# Biotechnology business models work: Evidence from the pharmaceutical marketplace

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## Abstract

A study was undertaken that validates the business models of biotechnology companies that compete in the pharmaceutical marketplace. Strategic alliances, largely with established pharmaceutical companies, have enabled biopharmaceutical companies to obtain revenues prior to achieving their goal of manufacturing and marketing their own products. As a result, despite the generally long lead-times to commercialisation, an increasing number of biopharmaceutical companies are demonstrating financial success in the marketplace, particularly with respect to revenues, at a faster pace than occurred for both the traditional pharmaceutical and the specialty pharmaceutical companies. There were 244 biopharmaceuticals approved for 366 indications from 1982 to 2005, of which 48 per cent of the approvals for both the products and the indications occurred in the period 2001–2005 (representing just 21 per cent of the 24-year period). From 1990 to 2005, the ten largest US biopharmaceutical companies increased their total revenues from $1.1bn to $31.7bn and turned a combined loss of $0.3bn to net income of $6.2bn. During this time-frame the number of US biopharmaceutical companies reporting revenues in excess of $1bn increased from zero to eight.

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## INTRODUCTION

For many investors the biotechnology industry is an enigma and biotechnology investing an oxymoron. A decade ago it was observed that '… most biotech firms are in the product development stage and in the short term are burning capital without generating income. They are typically subject to extensive government regulation and require long gestation periods (frequently exceeding 10 years for a single product) before a product can be developed to the point of commercialisation. Therefore, the biotechnology industry as a whole has never recorded a net profit'.[1] That statement still holds true today, and as a result, critics argue that the biotechnology industry's structure is flawed, that unless there is fundamental change in this structure, 'biotech won't be

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able to attract the investments and talent required to realize its potential for transforming healthcare'.[2]

Pisano, in particular, posits that '… the business models of biotech have worked poorly because they were based on the wrong inferences about the science'.[3] He has argued that 'biotech has produced no breakthrough in R&D productivity',[2] and that 'industrialized R&D has yet to deliver for biotech'.[2] While on the surface it would appear that one could reasonably question the validity of the business models of biotechnology, an unprofitable industry over 30 years old, digging beneath the surface leads one to the opposite conclusion. Indeed, a counter argument can be made, namely that 'the business models are indeed valid because they are based on the correct inferences about the science'.[4]

For example, regarding R&D productivity, Pisano's own data show that for publicly held biotechnology companies, R&D spending per new drug launched (in constant dollars) decreased from $2.0bn in 1985 to $1.2bn in 2004, and for the top 20 pharmaceutical companies worldwide it decreased from $4.3bn in 1985 to $1.3bn in 2004.[2] These figures thus demonstrate an increase in R&D productivity, as indicated by a decrease in R&D spending per new drug launched, and suggest that pharmaceutical companies now use the same biotechnology techniques pioneered by the biotechnology industry.[4]

The current study examines the evidence that supports the counter argument. A prerequisite for gathering such evidence is to place biotechnology in its proper context. Biotechnology, including genetic engineering, 'originated thousands of years ago with the cultivation of plants, domestication of animals and fermentation…. The oldest examples of genetic engineering include the breeding of animals, cross-breeding of plants and selection of microbial mutants'.[5] Selection of microbial mutants and fermentation, for example, were involved in making alcoholic beverages, antibiotics and industrial chemicals well before the discovery of recombinant DNA (rDNA) in 1972, the seminal event of modern biotechnology. Today, biotechnology encompasses a plethora of techniques and applications that are practiced by a variety of industries, including the pharmaceutical, agricultural, food processing, chemical, energy, and waste treatment industries, in addition to that industry known as 'biotech'. It is abundantly clear from the widespread practice of biotechnology across established industries that both the science and the economics are sound.[6]

## METHODOLOGY

The current study focuses on that sector of the biotechnology industry that requires the most government regulatory approval, the sector that competes in the pharmaceutical marketplace. Biotechnology companies in this sector are typically called biopharmaceutical companies (or biopharma), but as will be explained below, for the purposes of this study not all biotechnology companies developing and commercialising therapeutics are considered to be biopharma. In addition, in order to facilitate access to data from this sector, the study was limited to US companies publicly traded on US stock exchanges.

*Nature Biotechnology* publishes annual surveys of public biotechnology companies worldwide. These surveys provide revenues, R&D expenses, and profits or losses of the companies listed. While the surveys are fairly comprehensive, not all public biotechnology companies are included, especially small companies that are traded over-the-counter. Moreover, some companies listed in the surveys may mistakenly be identified as biotechnology, such as instrumentation and equipment manufacturers selling to biotechnology companies, or the same company being listed under both its previous name and its current name, or a company with absolutely no biotechnology connections. Nevertheless, since the surveys include almost all public US biotechnology companies (omitting primarily those public biotechnology companies that are delinquent in filing reports with the Securities and Exchange Commission

(SEC)), they represent a good starting point to screen for biotechnology companies meeting certain criteria. Surveys undertaken for the years 1995,[7] 2000,[8] 2005,[9] and 2006,[10] listed 228, 361, 402, and 419 companies, respectively.

Every company appearing in these surveys was screened in the following manner. The archives of the US SEC[11] were accessed to determine which of these companies were US companies and from their Form 10-K Annual Reports which of them fit the criteria of biotechnology companies competing in the pharmaceutical marketplace. In some cases, company histories archived by FundingUniverse were accessed.[12] Analyses of financial data were performed only with financial data obtained from the 10-K Annual Reports, not from the *Nature Biotechnology* surveys nor from Funding Universe.

Companies listed in the *Nature Biotechnology* surveys that were considered for inclusion in this study had to have products either under development or already in the marketplace that require approval by the US Food and Drug Administration (FDA) of either a new Drug Application (NDA) or a Biologics License Application (BLA). Companies excluded included those better characterised as specialty pharmaceutical companies (ie generic drug companies, drug delivery companies, and companies that license in and market drugs developed and manufactured elsewhere), as well as those companies focused on human blood products, human cellular and tissue-based products, or medical devices. FDA has different regulatory requirements for the latter two categories. Diagnostics companies were also excluded, but biotechnology companies that had significant programmes in both pharmaceuticals and diagnostics were included.

In summary, this study was limited to biopharmaceutical companies that were developing or commercialising products, subject to approval of an NDA or BLA, that fit one or more of the following five categories: rDNA-derived protein therapeutics, therapeutic monoclonal antibodies (mAbs), nucleic acid therapeutics, therapeutic vaccines, and smaller molecules requiring specialised techniques intrinsic to modern biotechnology. A database of all FDA-approved biotechnology-derived therapeutics, maintained by the Biotechnology Industry Organization (BIO), was accessed in order to analyse the growth of such approvals.[13,14]

## RESULTS

In 1982, rDNA-derived human insulin became the first biotechnology therapy to be approved by FDA.[13] From 1982 to 31st October, 2006, a total of 254 biotechnology-derived drugs (including 106 recombinant and mAb products and a few tissue-engineered products) were approved by FDA for 392 indications.[14] An indication of the practical impact of the science behind biotechnology can be gleaned from an analysis of the pattern of approvals since 1982. BIO has reported the number of new biotechnology drug and vaccine indication approvals for each year from 1982 to 2005.[13] As demonstrated in Table 1, which groups the data by five-year periods (except for the first period, 1982–1985), the number of approvals has consistently accelerated from one five-year period to the next. Of the 366 approvals (for 244 drugs) over the 24-year period from 1982 to the end of 2005, 176 or 48 per cent occurred over the final five-year period ending December 2005 (representing just 21 per cent of the 24-year period). The acceleration in the number of approvals was due not only to increasing numbers of approved indications for pre-existing drugs

**Table 1:** New biotechnology drug and vaccine indication approvals from 1982 to 2005

| Years | Number of approvals | % of all approvals |
|---|---|---|
| 1982–1985 | 3 | 1 |
| 1986–1990 | 22 | 6 |
| 1991–1995 | 42 | 11 |
| 1996–2000 | 123 | 34 |
| 2001–2005 | 176 | 48 |
| Total | 366 | 100 |

but also to increasing numbers of new drugs approved. Of the 244 drugs approved, 117 or 48 per cent occurred in the 2001–2005 period.

Typically, biotechnology companies implement strategies for achieving revenues prior to achieving product sales. Such strategies may include marketing technical services to government and industry, procuring R&D contracts from government, and in almost all cases forming strategic alliances with industrial partners – mostly corporations in the pharmaceutical, agricultural, food processing, chemical, energy, or waste treatment industries. In 2005 alone, 564 strategic alliances were formed between biotechnology and pharmaceutical companies, and another 354 such alliances were formed solely among biotechnology companies.[13] Moreover, over the years this author has collected annual reports from over 330 biotechnology companies, all of whom had reported strategic alliances. All of the reports were provided by a service operated by *The Wall Street Journal* and were from all the companies that were listed in its biotechnology category.

Strategic alliances with industrial partners usually provide for a mix of fees based on R&D performed and milestones achieved. More importantly, the major objective for the biotechnology company in such alliances is to obtain either (a) significant royalties on products it has developed that are sold by its strategic corporate partner, or (b) co-promotion revenue, which amounts to a sizable share of the profits from the sale of such products. In addition, a few biotechnology companies have jump-started their commercialisation activities by acquiring a product already in the marketplace, or by acquiring or merging with an entity producing such a product. Most importantly, the success of a biotechnology company's business model may be defined by how well the company hones its core competencies, markets them to potential strategic partners, and structures the resulting strategic alliances so as to mesh its core competencies with those of its partners and provide for a series of increasing revenue streams.

Tables 2 and 3 provide some of the financial evidence of the validity of biotechnology's business models. Based solely on historical data obtained from 10-K Annual Reports, Table 2 lists all those publicly traded US biopharma companies (as defined in the methodology section) that were able to grow their annual revenues past the $100m mark. As indicated above, revenues include the total of all applicable R&D contract and technical services fees, upfront license fees, milestone fees, royalties, co-promotion fees, and product sales. In 1986, the oldest of these companies, Genentech, which was formed in 1976, was the first such company to reach $100m. Through the end of 2006, 31 companies had met this goal. As disclosed in their 10-K Annual Reports, all of the companies listed in Table 2 had formed strategic alliances that were prerequisite to achieving $100m of annual revenues.

Table 3 groups the number of biopharma companies by five-year periods with respect to when they first achieved annual revenues of $100m. The number of companies achieving this goal has also accelerated from one five-year period to the next. Of the 29 companies that reached this goal over the 20-year period from 1986 to the end of 2005, 14 or 48 per cent occurred over the final five-year period ending December 2005 (representing just 25 per cent of the 20-year period).

Returning to Table 2, this table also indicates which companies were able to reach $100m of product sales prior to 2007. It is clear that the companies listed were typically focused on becoming fully integrated pharmaceutical companies and by and large have mostly achieved that goal (as evidenced by their own product sales). Of the 31 companies that achieved revenues exceeding $100m, 25 concomitantly or subsequently attained product sales also exceeding $100m. Two companies were merged or acquired

**Table 2:** Biopharma companies with $100m annual revenues prior to 2007

| Year formed | Company | No.of years to reach $100m revenues (product sales) | No. of years to reach $1bn revenues (product sales) | No. of years to be acquired | Acquired by/ merged into |
|---|---|---|---|---|---|
| 1976 | Genentech, Inc. | 10 (11) | 22 (23) | | |
| 1978 | Biogen, Inc. | 14 (19) | 23 (24) | 25 | IDEC |
| 1979 | Centocor, Inc. | 13 (17) | M/A | 20 | Johnson & Johnson |
| 1980 | Amgen, Inc. | 10 (10) | 12 (12) | | |
| 1980 | Genetics Institute, Inc. | 13 (16) | M/A | 16 | Wyeth |
| 1981 | Chiron Corporation | 10 (11) | 14 (15) | 25 | Novartis AG |
| 1981 | Enzon, Inc. | 22 (23) | N/Y | | |
| 1981 | Genzyme Corporation | 10 (11) | 20 (20) | | |
| 1981 | Immunex Corporation | 12 (12) | M/A | 21 | Amgen |
| 1981 | Scios Inc. | 21 (21) | M/A | 22 | Johnson & Johnson |
| 1983 | OSI Pharmaceuticals, Inc. | 22 (23) | N/Y | | |
| 1984 | ImClone Systems Incorporated | 20 (N/Y) | N/Y | | |
| 1985 | IDEC Pharmaceuticals Corporation | 14 (M/A) | M/A | 18 | Biogen |
| 1986 | Celgene Corporation | 10 (10) | N/Y | | |
| 1986 | PDL BioPharma, Inc. | 19 (19) | N/Y | | |
| 1987 | Alkermes, Inc. | 19 (N/Y) | N/Y | | |
| 1987 | Amylin Pharmaceuticals, Inc. | 18 (19) | N/Y | | |
| 1987 | Cephalon, Inc. | 14 (15) | 17 (18) | | |
| 1987 | Gilead Sciences, Inc. | 9 (10) | 17 (17) | | |
| 1987 | Ligand Pharmaceuticals, Inc. | 15 (15) | N/Y | | |
| 1988 | COR Therapeutics, Inc. | 12 (M/A) | M/A | 14 | Millennium |
| 1988 | MedImmune, Inc. | 10 (10) | 15 (16) | 19 | AstraZeneca PLC |
| 1989 | Vertex Pharmaceuticals Incorporated | 16 (N/Y) | N/Y | | |
| 1991 | Myriad Genetics, Inc. | 15 (N/Y) | N/Y | | |
| 1991 | NeXstar Pharmaceuticals, Inc. | 7 (7) | M/A | 8 | Gilead |
| 1992 | Cubist Pharmaceuticals, Inc. | 13 (13) | N/Y | | |
| 1993 | Millennium Pharmaceuticals, Inc. | 5 (11) | N/Y | | |
| 1994 | ViroPharma Incorporated | 11 (11) | N/Y | | |
| 1996 | United Therapeutics Corporation | 9 (9) | N/Y | | |
| 1998 | Emergent Biosolutions, Inc. | 7 (7) | N/Y | | |
| 1998 | InterMune, Inc. | 4 (4) | N/Y | | |

Note: N/Y = not yet, M/A = merger/acquisition prior to reaching revenue goal.

**Table 3:** Number of biopharma companies with annual revenues first exceeding $100m between 1986 and 2005, grouped by five-year periods

| Years | Number of companies (%) |
|---|---|
| 1986–1990 | 2 (7) |
| 1991–1995 | 6 (21) |
| 1996–2000 | 7 (24) |
| 2001–2005 | 14 (48) |
| Total | 29 (100) |

before being able to achieve the latter goal, leaving only four independent companies that had not reached $100m of product sales prior to 2007.

Table 2 further shows that all of the companies that surpassed $1bn in revenues (which took an average of 17.5 years following incorporation) also recorded product sales exceeding $1bn (which averaged around 18 years following incorporation). Five companies whose product sales exceeded $100m were merged or acquired before reaching the $1bn level. In addition, three companies whose product sales had surpassed $1bn were merged or acquired. In total, five acquisitions were made by four large international pharmaceutical companies, and the remaining five mergers or acquisitions were entirely within the biotechnology sector.

Of particular interest is how four of the companies listed in Table 2, all four having been created after 1990, achieved annual product sales exceeding $100m in relatively short periods of time, within 4–9 years. United Therapeutics Corporation and InterMune, Inc. were able to jump-start their commercialisation strategies by acquiring rights to products that had been developed by other companies. United Therapeutics also acquired the contract manufacturer of the active ingredient of its first product. Emergent Biosolutions, Inc. implemented its commercialisation strategy by acquiring the rights and manufacturing capabilities to produce an FDA-approved anthrax vaccine, and then entering into multiyear contracts to provide the vaccine to the US Department of Defense and the US Department of Health and Human Services. NeXstar Pharmaceuticals, Inc. acquired a company that had existing products in the marketplace. NeXstar was subsequently merged into Gilead Sciences, Inc. in 1999, one year after it had achieved $100m of product sales. Gilead, which had not reached the $100m revenue mark prior to its merger with NeXstar, subsequently restated its revenues for prior years to reflect the merger that was accounted for as a pooling of interests. If revenues had not been restated, Gilead would not have reported $100m of revenues and of product sales until 1999, 12 years after its formation (versus 9 and 10 years, respectively, as shown in Table 2).

It should be noted that a number of specialty pharmaceutical companies commercialising human therapeutics were included in the *Nature Biotechnology* surveys because they were considered to be biopharmaceutical companies. Some of those companies have surpassed $100m in annual revenues but are not listed in Table 2 because of the limiting definition of biopharma employed in this study. For example, Alza Corporation, noted for its leading drug delivery technologies, exceeded revenues of $100m in 1991 and almost reached $1bn in 2000, before being acquired by Johnson & Johnson in 2001. Endo Pharmaceutical Holdings Inc. and Medicis Pharmaceutical Corporation first exceeded $100m revenues in 1998 and 1999, respectively. Kos Pharmaceuticals, Inc. first exceeded $100m revenues in 2002 and was acquired by Abbott Laboratories in 2006. Sepracor Inc. exceeded revenues of $100m in 2001 and $1bn in 2006.

Other biopharma companies were excluded from Table 2, even though at some point in their history they had achieved $100m revenues, because for various reasons those revenues were unsustainable. For example, Nabi Biopharmaceuticals, which was founded in 1969 as North American Biologicals, Inc.,[15] was originally a blood plasma supplier whose revenues eventually grew beyond the $200m mark. In 2001, Nabi sold the majority of its plasma collection centres in order to focus on becoming a fully integrated biopharmaceutical company. As a result its revenues began to fall, dropping below $100m in 2005 and 2006.

Three other biopharma companies not listed in Table 2 are Incyte Corporation, Neurocrine Biosciences, Inc., and Pharmacopeia Drug Discovery, Inc. Incyte evolved from a company created in 1991 to provide genomic information-based tools and services to pharmaceutical and biotechnology companies. Operating in this niche, Incyte grew rapidly, reporting revenues exceeding $200m in 2001. The company, however, discontinued most of this business in 2004 in order to focus on drug discovery and development with a wholly owned pipeline of compounds. As a result, its revenues dropped over 90 per cent from those reported for 2001 and in 2006 were around $28m. Neurocrine was formed in 1992. Owing to a strategic alliance with Pfizer Inc., Neurocrine's revenues topped $100m in 2003 and 2005 but dropped to $39m in 2006, following termination of its collaboration with Pfizer, and plunged to only $152 thousand for the first six months of 2007. Pharmacopeia Drug

Discovery, Inc. originated in 2004 as a spin-off from Pharmacopeia, Inc. Formed in 1993, Pharmacopeia, Inc. created two subsidiaries – one commercialising scientific software, and the other providing drug discovery services for pharmaceutical and biotechnology companies. Pharmacopeia, Inc. grew to over $100m in annual revenues by 2000, with the bulk of the revenues attributed to the scientific software business. In 2006, Pharmacopeia Drug Discovery, Inc. reported revenues of just $17m.

Tables 4–7 summarise the financial results for publicly traded US biopharma companies with the ten largest revenues reported for 1990 (Table 4), 1995 (Table 5), 2000 (Table 6), and 2005 (Table 7). The annualised growth rates for total revenues and product sales over this 15-year period were 25 and 28 per cent, respectively, resulting in total revenues and product sales of almost $32bn and $28bn, respectively, for 2005. When product sales as a percentage of total revenues were determined for each company, the average percentage grew from 40 per cent in 1990 to 81 per cent in 2005, thereby indicating that over time substantial portions of most companies' revenues were converting to product sales.

The number of companies reporting product sales exceeding $1bn grew from 0 in 1990 to 2 in 1995 and 2000 to 8 in 2005.

**Table 4:** Financial results of biopharma companies with the ten largest revenues for fiscal 1990

| Company | Total revenue ($ in millions) | Product sales ($ in millions) | Product sales (% of revenue) | Net income ($ in millions) |
|---|---|---|---|---|
| Genentech | 447 | 367 | 82 | (98) |
| Amgen | 299 | 281 | 94 | 4 |
| Chiron | 99 | N/A | N/A | 8 |
| Centocor | 65 | 33 | 51 | (132) |
| Genzyme | 62 | 32 | 52 | (26) |
| Biogen | 59 | 0 | 0 | 8 |
| Genetics Institute | 40 | 0 | 0 | (25) |
| Immunex | 35 | N/A | N/A | (10) |
| Scios | 12 | N/A | N/A | (5) |
| Liposome Company | 6 | 0 | 0 | (5) |
| Total | 1,124 | 713 | | (281) |
| Mean±SEM | | | 40±15 | |

Note: Total revenue excludes interest or investment income. N/A = data not readily available; SEM = standard error of the mean. Financial records of a number of small companies, whose revenues were under $10m in 1992, were not always accessible online for years prior to 1991 or 1992. In particular, three other companies may have been larger than the smallest company listed above. Two of these companies each reported revenues of $8m in 1991, and one reported revenues of $7m in 1992.

**Table 5:** Financial results of biopharma companies with the ten largest revenues for fiscal 1995

| Company | Total revenue ($ in millions) | Product sales ($ in millions) | Product sales (% of revenue) | Net income ($ in millions) |
|---|---|---|---|---|
| Amgen | 1,940 | 1,819 | 94 | 538 |
| Chiron | 1,101 | 923 | 84 | (512) |
| Genentech | 857 | 635 | 74 | 146 |
| Genzyme | 384 | 304 | 79 | 22 |
| Genetics Institute | 172 | 83 | 48 | (22) |
| Immunex | 157 | 138 | 88 | (11) |
| Biogen | 135 | 0 | 0 | 6 |
| Centocor | 79 | 65 | 82 | (57) |
| NeXstar | 61 | 58 | 95 | (37) |
| Athena Neurosciences | 53 | 43 | 81 | (30) |
| Total | 4,939 | 4,068 | | 43 |
| Mean±SEM | | | 73±9 | |

**Table 6:** Financial results of biopharma companies with the ten largest revenues for fiscal 2000

| Company | Total revenue ($ in millions) | Product sales ($ in millions) | Product sales (% of revenue) | Net income ($ in millions) |
|---|---|---|---|---|
| Amgen | 3,629 | 3,202 | 88 | 1,139 |
| Genentech | 1,646 | 1,278 | 78 | (74) |
| Chiron | 972 | 627 | 65 | 9 |
| Biogen | 926 | 761 | 82 | 334 |
| Genzyme | 903 | 812 | 90 | (63) |
| Immunex | 862 | 829 | 96 | 154 |
| MedImmune | 540 | 496 | 92 | 111 |
| Gilead | 196 | 150 | 77 | (57) |
| Millennium | 196 | 0 | 0 | (310) |
| IDEC | 155 | 0 | 0 | 48 |
| Total | 10,025 | 8,155 | | 1,291 |
| Mean±SEM | | | 67±11 | |

**Table 7:** Financial results of biopharma companies with the ten largest revenues for fiscal 2005

| Company | Total revenue ($ in millions) | Product sales ($ in millions) | Product sales (% of revenue) | Net income ($ in millions) |
|---|---|---|---|---|
| Amgen | 12,430 | 12,022 | 97 | 3,674 |
| Genentech | 6,633 | 5,488 | 83 | 1,279 |
| Genzyme | 2,735 | 2,453 | 90 | 441 |
| Biogen Idec | 2,423 | 1,617 | 67 | 161 |
| Gilead | 2,028 | 1,809 | 89 | 814 |
| Chiron | 1,920 | 1,421 | 74 | 180 |
| MedImmune | 1,244 | 1,221 | 98 | (17) |
| Cephalon | 1,212 | 1,157 | 95 | (175) |
| Millennium | 558 | 192 | 34 | (198) |
| Celgene | 537 | 446 | 83 | 64 |
| Total | 31,720 | 27,826 | | 6,223 |
| Mean±SEM | | | 81±6 | |

The profit picture also changed dramatically over this 15-year period. The percentage of profitable companies in 1990, 1995, 2000, and 2005 were 30, 40, 60, and 70 per cent, respectively. Tables 4–7 show an overall loss in 1990, a small profit in 1995, and total net income of $1.3bn and $6.2bn in 2000 and 2005, respectively.

Over the 15-year period between 1990 and 2005, from one five-year period to the next, there was considerable turnover in the groupings comprising the ten largest biopharma companies. All of the top ten companies in 1990 (Table 4) were created between 1976 and 1981. Companies formed between 1985 and 1993 gradually replaced half of those companies. In 1995 (Table 5), 2000 (Table 6), and 2005 (Table 7), the number of younger companies (incorporated in 1985 or later) among the top ten grew from two to four to five. In 2006, one of the older companies, Chiron Corporation, was acquired by Novartis AG, and a slightly younger company, ImClone Systems Incorporated, which had been formed in 1984, became one of the top ten, joining the remaining nine companies from the top ten in 2005. ImClone's revenues for 2006 were $678m, versus only $6m in 2000.

Only two companies that at some point in time were among the top ten, The Liposome Company, Inc. in 1990 (Table 4, but see the footnote) and Athena Neurosciences, Inc. in 1995 (Table 5), did not reach $100m in revenues as independent companies. Both companies were acquired by Elan

**Table 8:** Comparison of the largest companies in the biopharma sector with those in the specialty pharmaceutical sector, based on 2006 revenues

| Biopharma companies | | | Specialty pharmaceutical companies | | |
|---|---|---|---|---|---|
| **Company** | **Year formed** | **Fiscal 2006 revenues ($ in millions)** | **Company** | **Year formed** | **Fiscal 2006 revenues ($ in millions)** |
| Amgen | 1980 | 14,268 | Allergan | 1948 | 3,063 |
| Genentech | 1976 | 9,284 | Forest | 1956 | 2,912 |
| Genzyme | 1981 | 3,187 | Watson | 1985 | 1,979 |
| Gilead | 1987 | 3,026 | Barr | 1970 | 1,314 |
| Biogen Idec | 1978 | 2,683 | Mylan | 1961 | 1,257 |
| Total | | 32,448 | | | 10,525 |

Corporation, plc., the Irish biopharma company. Athena Neurosciences, formed in 1986, was acquired in 1996, the year after it had become one of the top ten. The Liposome Company, formed in 1981, was acquired in 2000, having attained revenues of $92m, including product sales of $86m and net income of $13m in 1999.

There has also been turnover among the top five biopharma companies. Just three companies in the top five in 2005 were in the top five in 1990. That neither early nor rapid market entry is a prerequisite for impressive market penetration is illustrated by the rise of Gilead Sciences, Inc. Formed in 1987, Gilead achieved annual revenues of only $4m in 1993, 1994, and 1995. The following three years it reached a higher plateau, with revenues of $33m, $40m, and $33m in 1996, 1997, and 1998, respectively. In 2000, subsequent to its merger in 1999 with NeXstar, it reported $196m of revenues, $150m of which were from product sales. Then, its growth really accelerated, resulting in revenues in 2005 of over $2bn and in 2006 of over $3bn, including product sales of over $2.5bn. One of the smaller biotechnology companies in 1995, Gilead became the eighth largest US biopharma company in 2000, the fifth largest in 2005, and the fourth largest in 2006.

Finally, an interesting perspective on the validity of biotechnology business models may be gleaned from a comparison with the specialty pharmaceutical industry, which is younger than the traditional pharmaceutical industry but older than the biopharmaceutical industry. Table 8 compares the five largest US biopharma companies with the five largest US specialty pharmaceutical companies with respect to dates of origin and fiscal 2006 revenues. It is clear that the biopharma companies have truly outpaced the specialty pharmaceutical companies. Even though four of the five specialty pharmaceutical companies are older than all of the biopharma companies, with three of the five having been formed prior to 1962, as a group the specialty pharmaceutical companies reported revenues only one-third of that reported by the biopharma companies.

## DISCUSSION AND CONCLUSIONS

The prevalent business model among biotechnology companies is the formation of strategic alliances with corporate partners that are well established within their industry, The rationale for forming such alliances is twofold: (i) to increase the likelihood of success in product development and commercialisation and (ii) to enhance the biotechnology company's market valuation. Nicholson *et al.*[16] have provided considerable evidence supporting this rationale with respect to biopharma companies forming alliances with large pharmaceutical companies. The data provided in the Results section focuses on biotechnology companies adhering to this business model, that have succeeded in the pharmaceutical marketplace.

There are many other examples of biotechnology companies succeeding in both related and unrelated vertical markets, including human diagnostics, human blood products, veterinary applications, agriculture, industrial processes, consumer applications, and R&D products and services. For example, Invitrogen Corporation, formed in 1987, is a biotechnology company that provides products and services to university and government research laboratories, and biotechnology and pharmaceutical company R&D centres. With an aggressive external growth strategy it exceeded the $100m mark for the first time in 2000, when it reported revenues of $246m. Four years later it reported revenues of $1bn.

A completely different example is a chemical company that transformed itself to a bioagricultural company. Monsanto Company, originally a chemical company that targeted the agricultural marketplace but diversified into pharmaceuticals and nutrition products, was merged in 2000 into a pharmaceutical company, the combined entity becoming Pharmacia Corporation. Two years later, Pharmacia spun off Monsanto to its shareholders, thereby making Monsanto an independently owned company again. Reinventing itself, Monsanto is now a company devoted solely to the agricultural marketplace, whose growth is biotechnology-driven. It has two operating divisions: Agricultural Productivity and Seeds & Genomics. From fiscal 2003 to 2006, total revenues grew from $4.9bn to $7.3bn, with almost all the growth occurring in Seeds & Genomics, where revenues grew from $1.9bn to $4.0bn.

The current study was limited to US companies, but there are biopharma companies in other countries, whose revenues have grown past $100m. Two such companies, Celltech Group plc in England and Serono S.A. in Switzerland, were acquired by the Belgian company, UCB S.A., in 2004 and by the German company, Merck KGaA, in 2007, respectively. Celltech, which was formed in 1980, had revenues of $545m in 2003. Serono, whose origin as an Italian company dates back to 1906, eventually transformed itself into a modern biotechnology company with revenues of $2.6bn in 2005, up from $1.2bn in 2000.

To put into perspective how fast the leading biotechnology companies have grown, one should compare them with the leading traditional pharmaceutical companies. Whereas the biotechnology industry began in the 1970s, the pharmaceutical industry dates back to the 19th century.[12] Merck & Co., Inc. originated in 1887 as the US sales office of E. Merck AG, which was established in Germany in 1827 as a drug manufacturer. The US sales office evolved into a drug manufacturer in 1903 and as a result of World War I subsequently became completely independent of E. Merck AG. Schering-Plough Corporation also traces its origin to a German company, incorporated in 1871, which later became known as Schering AG, and which in 1876 established a US presence to distribute its products. The US operations of Schering AG were suspended during World Wars I and II, and in 1952, the US subsidiary was sold off, resulting in an independently owned Schering Corporation. The next three companies all originated in the United States. Pfizer Inc. was founded in 1849 and incorporated in 1900 as Charles Pfizer & Company Inc. Eli Lilly and Company was founded in 1876 and incorporated in 1881. Bristol-Myers Squibb Company began in 1887 as the Clinton Pharmaceutical Company and changed its name to Bristol-Myers Company in 1900. The merger with Squibb occurred in 1989.

Revenues reported for fiscal 2006 by the aforementioned US pharmaceutical companies were as follows: Pfizer- $48.4bn; Merck- $22.6bn; Bristol-Myers Squibb- $17.9bn; Eli Lilly- $15.7bn; and Schering-Plough- $10.6bn. It should be noted that a major reason for Pfizer's revenues being so large is the result of two acquisitions it had previously made: Warner-Lambert Company in 2000 and

Pharmacia Corporation in 2003. Warner-Lambert's revenues in 1999 were $12.9bn, and Pharmacia's revenues in 2002 were $14.0bn. In 2006, the two largest biopharma companies were Amgen and Genentech, with revenues of $14.3bn and $9.3bn, respectively. Amgen, founded in 1980, was almost as large as Eli Lilly, founded in 1876, and larger than Schering-Plough, whose US origin also dates back to 1876. Genentech, founded in 1976, was almost as large as Schering-Plough.

The results of the current study support the conclusions drawn from an earlier study, in which the biotechnology industry was compared with the semiconductor industry at similar time intervals following the seminal events for those industries (the seminal event for the semiconductor industry being the invention of the transistor in 1947).[5] The semiconductor industry was selected, because fuelled by radical innovation, as was the biotechnology industry, it became commercially successful, impacting positively on other industries. Twelve years after their respective seminal events, biotechnology product sales (in 1984) were 20 per cent lower in constant dollars than semiconductor sales (in 1959), but then biotechnology product sales began to grow faster than semiconductor sales, eventually surpassing semiconductor sales in constant dollars by 3 per cent, 19 per cent, 29 per cent, 51 per cent, 59 per cent, and 63 per cent at 17, 18, 19, 20, 21, and 22 years, respectively.[4,5]

Indeed, 33 years after their respective seminal events, biotechnology product sales of all US public companies (in 2005) still were 61 per cent higher than all semiconductor sales of US companies (in 1980) in constant dollars.[13,17,18]Of the total $50.7bn of revenues reported by 329 public US biotechnology companies in 2005, $32.1bn were attributed to product sales.[13] In 1980, semiconductor sales of US companies totalled $8.4bn,[17] which is equivalent to $19.9bn in 2005 dollars.[18] In other words, contrary to the stereotypical view of biotechnology being an industry constantly developing products with limited commercial successes, it really is delivering the goods.

The fact that just five companies representing 0.35 per cent of all 1415 private and public US biotechnology companies in 2005[13] dominated the biotechnology industry by accounting for 36 per cent of total industry revenues of $72bn[19] does not invalidate the industry's business models. 'It simply means that there are winners, challengers, and losers at any point in time. Who is ahead at that point in time by no means guarantees who will be ahead 5 years later'.[4] Entrepreneurship results in what Schumpeter called 'creative destruction'.[20]

The semiconductor industry also provides evidence of creative destruction.[4] In 1982, 35 years after the semiconductor industry's seminal event, five US semiconductor companies, representing only 0.65 per cent of all 766 US semiconductor firms at that time,[21] accounted for 38 per cent of the value of all semiconductors produced by US companies.[22] These percentages are similar to the corresponding percentages for the biotechnology industry, 33 years after the biotechnology industry's seminal event. In terms of revenues, the world's largest semiconductor company today, Intel, ranked only seventh in market share in 1982, and three of the five largest semiconductor companies in the world at that time were not among the five largest ten years earlier.[22] With respect to the biotechnology industry, of the five largest US biopharma companies in 2005, only three were among the five largest in 1990.

Finally, the investment community apparently has concluded that biotechnology's business models are valid.[4] In 2005, the US biotechnology industry raised almost $35bn,[19] whereas ten years earlier it raised around $8bn.[23] In fact, Pisano reported that 'an investor who bought all 340 biotech IPOs from 1979 to 2000 and held on to those shares until January 2001 (or until a company was acquired) would have realized an average annual return of 15 per cent'.[2] This return surpasses the comparative returns over the

same period of time for the S&P 500 Index, the Dow Jones Industrial Average, and the National Association of Securities Dealers Automated Quotations (NASDAQ) Composite, which were 12.6, 12.5, and 14.8 per cent, respectively.[24] Moreover, the average annual returns for the NASDAQ Biotechnology Index and the AMEX Biotechnology Index for the first full 11 years data from those indexes were available (1995 to 2005) were 19.3 and 21.2 per cent, respectively, versus 9.5, 9.8, and 10.3 per cent during the same time period for the S&P 500 Index, the Dow Jones Industrial Average, and the NASDAQ Composite, respectively.[24]

Pisano's concern,[2] as to whether biotechnology will continue to be able to attract investment capital because of the generally long lead-time to commercialisation, is a moot point because of what is now a substantial track record on the part of the leading biotechnology companies. What may be a more pertinent question is how does one predict the future leaders. That requires specialised in-depth analyses and has been discussed elsewhere.[1,25,26]

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