Incumbent Pharmaceutical Firms Integration of Biotechnology:

Choices of Internal R&D vs Alliances and Acquisitions

By John Lewis

Abstract:

The emergence of new biologically based techniques preceded the development of a new segment of the pharmaceutical industry. It was initially dominated by small start-up companies. This gave way to a network of technological alliances between the new biotechnology firms, NBFs, and the incumbent firms. This paper looks at how those relationships changed over time and discusses possible reasons for the industries current state.

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Introduction

Alliances are not a new form of cooperation in business. They have been common in high technology growth industries [1, 2]. The pharmaceutical industry saw the largest explosion of alliances in current history during the 1980's. Previous to this, the sector's dominant firms were associated with consistent in-house R&D drug development, despite the industry having experienced several cycles of innovation [3]. During this period, using organic chemistry to create small molecular structures that imitated biological substances were beginning to come into their own [4]. However, the same period, 60s and 70s, saw significant advances in the biological sciences. A wave of new biotech firms, NBFs, sprang up, largely based on two major advances, recombinant DNA and hybridoma techniques[5]. Recombinant DNA techniques allow a gene or sections of DNA from one organism to be cut out and pasted into the DNA of another organism. Hybridoma techniques hybridize two cells, essentially fusing two cells into one. This technique is used to create monoclonal antibodies, antibodies that bind to a specific substance and are extremely useful throughout the industry. Both of these advances were novel innovations creating a new technological regime[5]. However, these were just the first advances in biotechnology, or "biotech". During the 90s, techniques that built on those advances and novel advances were created. Along with gaining the ability to synthesis DNA and knockout specific genes we also began mapping the human genome. These techniques and their ability to manipulate nature have the potential for large wealth creation and the ability to make current medicines largely obsolete. However, our familiarity and knowledge of the interworking of our biology is not, and for the foreseeable future will not be, there yet.

Pharmaceutical firms historically used university research in early stage development [3, 4] but this new discipline was wholly out of their current knowledge base and infrastructure. The knowledge gap between chemical and biological production is vast and would have required significant new

investment in R&D [4, 6]. Many of the firms had very promising New Molecular entities, NME, in their product development pipeline that would become their blockbuster drugs of the 80s and 90s [3]. Combined with the uncertainty that the patent rights of most new biological techniques would hold up and doubt around the potential of biotech itself [4, 5], most companies largely left biotech research alone during the 60s, 70s and most into the 80s [4]. This left the door open for a unique development in the pharmaceutical industry, the creation of many small venture capital start-ups[5]. These start-ups owe some credit to the passage of the Bayh-Dole act of 1980, which enabled universities or non-profits to own and profit from the patents created through public funding [3]. Many start-ups where created by professor's who developed a useful product through their research [4].

These new biotechnology firms, or NBFs, had a new superior technology. In situations like these, Schumpeter predicted the new improved paradigm should preclude the old one[2]. However, the emergence of biological techniques, while potentially superior to current techniques, has not resulted in Schumpeterian creative destruction. This may be because the technology is not far enough along but the pharmaceutical landscape also created two large obstacle to entry[6]. In order to get a drug to market, it must pass FDA review. This includes a preclinical trial and then three phases of FDA reviewed trials before being finalized and given permission to market. The onus for these trials is on the firms. After this expense, it has to market the drug to gain market share. If it is competing in an area already dominated by the larger pharmaceuticals it would be even harder. The NBFs were often created out of one or a few patents on novel techniques [7] and therefore had a significant advantage in the development stage but could not cope with traversing trials and marketing [1, 8, 9]. The large firms had experience and capital to handle regulation and marketing and so held a significant advantage during downstream development [9, 10]. Indeed, the biotechnology literature, which influenced the creation of this paper, views biotech as the "product innovators and the pharmaceutical companies as the market deliverers" [1, 11].

One of the first alliances that solved this duality was between Pharmaceutical Eli Lilly and Biotech Genentech in the early 80s. Genentech had created E. coli, a microorganism, which produced human insulin. This method was cheaper and more efficient than production before it. Eli Lilly held most of the US market share in insulin and was concerned that the innovation would hurt their sales [4]. They therefore licensed the technology, and helped carry it through trials. Several other incumbents followed Eli Lilly and began licensing specific products or creating technological and R&D alliances with biotech companies. Many of these early alliances were for a specific goal and short lived. As alliances became more common and the incumbent industry began to realize the worth of biotechnology, these alliances were more frequently associated with equity purchases in the young companies. The 80s and 90s saw a drastic increase in the number of alliances and licensing[6]. This period also saw a steady increase in NBFs, increasing dramatically near the end of the decade.[12] Throughout, there were significant acquisitions of NBF by incumbents as well as mergers both in the incumbents and in the NBFs [13].

The sector, which had previously been well defined, was in a state of transition. The newcomers had the advantage of the winner take all patent system [14], but their lack of capital, experience and the infrastructure to take a product through the existing system and develop it, meant that the incumbent firms still had a significant advantage. The division in market power here led to the dynamic system of R&D where incumbent firms began to utilize external as well as internal R&D. Large networks of alliances are technological partners arose [3, 15]. However, due to increased expenses from transaction costs and the uncertainties from informational asymmetries [14], let alone the imbalanced nature of the relationships, I expect that the system of alliances should be an unstable state. My hypothesis is that a firm which successfully adapts to the radically new technology will have adopted ties with technological upstarts early. It will have been important for a firm to pursue a high level of external R & D initially to flexibly explore and fill the void in their program. However, over time, this should give way to more and more substantial in house R & D programs from either internal development or external acquisitions.

I had initially hoped to examine the set of dominant firms from 1980 through to the present to study what characteristics succeeded and which failed. However, this period was distinguished by remarkably high levels of consolidation. Of the top 50 companies only five companies survived the period without merging into another entity, being acquired or being liquidated. Another four companies were the product of major mergers. Where I had originally intended to statistically test data on this entire set; I will instead analyze qualitatively the data on those nine companies and utilize a review of previous literature to explore my predictions.

If I am correct I should see the level of Alliances start high and then decrease and the level of R&D steadily increase as capabilities are built and then fall back to normal levels. This should be accompanied by flourishing of small biotech firms and then a steady decrease. The previous literature should also support that the incumbent firms do better with internal R&D.

Data

Data is compiled from the Compustat's North American Annual fundamentals database through WRDS as well as Thomson Reuters Database via the excel plug-in. Further Mergers and acquisition data was derived from the Thomson One Bankers database online.

Research and Development Data was defined as expenses, direct and indirect, related to creation and development of new processes, techniques, and applications of products for commercial possibilities.

Technological Alliances and Joint Ventures were represented by Purchase of Investment. This category contained all cash outflows towards investments in affiliates, joint ventures, limited partnerships. However, it did not distinguish between the types of partners in the alliance. This variable wouldn't capture technology trade, but the more common case is a money transfer for technology or

distribution rights. It is also potentially a good and bad representative of this category because it includes expenses relating to buying partial equity in a company. This is often associated with alliances; however, it does not distinguish between biotech and small pharmaceutical firms. Although buying a controlling interest would be under the next variable. Loans and other debt related investments were categorized separately under investments.

Mergers and Acquisitions were classified under Acquisition of Businesses. This included any reported outflows towards acquiring a new business however, could be incomplete as some companies report the each component in assets and liabilities. This was the case for Novartis.

Results

To derive the set of incumbent companies to be used in this study, the Market Cap of every company classified under SIC codes as a Pharmaceutical company, SIC 2846, was downloaded from WRDS. This was organized and the top fifty firms were selected. However, the Thomson Reuters database will only collect information on active parent companies. After tracing the fate of those original 50 companies, in 2009 seven companies existed in their original form and six had merged into new entities. In 2012, seven decreased to five while new merged entities were down to four. The surviving companies are: Sanofi (formerly Sanofi-Aventis), Merk & Co, Pfizer, Eli Lilly, GlaxoSmithKline, Bristol-Meyer Squibb, Novo Novartis, Abbott Laboratories, and Johnson & Johnson. Without exception, the other original companies were acquired or merged into those companies.

This is the first interesting result and it mean that statistical analysis will be impossible. I cannot run a fair regression on a sample size of 9. However, my original question can still be examined through the time series data presented by these eight case studies. (Eight instead of all 9 because Johnson &

Johnson's diverse product array implied that the broad data I am using would not be reliable in capturing the "biotech" effect.)

I analyzed the time series for R&D, Alliances, and Acquisitions for each company and then as a composite to reflect the general trend of the incumbents. All data was deflated to 1985 dollars. R&D showed the strongest and most consistent pattern between all of the companies. It was growing on average at roughly 10% percent of R&D. When the percent change in R&D is regressed against the companies percent change in Market Cap lagged one year, there is a mild correlation that is significant. Both variables are stationary and lack a trend.

The variable representing Alliances and Joint Ventures also showed significant growth during the 2000s. It was growing at a steady pace through the end of the 80's and most of the 90's. However, during 98 it began to grow more rapidly. It peaked in 2004 but has been declining since; although, it did have another upturn last year.

Acquisitions were the only category that seemed to be affected by the downturn of 2008. For those companies with consistent data back that far, the investment in acquisitions began to increase from the 80's and 90's level after 1996 and especially going into the turn of the century. Acquisitions are less consistent than R&D or even the level of Alliances, with spikes for several companies in 2004 or 06 and another series in 2009. The acquisitions in 2009 correspond with several large mergers of major companies such as Pfizer acquiring the Wyeth for 68 Billion and Schering Plough merging into Merck. With the exception of Eli Lilly, there were very few significant biotech acquisitions by these companies. Since 2010 Sanofi has been acquiring large biotech interests, but previous to that it, along with the others, have been buying up Pharmaceuticals and especially ones within their "niche" focus.

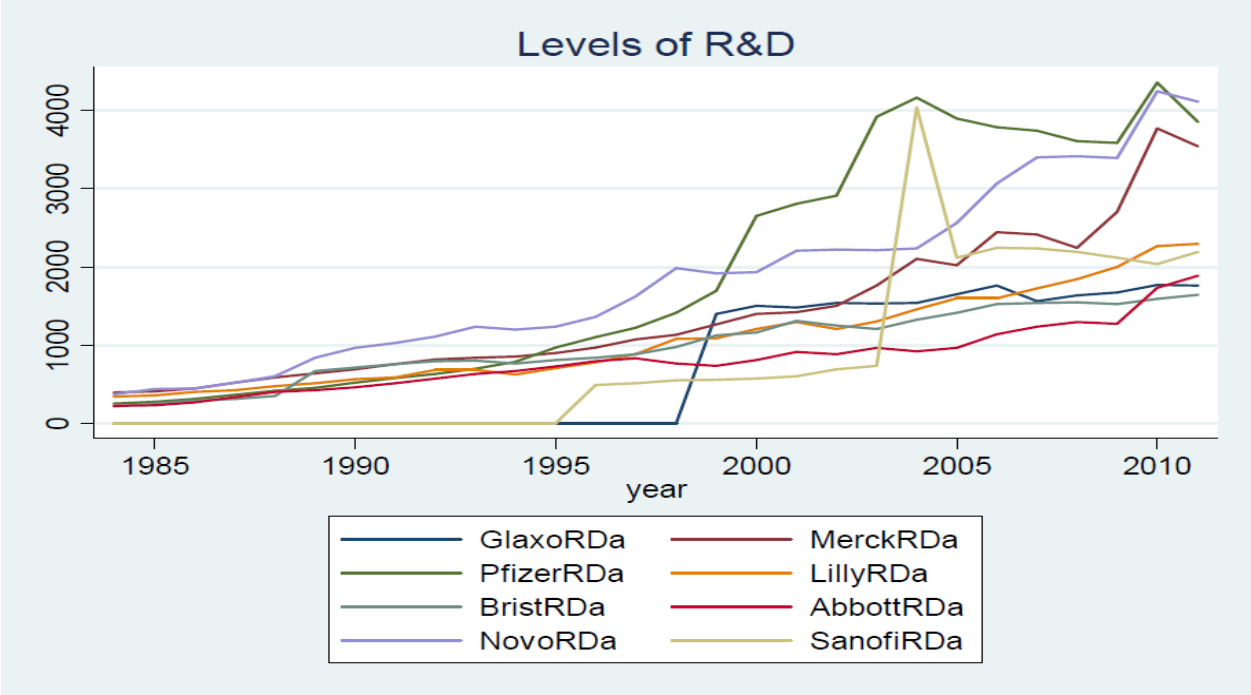
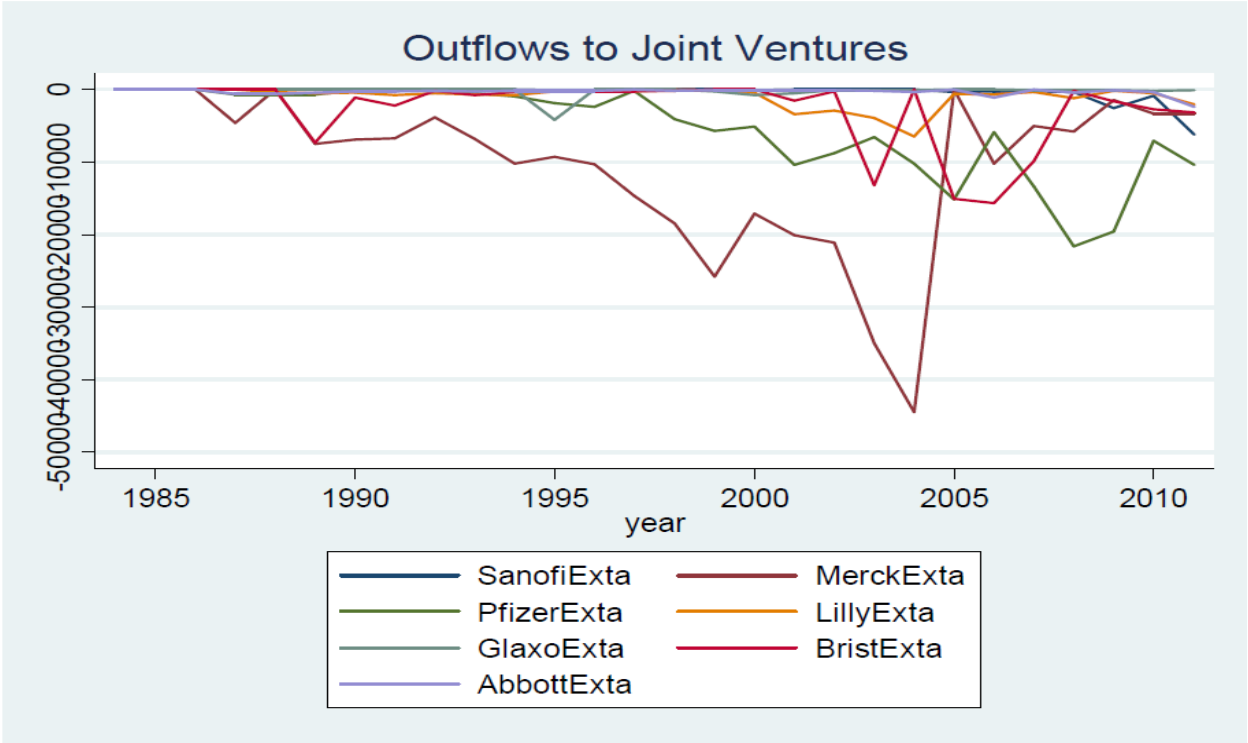


Figure 1: Research and development expenditures of the eight surviving firms in millions of US dollars.

Both graphs are adjusted to 1985 dollars.

Figure 2: Reported expenditures towards alliances, joint ventures and investment in affiliated companies, in millions of US dollars.



Discussion

The results partially correspond with my expectations; however, they significantly contradict them in several ways. There were significantly higher levels of R&D during the last decade- in accordance with my theory. However, the rising R&D expenditures are partially explained by the consolidation of the industry, which is supported by its correlation with market cap. The spending was also growing at a more or less constant rate, with growth rates dropping slightly in the latter half of the last decade. This may support my hypothesis. It might also reflect the economic downturn, which decreased spending in general. Next, joint ventures and alliances grew more in the latter half of the 90's and halfway into the next decade. While this is what I expected, the timing does not correspond to my reasoning. This result suggests biotech interactions became more, not less, important. Although the decline after 2005 might imply this method of interaction is not a permanent arrangement. Future data is required to tell if it is dropping to an equilibrium level, experiencing a swing, or dropping away entirely. Finally, while acquisition numbers have been rising, lending further credence to the initial hypothesis, the company level detail does not. Although these firms have been accumulating subsidiaries in the last decade, they have been largely pharmaceutical in nature. This observation seems to strongly contradict the original hypothesis. The Pharmaceuticals are entrenching their technological position or, to a smaller financial extent, expanding their repertoire but not investing in new biological expertise.

It is clear that firms have not been investing themselves more heavily into Biotechnology. It is important then to try to understand why they haven't done so and what is causing the trends I predicted if it is not the introduction of a new technology.

I must address the possibility the initial reasoning was essentially correct but applied to the wrong time-period. There was a similar trend to what was predicted because it was the trend but offset in time. First, consider that the biopharm sector of the late 80's and early 90's appeared very swiftly [3]. Yet, research and the approval process are long and slow. It takes years of development then a drug needs to pass a pre-clinical stage before clearing three clinical trials. This will introduce a significant lag into drug development. If pharmaceuticals did not partner with start-ups early on, such as in preclinical and clinical trial stage 1, but instead chose to ally with the later stage III drugs for their higher probability of success [14], then the hypothesis needs to be shifted to a later period but is still correct. The incumbent firms are utilizing smaller firms to supplement their pipeline. However the hypothesis states this use is as a substitute more so than a complement, to their internal R&D. The data does not back up the substitute hypothesis as joint ventures/alliances and internal research rose together and is positively correlated implying complements. This is further rejected by the literature.

Previous studies of R&D allocation in the industry found that pharmaceuticals partnered early on with biotech firms but build internal R&D [4, 16]. After this was accomplished, they increased involvement with NBFs but in the area they had built up. The partnerships were designed to help guide their internal R&D building [16]. This is in line with Hagedoorn et all, who found external R&D was a supplement only for companies with low internal R&D but became complementary with high internal R&D [8]. Similarly, another study showed that licensing a drug has a proportional benefit to the extant level of in-house R&D [17]. One paper noted the prevalence of licensing in each phase has changed historically. Modern companies are moving away from the relatively cheaper but riskier bet of investing in stage I and

preclinical drugs, toward the more expensive, safer stage III drugs [17, 18]. The firms are mature enough in their capabilities to identify and then use licensing to buy out potential therapeutic or drug competitors [16]. These revelations will help us answer the following questions

Why have Pharmaceuticals only marginally adopted biotechnology as the innovating technology? There are several possibilities. The initial ideas in this paper must be wrong and biological techniques are not a paradigm shifting Schumpeterian advance but will be a helpful albeit minor addition to the field of medicine. The current culture of Pharmaceuticals is underutilizing this technology. Its potential has not become economically feasible. Or finally, the initial startups cornered the market while these companies ignored it.

The expectation for biological manipulation is no doubt overblown. However, the technology is very flexible and capable of a lot more than is currently being done [7]. Growth is unlikely to slow and is showing no signs of doing so [17]. Therefore the author still believes the premise that this technology will be a major part of the industry in the future. Next, the industry has not ignored biotech as a whole, and it is unfair to refer to it as a homogenous entity as I have been doing [14]. There are firms, such as La Roche, that have embraced biotech to a larger degree than their peers [4]. If any firms were significantly underutilizing the technology, they would be outcompeted by La Roche and other biotech firms. The industry would follow the winning strategy to the correct level of integration. Efficiency theories make the underutilization explanation highly suspect. In contrast, the final two hypotheses deserve closer scrutiny.

It is almost certain that biological techniques have not reached their full potential [19]. Yet, mature profitable biotech firms like Amgen, Biogen and others show that the industry is economically feasible [3]. Even so, the technology might not currently be economically logical for entrenched pharmaceuticals. The biological revolution took two practical directions, generalized techniques like better information collection and sampling, or very specific techniques [15]. The very specific biotechnology products do better in some areas and not in others, therapeutics being a strong biotech market [11, 16]. Galambos et all, found that specialist firms, such as those who would adopt the later technologies, often had more difficulty and spent more to generalize their operations towards biotechnology [4]. Therefore, those companies who would incorporate biological are in a worse position to do so.

It has also been shown that new technologies are integrated best and are more likely to be beneficial if the acquiring firm already has a solid general knowledge base [11] [8, 20]. A phenomenon referred to as capacity absorbance [8, 21, 22]. This is part of the reasoning behind large mergers in the industry. The fact that almost every firm did some investment in the 90s reflects easy increases in capacity absorbance from general biotech techniques like high-throughput screening and bioinformatics [3, 4]. The incumbent firms in his industry have shown they are adept adapters [4], so the opposite pulls of increasing capacity absorbance and costs associated with doing so is fair explanation. The incumbent firms allied with those firms that could complement their production process or current product lines then ceased further integration as the economies of scope no longer outweighed the costs [11]. Further advancing this hypothesis, the current level of investment is in bio-firms that can provide services relating directly to current projects or specific expertise rather than new or general capabilities [8, 16].

The industry requires more specific expertise so NBFs will succeed or fail in attaining alliances based on their compatibility to an incumbent. Due to their ability to capture new innovation with patent rights, this should remain a viable strategy for start-ups.

The second explanation, that NBFs grabbed the market share, comes with a caveat. The large pharmaceuticals have not significantly adapted their development strategies away from small molecule drugs [16], nevertheless, through licensing and their in-house capabilities they hold roughly half of the profit from biologics[17]. But their slow adoption did allow several large firms to become established. These firms are now merging and acquiring smaller firms to become large diversified firms in their own right [11, 13]. Biotech alliances between biotech firms even surpassed biotech to pharmaceutical alliances in 2002 [16]. The creation of NBFs has followed market cycles, but is still growing. [12] However, the largest pharmaceuticals are still several folds larger than the largest biotech, with the respective leader's revenue in 2008 as 70 million v 15 million[17]. However, the acquisitions of Genentech and Genzyme, the next two largest biotech firms, show there is no such thing as entrenched in this industry [13].

Shifting gear, let's consider the observed trends. The boom in NBFs could have created a similar surge in products. The first wave of alliances built for several years until 2004, or approximately the 14 year developmental period of a drug. The increase in alliance spending therefore represents the increasing number of drugs becoming viable candidates to license. This explains the spike and subsequent decrease in external R&D up to 2004. The decrease is the first wave of drugs passing to the market without enough later projects far enough through the approval process to replace them. The literature reveals the approved number of new

chemical entities, NCE, peaked in 1995 but new biologics, NBE peaked in 2003 and 05. (Fig 3) [13]. Licensing most likely contributed but is not the full story.

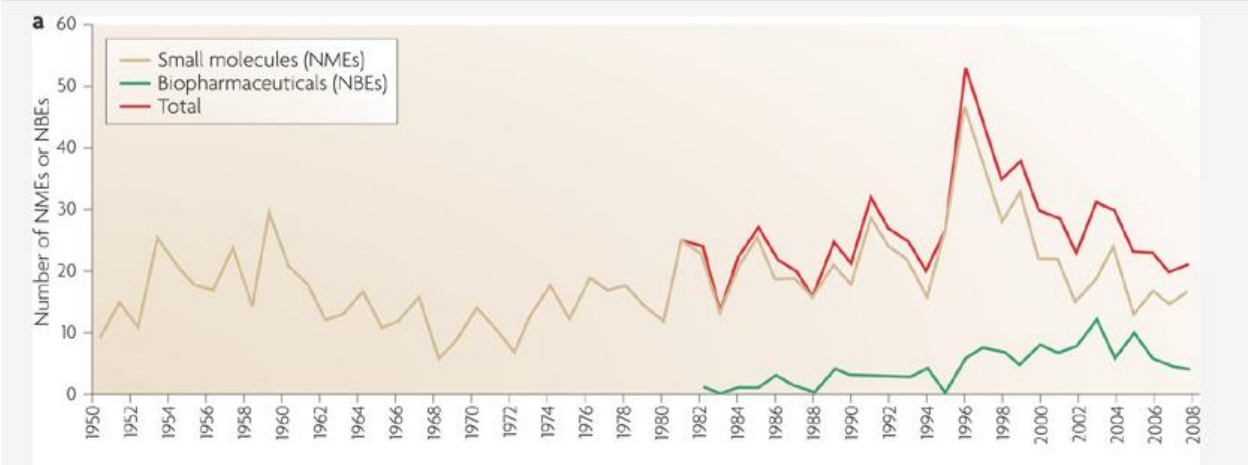


Figure 3: Source: Munos [13]. Amount of New Molecular Entities and New Biological Entities per year.

The literature also suggests that the increase in alliances from both biotechnology and pharmaceutical companies, which is line with my data. The industry has been facing an "innovation deficit" that is likely causing the increasing trend toward partnerships, as well as the consolidation in the industry [3]. While it is controversial whether cooperatively developed products are more successful [11, 21], most investigations suggest that it is [1, 10]. Generally, drugs created in an alliance have a lower probability of clearing the first clinical stage but are then more likely to have a greater acceptance rate and eventual payoff [10]. This form of pipeline creation is more expensive but much faster and so helps smooth innovation shortfalls [8, 11].

There are several factors to account for the steady increases in R&D and acquisitions. First and foremost, the major firms are about to lose the blockbuster drugs they have sustained their growth with. Indeed, 9 of the top 10 best selling drugs go off patent within 5 years [18].

Generic brand companies are becoming more prevalent and profitable [18]. They need to increase development of new patent protected products so they are increasing R&D. To compound this, the price of creating a drug has increased, further pushing up R&D [13]. These two major factors present a serious problem for drug producers. The large consolidation is a reaction to try to create a larger portfolio of drugs and create economies of scale and scope [4, 7, 20]. Some of the literature has argued this will not solve the pipeline issue [13, 18]. The fragmentation of knowledge is so create that partnerships are more necessary [17]. Alliances and acquisitions have been increasing as incumbent firms associate with small pharmaceutical companies and NBFs. It makes sense to acquire similar products if you believe you will lose the monopoly on the ones you already own. You then maintain your brand in an area where it has more recognition and therefore value and were more efficient working from your existent knowledge base.

If these companies are growing, which they are through sales as well as acquisitions, they require a larger R&D budget to accompany their greater size. This is further supported by the correlation in market cap growth and R&D growth. However, further consolidation of the industry is untenable. Expecting further increases in R&D coupled with the constant creation rates of new drugs [3], the industry will face economic difficulties in the future [11, 18, 23]. In order for these large companies to continue to grow they are integrating every option available to them. They are increasing all forms of R&D to increase efficiency [13, 22], with an emphasis on internal R&D [13]. Biotechnology will contribute to this effort as part of both internal and external sources [8, 21].

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