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US Biopharmaceutical Finance and the Sustainability of the Biotech Boom

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ABSTRACT

In the decade before the current economic crisis, the US biotechnology industry was booming. In a 2006 book, Science Business: The Promise, the Reality, and the Future of Biotech, Gary Pisano implies that, given the 10-20 year time-frame for developing biotech products and the lack of profitability of the industry as a whole, the US biotech boom should not have happened. Yet the biotech industry has received substantial funding from venture capital firms as well as from established companies through R&D alliances. Why would money from venture capitalists and big pharma be flowing into an industry in which profits are so hard to come by? The purpose of this article is to work toward a solution of what might be called the "Pisano puzzle", and in the process to provide a basis for analyzing the industrial and institutional conditions under which the growth of the US biopharmaceutical (BP) industry is sustainable. One part of the answer has been the willingness of stock-market investors to absorb the initial public offerings (IPOs) of a BP venture that has not yet generated a commercial product, and indeed may never do so. The other part of the answer is that the knowledge base that BP companies can tap to develop products comes much more from government investments and spending than from business finance. Indeed, we show that, through stock buybacks and dividends, established corporations in the BP industry have been distributing substantial sums of cash to shareholders that may be at the expense of R&D. We use the framework that we have developed for analyzing the sustainability of the US BP business model to pose a number of key areas for future research, with an emphasis on the implications of the financialization of this business model for the generation of safe and affordable BP drugs.

1. The "Pisano Puzzle"

In the decade before the current economic crisis, the US biotechnology industry was booming. According to Ernst & Young's annual global biotechnology reports,[1] measured in 2008 dollars, US biotechnology revenues increased from $20 billion in 1996 to $70.1 billion in 2008, while R&D spending in the industry increased from $10.8 billion to $30.4 billion. In 1996 the industry had 1,308 biotech firms, of which 260 were publicly listed; and in 2008, 1,754 companies, of which 371 were publicly listed. Employment in the industry increased from 118,000 in 1996 to a peak of 198,300 in 2003, before declining to 187,500 in 2004 and 170,500 in 2005, and then rising again to 190,400 in 2008.

In a book, Science Business: The Promise, the Reality, and the Future of Biotech, published in 2006, Gary Pisano, a long-time student of the biotech industry, implies that, given the lack of profitability of the industry as a whole, the US biotech boom should not have happened. The development of biotech drugs requires the organizational integration of diverse capabilities in a cumulative learning process that can take 10-20 years to yield a commercial product with highly uncertain prospects for success. In a Harvard Business Review article, adapted from the book, Pisano (2006a, 114-115) observes that after 30 years "biotech still looks like an emerging sector":

> Despite the commercial success of companies such as Amgen and Genentech and the stunning growth in revenues for the industry as a whole, most biotechnology companies earn no profit. Nor are they significantly more productive at drug R&D than the much maligned behemoths of the pharmaceutical industry.

Pisano (2006b, 205-209) combines data for 293 US biotech companies that were publicly held in 2004 to generate totals for revenues and operating income for these companies for 1975 through 2004. In 2004 combined revenues were $35.8 billion and operating income $2.5 billion. When results for Amgen – the largest dedicated biotechnology firm – are dropped from the totals, combined revenues fall to $25.2 billion with a combined loss from operations of $2.1 billion (Pisano 2006a, 119). Moreover, one can assume that the biotech companies in existence that remained privately held in 2004 were in general less profitable than those that were publicly held.

Technological innovation in the biotech industry depends on a process of cumulative and collective learning. Yet, Pisano (2006b, 155) argues, "[t]he high rate of firm formation means that there are many inexperienced firms in the industry."

> The typical start-up in biotech is simply going to lack the capabilities of a Genentech, which has accumulated R&D experience for more than thirty years. In addition, because newer ventures have limited financial resources, they simply cannot afford to learn from experience….[G]iven that venture capitalists are focused on a liquidity event in a three-year time frame, they have little incentive to promote learning at the organizational level. Finally, the market for know-how may also impede learning from experience. The average R&D alliance in

[1] See www.ey.com/beyondborders for the latest report.

> biotechnology lasts less than four years (about one-third the expected product development cycle). Alliance partners are interested in the firm achieving its next milestone, not in building long-term capabilities. If the biotech firm cannot achieve its milestones, the partners have an easy option to terminate the relationship.

In other words, given its current organization, Pisano sees the US biotech industry as beset by "short-termism", whereas what this industry needs more than any other is "patient capital".

Given these characteristics of the industry, one would think that biotech would have had difficulty securing investment finance from the business sector. Yet as Pisano (2006b, ch. 8) himself shows, biotech has received substantial funding from venture capital firms. For the period 1978 through 2004, measured in 2004 dollars, venture capital invested $38 billion in US biotechnology companies. About two-thirds of the venture capital investment (measured in 2004 dollars) occurred after 1998, with 27 percent in 2000 and 2001 alone (Pisano 2006b, 141).

Once these new ventures are formed, moreover, they often receive funding from R&D alliances with established pharmaceutical companies. Average annual expenditures (in 2006 dollars) on corporate partnering in the biotech industry, of which R&D alliances are an important form, increased from $7.9 billion in 1999-2001 to $10.0 billion in 2002-2004 to $17.2 billion in 2005-2006 (Burrill 2005; Rosen 2006). An R&D alliance typically includes an R&D contract from the established company for the startup to engage in drug development in exchange for intellectual property rights and, if and when the drug is approved, certain marketing rights. For almost all young biopharmaceutical companies, R&D alliances and other forms of corporate partnering represent their major, if not only, source of income (as distinct from equity investments) prior to an IPO. An R&D alliance also typically includes a capital injection into the startup that gives the established company an equity stake.

Hence what might be dubbed the "Pisano puzzle": Why would money from venture capitalists and big pharma be flowing into an industry in which profits are so hard to come by? The purpose of this article is to work toward a solution of the Pisano puzzle, and in the process to provide a basis for analyzing the industrial and institutional conditions under which the growth of the US biopharmaceutical (BP) industry is sustainable.

One part of the answer, which we explore in Section 2 of this paper, is the willingness of stock-market investors to absorb the initial public offerings (IPOs) of a BP venture that has not yet generated a commercial product, and indeed may never do so. According to Pisano (2006b, 141), for the period 1978 through 2004, measured in 2004 dollars, public equity markets absorbed $168 billion of IPOs and secondary stock issues by US biotechnology companies, with about two-thirds of these funds raised after 1993 and most of the money flowing into the industry in the speculative boom of 1999-2000. Besides enabling the BP venture to raise funds for further drug development, a stock-market listing also creates the opportunity for venture capitalists and other parties, such as R&D partners, with equity stakes in the BP venture to exit from their investments, often with a substantial return despite the absence of a commercial product.

The other part of the answer, which we explore in Section 3, is that the knowledge base that BP companies can tap to develop products comes much more from government investments than

from business investments. We outline the modes and extent of government support for the US BP industry, emphasizing the roles of government research funding, subsidies, regulation, and spending in enabling an industry that depends on investments in a complex knowledge base to exist and grow.

Then in Section 4, we combine the analyses in the previous two sections to highlight the limits to the sustainability of the growth of the US BP industry based on its current financing model. In particular, we emphasize the financial behavior of US BP firms that, to boost their stock prices, allocate resources to stock repurchases at the expense of investments in productive capabilities and to the benefit of the corporate executives who make these allocative decisions.

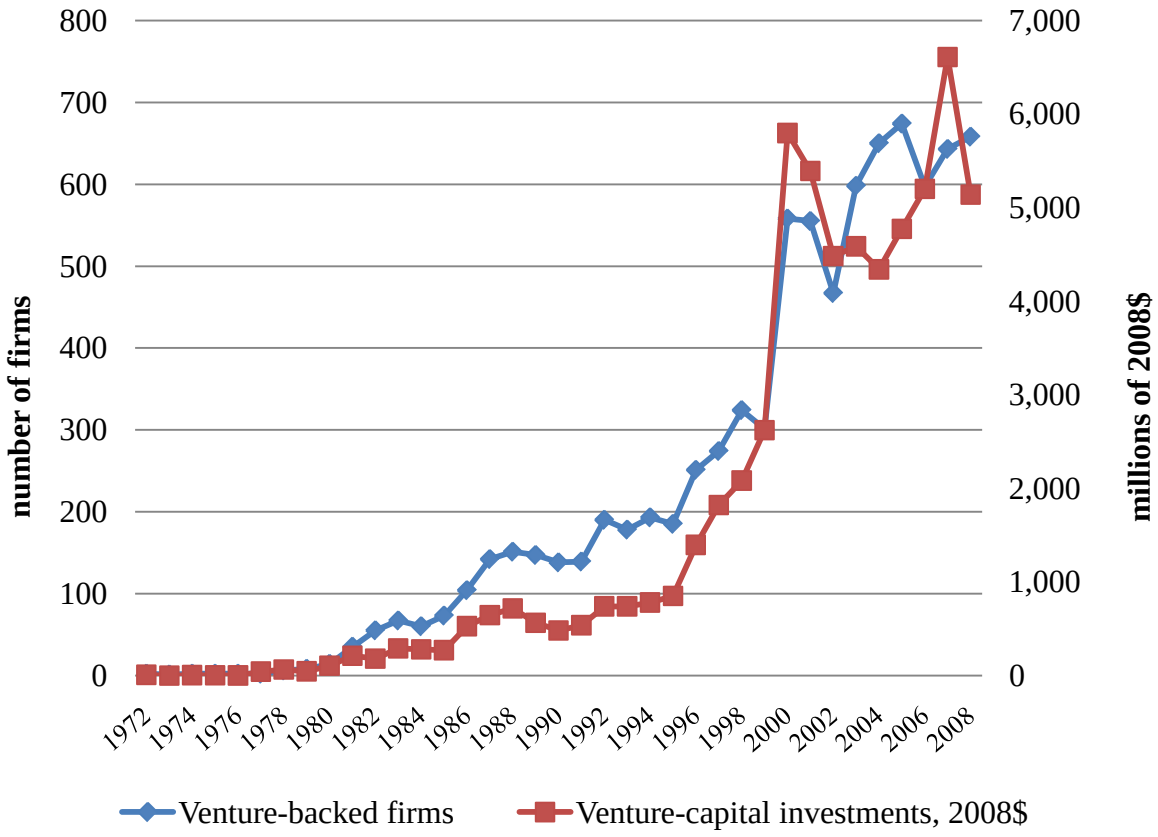
Finally, in Section 5, we use the framework for analyzing the sustainability of the US BP business model to pose a number of key areas for future research, with an emphasis on the implications of the financialization of this business model for the generation of safe and affordable BP drugs.

2. The US Biopharmaceutical Financing Model

The development of BP drugs requires a unique knowledge base that depends on intense interactions among scientists in research institutes and business enterprises. As a result, localities in which these knowledge bases have been built have become centers for new firm formation and the growth of BP firms. There are a number of main centers of BP growth in the United States, of which the Boston-Cambridge area is the most concentrated and important (see Cortright and Mayer 2002; Feldman 2003; Owen-Smith and Powell 2004; Porter et al. 2006; Lazonick et al. 2007).

Venture capital has become integral to the growth of these regional BP industries. Of $27.6 billion in venture-capital investments in the US BP industry in 2001-2006, 24.8 percent was in the San Francisco area, 17.6 percent in the Boston-Cambridge area, 12.8 percent in the San Diego area, and 12.4 in the New York City-Northern New Jersey area (Lazonick et al. 2007). For the BP industry as a whole, since 2000 venture-capital investment in the BP industry has been at extraordinarily high levels. Figure 1 shows the general rise from the late 1970s to the late 1990s in the number of venture-backed biotech firms and the value of disbursements in 2008 dollars. After accelerations in both firm and disbursement levels in the last half of the 1990s, venture creation and venture funding jumped dramatically in 2000s and have remained high throughout the decade. The average annual number of venture-backed companies almost doubled from 288 in 1996-1999 to 545 in 2000-2003, and averaged 644 for 2004-2008; while the average annual amount of disbursements in 2008 dollars increased 2.6 times from $1,981 million in 1996-1999 to $5,066 million in 2000-2003, and averaged $5,431 million in 2004-2008.

Figure 1. Venture-backed companies and venture-capital investments (in 2008 dollars) in US biotechnology, 1978-2008



Source: Thomson Financial, Venture Xpert

The development of BP drugs is a costly process (Grabowski et al. 2002; DiMasi et al. 2003; Light and Warburton 2005a and 2005b; DiMasi et al. 2005a and 2005b; Adams and Brantner 2006). Replicating the calculations of DiMasi et al. (2003), Adams and Brantner (2006) argue that the cost of developing a new molecular entity varies between $500 million and $2 billion in 2000 dollars. A subsequent study by DiMasi and Grabowski (2007) estimates the average cost (in 2005 dollars) of developing biologics as $1.24 billion and pharmaceuticals as $1.32 billion. The US BP industry has adopted the formula (suggested by Ligand Pharmaceuticals) that during the first decade of its existence, 10 percent of a BP firm's funding comes from venture capital, 50 percent from R&D alliances with established pharmaceutical companies, and 40 percent from public equity markets (Hess and Evangelista 2003).

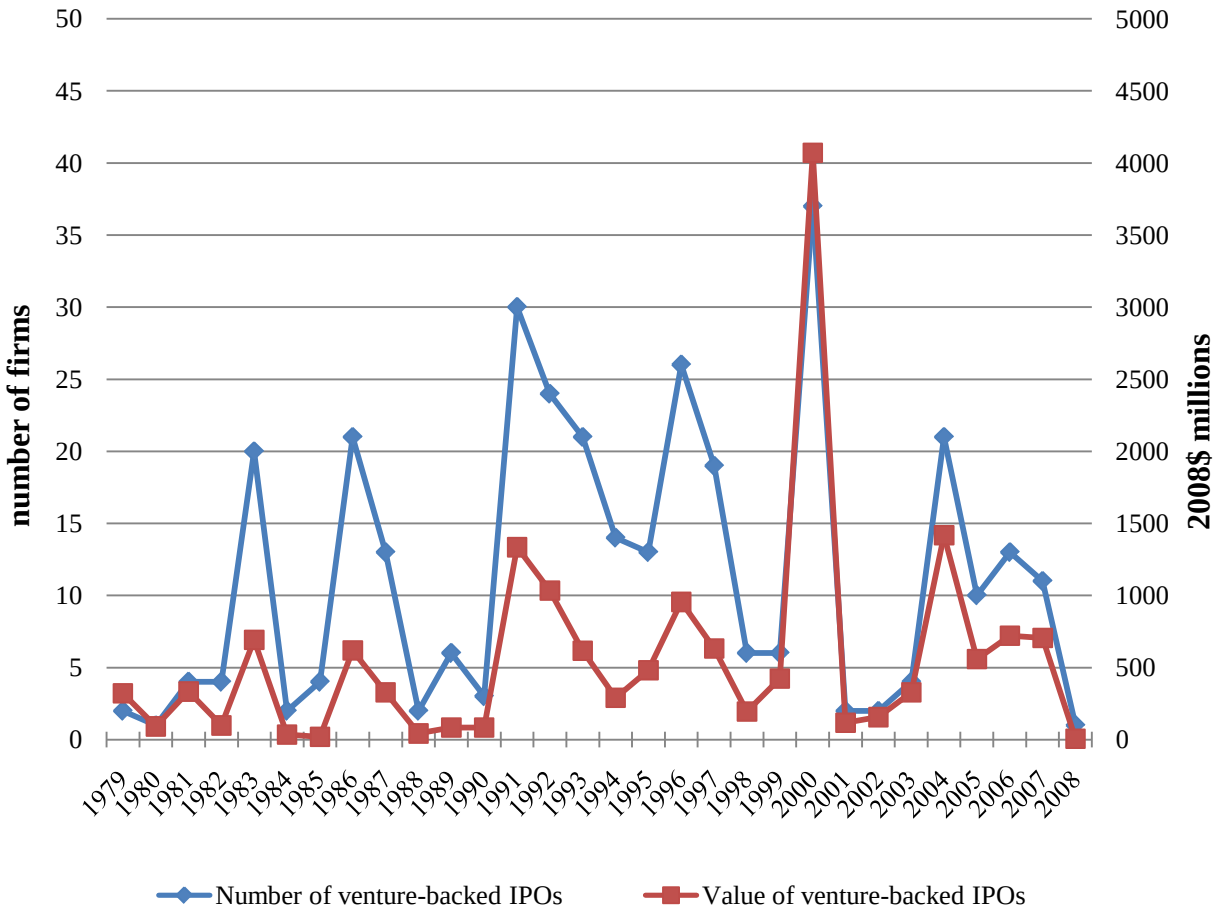
A study by Cortright and Mayer (2002) found that, across nine major metropolitan areas in the United States, R&D alliances accounted for $769 million in funding prior to 1990, $4,481 million from 1991 through 1995, and $9,798 from 1996 through 2001. Data already cited suggests that for the United States as a whole average annual expenditure on R&D alliances was more than two times greater in 2005-2006 than it had been in 1999-2001 (Burrill 2005; Rosen 2006). In entering into an R&D alliance, the "startup" (which may have been in existence for decade or more) gives up certain property rights to its drug, if and when it is ever approved for

sale (Wakeman 2004, 2008). Typically the startup is able to use the revenues and capital injections from one or more R&D alliances to convince stock market investors that it is worthy of an IPO (as we show in the example of Affymax below). Subject to achieving milestones, the R&D alliances can continue to provide income after the IPO (see also Nakajima and Loveland 2007). Alternatively, R&D alliances can provide the funding for a startup to develop its drug to the stage at which an established company deems it worthwhile to acquire it, even though a commercial drug has yet to be generated.

Virtually all BP companies that do IPOs are product-less. Pisano (2006b, 143) argues that "only approximately 20% of *all* publicly held companies in existence today have any products on the market or are earning royalties based on products commercialized by partners. Thus the vast majority of publicly held biotech firms are essentially R&D entities." Schiff and Murray (2004) underline the importance of Special Purpose Entities (SPE) and the role that they have played in developing several blockbuster drugs. Since the early 1980s investments in R&D have been made through SPEs in which a technology developer (inventor) and a sponsor (investor) each have equity stakes in a new joint venture founded in the form of an R&D limited partnership or Special Purpose Corporation (SPC). The purpose of this strategy is to give up certain rights on intellectual property by transferring part of the technology to the new SPE and generating the finance necessary for further R&D activities. Special Purpose Accelerated Research Corporation (SPARC) and Stock and Warrant Off-Balance-Sheet Research and Development (SWORD) are two well-known brand names of SPEs. Companies such as Amgen, Genzyme, Genentech, and Biogen made use of SWORD to finance the initial phase of the R&D processes that ultimately generated blockbusters (Solt 1993; Schiff and Murray 2004).

If, to generate returns on their investments, venture capitalists and established pharmaceutical companies had to wait for a BP drug to be approved for sale on the market, they may not have made the investments in the first place. Rather than waiting 10 to 20 years to see whether a commercial drug will in fact be produced, the existence of a speculative stock market provides them with a mode of exit from their investments by means of an IPO. Figure 2 shows the number and value (in 2008 dollars) of venture-back BP IPOs in the United States from 1979 through 2008. As can be seen, venture-capital investments are highly variable from year to year, with sharp peaks in 1983, 1986, 1992, 1996, 2000, and 2004.

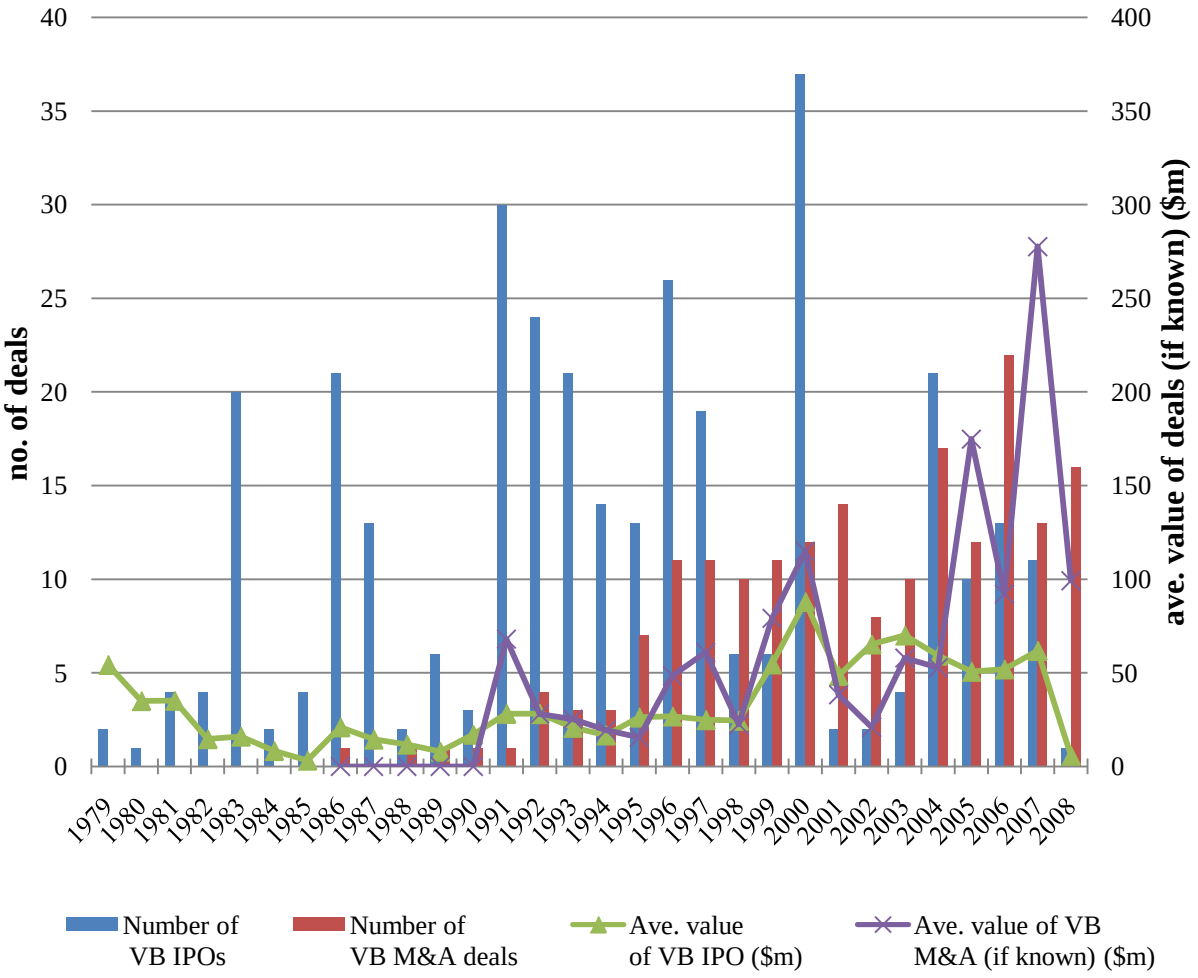
Figure 2. Venture-backed initial public offerings in biotech, 1979-2008



Source: Thomson Financial, Venture Xpert

Alternatively, equity holders can exit through the private sale of the startup to an established company, receiving payment in cash or in the company's listed shares. As Figure 3 shows, such M&A deals have become particularly important as a mode of exit in the 2000s. Indeed, in 2006-2008 the average value of an M&A deal far surpassed the average value of an IPO. Further research will be required to determine whether, as one would assume, the startups that do M&A deals are further advanced toward the development of a commercial drug, and hence less speculative investments.

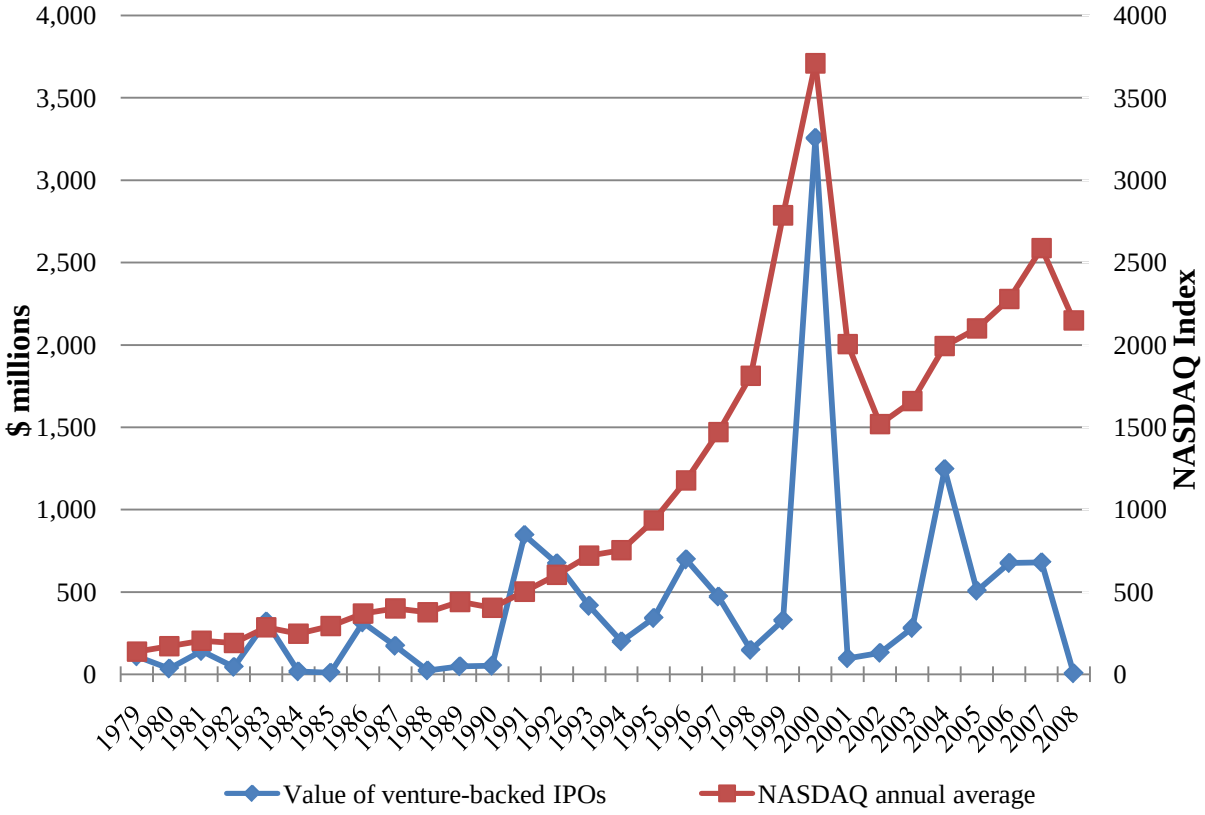
Figure 3. Number and value of IPOs and M&A deals in biotechnology, 1979-2008



Source: Thomson Financial, Venture Xpert

Note in Figures 2 and 3, the extraordinarily high number and average value of IPOs in 2000, at the height of the "New Economy" boom. The speculative character of these investments is confirmed in Figure 4, which shows the relation between the annual average movements of the NASDAQ Composite Index and the value of venture-backed BP IPOs in current dollars. Especially over the past decade, it would appear that stock market speculation has been a critical inducement to venture financing of the BP industry. By the same token, the current financial crisis has lowered expectations of returns from IPOs (Moore 2008). In 2008 there was only one venture-backed IPO in the US biotech industry, and in 2009 thus far (as of July 8) there have been none.

Figure 4. Value of venture-backed IPOs in current dollars and movements in the NASDAQ Index, 1979-2008



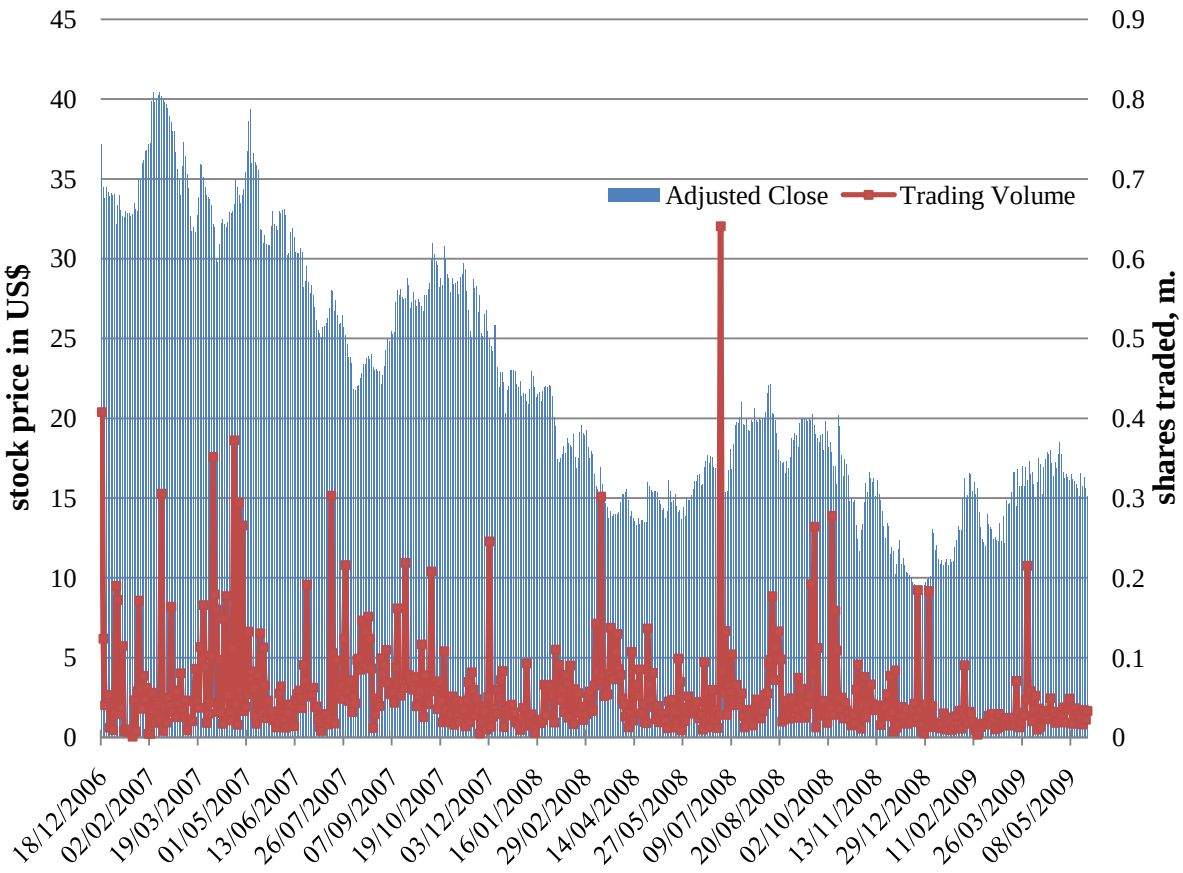
Sources: Thomson Financial, Venture Xpert; Yahoo! Finance

As an example of the relation between venture financing, R&D contracts, and IPOs, on December 15, 2006, Affymax, a venture-backed BP company based in Palo Alto, California that had been created in 2001 as a spinout from GlaxoSmithKline, did an IPO, raising $92 million (Lorenzo 2006).[2] From its founding to its IPO, Affymax recorded a total of $11.7 million in revenues, virtually all of it from an R&D partnership worth up to $102 million, inked in February 2006, with Japan-based Takeda Pharmaceutical (Phil-Carey 2006). At that time, Affymax had a therapeutic product under development in the late stages of Phase II clinical trials, with the expectation of moving into Phase III trials in early 2007 and the possibility of gaining Food and Drug Administration (FDA) marketing approval for the drug in 2010; that is, three to four years after the IPO. At that point, Takeda will have exclusive rights to market the drug outside of the United States. But Takeda, as well as Affymax's venture capitalists, do not have to wait until a product actually goes to market to generate returns from their investments. As part of the R&D partnership, Takeda purchased 2.1 million Affymax shares for $10 million in February 2006. At the IPO some ten months later, Takeda's shares were worth $63 million.

[2] Affymax had actually been founded in 1988 in The Netherlands in 1988 with a research lab in Palo Alto, California. GlaxoSmithKline acquired Affymax in 1995 (Kornberg 1995, 93-94)

Takeda was able to reap this return on its shareholdings because of the existence of public investors who were willing to speculate in the shares of a company like Affymax which was still years away from a commercial product. Indeed, from an IPO price of $30.00 on December 15, 2006, Affymax's stock rose to a peak price of $41.00 on February 12, 2007, and then began a general decline to a low (at the time of writing) of $9.03 on December 23, 2008. As can be seen in Figure 5, both the Affymax stock price and the trading volume in its shares have been very volatile, with speculators going into and out of the market in the attempts to lock in speculative gains. The existence of stock market investors looking to make speculative gains on a stock such as Affymax is what enables the IPO, which in turn attracts venture capital and big pharma money into the BP industry.

Figure 5. Stock-price movements and trading volume of Affymax shares, December 2006-May 2009



Note: Excludes trading volume of 1,997,500 shares on the IPO date, December 15, 2006.
Source: Yahoo! Finance

3. US Government Support for Biotech

Pisano (2006b) does not mention the possibility that such speculative investments in IPOs may be responsible for a substantial proportion of the venture, R&D, and public equity funds that has flowed into the biotech industry. Even then, the fact that the speculative stock market can enable financiers to reap returns on young biotech companies long before they have generated a commercial product is only one part of the solution to the "Pisano puzzle". The other part is the role of the government in the biotech industry

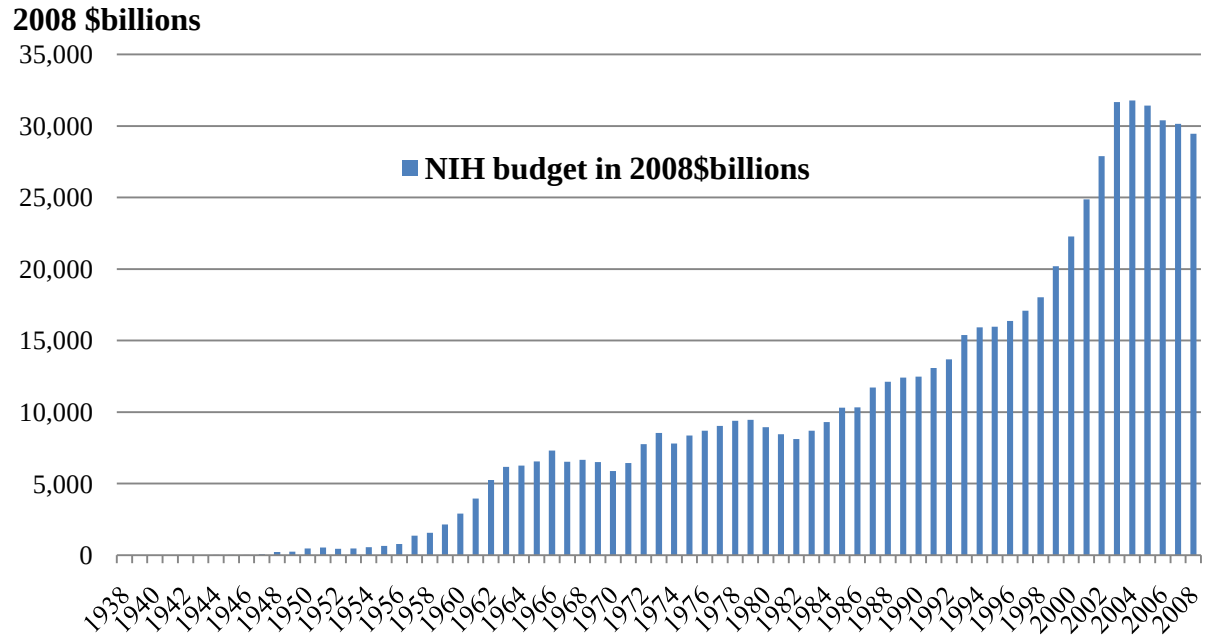
It is only in the concluding chapter of the book, where he devotes a few pages to a discussion of "the institutions of basic science" that Pisano (2006b, 186) recognizes in a general way the centrality of government funding to the biotech industry:

> The institutions of basic science include academic research laboratories, government research institutes, and government funding of science. These institutions have played an important role in advancing the underlying sciences of biotechnology. It is hard to imagine what the life sciences would look like today without the National Institutes of Health, the University of California, Stanford, MIT, Columbia, University of Washington, Harvard, the Whitehead Institute, the Institute of Genomic Research, the Human Genome Project, the MRC Laboratory of Molecular Biology, dozens of academic medical centers, countless other governmental and academic laboratories around the world and journals such as *Science* and *Nature*.

While Pisano calculates the cumulative flows of venture capital and stock market funds into the biotech industry for the period 1978-2004, he attempts no such parallel calculation for government funding, notwithstanding his "hard to imagine what the life sciences would be like" statement in the paragraph just quoted. In fact, from 1978 through 2004, NIH spending on life sciences research totaled $365 billion in 2004 dollars (which can be compared with his figures for venture capital and public equity funding cited above).[3] Moreover, unlike venture capital and stock market investments, which have fluctuated widely from year to year, NIH funding has increased in nominal terms in every single year from 1970 to 2008, except for a small decline in 2006. The rate of increase in funding in real terms was particularly large in 1999-2003 when it averaged almost 12 percent per annum. In 2004 NIH funding in real dollars was double its level in 1994 (see Figure 6). Since its inception in 1938 through 2008, US taxpayers invested $668 billion in 2008 dollars in the work of the NIH. For the 33 years since 1976, when Genentech was founded as the first biotech company to take advantage of the new techniques of rDNA, NIH funding totaled $555 billion in 2008 dollars. Through the NIH, the US government, and by extension the US taxpayer, has long been the nation's (and the world's) most important investor in knowledge creation in the medical fields. Without NIH funding to create the indispensable knowledge base, venture capital and public equity funds would not have flowed into biotech.

[3] NIH, Office of Extramural Research: http://grants1.nih.gov/grants/award/HistoricRankInfo.cfm.

Figure 6. National Institutes of Health funding, 1938-2008, in 2008 dollars



Source: National Institutes of Health 2009

For 2009 the US Congress has provided the NIH with a budget of $30.4 billion. The NIH uses 16 percent of its budget to directly employ 19,000 people, of whom almost 6,000 are scientists based mainly at the NIH's 27 centers and institutes in Bethesda, Maryland. The other 84 percent of the budget "supports over 325,000 extramural scientists and research personnel at more than 3,000 institutions nationwide."[4]

As one of the NIH's 27 centers, the National Human Genome Research Institute (NHGRI), created in 1989, was allocated $487 million in 2008, and since its inception its funding has totaled over $6.6 billion in 2008 dollars. The most recent addition to the growing number of NIH centers and institutes is the National Institute of Biomedical Imaging and Bioengineering (NIBIB). It began receiving appropriations in 2002, and through 2007 had total funding of $2.0 billion in 2008 dollars, including $299 million in 2008. NHGRI and NIBIB are relatively small programs within NIH, together absorbing 2.7 percent of total NIH funds in 2008. The top three centers, together accounting for 41.7 percent of the NIH's total funds in 2008, are the National Cancer Institute (NCI) with 16.3 percent of the total; the National Institute of Allergy and Infectious Diseases (NIAID) with 15.4 percent; and the National Heart, Lung, and Blood Institute (NHLBI) with 9.9 percent. These knowledge-creating programs are all highly relevant to the biotech industry.

A number of important changes in government regulation in the late 1970s and early 1980s made this knowledge base both more valuable and more accessible to high-tech business interests. The

[4] http://www.nih.gov/about/index.html

powerful high-tech lobby, led by the American Electronics Association and the National Venture Capital Association, that had by the late 1970s emerged from the microelectronics industry centered in Silicon Valley convinced the US Congress to alter tax laws that provided financial incentives for the allocation of capital and labor to high-tech startups (see Lazonick 2009a, ch. 2). Then in the early 1980s, a number of regulatory changes, all connected with intellectual property rights, specifically encouraged new ventures in biotech.

The Bayh-Dole Act of 1980 enabled biotech startups to tap the federally-funded knowledge base. By giving universities and hospitals clear property rights to new knowledge that resulted from federally funded research, Bayh-Dole facilitated the transfer of this knowledge to support the creation and growth of new technology firms (Mowery et al. 2004). The motivation for Bayh-Dole was the growing number of biotech inventions that, it was argued, would be left unexploited unless the conditions for the transfer of intellectual property were made less restrictive.

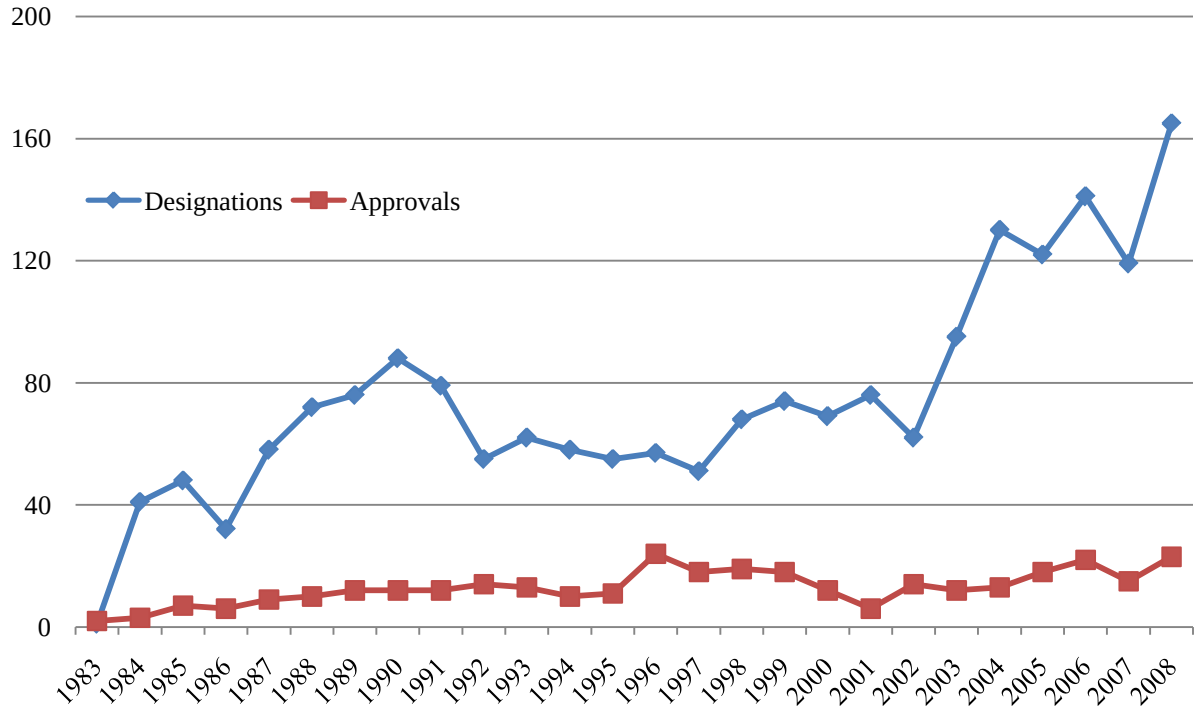
In 1980 as well, the Supreme Court decision in Diamond v. Chakrabarty that genetically engineered life forms are patentable greatly enhanced the opportunity for the types of knowledge transfers that Bayh-Dole envisioned. The decision itself was a 5-4 ruling, and has since been the subject of debate (Lewin 1982; Eisenberg 2002; Garcia 2002). Nevertheless, it set a precedent for the patenting of genes. In the early 1990s, in the context of the Human Genome Project, even the NIH began patenting partial complementary DNA sequences on the grounds that patent licenses to biotech companies would encourage product development (see Eisenberg 1992).

In 1983 the passage of the Orphan Drug Act provided another important inducement to biotech investment. Designed to encourage pharmaceutical companies to invest in the development of drugs for "rare" diseases, the Orphan Drug Act gives companies generous tax credits for research and experimentation as well as the possibility of market exclusivity for seven years from the time that a drug is approved for commercial sale by the FDA.[5] It was argued that without these financial incentives many potential medicinal drugs that could be developed for relatively small markets would remain "orphans": companies would not have been willing to make the large financial commitments required to nurture these drugs from infancy to adulthood. Through 2008, the FDA designated 1,954 orphan drug submissions and had granted market exclusivity on 335 drugs that had reached approval (see Figure 7).

As shown in Figure 7, the annual number of designations climbed in the 1980s to reach a local peak of 88 in 1990, with an annual average of 79 over 1988-1991. The annual average fell to 56 in 1992-1997, and then rose somewhat to 70 in 1998-2002. Since 2003 the annual numbers of designations have reached new heights, with a record 165 in 2008. The 24 approvals in 1996 remain an all-time annual high, while the six approvals in 2001 were the fewest since 1986. From 2002-2008, the average annual number of approvals was 17. Given the high levels of designations since 2003, we can expect that approvals will be at much higher levels over the next decade or so.

[5] http://www.fda.gov/orphan/oda.htm

Figure 7: Number of orphan drug designations and approvals per year, 1983-2008



Source: Food and Drug Administration 2009

An orphan drug may or may not be covered by a patent. In its original formulation in 1983, the Act only covered drugs that were not patentable, but an amendment to the Act in 1985 made patented drugs potentially eligible for Orphan Drug benefits as well. While the duration of a patent is for 20 years and market exclusivity under the Orphan Drug Act is only seven, the latter becomes effective once a drug has already been approved by the FDA for sale while, given the typically long duration of the drug development process, a patent may well be close to expiration, or even expired, by the time a drug is ready to be sold to the public.

What makes a disease "rare"? The Act of 1983 defined a rare disease as one that "occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available…a drug…will be recovered from sales in the United States (Hogan 1995, 534). In an amendment to the Act in 1985, the definition was changed to either a disease that affects less than 200,000 people, or, if it affects more, a disease for which a drug cannot be developed profitably. A company retains its right to market exclusivity even if the number of people with the disease becomes greater than 200,000 during the seven-year exclusivity period.

Moreover, a company can file for orphan drug designation for multiple indications of the same drug. For example, an orphan drug designation for "the treatment of chronic myelogenous leukemia" that Novartis obtained on January 31, 2001 was approved by the FDA, with market exclusivity, on May 10, 2001 under the tradename Gleevec. During the last five months of 2005

Novartis filed for five other orphan drug designations, and won approval for all five on October 19, 2006, each one under the tradename Gleevec. There may be long time-lags between an original orphan drug designation and subsequent ones for the same drug. For example, in 1988 the Danish pharmaceutical company, NovoNordisk, received an orphan drug designation for "the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX", which was approved by the FDA in 1999 and marketed under the tradename NovoSeven. In 2004 NovoNordisk filed for seven more indications for NovoSeven, of which three won FDA approval in 2005.

In addition, a company that has received FDA approval for an orphan drug may subsequently find that it has one or more non-orphan applications. For example, Allergan filed for two orphan drug designations in 1984, one in 1986, and one in 1991 for a drug known as Botox. FDA approval for the two 1984 designations came in 1989 and for the 1986 designation in 2000. The indication approved in 2000 was for "treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia". But Allergan had also discovered that Botox could be used for "the temporary treatment of moderate to severe frown lines between the brows",[6] and had made the drug a leader in cosmetics. The company also markets Botox as a treatment for severe under arm sweating. Indeed, according to Allergan (2008 10-K, 8), Botox "is currently approved in 75 countries for up to 21 unique indications." In 2008 Botox generated $1,310 million in revenues (representing 30 percent of the company's product sales), of which therapeutic uses were 50 percent and cosmetic uses the other 50 percent (Allergan 2008 10-K, 64, 66).

A brochure published in June 2005 by the Genetic and Rare Diseases Center of the NIH states that there are more than 7,000 rare diseases that afflict a total of 25 million Americans – or 1 in 12 of the total population and an average of about 3,600 people per rare disease (NHGRI and ORD 2005). The National Organization for Rare Disorders (NORD) database contains reports on 1,150 rare diseases.[7] Rare diseases are often genetic, and, especially given that its enactment coincided with the first wave of biotech startups, the Orphan Drug Act has been of particular importance to small biotech companies. One role that NORD has played has been to encourage large pharmaceutical companies that have been reluctant to use their proprietary knowledge to develop specific orphan drugs to license that knowledge to smaller companies (Meyers 2000).

Table 1 shows the number of orphan drug designations and approvals of companies that as of the May 2009 had control over at least 15 designations, including designations obtained by companies that subsequently were acquired. The fifteen companies listed in Table 1 accounted for 23 percent of the 2,000 designations and 38 percent of the 335 approvals from 1983 through May 5, 2009. Among these companies are many of the world's largest pharmaceutical companies such as Novartis, Roche, Johnson & Johnson, GlaxoSmithKline, Pfizer, Bayer Schering, AstraZeneca, Merck Serono, Bristol-Meyers-Squibb, Abbott, and Novo Nordisk as well as few dedicated BP companies including Amgen, Genzyme, Biogen Idec, and Immunomedics. Dedicated BP companies MedImmune and Genentech would have been on the list had they not been acquired, respectively, by AstraZeneca in 2007 and Roche in 2009.

[6] www.botoxcosmetic.com
[7] www.rarediseases.org

Table 1. Orphan drugs designations and approvals, companies with 15 or more designations, 1983-2009, as of May 5, 2009

Company	DES	APP	Tradenames
Novartis (including Sandoz and Chiron)	47	17	*Cibacalcin, Lamprene, Zometa/Zabel, Gleevec (6), Simulect, Sandostatin LAR (3), Exjade, Betaseron, Proleukin (2)*
Roche* (including Behringer Mannheim, Genentech, Hoffmann-Laroche)	47	15	*Roferon-A (2), Lariam (2), Hivid, Vesanoid, Zenapax, Protropin, Nutropin (4), Nutropin Depot, Pulmozyme, Rituxan*
Johnson&Johnson (including ALZA, Centocor, R. W. Johnson Pharmaceutical Research Institute, OMRIX, Scios, Scios Nova, Tibotec)	45	5	*Procrit, Leustatin Injection, Remicade (2), Elmiron, Doxil*
GlaxoSmithKline (including Burroughs Wellcome, Genelabs, Glaxo Wellcome, Sirtris, SmithKline Beecham)	44	18	*Digibind, Retrovir (2), Exosurf Neonatal for Intratracheal Suspension (2,) Alkeran For Injection, Mepron (2), Flolan (2), Lamictal, Bexxar, Arranon, Triostat, Halfan, Albenza (2), Promacta*
Pfizer (including Coley, Pharmacia, Pharmacia & Upjohn, G. D. Searle, Sugen, Upjohn, Warner-Lambert)	43	9	*Zinecard, Genotropin (3), Aromasin, ATnativ, Ellence, Cyklokapron, Cerebyx*
Bayer Schering (including Berlex)	40	11	*Intron A, Rebetol, Betaseron, Fludara, Betapace, Prolastin, Thrombate III, Kogenate, Gamimune N, Trasylol, Nexavar*
Amgen (including Immunex)	28	12	*Epogen (2), Neupogen (4), Sensipar, Leucovorin calcium (2), Leukine (2), Enbrel*
AstraZeneca (including MedImmune)	29	5	*Respigam, Hexalen, Neutrexin, Ethyol (2)*
Genzyme (including ILEX Oncology and Peptimmune)	28	7	*Ceredase, Cerezyme, Thyrogen, Campath, Fabrazyme, Clolar, Myozyme*
Biogen Idec (including Syntonix)	25	2	*Zevalin, Avonex*
Immunomedics (including IBC)	22	0	
Merck Serono	20	10	*Novantrone (3), Metrodin, Serostim, Geref, Gonal-F, Zorbtive, Luveris, Saizen*
Bristol-Myers-Squibb	17	8	*Sprycel (2), Ifex, Vumon for injection, Megace, Blenoxane, Taxol, Droxia*
Abbott Laboratories (including Knoll)	17	2	*Panhematin, Humira*
Novo Nordisk	15	5	*Norditropin, NovoSeven (4)*

DES=designations / APP=approvals

Note: Data on designations and approval for each company are as of May 2009, and include designations and approvals in the name of firms that were subsequently acquired by the company.

* On March 26, 2009 Genentech became a wholly-owned subsidiary of Roche. Prior to the acquisition, Genentech had 22 designations and eight approvals.

Source: Food and Drug Administration 2009

Most orphan drugs are expensive. Even when the size of the market for a drug is small, the revenues can be substantial. To take some examples of leading therapeutic drugs, the average annual cost of Amgen's Epogen and Neupogen (for anemia) is $5,000 to $20,000; Genentech's Rituxan (for rheumatoid arthritis), $15,000-$20,000; Genzyme's Cerezyme (for Gaucher's disease), $150,000-$225,000; Biogen Idec's Avonex (for multiple sclerosis), $20,000-$24,000; Merck Serono's Rebif (for multiple sclerosis), $20,000-$24,000; Gilead Sciences' AmBisone (for AIDS), over $15,000; Novartis's Gleevec (for cancer), over $40,500; and Millennium's Velcade (for cancer), over $50,000 (see Caremark 2006, 25; Stern and Reissman 2006, 737).

Table 2 shows the dependence on revenues from drugs that have had orphan status of the leading dedicated BP companies. Note that (similar to the case of Botox outlined above) a portion of the revenues included in the "orphan drug" revenues in Table 2 are from non-orphan applications of drugs that have had orphan drug status. The point is that at formative periods in their histories, several leading biotech companies have achieved significant growth through the development

and marketing of drugs with orphan status. As can be seen in the row labeled TOTAL 1 in Table 2, in 2008 orphan drugs represented 59 percent of the total revenues and 61 percent of the product revenues of the six leading dedicated BP companies. Note that Amgen's two most recent blockbuster drugs, Aranesp with 2008 revenues of $3.1 billion and Neulasta with 2007 revenues of $3.3 billion, are second-generation low-dosage derivatives of Epogen and Neupogen respectively. If we treat these two drugs as products with "orphan" origins, then in 2008 orphan drugs were 74 percent of the total revenues and 74 percent of the product revenues of the six leading companies.

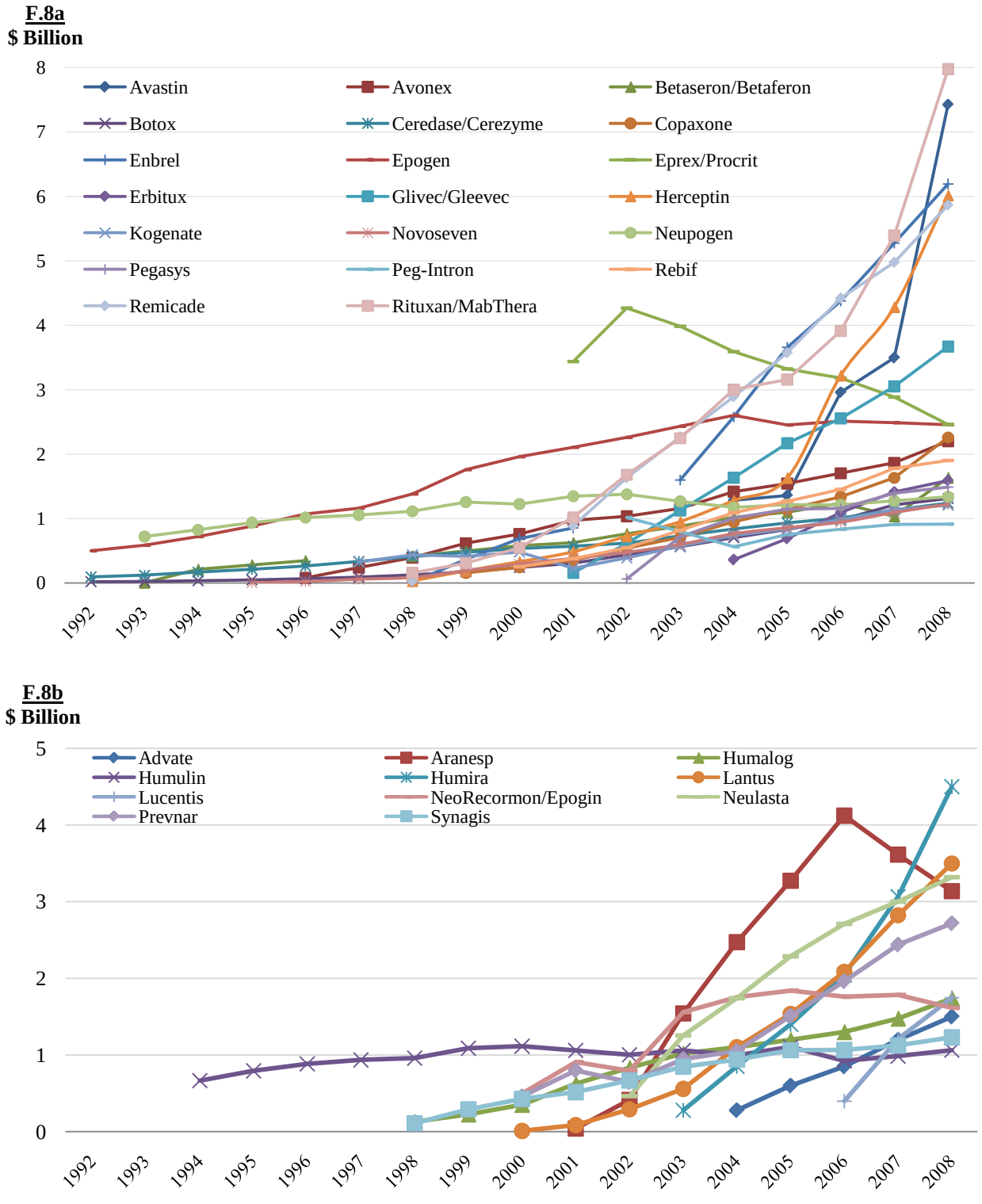
Table 2. Orphan drugs as a percentage of revenues of leading biotech companies, 2007 and 2008

	Total revenues, $m. (A)		Product revenues, $m (B)		Orphan drug revenues, $m (C)		C as % of A		C as % of B	
	2008	2007	2008	2007	2008	2007	2008	2007	2008	2007
Amgen	15,003	14,771	14,687	14,311	7,992	6,182	**53**	**42**	**54**	**43**
Genentech	13,418	11,724	13,070	11,427	10,235	8,089	**76**	**69**	**78**	**71**
Gilead Sciences	4,605	3,813	4,197	3,457	2,580	2,064	**56**	**54**	**61**	**60**
Genzyme	4,098	3,172	4,079	3,147	3,331	2,794	**81**	**88**	**82**	**89**
Biogen Idec	5,336	4,230	5,303	4,201	1,024	897	**19**	**21**	**19**	**21**
Cephalon	1,975	1,773	1,944	1,727	1,064	852	**54**	**48**	**55**	**49**
Millennium		528		528		397		**75**		**75**
TOTAL 1	44,434	40,011	43,279	38,798	26,225	21,275	**59**	**53**	**61**	**55**
TOTAL 2*	44,434	40,011	43,279	38,798	32,662	27,889	**74**	**70**	**75**	**72**

Orphan drug revenues by company and tradename (2008 and 2007 sales in $millions in parentheses):
Amgen: Enbrel (3598; 3230), Epogen (2456; 2489), Neupogen (1341; 1277); Sensipa (597; 463)
Genentech: Rituxan (2851; 2285), Avastin (2908; 2296), Herceptin (1819; 1287), Nutropin (375; 371), Tarceva (457; 417), Activase (-; 268) Pulmozyne(302; 223)
Gilead Sciences: AmBisome (289.7; 263); Letairis(112.9; 21.0); Viread (621.2; 613.2)
Genzyme: Cerezyme (1239; 1133), Fabrazyme (494.3; 424), Thyrogen (148.4; 114), Thymoglobolin (149.1; 127), Campath/Clolar/Mozobil (101.2; 65); Myzyme (296.2; 200.7); Aldurazyme (151.3; -)
Biogen Idec: Avonex (2202.6; 1,868), Rituxan (1128.2; 926.1)
Cephalon: Provigil (988.4; 852) Treanda (75.1; -)
Millennium: Velcade (265, 327) (includes revenues from strategic alliances and royalties)
Note: In May, 2008, Millennium was acquired by Takeda Pharmaceutical Company Limited.
* Total 2 treats Amgen's Aranesp (3119; 3614) and Neulasta (3318; 3000) as derivative of orphan drugs.
Sources: Company SEC filings and annual reports

The financial histories of these companies show that orphan drugs were of even greater importance to revenues in the earlier phases of enterprise growth. More generally, the importance of orphan drugs in the growth of the BP industry can be seen by comparing the timing and growth of revenues for orphan and non-orphan blockbusters, as is done in the two panels of Figure 8. Comparing the two panels, orphan drugs are more numerous, their revenue growth began earlier, and many of them have greater 2007 sales than the leading non-orphan drugs. If we were to transfer Amgen's Aranesp and Neulasta to the orphan drug panel, the centrality of orphan drugs in driving the development of the biotech industry would become even more apparent.

Figure 8a & 8b. Blockbuster biopharmaceutical orphan (8a) & non-orphan (8b) drugs, 1992-2008



Source: Company SEC filings and annual reports

We have already seen an indication of the important role of big pharma in BP in Table 1 above. The growing importance of big pharma to the biotech industry, and vice versa, becomes apparent when we attach company names to the blockbuster drugs displayed in Figure 8. Table 3 lists the companies for which these BP drugs, orphan and non-orphan, generate revenues, with big pharma in italics.

Table 3. Companies with blockbuster biopharmaceutical drugs through 2008

ORPHAN BLOCKBUSTERS		NON-ORPHAN BLOCKBUSTERS	
COMPANY	**Trade name**	**COMPANY**	**Trade name**
Amgen & *Wyeth*	Enbrel	*Baxter*	Advate
Genentech	Avastin	Amgen	Aranesp
Biogen Idec	Avonex	*Eli Lilly*	Humalog
Bayer (Schering AG)	Betaseron/Betaferon	*Abbott*	Humira
Allergan	Botox	*Eli Lilly*	Humulin
Genzyme	Ceredase/Cerezyme	*Sanofi-Aventis*	Lantus
Sanofi-Aventis/Teva	Copaxone	Genentech (*Roche*)/*Novartis*	Lucentis
Amgen	Epogen	Genentech/*Roche/Chugai*	NeoRecormon/Epogin
*Merck-Serono/Bristol-Myers/Eli Lilly (*ImClone*)*	Erbitux	Amgen	Neulasta
Novartis	Gleevec	*Wyeth*	Prevnar
Genentech/*Roche*	Herceptin	*Abbott*/MedImmune	Synagis
Bayer	Kogenate		
Amgen	Neupogen		
Novo-Nordisk	NovoSeven		
Roche	Pegasys		
Schering-Plough	PEG-INTRON		
*Johnson&Johnson/*Ortho Biotech	Procrit/Eprex		
Serono	Rebif		
Johnson&Johnson	Remicade		
Genentech/Biogen/*Roche*	Rituxan/MabThera		

Note: Big Pharma in italics
Source: Company SEC filings and annual reports

The distinction between big pharma and big biopharma has become blurred. For both, in the 2000s, the US government still serves as an investor in knowledge creation, subsidizer of drug development, protector of drug markets, and, last but not least – as we shall discuss in the next section – purchaser of the drugs that the biopharmaceutical companies have to sell. The BP industry has become big business because of big government, and, as we shall now show, remains highly dependent on big government to sustain its commercial success.

4. Sustainability of the US Biotech Boom

On the supply side, the biotech boom has depended on technological innovation in the development of new drugs for the treatment of diseases, many of which were previously untreatable. In the forefront have been NIH funding of the life sciences knowledge base and an emphasis on the part of business enterprises on finding cures for "genetic and rare diseases" that fall within the purview of the Orphan Drug Act. The sustainability of the US biotech boom depends in part on the ability of the United States to continue to innovate in the BP industry, especially given an inevitable increase in global technological competition.

On the demand side, the US biotech boom has depended on the ability of those afflicted by these diseases to acquire the new biopharmaceuticals. Unlike the demand for most innovative goods and services, the demand for biotech drugs is not directly dependent on personal disposable income and consumer choice. The richer households that have the money to pay both the higher taxes needed to support public insurance plans and the higher premia needed to fund private insurance plans are not necessarily the same households that are in need of the drugs.

On the demand side, the key question is whether there will be sufficient medical coverage for the nation's population to absorb the industry's supply of BP drugs, *especially* when innovations in the BP industry have been transformed into approved drugs that are often very expensive. In the 2000s the richest nation in the world is already straining to afford the wonders of modern medical technology. Prescription drug expenditures (PDE) have been increasing as a proportion of national health expenditures (NHE). NHE rose from 5.2 percent of GDP in 1960 to 9.1 percent in 1980 and 13.8 percent in 2000, and continued their climb to 16.2 percent in 2007. A rapidly increasing component of the rise in NHE is prescription drugs. Since 1981, when they reached a low for the whole period of 4.6 percent, PDE as a proportion of NHE have been on the rise, averaging a record 11.4 percent for the period 1997-2007.

An increasing proportion of NHE has been borne by public funds. Government expenditure as a proportion of NHE was 24.8 percent in 1960 but jumped to 37.7 percent in 1970 as a result of the introduction of Medicare and Medicaid in 1965 as policy pillars in the "War on Poverty" (NCHS 2006, 374). This proportion stood at 42.1 percent in 1980, 40.4 percent in 1990, and 44.3 percent in 2000. In 2007 the government share of NHE was 46.2 percent.

Since the early 1980s, prescription drug expenditures (PDE) as a proportion of NHE have been on the rise, averaging a record 10.1 percent for the period 2003-2005. Plan D of Medicare, introduced on January 1, 2006 to implement the Medicare Prescription Drug, Improvement and Modernization Act of 2003, further increased PDE as a proportion of NHE to 10.3 percent in 2006. In total, at the beginning of January 2008, 39.6 million people received comprehensive prescription drug coverage under Medicare, including 24.4 million under Plan D, of which over 9 million were low-income beneficiaries who receive the drugs at little if any cost (O'Sullivan 2008, 39; see also Montgomery and Lee 2006; CMS 2007).

More generally, as a proportion of GDP, the United States spends far more than any other nation on health care; in 2006 the US figure was 15.3 percent, followed by Switzerland at 11.3 percent, France at 11.1 percent, and Germany at 10.4 percent (www.who.int/whosis/data/Search.jsp). The

high cost of US health care raises the question of whether, going forward, there will be sufficient public and private medical coverage for the nation's population to absorb the industry's supply of BP drugs, *especially* when innovations in the BP industry have been transformed into approved drugs that are for relatively small populations and that are very expensive. As was shown in Figure 7, in the United States the past few years have seen a quantum increase in the number of orphan drug designations, which means that there are greater numbers of drugs for genetic and rare diseases in the pipeline. Moreover, with some 7,000 such diseases having been identified and an estimated 25 million Americans who can potentially make use of them, the need for new drugs remains far from being met.

In the 2000s the limits to effective demand for BP drugs in the United States have been transcended to some extent through exports (Lazonick et al. 2007). Europe is the biggest foreign market for US BP exports. Among Harmonized System (HS) 6-digit export classifications, the second largest product category to the EU15[8] in 2007, with 3.2 percent of the total, was "Other medicaments, packaged for retail sale" (HS-300490). Of US HS-300490 exports to the world, 57 percent went to the EU15. The seventh largest product classification, with 2.1 percent of the EU15 total, was "Antisera and blood fractions/immunological products" (HS-300210); that is, materials for the manufacture of BP products. Of US HS-300210 exports to the world, 80 percent went to the EU15. In 1997 these two classifications combined had accounted for only 0.9 percent of all US exports to the EU15; a decade later, 5.3 percent.

The sustainability of the growth of the BP industry in the United States, therefore, depends in part on whether US BP firms can continue to capture European demand. In 2001 the European Union passed its own Orphan Drug Act as part of an effort to catch up to the United States in biopharmaceuticals (Young 2007; Heemstra et al. 2008). Reflecting perhaps a process of European import substitution in BP, US exports of hormones (HS-293790), which had risen from 0.02 percent of all US exports to the EU15 in 1996 to 0.97 percent in 2004, fell sharply to 0.59 percent in 2005 and were down to 0.45 percent in 2007. According to the Ernst & Young annual biotech report, in 2008 Europe had more biotech companies than the United States (1,836 to 1,754), although the United States had more than twice as many publicly listed companies than Europe (371 to 178). The US BP industry has had access to much more venture financing than the European industry, but the Europeans are catching up (Ernst & Young 2009, 25).

Many leading European pharmaceutical companies are tapping into US biotechnology research through R&D alliances, acquisitions of US companies, and R&D facilities in the United States. For example, in 2002, Novartis, the Swiss pharmaceutical company, established its worldwide R&D headquarters in Cambridge, Massachusetts, next to MIT (Griffith 2002). As already mentioned, the regional concentrations of biotech research and companies that can be found in the vicinity of Boston-Cambridge, San Francisco, San Diego, and Washington-Baltimore are of utmost importance to the commercialization of the findings of NIH-funded knowledge base (see Cortright and Mayer 2002; Owen-Smith and Powell 2004; Porter et al. 2006), and remain a distinctive source of competitive advantage for the firms that operate in these dynamic industrial districts. Nevertheless, given the European presence in the US BP industry, we can expect that

[8] Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom

the latest knowledge and cutting-edge technology will continually flow from the United States to Europe.

The subsidies and protection provided by the Orphan Drug Act along with the NIH-funded knowledge base and non-orphan patent protection will continue to entice the business sector, including venture capital, to invest in an industry characterized by extraordinarily long product development cycles with highly uncertain prospects for commercial success. Such will especially be the case, as we have argued, if venture capitalists and established pharmaceutical companies expect that a speculative stock market will enable them to secure returns on their biotech investments long before the actual products in which they have invested generate substantial sales.

At the same time, however, the very importance of the stock market to biotech firms in particular and high-tech companies in general may serve to undermine the extent of the investments that BP companies make in generate innovative products. Over the past two decades, but especially in the 2000s, the executives of US business corporations, encouraged by Wall Street, have become committed to the practice of allocation substantial corporate resources to buy back their own corporate stock (Lazonick 2008; 2009a, ch. 6; and 2009b).

Many of the major pharmaceutical companies and the dedicated BP companies are very active stock repurchasers. Yet in the pharmaceutical industry writ large, there has long been a debate over the high prices of prescription drugs in the United States compared with over parts of the world including Japan and the high-wage nations of the European Union. The pharmaceutical companies argue that, since so much of the research on these drugs is done in the United States, they need to charge higher prices to fund R&D. Back in 1990 President George H. W. Bush vetoed a Congressional bill to modify the Orphan Drug Act in order to create more competition and keep down drug prices (Gibbons 1990). In recent years Congress has been debating whether, under Plan D of Medicare, the government should use its purchasing power to step in and negotiate prices with the drug companies. Then, as now, the pharmaceutical companies have argued that any attempt to regulate drug prices will cut into company profits, which will in turn diminish the amount of resources that companies have available to invest in R&D and, thereby, generate a flow of innovative products.

Yet, as shown in Tables 4 and 5, if one looks at the financial behavior of many big pharma and dedicated BP companies, a number of them use substantial portions of their profits to buy back their own stock. Among big pharma companies, over the decade 1997-2008, Pfizer did repurchases equal to 73 percent of R&D expenditures, Merck 72 percent, and Johnson & Johnson 60 percent. When the substantial dividends that these companies pay are added to their repurchases, the ratio of distributions to R&D shoots up to 1.63 at Merck, 1.42 percent at Pfizer, and 1.17 percent at Johnson & Johnson.

Table 4. Distributions to shareholders in the forms of stock repurchases and dividends by major US-based pharmaceutical companies, 1997-2008

	Sales, 2008	Fortune 500 rank	RP/ NI	(TD+RP)/ NI	RP/ R&D	(TD+RP)/ R&D
	$m	2008	1997-2008	1997-2008	1997-2008	1997-2008
Johnson & Johnson	63,747	29	0.40	0.79	0.60	1.17
Pfizer	48,296	46	0.73	1.41	0.73	1.42
Abbott	29,528	80	0.18	0.71	0.27	1.04
Merck	23,850	103	0.41	0.93	0.72	1.63
Wyeth	22,834	110	0.15	0.67	0.16	0.71
BMS	20,597	120	0.23	0.91	0.26	1.03
Eli Lilly	20,378	122	0.29	1.03	0.22	0.77
Schering-Plough	18,502	138	0.13	0.75	0.08	0.45
Allergan	4,403	517	0.68	0.93	0.32	0.43

TD=total (preferred plus common) dividends; RP=stock repurchases; NI=net income after taxes, before extraordinary items; R&D=research and development
Sources: Compustat database; 2009 Fortune 500 list
(http://money.cnn.com/magazines/fortune/fortune500/2009/full_list/)

Table 5 charts the stock repurchase activity for 1997-2008 for leading dedicated BP companies. Amgen has repurchased stock in every year since 1992, for a total of $26.7 billion through 2008. In many years the cost of Amgen's stock buybacks has surpassed the company's R&D expenditures, and for the period 1997-2008 were equal to 97 percent of R&D outlays. Genentech only began to do repurchases in 2001. From 2001 through 2008, the company allocated $7.4 billion to stock buybacks and $10.2 billion to R&D expenditures, for a repurchase to R&D ratio of .73. Genzyme did its first repurchases in 2007 and 2008, representing 42 percent of its net income.

Table 5. Distributions to shareholders in the forms of stock repurchases and dividends, leading dedicated biopharmaceutical companies, 1997-2008

	Sales, 2008	Fortune 500 rank	RP/ NI	(TD+RP)/ NI	RP/ R&D	(TD+RP)/ R&D
	$m	2008	1997-2008	1997-2008	1997-2008	1997-2008
Amgen	15,003	168	1.15	1.15	0.97	0.97
Genentech	13,418	201*	0.72	0.72	0.63	0.63
Gilead Sciences	5,336	444	0.84	0.84	0.50	0.50
Genzyme	4,605	502	0.18	0.18	0.06	0.06
Biogen Idec	4,098	546	2.63	2.63	0.86	0.86

* Genentech is not on the 2009 Fortune 500 list. If it had been, it would have ranked 201st in revenues.
For definition of acronyms, see Table 4.
Notes: Biogen Idec includes only Biogen repurchases and R&D before the 2003 merger of the two companies.
Sources: Compustat database; 2009 Fortune 500 list
(http://money.cnn.com/magazines/fortune/fortune500/2009/full_list/)

Why do companies do stock buybacks? Their purpose is to raise stock prices. Prime beneficiaries of stock repurchases, and the consequent boosting of stock prices, are the high-level corporate executives who make these allocative decisions (see Lazonick 2008; 2009a; and 2009b). Gains from the exercise of stock options are the main component of the well-known explosion of top executive pay that has occurred since the 1980s (see Hall and Leibman 1998; Jensen et al. 2005). Table 6 shows the average gains per person from the exercise of stock options over the past decade by the CEO and other four highest paid executives of six leading dedicated biotech firms, including Amgen and Genentech. Aided by stock buybacks, the CEO and other four highest paid executives at Amgen reaped an average of $105.3 million from gains from stock options for the period 1997-2008, while the top 5 at Genentech averaged $116.2 million for the period 1995-2008. Among big pharma companies that are large-scale repurchasers of stock, the average gains of the top 5 from the exercise of stock options for 1997-2008 were $30.0 million at Johnson & Johnson, $32.4 million at Merck, and $46.6 million at Pfizer.

Table 6. Gains from the exercise of stock options, average for CEO and other four highest paid executives, 1995-2008 (in US dollars)

	AMGEN	GENENTECH	GILEAD SCIENCES	GENZYME	BIOGEN IDEC
1995	6,817,627	825,701	*	465,309	2,464,961
1996	5,279,364	$325,679	411,250	721,100	298,066
1997	3,010,156	0	832,369	$44,373	4,293,557
1998	11,307,884	$592,149	491,235	1,471,548	615,541
1999	13,330,697	10,763,997	633,146	4,652,625	8,132,058
2000	42,131,827	23,414,861	2,227,746	1,846,424	9,070,194
2001	4,321,772	371,803	4,747,643	5,344,364	1,841,877
2002	2,951,349	0	2,530,736	0	736,089
2003	2,787,683	14,253,173	6,437,089	4,897,291	1,848,609
2004	1,729,808	24,175,200	7,563,908	2,116,807	14,221,925
2005	9,444,582	31,149,362	9,535,369	10,662,508	2,378,898
2006	1,036,550	4,445,274	13,967,766	0	1,695,916
2007	149,045	5,909,682	14,218,719	4,722,735	3,247,255
2008	1,190,447	**	767,552	2,057,562	4,235,246
1995-2007		**$116,226,881**			
1996-2008			**$64,364,528**		
1995-2008	**$105,488,791**			**$39,002,646**	**$55,080,192**

* Gilead Sciences did not report these data for fiscal 1995.
** In 2009 Genentech was acquired by Roche and did not release these data for 2008
Sources: SEC filings and Compustat database

Stock buybacks represent a manipulation of the stock market, and can come at the expense of meeting the challenges of drug development. In May 2007 Amgen borrowed $3.2 billion ($2.0 billion due in 2008, $1.1 billion in 2017, and $0.9 due in 2037) to help finance a $5.0 billion stock repurchase, the largest annual purchase that the company had ever done (Amgen 10-Q, period ending June 30, 2007). At the same time, as Amgen reported in its quarterly financial filing, sales of its blockbuster anemia drug, Aranesp, declined by 19 percent because of an FDA

ruling that dosage levels had to be cut because of cases of heart attacks from high doses (Chase 2007).

On August 13, just after Amgen issued its second quarter 10-Q filing, an analyst at Bernstein Research wrote: "Amgen will likely lose at least 40 percent of their US Aranesp revenue by 2008 with even greater downside possible for both Aranesp and Epogen if upcoming [Medicare and Medicaid] reimbursement and regulatory decisions go against them." But the analyst reportedly added: "If Amgen cuts costs, continues to buy back stock and improves its tax rate…it could increase its earnings per share by 10-12% each year from 2008 to 2011, even if it does not develop any significant drug candidates."[9]

Four days later, Amgen announced that it would reduce its workforce by 14 percent, or 2,600 jobs, cut capital expenditures by $1.9 billion, close some of its production facilities, and reduce R&D expenses (which had been at 27 percent from 2003 through 2006) to 20 percent of sales. It may well be that Amgen borrowed money to do the $5-billion stock repurchase because it wanted to offset the adverse impact of the Aranesp news on its stock price. In any case, the priorities of Amgen's top executives in their allocation of corporate resources seem clear.

In assessing the arguments of the relation between drug prices and BP investments in R&D, government policy makers should take seriously two salient issues that business proponents of a "free market" economy prefer to ignore. The first issue is the fact that government investment in research is more important than business investment for supporting innovation in the BP industry. The second issue is that when US BP companies get high profits from high prices they do not necessarily invest those high profits in R&D.

These two issues are intertwined. Given the role of government in funding the biotech industry, the government should take an active role in the governance of companies that make use of this support. Since the 1980s the US business community, the BP industry included, has embraced the ideology that the performance of their companies and the economy are best served by the "maximization of shareholder value" (see Lazonick and O'Sullivan 2000; Lazonick 2008 and 2009a, ch. 6). It is an ideology that, among other things, says that any attempt by the government to interfere in the allocation of resources can only undermine economic performance. In practice, what shareholder ideology has meant for corporate resource allocation is that when companies reap more profits they spend a substantial proportion of them on stock repurchases in an effort to boost their stock prices, thus enriching first and foremost the corporate executives who make these allocative decisions.

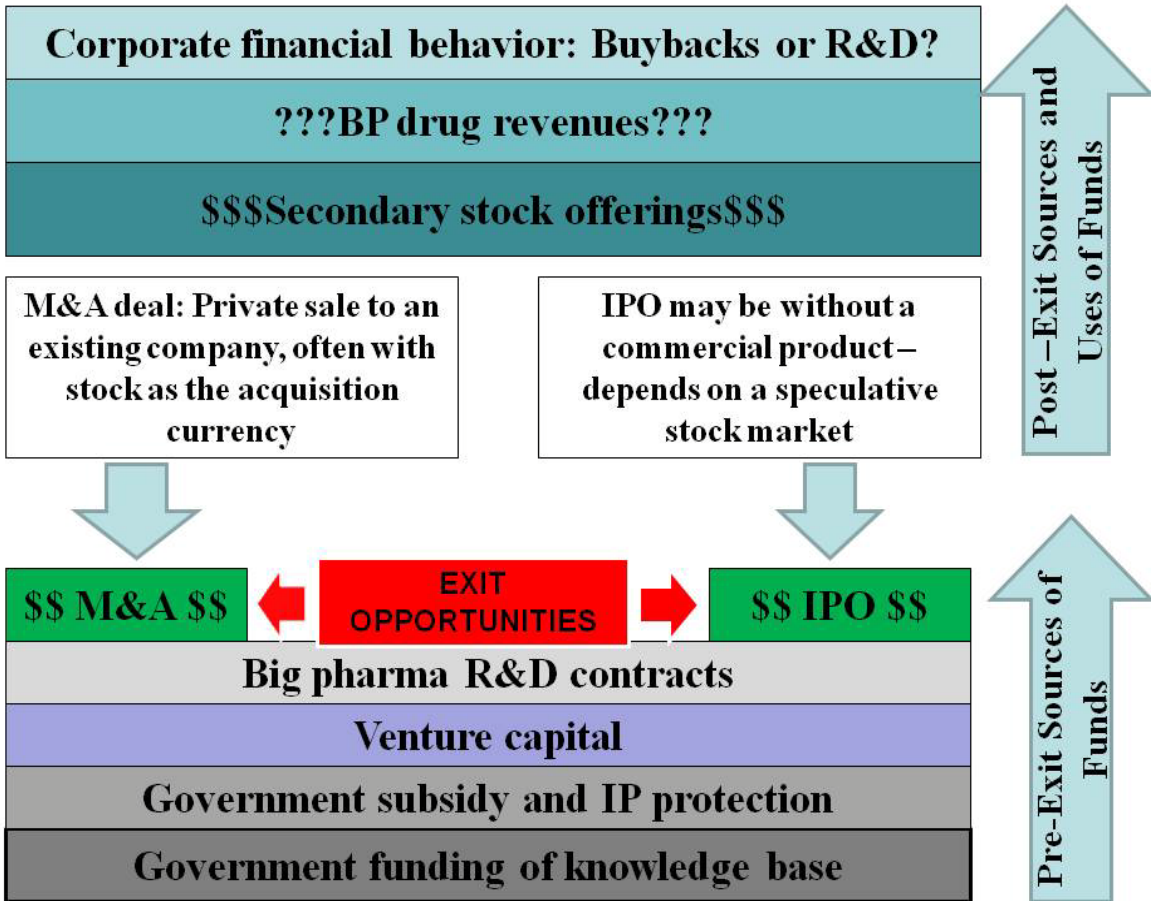
5. Financialization and Innovation: A Research Agenda

As outlined in this paper, and as depicted in Figure 9, the US BP finance model rests on NIH funding of the knowledge base as its foundation complemented by various types of government subsidies, of which those available to BP firms under the Orphan Drug Act appear to be of particular importance. Building on the availability of government funding and subsidies, venture capitalists and established pharmaceutical companies provide cash for BP startups to develop

[9] "Amgen moves up after analyst says company will restructure to increase earnings," Associated Press Financial Wire, August 13, 2007.

drugs. In terms of the time required to develop a commercial drug, it is not unusual for the BP firm that is being funded to remain a "startup" for two decades or more. Through M&A deals and IPOs, however, the venture capitalists and the established pharmaceutical companies that fund drug development often are able to secure returns on their investments long before the BP startup actually develops a commercial drug, and in many cases even if the BP firm never develops a commercial drug.

Figure 9. The US biopharmaceutical funding structure



Ernst & Young's press release for its 2009 Beyond Borders biotechnology report observed that. "the prolonged and systematic funding drought is placing the business model that fueled biotech growth for the past 33 years under unprecedented strain." Yet, according to Ernst & Young, in 2008 the revenues of publicly traded biotech companies grew by 12 percent over the previous year, reaching $89.7 billion, and taken together these companies showed a profit. The flow of venture capital into the industry remained strong in 2008, down only 19 percent from a record high of $6 billion the previous year. Meanwhile, the total value of M&A deals in biotech was $28.5 billion, an unprecedented amount if one excludes megadeals. The Ernst & Young press release might have added that in 2008, NIH funding, the backbone of the industry, was $30 billion, about the same as the previous year.

What then is the source of "the prolonged and systematic funding drought" that is placing the biotech business model under strain? According to Venture Xperts (see Figure 3 above), in 2008 there was only one venture-backed biotech IPO in the United States, worth less than $6 million, down from 21 deals for $1,245 million in 2004, 11 deals for $671 million in 2005, 14 deals for $714 million in 2006, and 11 deals for $679 million in 2007 (see also Ernst and Young 2009, 24). Through the first half of 2009, there were no venture-backed biotech IPOs in the United States. In the absence of a speculative stock market that will absorb product-less IPOs, the BP business model is not providing venture capitalists and big pharma who make equity investments in BP startups with the exit opportunities that they have enjoyed in the past. The fear is that if this "funding drought" persists, the flow of venture capital and big pharma equity investments will start to dry up as well.

From the perspective that we have set out in this paper, there are a number of questions concerning the sustainability of the BP business model that require in-depth research on the sources and uses of funds that characterize the US BP business model, and on the implications of the combination of government funding and the speculative stock market for the successes and failures of companies and products over the BP industry's three decades long history.[10]

- At the base of the funding structure depicted in Figure 9, how tightly linked is NIH funding to the emergence of successful drugs, such as the blockbusters shown in Figures 8a and 8b?
- How important have subsidies and protection under the Orphan Drug Act been to successful drug development?
- As we move up the funding structure, how successful have venture capitalists and big pharma been in extracting value from their investments in startups in advance of the generation of commercial products?
- What impacts does this value extraction have on the commitment of finance to the drug development process subsequent to an IPO? Put differently, does it matter to the success or failure of the drug development process if key actors in the formation and growth of BP firms have more to gain from a speculative stock market than from the commercialization of a drug?
- Is a startup acquired through an M&A deal, that inherently becomes a real asset on the books of the acquiring drug company, of a higher quality (that is, further down the road toward developing a commercial product) than an IPO in which speculative investors in publicly traded stock can easily dispose of their investments?
- How does this mode of BP finance affect that ultimate cost of drug development, and the distribution of the costs and benefits of the drug development process?
- And when a BP company develops a profitable drug, how does a stock-market orientation, as manifested in stock buybacks and stock-based remuneration of executives, affect the commitment of finance to the further growth of the firm?

[10] We are doing this research as part of the European Commission's Seventh Framework project on Finance, Innovation, and Growth (FINNOV) in collaboration with Mariana Mazzucato of The Open University; Claude Dupuy, Yannick Lung, and Matthieu Montalbon of Université Montesquieu-Bordeaux IV; and Mustafa Erdem Sakinc, formerly a graduate student in the Department of Regional Economic and Social Development of the University of Massachusetts Lowell, who is working on FINNOV as part of the Bordeaux team. Related research on Ireland is being carried out by the authors of this paper under a collaborative agreement between the Centre for Innovation and Structural Change of the National University of Ireland Galway, directed by Paul Ryan, and the UMass Lowell Center for Industrial Competitiveness under a European Commission Sixth Framework Marie Curie actions grant for the Transfer of Knowledge.

In seeking to answer these questions, our analysis will be guided by "the theory of innovative enterprise", with its focus on strategic, organizational, and financial factors in the growth of the firm (see Lazonick 2002; 2004; and 2007). In our view, the only way to implement this research agenda in a way that can generate reliable answers to these questions is through the accumulation of company case studies on the basis of a common template. This analytical framework permits us to ask how the prevailing mode of finance affects the strategic decisions of those who exercise control over the allocation of the BP firm's resources as well as the organizational integration of people with diverse capabilities into the cumulative and collective learning process that is essential for successful drug development.

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