Chapter 17
Technology Intelligence Map: Biotechnology

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Recently, biotech companies are increasingly attracting the attention from investors. From 2016, of the top 10 performers in the NASDAQ-100 (index consisting of 100 largest non-financial companies listed on NASDAQ), six were biotech. However, the reasons behind their success, or the actions that lead them to be successful, are still ambiguous. This chapter aims to give insights into the critical success factors in the biotech industry by analyzing the strategic and market data of the 10 biotech companies included in NASDAQ-100. Thus, the enterprise value (EV) of companies from 2002 to 2016 was considered to identify fluctuations that can be associated with key indicators such as R&D expenditure, corporate deals, patent portfolio, pipelines, and additional indicators. Our results give an overview of the main critical success factors and strategic actions, in a temporal manner, which the top-valued biotech firms fall into. The factors of highest importance included constant and high investment on R&D, intense transactions related to mergers and acquisitions for big biotech companies, and a favorable regulatory environment for drug approvals. Additional relevant factors involve the company's focus and a proper management of their innovations. This chapter opens a new perspective by understanding the consolidated critical factors among the top US biotech companies, indicating what they are dependent on to steer them to failure or success.

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17.1 Introduction

Biotechnology involves the integration of biological systems, living organisms, or genetic engineering to develop technologies on a wide range of applications in major areas, which include healthcare (medical), food and agriculture, environmental, and industrial. The worldwide biotech market was estimated at USD 369.62 billion in 2016 and is projected to reach USD 727.1 billion by 2025 (Grand View Research 2017). The sector is facing an unprecedented growth lately, and it is remarkably transforming the economy of the United States, the country with the largest biotech sector. Its contribution to the US economy was estimated to represent more than 2% of the gross domestic product (GDP), and from 2007 to 2012, the biotech aggregates' revenues have grown on an annual average rate of more than 10%, much faster than the US economy as a whole (Carlson 2016). The growth of biotechnology is largely driven by its applications in healthcare, which differs from the traditional pharmaceutical companies through the nature of their drugs. While biotechnology companies develop their drugs on a biological basis, the pharmaceuticals use traditional chemical-based drugs. However, both sectors intersect and complement each other to develop the so-called biopharmaceuticals (Rader 2008).

The progress of the industry is mainly motivated by factors such as massive R&D investments, intense protection of intellectual property rights, and also the establishment of cooperations and strategic alliances (Evens and Kaitin 2014). Moreover, advances in our understanding of the disease's molecular level triggered by the OMICs have led to significant improvements in drug discovery, consisting of identification of new targets and therapeutic molecules (Bilello 2005).

The huge R&D expenditure is the hallmark for the biotechnology industry, known to be one of the most R&D-intensive industry sectors in the world. Among the US industries, biopharmaceuticals have the highest R&D reinvestment as a percentage of the revenue, a rate of 21.3%, i.e., nearly 3 percentage points ahead of the semiconductor industry. The steps in the discovery and development through market approval are known to be costly and lengthy, besides being marked by financial risks due to failure in obtaining approval by regulatory agencies. The capitalized R&D cost for a newly approved biopharmaceutical was estimated at 2558 billion in 2014 (2013 US dollars), two times more than the cost 10 years from that time (DiMasi et al. 2016). Most of the R&D expenses go to the clinical phases to develop a drug's pipeline. Each stage can be very costly due to the complexity of human health, compounding, and response to treatment (Morgan et al. 2011). The surge in R&D expenses over the years resulted in an increased number of biopharmaceuticals in clinical development. In 2001, there are 369 biopharmaceuticals in the clinical phase, compared to 901 in 2012, an increase of 245% in the number of drug candidates (PhRMA 2013). The biggest increase was seen by the monoclonal antibody class, which grew 351% over the 11 years of analysis consisting of 338 from the 901 biologics in development in 2012. Monoclonal antibodies are not only the highest biopharmaceuticals class in development, but they are also the most approved in the USA and Europe (Walsh 2014). Thus, the high R&D expenditure,

as a consequence, allows companies to leverage their discoveries, submit new candidates for clinical evaluation, and if it fulfills all stages successfully, new drugs are approved, leading to revenue for companies.

Behind the steps of preclinical and clinical phases resides the strength of intellectual property rights. The healthcare biotechnology benefits the most from the patent system, which guarantees exclusivity in the commercial exploration of their technologies. The biotechnology intellectual property rights also take advantage from some peculiarities of the market, a biopharmaceutical product can carry multiple patents from the molecule involving different process and improvements (Evens 2016), also by changes in law in 2010 (by the Patient Protection and Affordable Care Act) awarded 12 years of data exclusivity from the approval date to biotech patents. On the other hand, more recently, the industry has been facing a patent cliff, with the expiry of patents of some top-selling biological drugs. This phenomenon opens up an opportunity for biosimilars, which are less costly and more long lasting than the reference biopharmaceuticals (Misra 2012).

Biopharmaceutical companies can disclose part of their knowledge stocks through patents (Erden et al. 2015). Besides the interest of biotech companies in protecting their products through patents, unexpected values from their patent portfolio can be extracted in many ways. A study led by Harlin and O'Connor (Harlin and O'Connor 2008) in 2008 discussed that biotech companies can leverage their intellectual property though nonexclusive or exclusive out-licensing, which is conducive for early-stage technology to raise capital and narrow the company's focus. By negotiating cross-licensing agreements with competitors promoting collaborations, the biotech companies can create opportunities to sell their intellectual properties or royalty streams to raise short-term capital and narrow the focus, and they can also obtain capital by using the patent assets as security for loans.

Another aspect of the biotech industry, which promotes the progress of the sector, is the frequent collaborations and mergers and acquisitions. In order to combine knowledge and resources for successfully developing a new product, biotech companies take advantage of alliances and cooperation (Haeussler et al. 2012). Historical data on R&D partnerships among pharmaceutical biotechnology companies revealed a pattern of overall growth since the mid-1970s (Roijakkers and Hagedoorn 2006). Cooperation is a common strategy of biopharmaceuticals; partnerships can arise from companies motivated by reasons related to sharing knowledge and R&D efforts to invest in a new path or drug class when the company has no expertise and to enter into a new market location through cooperation with firms that are geographically distant (Moorkens et al. 2017). Besides the high cooperation rate in biopharmaceuticals, the sector is massively influenced by its mergers and acquisitions. From Big Pharma's perspective, an interest in the market segment of biotechnology resulted in several acquisitions in order to achieve the right infrastructure and knowledge to develop their biopharmaceuticals (Moorkens et al. 2017). In 2016, the acquisition of biotech companies comprised 55% of all potential merger and acquisition value. The years of 2011, 2013, 2015, and 2016 were marked by mega deals (>US$ 5 billions) among biotech companies (Ernst and Young 2016). In

2015, mergers and acquisitions in the USA and Europe reached a high in terms of total potential value and volume records.

The biotech sector is dependent on mergers and acquisitions to accomplish their growth goals and during its life cycle, the initial public offering (IPO) is an important stage (Quintana-García and Benavides-Velasco 2016). Most of the US biopharmaceuticals, involved in the greatest deals, went public years ago on NASDAQ (National Association of Securities Dealers Automated Quotation System). NASDAQ differs from traditional stock exchanges because it is an electronic stock exchange, in which only shares of technological companies known as "New Economy" such as Apple, Google, Microsoft, Intel, and others are traded. The NASDAQ-100 Index includes the top 100 US and international nonfinancial companies listed on the stock market based on market capitalization. The index is updated quarterly and reflects companies in all major industry groups, including hardware and software, telecommunications, retail/wholesale, and biotechnology. By the end of 2016, six of the ten performers of the NASDAQ-100 index were from biotechnology. Overall, 10 biotech companies with a weight of 8.6% comprised the index by November of 2016, which includes Alexion Pharmaceuticals, Inc. (ALXN), BioMarin Pharmaceutical Inc. (BRMN), Incyte Corporation (INCY), Regeneron Pharmaceuticals Inc. (REGN), Vertex Pharmaceuticals Incorporated (VRTX), Biogen Inc. (BIIB), Celgene Corp. (CELG), Amgen Inc. (AMGN), Gilead Science Inc. (GILD), and Illumina Inc. (ILMN). As mentioned above, the NASDAQ-100 included companies based on its market capitalization; however, the metric does not represent the entire worth of the company such as the enterprise value (EV). Since the sector is marked by acquisitions, an accurate valuation of the company is very important for the negotiations.

EV is an economic metric used by economists and financial analysts to measure the value of a publicly traded organization. It is a way through which the market can determine the entire worth of a company, instead of just looking at its market capitalization (market cap) (Investopedia 2018). The EV formula includes extra information that balances out the sometimes-misleading figures provided by market capitalization. The measure of EV is given by the market value of common stock plus market value of preferred equity + market value of debt + minority interest minus cash and investments (A. H. CFA 2018). In more simple terms, EV would be the market cap plus the net debt. EV is a good indicator to measure an organization's value and it is especially useful when evaluating companies prior to a merger and acquisition (M&A), since it includes aspects such as debt and cash reserves, which could drastically change the actual value of a company in a potential deal. EV is sometimes referred to as the "takeover price" and it is considered to be more accurate than a regular market capitalization calculation (A. H. CFA 2018).

EV has also been consistently applied to value companies in academic studies. Aiming to compare US and Canadian equity markets and to assess whether those were integrated or segmented, King and Segal used statistical regressions, EV, and EBITDA (earnings before interest, tax, depreciation, and amortization) in order to compare companies' values (King and Segal 2008). Similarly, other studies also use EV and EBITDA in valuing companies for several purposes (Ribal et al. 2010;

Chullen et al. 2015; Sareewiwatthana and Janin 2017). In a study conducted to identify and analyze crucial value drivers for players in the mining sector, MacDiarmid et al. used EV as the metric, mentioning that the metric is especially useful for comparing the value of different companies (MacDiarmid et al. 2018). Mariani et al. used EV as a way to account for the performance of University spin-offs and investigated how technology transfer efforts and investments would influence the EVs, using the University of Pisa as a case (Mariani et al. 2018). Njowa and Musingwini criticized standard financial methods and statements for not accounting for future perspectives and factors, and proposed a new framework using the mining sector as a case, while admitting that EV is a more adequate measure of value than market capitalization (Njowa and Musingwini 2018).

Taking into consideration the aspects discussed above, this chapter aimed to trace a historical profile of the 10 biotech companies included on NASDAQ-100 index (November 2016) in order to identify critical success factors that lead them to outperform in the industry. The evolution of the EV between 2002 and 2016 was analyzed to get insights of the company's performance. The factors are shown and discussed with highlights on the current scenario for biotech during the period and each company's decisions and strategies which likely reflect on its EV. At the end, the identified factors are consolidated for an overview of what biopharmaceuticals depend on and what lead the sector to fail and succeed.

17.2 Data Collection

The criteria for selecting the companies were based on the NASDAQ stock market considering the biotechnology firms listed on NASDAQ-100 index (NDX). Ten biotech companies comprised the index by November 2013 including Alexion Pharmaceuticals, BioMarin, Incyte Corporation, Regeneron Pharmaceuticals, Vertex Pharmaceuticals, Biogen Inc, Celgene Corp, Amgen Inc, Gilead Science, and Illumina.

Information regarding the companies was retrieved from three main sources.

17.2.1 Financial Data

The database Thomson EIKON™, from Thomson Reuters, was used to gather financial data of the companies from 2002 to 2016. Thomson Reuters Eikon™ has the broadest and deepest financial data and offers a comprehensive solution for establishing customizable benchmarks for the assessment of corporate performance (Reuters 2018). Data related to company's income statements, operating metrics, balance sheet, deals, merge and acquisitions, major costumers, ratio key metrics, ratios profile value, and risk were extracted from the database. Some key information including EV, net income, revenue, R&D expenditure, company's pipeline and

deals' description were compared among companies. Additional information available through the database was collected when needed.

17.2.2 Patent Data

The intellectual property assets from companies were collected from the Derwent Innovation (formerly Thomson Innovation) of *Clarivate Analytics*. The database provides access to global patent data covering more than 50 patent issuing authorities, with English translations from 30 languages (Clarivate Analytics 2018). The patent portfolio from all corporate tree members of each biotech company was collected based on the earliest priority data ranging from 2001 to 2016 and grouped by INPADOC (International Patent Documentations) families.

17.2.3 Company's Annual Reports

The annual reports from the 10 US biotech companies listed on NASDAQ-100 were manually downloaded from the company's website available to investors. The reports were used to gather detailed information regarding the company's strategies, decisions, purposes behind their deals, drug's pipeline performance, and company's future perspectives.

Additional information available online related to financial news, opinions from financial analysts and experts, reports from consulting firms to the sector was also used for supplementary support to our findings.

17.3 Results and Discussion

The EV for the ten companies analyzed in this chapter are shown in Fig. 17.1 for the years 2001–2017.

On the individual firm analysis level, Amgen started out as the most valuable company with an EV of $60 billion in 2002, while the remaining nine companies started out with EVs less than $10 billion. It is interesting to notice the evolution of Gilead overtime – the company's curve shows major spikes and ends up with an even higher EV than Amgen (around $110 billion). Celgene finishes the period with an EV of approximately $95 billion, while Biogen comes in fourth place with an EV of approximately $55 billion, both detaching themselves form the lower tier group of companies. After these four companies, Regeneron and Alexion show up with approximately $35 and $30 billion, respectively. The remaining four companies finish 2016 with EVs equal to or less than $15 billion. Although there are different patterns followed by each individual firm, one can notice that some patterns are

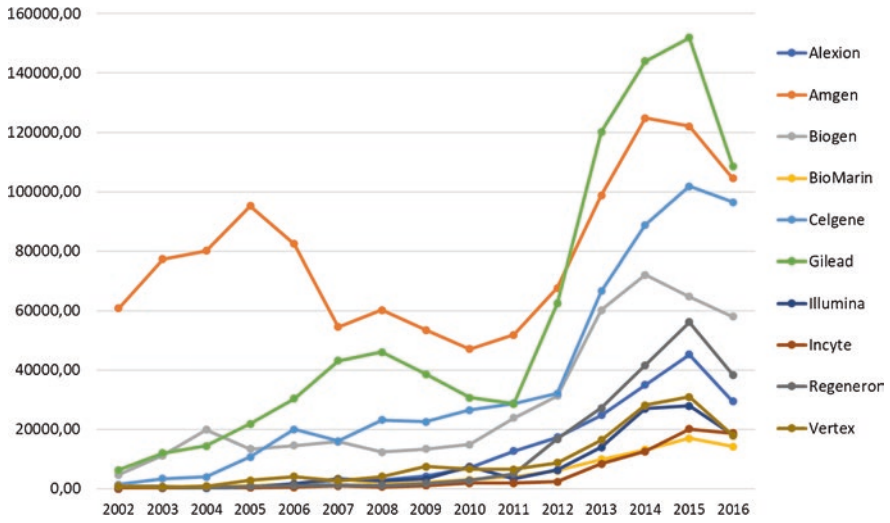

Fig. 17.1 Enterprise Values from 2002 to 2016 of US biotech companies

observed in the curves of all ten companies. For instance, it is noticeable that in the period 2011–2012, all ten companies experienced a spike in their EVs (to a greater or lesser extent, depending on each case). Additionally, precisely, the opposite is observed around 2015, when nearly all ten companies see their EVs fall down drastically and rapidly. All of these points are discussed in subsequent sections of this chapter.

A study published in 2010 showed that survival of a company on a stock market such as NASDAQ is directly dependent of the patents they hold (Wagner and Cockburn 2010). Since NASDAQ include high-technology companies and the biotech sector is absolutely dependent of intellectual property rights, the patent portfolio from each biotech company studied in the present research was plotted for further analysis. Figure 17.2 brings the patent family count the companies first filed from the period of 2001 to 2016. The chart shows that Incyte starting invested deeply in intellectual property in 1997 (almost 250 patents – data not shown) but quickly losing momentum and being surpassed by Amgen, which files the highest number of patents from that year until 2012, when Celgene starts catching up. Gilead, Biogen, and Vertex also show strong intellectual property output throughout those years, and Illumina and Regeneron get close to 50 patents in 2014. The remaining companies stay, for the most part of the reported period, below the line of 20 patents.

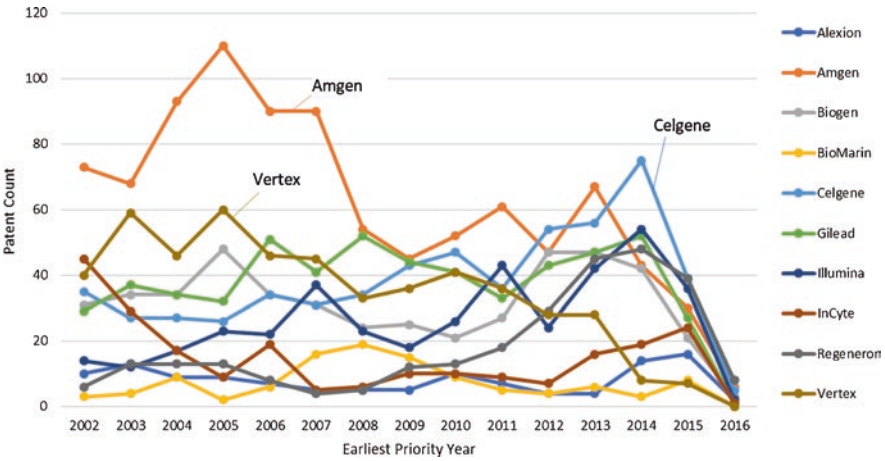

Fig. 17.2 Patent count from 2001 to 2016

17.3.1 Company's Features and EV Performance

17.3.1.1 Alexion

Alexion Pharmaceuticals Inc. is a Connecticut-based (moving to Boston in 2018) pharmaceutical company, founded in 1992 (IPO in 1996), best known for its development of Soliris (eculizumab), a drug used to treat rare disorders such as atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH). Soliris is considered one of the world's most expensive drug (Z. I. Research 2018) approved by FDA in 2007 which subsequently reflected the company's EV's historical rise since then. The hemolytic–uremic syndrome epidemic in 2010 also helped to boost Soliris sales impacting on Alexion's EV from about $10 billion to more than $40 billion in less than 5 years and landing it in NASDAQ-100 in 2011. Alexion has completed three major acquisitions to date, which are antibody, hypophosphatasia treatment, and rare disease-related drug. The company has been raising its R&D spending every year with bigger leaps starting after 2007 (going from $10 million to $757 million from 2002 to 2016). The company has done a total number of 13 deals (including M&A (7), Equity (2), and loans (4)) with the biggest acquisition being Synageva Biopharma Corp for $7.6 billion in 2015. Alexion's main strategy is to target rare diseases. With this purpose, Alexion shortened FDA approval times and cut trial costs, leading to a more productive pipeline in addition to the fact that rare diseases are normally ignored by big pharma companies. Although Alexion's drug prices are high, it approaches public relations firms to help families institute campaigns to pressure their governments to pay for the drug ("How a pharmaceutical firm priced its life-saving drug at $500K a year" CBC News. [Online].). Alexion's second drug Strensig received FDA approval in 2015, which was part of their 2011 acquisition of Enobia. Also, Kanuma drug was

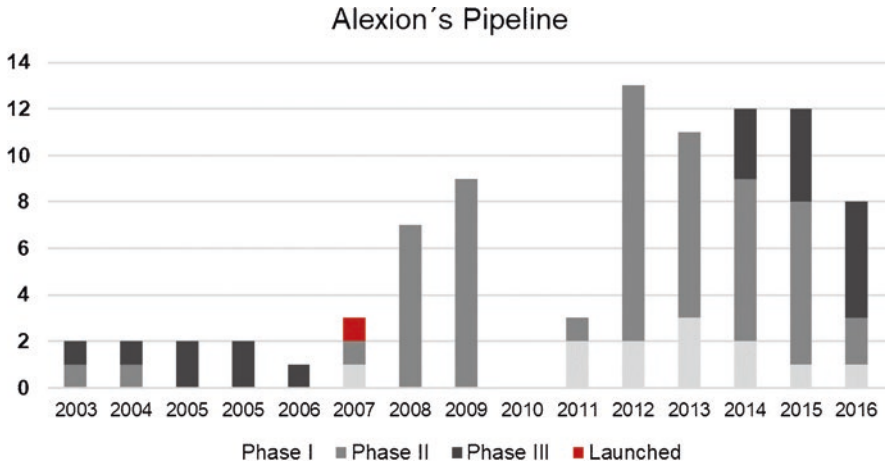

Fig. 17.3 Alexion pipeline from 2003 to 2016

approved in 2015 and was connected to their Synageva acquisition (with $1 billion in projected annual sales ("Biotech blastoff: Synageva up 112% on $8B Alexion deal," USA TODAY. [Online].)). In October 2017, the FDA approved the use of Soliris to treat adult patients with generalized myasthenia gravis (gMG) and in November 2017, the company received a patent for Soliris from the Japanese Patent Office. Figure 17.3 brings the company's pipeline evolution in terms of drug candidates in phases I, II, and III.

17.3.1.2 Amgen

Amgen is one of the world's leading biotechnology companies focused on the treatment of serious disease through the discovery, development, and manufacturing of innovative treatments. Amgen is among the biopharma companies which spend the most in R&D. Besides the expense being very high, the percentage of the R&D of the revenue was constant between 2002 and 2016, around 20% of the revenue; recently, the ratio decreased in 2015 (18.7% of the revenue) and 2016 (16.7%).

The company's therapies are very diverse, consisting of sixteen drugs including six recombinant peptides, five monoclonal antibodies, and one oncolytic virus. The company is very intense in protecting their discoveries through patents, mostly international deposit (as PCT), besides new inventions falling dramatically after 2007 (Fig. 17.2). The drug discovery activity of Amgen is focused on drugs that hit a target or has a mechanism of action that no existing drugs address. The company is constantly testing new products in clinical trials as seen by the high number of late-stage drugs. After 2011, Amgen was with 10 (or more) candidates undergoing testing in phase III – Fig. 17.4.

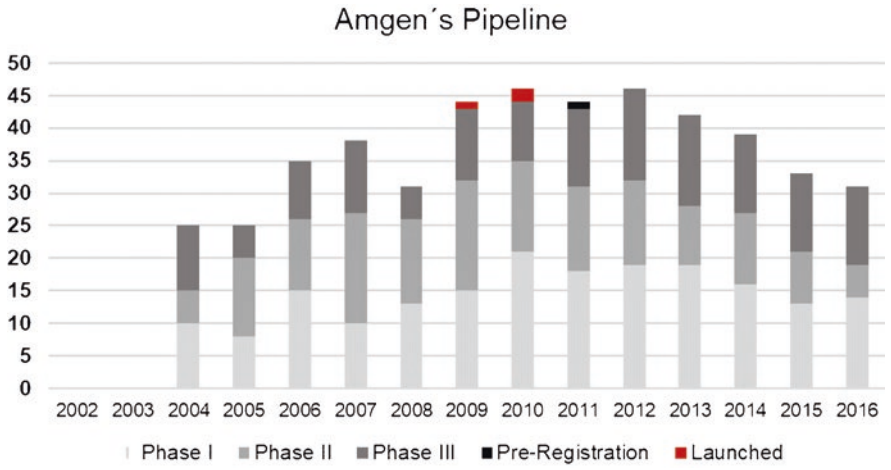

Fig. 17.4 Amgen pipeline from 2002 to 2016

The company had an expressive growth between 2002 and 2005 driven by significant merge and acquisitions (M&A). As in 2002, it was the world's largest biotechnology company, after completing the acquisition of Immunex Corporation, a leader in inflammation and one of biotechnology's premier companies. The acquisition on a $16 billion deal was the largest so far of one biotech company acquiring another. Two years later, Amgen acquired Tularik, a pioneer company in drug discovery related to cell signaling and the control of gene expression, for $1.3 billion. At the time, Amgen did not have any exciting new drugs under development to sustain its rapid growth, and with the acquisition, Amgen aimed at the Talariḱs research talents besides any specific molecule on its pipeline. In 2005, Amgen agreed to acquire Abgenix for approximately $2.2 billion. The acquisition gave Amgen full ownership of one of its most important advanced pipeline products, panitumumab, and consequently eliminated the need of royalty payment on denosumab, another important pipeline drug.

During 2006–2010, the company experienced a dramatic fall in EV for many reasons. One was about the concerns for the use of Aranesp, a flagship drug, in cancer patients, which showed on clinical trials that it could make cancer worse and shorten patient survival. As a result, in 2007, the FDA issued a black-box warning about the potential side effects of Aranesp, which led to sales decline in the following years. In subsequent years, Amgen faced a lawsuit about the Aranesp scheme, accused of boosting drug sales along with the International Nephrology Network and ASD Healthcare, a wholesaler owned by AmerisourceBergen Corp. There were some other issues that Amgen had to face from 2007 to 2009, such as FDA approval delays on its most promising drug at the time, the monoclonal antibody denosumab, followed by some failures on clinical trials for other drug candidates.

Amgen started rising in EV after 2011, thanks to the numerous mergers and acquisitions. At total, it was 8 M&A in 2011 totaling $7 billion, 4 in 2012 totaling

$2.6 billion, and 2, which included the acquisition of Onyx Pharmaceuticals in 2013, totaling $9.1 billion. Onix Pharmaceuticals developed carfilzomib, one of the major drugs on sales of Amgen. In 2011, Amgen acquired for $1 billion a venture-funded, biotechnology company named BioVex Group, Inc., owner of OncoVEX (GM-CSF), a novel oncolytic vaccine in Phase 3 clinical development to treat melanoma and head and neck cancer, which were approved by FDA in 2015.

In 2012, Amgen acquired Micromet ($1.1 Billion), a biotech company focused on the discovery, development, and commercialization of antibody-based therapies for the treatment of cancer. At the same year, Amgen acquired Mustafa Nevzat (700MM) to expand its presence in Turkey and the surrounding region. At the end of the year, the company acquired Decode Genetics ($415 million), a global leader in human genetics, to strengthen the identification and validation of human disease targets.

17.3.1.3 Biogen

Biogen Idec Inc. (NASDAQ: BIIB) is an American multinational biotechnology leader in the discovery, development, manufacturing, and commercialization of innovative therapies for the treatment of neurodegenerative, hematologic, and autoimmune diseases. The company R&D expenses turned around an average of 25% of the revenue from 2002 to 2016, and the ratio was nearly constant each year, but it dropped to an average of 18% of the revenue in 2014–2016.

Currently, the company has 12 therapies including three biosimilars and many other drugs under development on its pipeline. From the current therapies of Biogen, eight are immunotherapy-based, being six monoclonal antibodies (natalizumab, daclizumab, obinutuzumab, rituximab, and the biosimilars infliximab and adalimumab) and two interferons: one interferon beta1-a and its pegylated form. Before 2002, the company had two FDA approvals (Avonex and rituximab) and two approvals for other companies of drugs licensed from Biogen. It is worth mentioning that in-licensing of drugs is also a key part of building Biogen's pipeline. There are also three phase III drugs on its pipeline, a monoclonal antibody (aducanumab) and a BACE1 inhibitor for Alzheimer disease, and a monomethyl fumarate prodrug for multiple sclerosis. The company had a powerful drug development engine which resulted in several FDA approvals of drugs independently commercialized, in cooperation with biotech and pharmaceutical companies and also drugs which were sold/transferred to other companies, resulting in royalties for their commercialization. Its pipeline consisted of several new candidates being tested, late-stage drugs, and many on pre-registration phase since 2011, which could possibly lead to an increase in EV after this year – Fig. 17.5.

The second largest acquisition involving two biotech companies was the merging of Biogen with Idec Pharmaceuticals on a $6.8 billion deal in 2003; the first was Amgen's acquisition of Immunex which has been described previously. With the merger, two blockbuster drugs were commercialized by the newly Biogen Idec company, rituximab originally from Idec (U.S. sales shared with Genentech) and

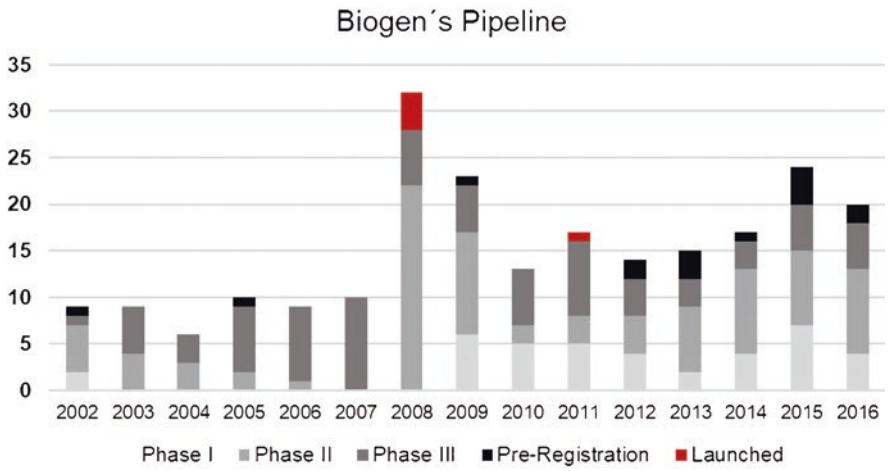

Fig. 17.5 Biogen pipeline from 2002 to 2016

Avonex from Biogen. Idec also had another drug named Zevalin, which was sold to Cell Therapeutics in 2007 for up to $30 million. The merger resulted in a growth of 78% of EV in 2004 driven by significant achievements: one was the first full year as a combined organization and also the outstanding performance of Avonex and rituximab. Another major acquisition by Biogen was the European Fumapharm AG, which develops therapeutics derived from fumaric acid esters. The acquisition provided support to the company's interest in treating multiple sclerosis, since Fumapharm had a co-developed drug with Biogen named at the time BG-12 (later Tecfidera), which would become one of the top sellers for Biogen. Also in 2007, Biogen acquired Syntonix Pharmaceuticals, which at the time had two drugs to treat hemophilia, Eloctate and Alprolix, and the acquisition resulted in intense sales for Biogen and in 2016, Biogen announced the spin-off Bioverativ for the its hemophilia business to keep the focus on its core multiple sclerosis portfolio. Biogen did also some small acquisition after 2007, and the largest was the Convergence Pharmaceuticals in 2015 for $675 million.

The year 2012 was very successful for the company, driven by the progress to late-stage pipeline in clinical trials and upcoming product launches (Tecfidera and hemophilia drugs). The revenue growth of natalizumab and Avonex was also a significant factor for the EV growth in 2012.

17.3.1.4 Biomarin

BioMarin is a world leader in developing and commercializing innovative biopharmaceuticals for rare diseases driven by genetic causes. Its mission is to bring new treatments to market that will make a big impact on small patient population. A leading source for global clinical trial information, *Center Watch,* named Biomarin

as one of the fastest drug developers in the industry in its monthly report in September 2014.

The company's strength to develop new drugs is explained by its massive R&D investments each year. In 2002, the company had no revenue, but even then, it invested around 27 million in R&D. After the approval of Aldurazyme in 2003, the company started earning revenue and invested massively in R&D, reaching 445% of the revenue in this year. In 2004, 268% of the revenue was invested in R&D and 219% in 2005. After 2005, the company started increasing its revenue each year after drugs approval by FDA, and the expressive investment in R&D was still high. From 2012 to 2016, the company invested an average on 64% of revenue in R&D.

The giant R&D investments resulted in a series of successful therapies and FDA approvals initiated in 2003. The first drug to treat mucopolysaccharidosis type I (MPS I), Aldurazyme (which was commercialized by Genzyme Corporation), was approved in Europe and by the FDA in 2003. Two years later, the FDA approved Naglazyme, making the second drug to treat MPS and the first drug independently commercialized by the company. In 2007, the FDA approved Kuvan for the treatment of phenylketonuria (PKU); it was the first medication to treat this condition. Kuvan was also approved in Europe, Japan, and Canada in the following years. In 2014, Vimizim received FDA approval for Morquio A syndrome, the first treatment for this condition. At the same year, Vimizim was also approved in Europe, Canada, and Australia. Lastly, in 2017, the FDA and the European Commission approved Brineura to treat patients with CLN2 disease, a form of Batten disease. It is worth mentioning that Biomarin has no direct competitors for their products.

Biomarin did some major acquisitions during its history. The first one was Glyko Biomedical, a leading provider of carbohydrate-related research reagents, processing enzymes, and analytic products, for $228 million in 2002. In 2009, Biomarin acquired Huxley Pharmaceuticals, focusing to get access to a proprietary therapy to treat a rare autoimmune disease, the Lambert Eaton Myasthenic Syndrome (LEMS). The therapy, named Firdapse by Biomarin, was approved in Europe in 2010. The next major acquisition was Lead Therapeutics, an early-stage development company, with a key asset, a PARP inhibitor. Biomarin acquired Lead for 97 million in 2010, then sold the PARP inhibitor (BMN673), already in phase III to treat advanced breast cancer, 5 years later for 570 million, keeping its efforts on rare diseases. Still, in 2010, Biomarin also acquired ZyStor Therapeutics, a biotech company developing a novel class of targeted protein therapeutics enhanced with the company's proprietary glycosylation independent lysosomal targeting (GILT) technology, which was incorporated further by many drug candidates in clinical trials. The biggest acquisition was the Dutch Prosensa, which had as the key asset an experimental Duchenne muscular dystrophy treatment named Drisapersen (Kydrisa), which failed in phase 3 and was rejected by the FDA in 2016. Recently, there are some speculations about Biomarin being acquired by giant pharmaceuticals and biotech companies such as Gilead and Sanofi. Figure 17.6 brings the company's pipeline evolution in terms of drug candidates in phases I, II, and III.

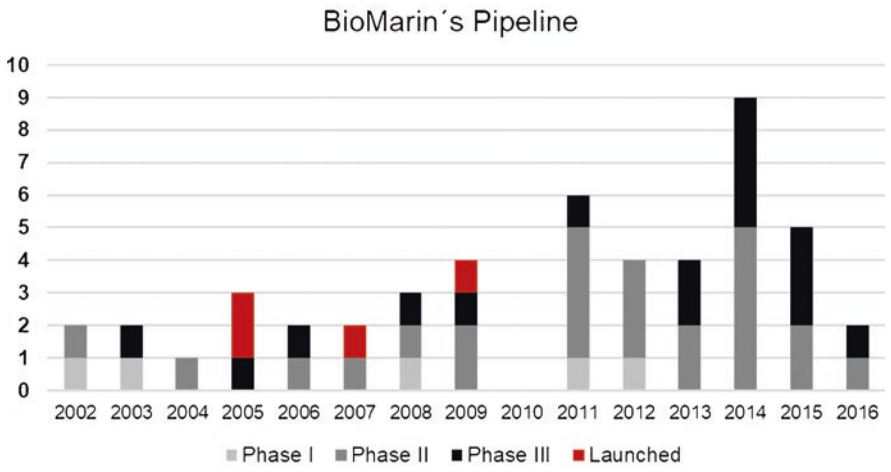

Fig. 17.6 Biomarin pipeline from 2002 to 2016

17.3.1.5 Celgene

Celgene, headquartered in Summit, NJ, was founded in 1986 with its initial public offering (IPO) 1 year later. Having received several recognitions and awards, including Fortune 500's fastest-growing pharmaceutical companies (Awards & Recognition 2016), the company focuses on oncology medicines and has multiple products in the pipeline, in the areas of multiple myeloma, leukemia, lymphoma, and others. The company has successfully developed several medicines in different areas and has three major centers for research and development: The Celgene Institute for Translational Research Europe (CITRE) in Seville, Spain; the Celgene Translational Development center in San Francisco; the Drug Discovery & Alliance Development center in San Diego.

The company is actively making deals, having completed 35 M&A in the period 2008–2017, totaling $45 billion. In 2010, Celgene acquired Abraxis BioScience in a transaction of almost $3,5 billion, in an attempt to enlarge their portfolio of oncology-related products. Abraxis had in its portfolio drugs that attack solid tumors, and although the transaction amount was considered very high, Celgene was confident that Abraxis was a perfect fit and also would be able to boost sales of Abraxis' existing drugs (Celgene to buy Abraxis BioScience for $2.9 billion 2010). In 2016, Celgene finalized a deal that had started in 2013 and acquired part of the assets of Acetyon Pharmaceuticals – a deal totaling $1.7 billion – bringing more cancer-related drug candidates to its pipeline (Xconomy 2016). In 2015, Celgene acquired Receptos for more than $7 billion. Expecting to attack markets with very large patient populations, Celgene yielded from Receptos medicines (candidates in the late stage of development) that address multiple sclerosis and inflammatory bowel disease.

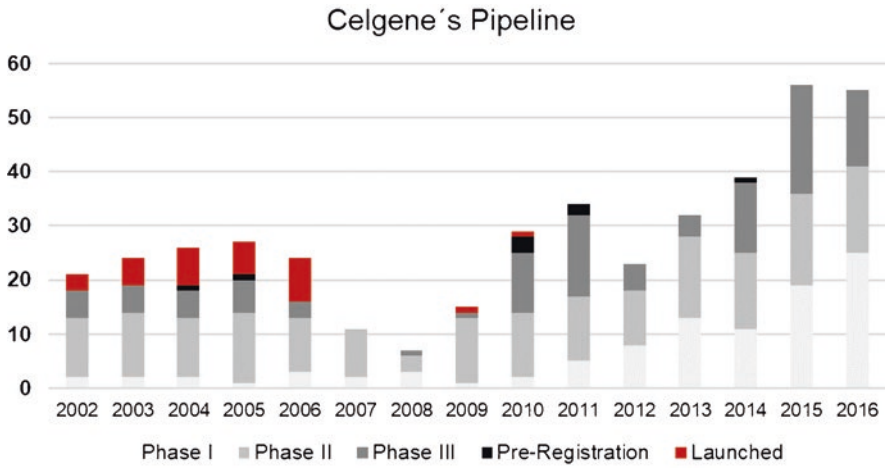

Fig. 17.7 Celgene pipeline from 2002 to 2016

Celgene's pipeline is large and had 14 products in clinical phase III as of 2016 as Fig. 17.7 shows. The company's portfolio is also large and it grows larger with every acquisition Celgene completes. Among the drugs within the portfolio, Revlimid, Abraxane, and Otezla could be listed as the most important ones – but some of their drug candidates are also considered to have an extremely high potential. Revlimid is a drug used to fight multiple myeloma (MM), myelodysplastic syndromes (MDS), and mantle cell lymphoma (MCL), and was first approved by the FDA in 2005, having had several subsequent approvals for different applications. Abraxane, originally developed by Abraxis BioScience, is a drug used to treat metastatic breast cancer, advanced non-small cell lung cancer and metastatic pancreatic cancer – this drug was approved by the FDA in 2005 for usage in metastatic breast cancer, but received other approvals in 2012 and 2013 for lung and pancreatic cancer. Otezla, the first pill to treat psoriasis, is prescribed to treat plaque psoriasis and active psoriatic arthritis, and it was approved by the FDA in 2014.

The income of Celgene has been steadily on the rise, going from $136M in that year to $11B in 2016. As opposed to other biotechnology companies, Celgene has not only achieved high income but also has enjoyed profits for most years since 2002 – profits have risen to almost $2 billion in 2016. In fact, between 2002 and 2016, the only year for which the company reported losses was in 2008 (a loss of $1,5 billion), and that is attributed to fees associated with the acquisition of Pharmion in the same year (Celgene swung back to profits in the first quarter 2009). Similar to the income, R&D investments have also been steadily increasing, going from $85 million in 2002 to $4,4 billion in 2016.

17.3.1.6 Gilead

Gilead Sciences is an American biopharma company based in Foster City, California. The company's main area of success and focus has been the treatment of Hepatitis C (Harvoni and Sovaldi), but allocates a great deal of R&D investment in treating antiviral drugs used in the treatment of HIV, hepatitis B, and influenza.

The already strong pipeline base and on top of that innovative drugs like Sovaldi and Stribild helped Gilead to become a gargantuan force in the biotech industry by increasing their shares by more than 400% since 2009 (Williams 2015). Initially, Gilead started with developing antisense with the help of Glaxo followed by their IPO in 1992 with about $86 million in raised proceedings. After selling the antisense IP, they started focusing on AIDS drugs through partnerships and acquisitions (1996–2002). However, in 2002, they shifted their concentration solely on antivirals and jettisoned their oncology knowledge to OSI Pharma for $200 million dollars. Gilead stayed focused on antivirals until 2006 where they added cardiovascular and respiratory drugs to their portfolio by acquiring Myogen Inc. and Corus Pharma Inc.. This helped them in having a steady rise in the EV from 2006 to 2008. In the meantime, acquisition of Raylo Chemicals Inc. helped them to increase their profits margin by bolstering their supply chain in terms of ingredients and intermediates. Gilead strengthened its position in the cardiovascular and respiratory fields by acquisitions in 2007 and 2009. In the meantime, they kept strengthening their portfolio through acquisitions of companies like Arresto Biosciences, CGI Pharmaceuticals, and Calistoga Pharmaceuticals. An important point in Gilead's success is definitely the acquisition of Pharmasset Inc. for about $10,8 billion. As a part of this acquisition, they got Sovaldi in their hands, which turned out to be phenomenal blockbuster drug for the treatment of Hepatitis C. This drug minimized the side effects of the previous drugs and raised the success rate to over 94% of the patients (Keating 2015). This acquisition helped their EV to rocket to over $140 billion from 2011 to 2015. The revenue generated from these drugs helped them to bolster their R&D spending from $142 million in 2002 to $4.2 billion in 2016. The M&A consequently led to the increase in the products in their pipeline as well (from 3 products in 2002 to 22 in 2011 and 25 in 2016). In 2015, the three acquisitions made by Gilead strengthened their explorations into nonalcoholic steatohepatitis, cancer therapy, and anti-inflammatory drugs, as they sensed the need to broaden their pipeline horizons. This action was taken as Gilead realized that they have more competition in the Hepatitis C field as Merck & Co. marketed Harvoni, which is the combination of Sovaldi and Ledipasvir, leading to litigations with Gilead. AbbVie launched a competing treatment for hepatitis C as well, which forced Gilead to sell at more competitive prices. They slowed down on the acquisitions in the recent years, missing out on the acquisitions of Pharmacyclics and Medivation in 2016 (Campbell 2018) and this chain of events added to other reasons decreased Gilead's EV to less than $110 billion in 2016.

Although the hepatitis C market seems to be leveling off, it should be taken into account that the addressable market for that is still huge. They finally made another big acquisition in the oncology field in 2017 with Kite Pharma ($11 billion), which

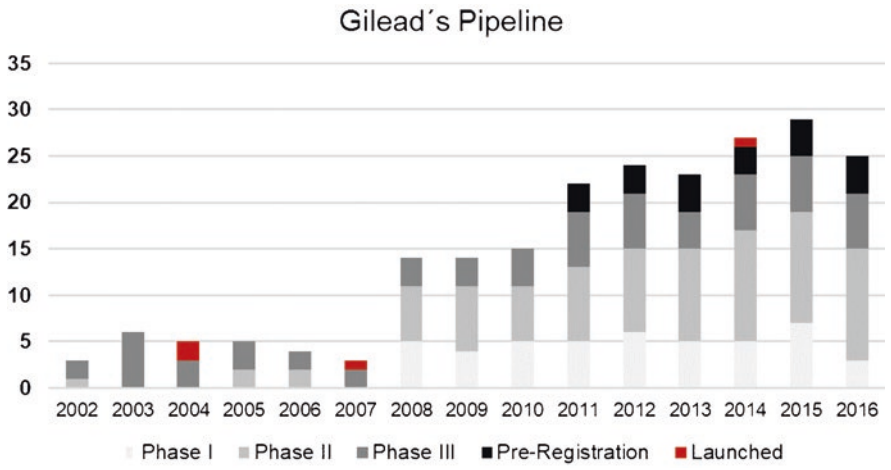

Fig. 17.8 Gilead pipeline from 2002 to 2016

has 14 clinical trials ongoing or planned targeting 10 cancer indications which can potentially boost Gilead's EV and maintain their sales with its drugs. All these new acquisitions and industry climate mean that hepatitis C is no longer going to be the sole focus of Gilead and they need to go after (already going) fields such as hepatitis B, cancer, and HIV more aggressively on a quest of finding their new blockbuster drug while their current cash cows are still standing. Figure 17.8 brings the company's pipeline evolution in terms of drug candidates in phases I, II, and III.

17.3.1.7 Illumina

Illumina Inc. is a San Diego-based company established in April 1998 (IPO 2000) that develops, manufactures, and markets integrated systems for the analysis of genetic variation and biological function. It produces a line of products and services revolving around sequencing, genotyping, and gene expression and proteomics markets. Illumina's biggest achievement is reducing Personal Full Genome Sequencing price from around $48,000 (June 2009) to around $4000 (May 2011) serving the academic, government, pharma, biotech, and other industries. Illumina was in the business of selling research instruments until 2010 before getting the FDA approval for BeadXpress for multiplex genetic analysis. This was the start of their EV increase going from $8 billion in 2010 to $28 billion in 2016. Illumina went through acquiring Epicentre Biotechnologies in 2011. The move was followed by the introduction of HiSeq X with cheaper and faster sequencing capabilities, helping them to own about three-fourths of the genome sequencing machines market by 2014 and producing more than 90% of the produced genome data (Regalado 2018). Since 2011, Illumina has been offering gene sequencing management and analysis platform (BaseSpace). The acquisition of GenoLogics in 2015 helped them

to bolster their lab info management capabilities. Illumina has been selling NovaSeq and HiSeq in a pretty stable way. Illumina has been following the goal of achieving $100 gene sequencing making its addressable market way bigger as discussed by its CEO de Souza. They have acquired 10 companies in total (biggest being Verinata Health Inc for $450 million in 2013). Their R&D spending has risen from $26.8 million in 2002 to $504.4 million in 2016 concurrent with widening the increase gap each year ($103 million increase in R&D spending between 2015 and 2016). Illumina has done 23 deals in total in which 20 of them are M&As ($9 billion), and 3 are equities.

17.3.1.8 Incyte

Incyte, founded in California (Palo Alto) in the early 1990s, is headquartered in Wilmington, Delaware. Focusing on oncology-related medicines, the company has several molecules under development and dozens of discoveries being further developed, some of which are in the clinical proof-of-concept stage. Being keen on the importance of collaborative research and development, the company has several license agreements and collaborations with important players in the industry, for example, Novartis and Eli Lilly, and has two medicines approved in 2016, one in the USA and one in Europe. Later in 2016, with the acquisition of ARIAD Pharms, a third drug – Iclusig – was added to the European portion of the company's portfolio.

In order to strengthen its pipeline and portfolio of oncology drugs, Incyte has reached a deal with Merus NV in 2016, a Dutch pharmaceutical company. The deal indicates that Incyte has exclusive rights for 11 of Merus antibody discovery initiatives, and Incyte has also bought $83 million worth of Merus shares – a total of 3.2 million shares. Also, in 2016, Incyte acquired ARIAD Pharmaceuticals, in a $274 million agreement, strengthening even further its presence in the market for oncology medicines. The deal gives Incyte exclusive rights for the commercialization of a kinase inhibitor called Iclusig (ponatinib) to fight chronic myeloid leukemia.

Analyzing Incyte's pipeline, it is very interesting to note that the company had, as of 2016, 21 drug candidates in the clinical phase II, as shown in Fig. 17.9. Provided the company is able to bring some of those drugs to the market, it might translate into a huge growth potential. However, it is also noteworthy that the number of early-stage development cases has been very low in the last few years, and the company has no drug candidates in phase I as of 2016. Incyte's portfolio has three drugs: Jakafi (ruxolitinib); Iclusig (ponatinib); Olumiant (baricitinib). Jakafi is used to treat myelofibrosis and polycythemia Vera, and was FDA approved for the first application in 2011 and for the second application in 2014. According to Incyte's annual report for 2016, Jakafi's sales have largely driven the company's spike in revenues in the past few years. Iclusig is indicated for adults suffering from different kinds of leukemia and also a specific type of abnormal gene (T315l-positive) – this drug is approved for markets in Europe, but has not received FDA approval. Olumiant, also approved for markets in Europe, is used to treat severe rheumatoid arthritis when previous therapies are not tolerated by the patient. Interestingly, FDA

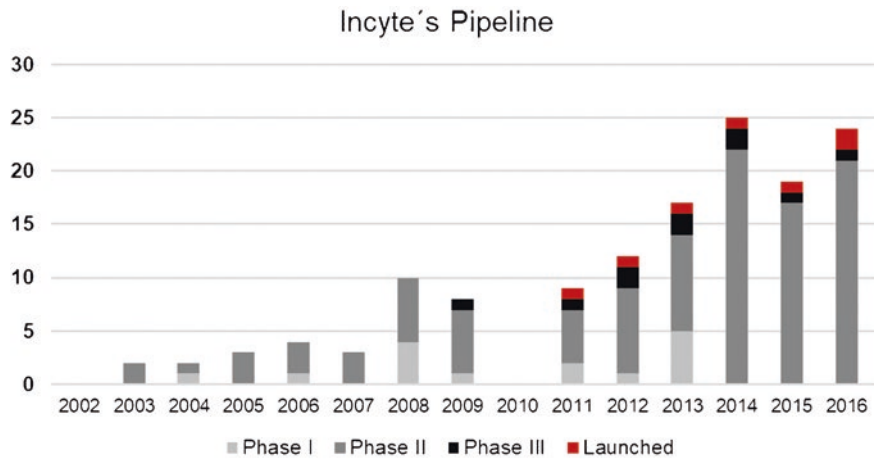

Fig. 17.9 Incyte pipeline from 2002 to 2016

did not approve this drug, rather asking for more data, which can severely delay the approval (U.S. FDA 2017).

In the period 2004–2009, the income has varied from $9M to $14M, and after 2010, the income has steadily increased, reaching $1,1 billion in 2016. In the period 2004–2016, the R&D investments have also increased steadily, reaching $581 million in 2016. Regarding profits, the company has presented losses until 2014. In 2015, Incyte has had small profits ($6,5 million) and in 2016, the company enjoyed over $100 million.

17.3.1.9 Regeneron

Regeneron was founded in 1988 and it is headquartered in Tarrytown, NY. The company employs more than 5,000 people – more than 700 of whom are PhD, MD, or PharmD candidates – and currently has 6 FDA-approved medicines in its portfolio, while also working on more than 15 different antibodies currently undergoing clinical trials. Regeneron has invented a series of technologies that aim to accelerate and improve the success rates of drug's R&D, with collaborations with big pharmas such as Sanofi and Bayer. Regeneron focuses on seven research areas for its drug development: cardiovascular and metabolism, infectious diseases, inflammation and immunology, oncology, ophthalmology, pain, and rare diseases.

In the period 2008–2017, Regeneron was part of eight deals, totaling $770 million dollars. In 2013, Sanofi acquired Regeneron shares, and in 2016, Regeneron acquired two companies: Intellia Therapeutics and Biomed Ritty. Intellia has developed treatments for numerous applications such as liver diseases, blood diseases, and cancer, and also is one of the pioneers in the Crisp-Cas9 technology, which focuses on gene identification and selection as a way to treat diseases.

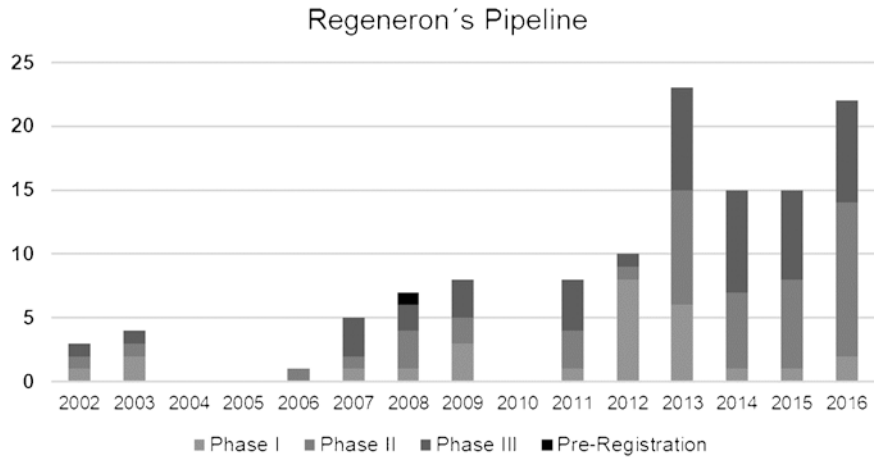

Fig. 17.10 Regeneron pipeline from 2002 to 2016

As demonstrated in Fig. 17.10, the company's pipeline was fairly modest until around 2011, when more candidates were introduced (in 2013, there were 23 candidates in the pipeline) and as of 2016, 22 products are either in phases I, II, or III. The portfolio of Regeneron is composed of five drugs, namely Arcalyst, Dupixent, Eylea, Kevzara, and Praluent. According to Regeneron's annual report for 2016, Eylea was responsible for the biggest share of the company revenues – $3.32 billion dollars. The drug is used to treat several types of macular degeneration and macular edema and it received FDA approval in 2011 for age-related macular degeneration.

Regeneron's income had been steadily increasing from 2007 to 2011, year in which the company had $445 million as revenue. In 2012, however, after the launch of Eylea partnered with Bayer, revenues skyrocketed to $1.3 billion dollars and it kept on growing – in 2016, the company had $4.8 billion in revenues. The investments in research and development have also been very strong and constantly growing. In 2002, the company invested $22 million, whereas in 2016, the amount of dollars spent in R&D was over $2 billion. With regard to profit, Regeneron has experienced losses in the period 2002–2011 (with the exception of 2004 when the company had a profit of a little over $40 million). In 2012, however, also after launching Eylea, profits came back and rose to $750 million in that year. In 2016, the net income was almost $900 million.

17.3.1.10 Vertex

Vertex was founded in 1989 and it is headquartered in Boston, Massachusetts. The company has employed more than 2000 people – two-thirds of whom actively work in research and development activities. Vertex has two approved medicines and several others in the pipeline, in the areas of cystic fibrosis, acute spinal cord injury,

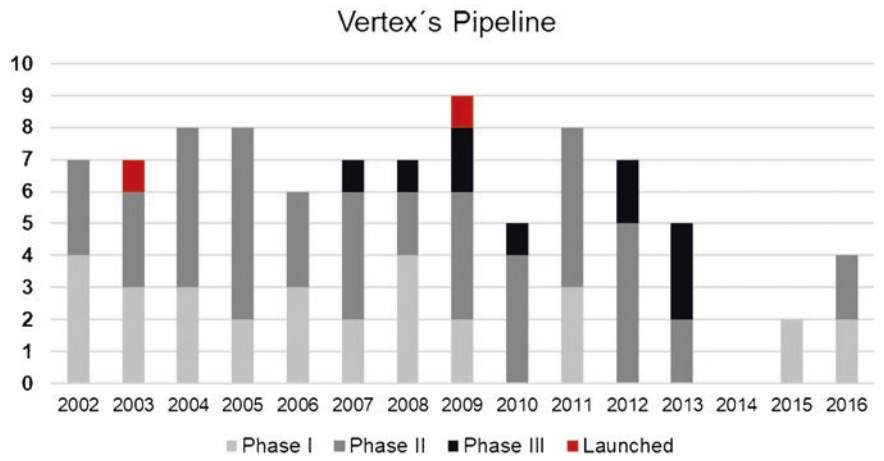

Fig. 17.11 Vertex pipeline from 2002 to 2016

oncology, pain and influenza. In 2009, Vertex had its drug Telaprevir undergoing development in Phase III, and in the same year, following their strategy of focusing on hepatitis C medicines, the company acquired ViroChem Pharma. ViroChem, another US-based biotech company, had at the time two promising drug candidates that tackled the hepatitis C virus, HCV (VCH-222 and VCH-759).

The pipeline variation in terms of clinical phases 1–3 for the years 2002 until 2016 is depicted in the Fig. 17.11. Vertex has developed a drug to tackle HCV called Telaprevir, in partnership with Johnson & Johnson and other companies, and is marketed by different companies and under different brands across the globe. Telaprevir received approval by the FDA in 2011. The company currently has two products in their portfolio: Orkambi (lumacaftor/ivacaftor) and Kalydeco (ivacaftor). Orkambi is a drug developed to target the root causes of cystic fibrosis and is administered to people who are 6 years of age and older and received approval from the FDA in 2015. Kalydeco, also developed to treat patients with cystic fibrosis, is administered to people who are 2 years of age and older and received approval from FDA in 2012.

Although the company has been obtaining increasing revenues (that jumped to more than $1 billion in 2011), the R&D investments are also massive ($1 billion in 2016) and the company has not enjoyed profits, except a small profit in 2011. New drug prospects and increased sales from existing drugs in their portfolio could change this scenario, however – the company's net income in 2014 was -$738 million in 2014, but has advance to -$112 million in 2016.

17.3.2 Companies' Key Success Factors

This chapter intended to identify the key factors that led biotech companies to success (NASDAQ 2016a). Our sample encompasses biopharmaceutical public companies listed on NASDAQ-100 index, since it aggregates the most actively traded US companies listed on the NASDAQ stock exchange. In November 2016, the healthcare sector represented 16% of the companies in the list and from the top 10 performers, six were biotechnology companies (NASDAQ 2016b). The consolidated descriptive analysis of the historical performance of the companies allows us to highlight some patterns and common success indicators according to their EV fluctuations. The main aspects are going to be discussed in the section below.

17.3.2.1 R&D Expenditure

High R&D expenditure seems to be one of the common strategies among these successful biotech companies. As an example, for Vertex, Incyte, and Biomarin, key success factors come from their massive and constant investments in R&D. They are the leaders among companies that spend the most on R&D relative to their revenue in the last 5 years of analysis (2012–2019) (Fig. 17.12). The biotech sector is highly demanding of R&D investment; thus, many of the selected companies were investing millions of dollars even before they had no revenues.

Heavy investments in research led to the development of some very important drugs for companies (such as Soliris for Alexion). Additionally, one of the reasons

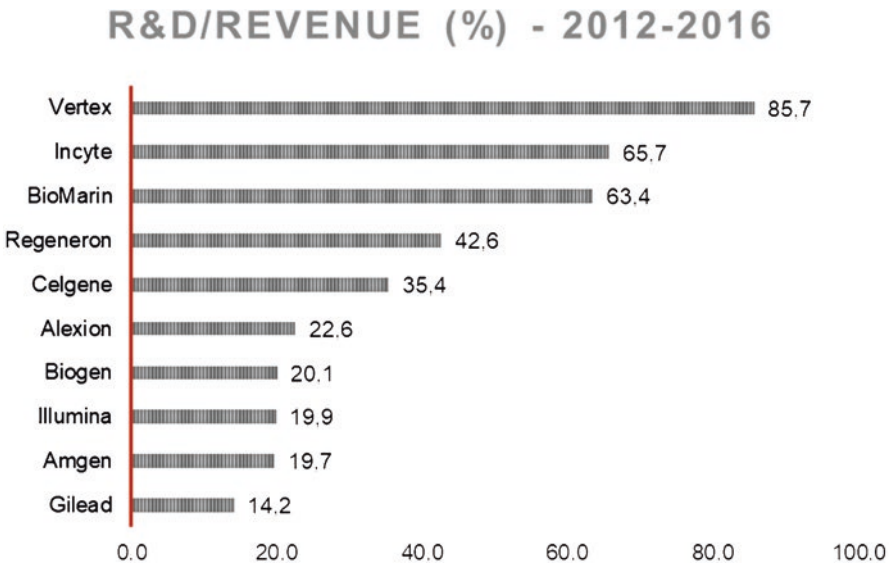

Fig. 17.12 Companies' R&D expenditure and revenues from 2002 to 2016

behind Gilead's success has been its massive R&D investment in different fields with hopes of expanding its pipeline horizons and penetrating different addressable markets for different diseases, which leads to a constant increase in the allocated budget for research (from $142 million in 2002 to over $4 billion in 2016). Along with R&D investments, Celgene's income has been increasing in a rapid and steady pace, and the company has enjoyed profits in most years since 2002.

Our data showed that most companies start with a high ratio of R&D expenditure compared to their revenue, but as time goes by, there is a changing point where the revenue would exceed the R&D expenditure. The overcoming point for revenue occurred post-2007 for Alexion, Biomarin, Illumina, Incyte, Regeneron, and Vertex. Also, as it can be seen in Fig. 17.13, the R&D expenditures for some companies are dramatically higher based on the ratio of the revenue. As an example, Alexion spent massive amount in R&D through consecutive years from 2002 to 2006, an average of 60 times more than the revenue, which consequentially may have led to the development of Soliris and its FDA approval in 2007 and the EV increase in the following years. From the other side, Biogen has a powerful drug development strategy and a diverse business core consisting of constant percentage of R&D expenditure of the revenue. In summary, R&D expenditure are crucial for companies to develop their products and launch them on market when approval occurs (Morgan et al. 2011; PhRMA 2013).

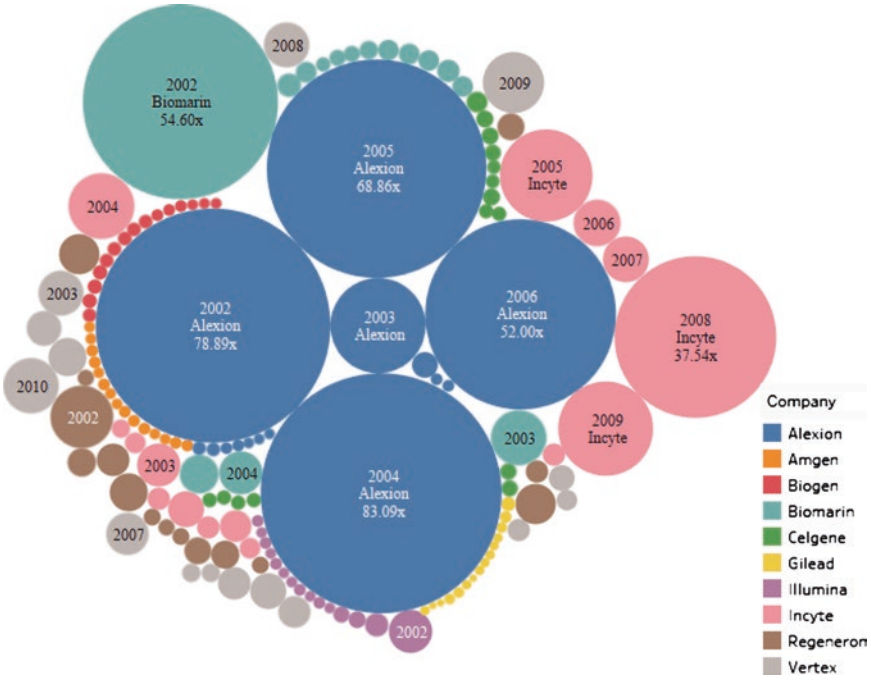

Fig. 17.13 R&D expenditure as a percentage of revenues (circle sizes show higher percentages)

17.3.2.2 FDA Approvals

The second theme should have naturally been common between companies, as getting the FDA approval would allow them to start selling their drugs and generating revenues. These drugs reflect the R&D and clinical trial results as being fruit of successful and strategic acquisitions. Thus, mergers and acquisitions focused on drugs with advanced pipeline should be positive to reach an FDA approval and consequently, revenue. This was the case for Alexion's second drug, Strensig, which received FDA approval in 2015 that resulted from the 2011 acquisition of Enobia; similarly, with its third drug, Kanuma, which was also approved in 2015 previously connected to their Synageva acquisition (with $1 billion in projected annual sales). Another example of this was the spike in the Regeneron's EV curve from 2011 to 2015, which probably was leveraged after their blockbuster drug, Eylea, was approved by the FDA in 2011. As for Incyte, Jakafi was approved by FDA for two different applications in 2011 and 2014, which indicates the spike we note in the EV curve for the period 2012–2015 due to the drug's launch leading to recurring revenue since then. Celgene also seems to have enjoyed an FDA approval-related success. The company's EV has had a big spike in the period 2012–2015, during which at least three of their drugs received approvals from the FDA, some of which for the first time (Otezla) and some for different kinds of treatment (revlimid and abraxane). Some of the rare disease-focused companies have been benefiting from FDA's faster approval times for orphan drugs. Biogen's strategy to focus on rare disease helped the company to get faster FDA approvals through orphan drug designations and a constant pipeline of drugs on advanced clinical development. It is also important to mention that Vertex had an increase in their EV value after 2011 due to the fact that two of their medicines received approval from the FDA – telaprevir and ivacaftor. The regulatory environment was very supportive to biotech during 2014 and 2015, but in 2016, the number of approvals fell dramatically (Moyer and Efram 2017), leading to a fall in EV in majority of companies.

17.3.2.3 M&As

Beside the already-mentioned impact of strategic M&A of companies with advanced pipelines on the companies' EV, the selected companies tend to have different behavior regarding this theme. Companies such as Vertex and Alexion tend to be less aggressive in terms of M&A compared to giant pharma Gilead. As an example, Vertex's M&A is rather focused and timely. The only acquisition made, in 2009, was conducted precisely because the company acquired had two very promising drug candidates in one of Vertex's focus areas – HCV infection. It seems that instead of growing out of acquisitions and mergers, the company prefers to selectively invest in their expertise areas and grow more organically based on blockbuster drugs that might come out of research in those areas. Alexion also was not a very busy player in the M&A area, but a very successful one, as two of their acquired companies resulted in fast FDA approved marketable drugs. Conversely, companies like Amgen, Gilead, and Celgene (which are the top three companies in terms of EV)

have taken a more aggressive approach in M&As. Amgen became a huge biotech company and the key success factor for Amgen EV is its strategy for mergers and acquisitions. The reasons behind were diverse but mainly driven by taking control of blockbuster drugs developed from other companies, to take advantage of a R&D team and expertise from the acquired company, improve its pipeline on a novel therapeutic class, expand its territorial presence, and strengthen the support on its own R&D team. Gilead also had their big break after acquiring Pharmasset in 2015 which handed them Sovaldi, which turned out to be their most successful drug. Gilead continues on its tradition of acquiring potential successful companies in order to delve into new domains and expand its currently gargantuan territory. A great part of Biogen's revenue also comes from joint business, royalties and partnership, which showed that cooperation is the key factor for Biogen success. According to our data, some M&As such as Illumina's acquisition of Genologics are not necessarily a drug company buying another drug company. Genologics is developer of industry leading laboratory information management systems that would intend to help Illumina to develop an analytic platform for their sequencing machines. In summary, a strategic M&A, even focused on a certain drug category or expertise, contributes strongly to the dynamicity of the sector.

17.3.2.4 Others (Innovations, Dynamic Capabilities, Analytic Services)

Some of the other spotted themes which were common among these companies were related to their innovation management. With the rise of Genomics, companies like Alexion, Incyte, Biomarin, and Illumina were leveraging this technology to target rare diseases while taking advantage of FDA's less strict and faster approval times for orphan drugs designation. In terms of managing the innovations, there have been instances of strategic shift in the history of these successful companies. Vertex was focused on cystic fibrosis and HCV infection, but started focusing also on pain relief, oncology, and acute spinal cord injury from 2015 while intensifying their strategic partnership initiatives. Another example can be Gilead's shift to focus only in antivirals in 2002 followed by jettisoning their oncology knowledge to OSI Pharma for $200 million followed by their move in 2006, when they added cardiovascular and respiratory drugs to their portfolio.

The trend seems to be that bigger companies pursue a more aggressive M&A strategy and as they get bigger, need to maintain their flexibility. Since it is harder for bigger companies to change, acquisitions facilitate these shifts for them. They also tend to occur after bigger addressable markets (Gilead's hepatitis B, hepatitis C, cancer, and HIV). Smaller companies, however, are leveraging the new technologies such as Genomics and focusing on smaller patient populations and rare diseases. One factor that can be seen in both types of companies is that biotech companies need to maintain a prolific and strong pipeline to survive. They can maintain it through great R&D expenditures or acquiring companies and talents. As a high-risk, high-reward industry with a high-velocity market, companies need to have different drugs and different stages (from discovery and preclinical to phase III) in order to be more successful and even survive. Even bigger companies' (like

Gilead) time is limited, as they need to maintain their multi-billion dollars of revenues by coming up with new blockbuster drugs before the cash cows run dry.

Despite the fact that these identified themes affect the success of the biotech companies, it should be taken into account that extrinsic events can have great impact on the performance of biotech companies that are studied in this paper. Some events related to that subject must be highlighted. The financial crisis in 2008 greatly affected the pharmaceutical and especially biotech industry as companies were faced with less budgets and many of them became weaker as a result of that. Moreover, many biotech firms had to reprioritize their R&D programs (cutting many drugs which were in the earlier phases of development) so as to cope with the economic crisis, as many had to go through big employee layoffs affecting the investors' interests in them. As a result and the aftermath of the crisis, biotech investors and founders were no longer looking for building the next biotech giant and were looking for establishing companies with hopes of getting acquired by bigger players in the industry (Russo 2008). Another event was in 2016 when Hillary Clinton slammed high price increase in the biotech industry (Egan 2015). Her tweet caused the NASDAQ Biotechnology Index to fall 5% in its ETF (IBB), as it scared the investors concerning the future of the sector Although she did not end up as the president of US, the pharma and biotech industries took a hard hit as result of her remarks. The nine biggest losers on the NASDAQ 100 were all biotech stocks, led by BioMarin and Biogen, which fell 6% each. Bigger biotech companies such as Regeneron, Gilead, and Celgene were not safe either and took big hits in their numbers (Egan 2015). However, as many companies survived the 2008 crisis, there are signs of their survival past the Clinton remarks as well. Despite the fact that the biotech industry has had a couple of rough years, there are signs of revival on the horizon and biotechnology had a solid year in 2017 (rise of about 20% in the December in NASDAQ biotechnology index) (Chandra 2017a, b). In January 2018, Sanofi and Celgene spent $20 billion on adding oncology and hemophilia-based drugs to their portfolio through acquisitions. These actions may encourage other biotech companies to become more active in 2018 as well. As an example, Gilead had become less active through years, but in 2015, the company raised US$10 billion in debt, increasing analysts' expectations that the big biotech would pursue an acquisition, but in 2016, they did not announce any major transaction. Consequentially, the US biotech sector dropped by 22%, led by Gilead (down 35%) due to investors' lack of trust on the company finding a new growth engine (Spence and Giovannetti 2017).

17.4 Conclusion

This chapter sheds a new light on the factors that lead the biotechnology industries to success. The methodology differs from other studies concerning the same subject through two major points: first, we use the enterprise value (EV) as a measure of reference to compare the US biotech companies, and second, the sample chosen

consists of biotech companies listed on NASDAQ-100 index – the 100 largest, most actively traded US companies on NASDAQ. The biotechnology companies contributed massively to the index by the end of 2016 through 10 companies, which were the object of this chapter.

It has been noted that the investment on intellectual property rights is an essential step as inventions take longer to achieve the developmental phase. Otherwise, companies can use that to raise capital in the early stage of development. Another interesting point for early-stage companies is the massive investment in R&D, even when there is no revenue. After a drug's approval, companies start earning revenue that is massively reinvested in R&D to develop more drugs from its pipeline, culminating in a rising cycle. The merger and acquisition are an essential step for biotech companies in whatever stage. Otherwise, the big acquisitions of companies with valuable assets are predominantly a transaction to big biotech companies, and it is also necessary to guarantee the investors' trust. In summary, the results discussed in this paper will contribute to R&D strategies for biotechnology industry, not only restricted to those with IPOs, but also start-ups and smaller companies, in order to drive their innovation management decisions that will consequently result in its growth.

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