Quo vadis, biotech? (Part 2)

Jurgen Drews

Those following the financial markets and the valuation of biotechnology companies recently might find themselves perplexed. Towards the end of 1999, during which the availability of capital for biotech initial public offerings and for private investment rounds seemingly withered, the markets suddenly turned around and gave the biotechnology industry its biggest bonanza ever.

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▼ The second part of this report continues to explain the financial dynamics of such a turbulent period and discusses how, over the next decade, biotechnology will remain the fastest growing industry in the healthcare arena.

Present status of the biotechnology industry

The biotechnology industry started with a small number of companies dedicated to the development and production of naturally occurring proteins by recombinant techniques. Since then, the industry has undergone a tremendous degree of diversification. Monoclonal antibodies, antisense molecules, ribozymes, gene therapy, cell therapy, natural products, drug delivery systems, genomics (gene mapping, sequencing, expression), pharmacogenomics (the assessment of drug responses on the basis of genetic dispositions), various forms of combinatorial chemistry, developmental biology, HTS techniques and bioinformatics have all found their way into the biotechnology industry. Every breakthrough in basic research that has any relevance to healthcare and related fields of industrial activity has given rise to the establishment of new companies. Therefore, the industry as a whole is very rich in methodology but also very fragmented from a strategic point of view.

Obviously, all these new approaches are funded by the customers of the biotechnology industry (e.g. the pharmaceutical industry) and by the financial markets on the basis of perceptions; how likely is it that any of these drug discovery or drug development approaches will make a strong and sustainable impact on the generation of value, and how soon will these impacts be felt?

Analysis of the cumulative revenue breakdown from deals made by 100 public biotechnology companies over the time period of 33 months, from 1997 to the third quarter of 1999, shows that 54% of the US$4.5 billion that was spent went into research allocated to technology platforms, whereas 39% was spent on disease-related research and 7% on drug delivery research (Fig. 1).

In technology platform companies, genomics has attracted the majority of funding over the past 33 months, followed by chemistry and drug screening. Gene therapy was only allocated with 8% of the total funding (Fig. 2). Interestingly, younger technology platform companies spend a substantial quantity of their money on informatics (Fig. 3). In disease-specialized public companies, most money was spent on cancer research (27%), followed by infection, CNS research and work on autoimmune diseases (Fig. 4).

However, in a group of 100 venture capital biotechnology companies, which of course represent earlier stages of development, cardiovascular research takes the top position with 32% of total revenue (Fig. 5). This finding might indicate the growing importance of biotechnology to cardiovascular research.

The availability of capital for the biotechnology industry has followed a cyclical pattern. The level of capital raised by the industry fluctuated considerably between 1996 and 1998. With the exception of the last quarter, 1999 was not a particularly good year for the

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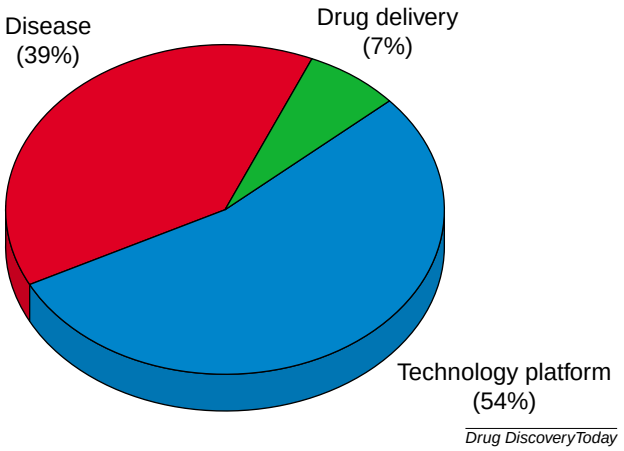

Figure 1. Biotechnology companies 1997–1999 (third quarter) partnering revenue breakdown (revenue = US$4.5 billion). Source: Recombinant Capital (Walnut Creek, CA, USA, www.recap.com).

industry. The markets for private equity (venture capital) dried up rather quickly, as much of the available capital has shifted into Internet companies (Fig. 6).

A correlate of this development can be seen in the scarcity of initial public offerings (IPOs) and in the clear preference of the markets for offerings resulting in a capital value of at least US$200 million. The window of opportunity for private biotechnology companies to go public opened again in late 1999 and has remained open since. There did not appear to be much interest in financing small-capital enterprises (<US$300 million). In 1997, the number of small-capital companies reached a peak and has been declining since, whereas the large-capital companies

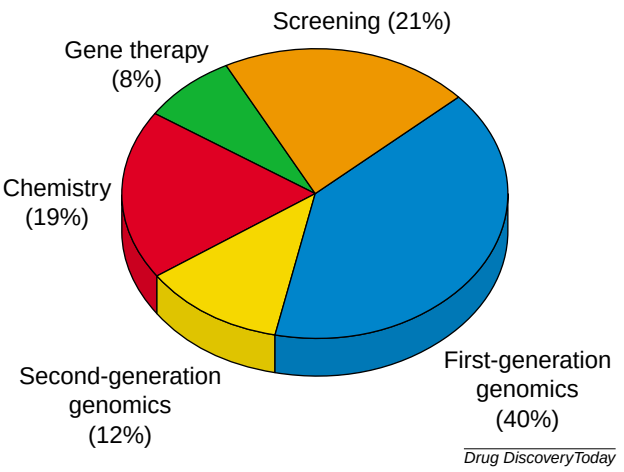

Figure 2. Technology platform companies 1997–1999 (third quarter) partnering revenue breakdown (revenue = US$2.4 billion). Source: Recombinant Capital.

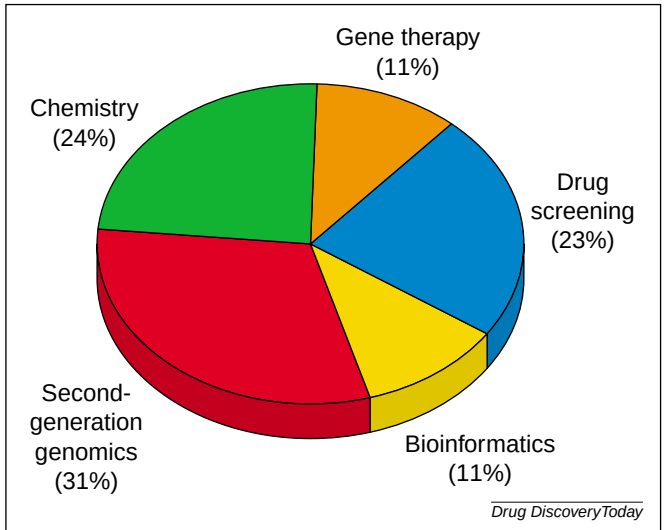

Figure 3. Venture capital-backed private biotechnology technology-platform companies 1997–1998 partnering revenue breakdown [revenue 1997 = US$366 million; revenue 1998 = US$415 million (+14%)]. Source: Recombinant Capital.

(>US$800 million) increased in number from 17 in 1997 to 29 in 1999. The crucial group is the intermediate-capital companies (US$300–800 million). Although this group appears poised for moving into the top tier, one untoward event such as the termination of a compound in development could relegate them back to the small-capital category. According to a recent analysis, there are now 19 biotechnology companies with a capital value of more than US$3 billion and the total number of companies with a capital value of more than US$800 million is greater than 50 (Fig. 7).

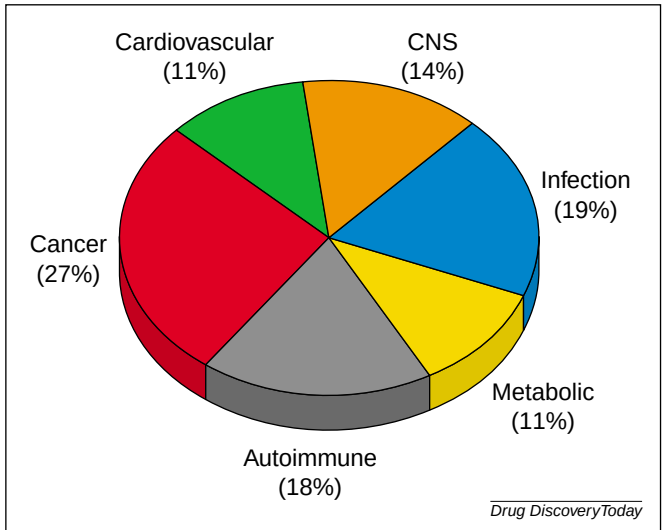

Figure 4. Disease-specialized companies 1997–1999 (third quarter) partnering revenue breakdown (revenue = US$1.7 billion). Source: Recombinant Capital.

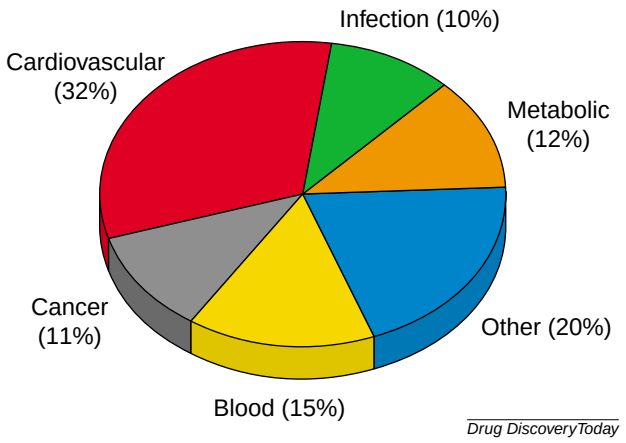

Figure 5. Venture capital-backed private disease-specialized biotechnology companies 1997–1998 partnering revenue breakdown (1997 revenue = US$224 million; 1998 revenue = US$238 million). Source: Recombinant Capital.

Biotechnology companies, in particular technology platform companies, are crucially dependent on deals with established industries, especially with large pharmaceutical companies. As with the financial markets, the ability and willingness of pharmaceutical companies to invest in biotechnology firms is subject to fluctuation. Pharmaceutical deal-making, both between biotechnology companies and between biotechnology and pharmaceutical companies, peaked in 1997 and has been decreasing ever since (Fig. 8), and the same is true for the inclination of large pharmaceutical companies to enter into collaborative deals with biotechnology companies. The merger and acquisition activity among pharmaceutical companies, which reached a preliminary peak in 1997 and appears ready to increase further in 2001, does not bode well for the ability of pharmaceutical companies to enter into collaborative deals with biotechnology firms (Fig. 9). The reasons for this are threefold. First, the process of merging two organizations places priorities on saving money, rather than on spending it. Second, the time managers spend worrying about the merging of two R&D organizations means less time to deal with technological and strategical issues. Third, the larger companies that result from mergers and acquisitions might have a greater tendency to do things in-house rather than seek further collaborations. It could be argued, however, that such impediments might be temporary. Large companies do not become more innovative because they increase in size. Furthermore, the intellectual climate that they provide for independent young minds is unlikely to improve as the result of mergers.

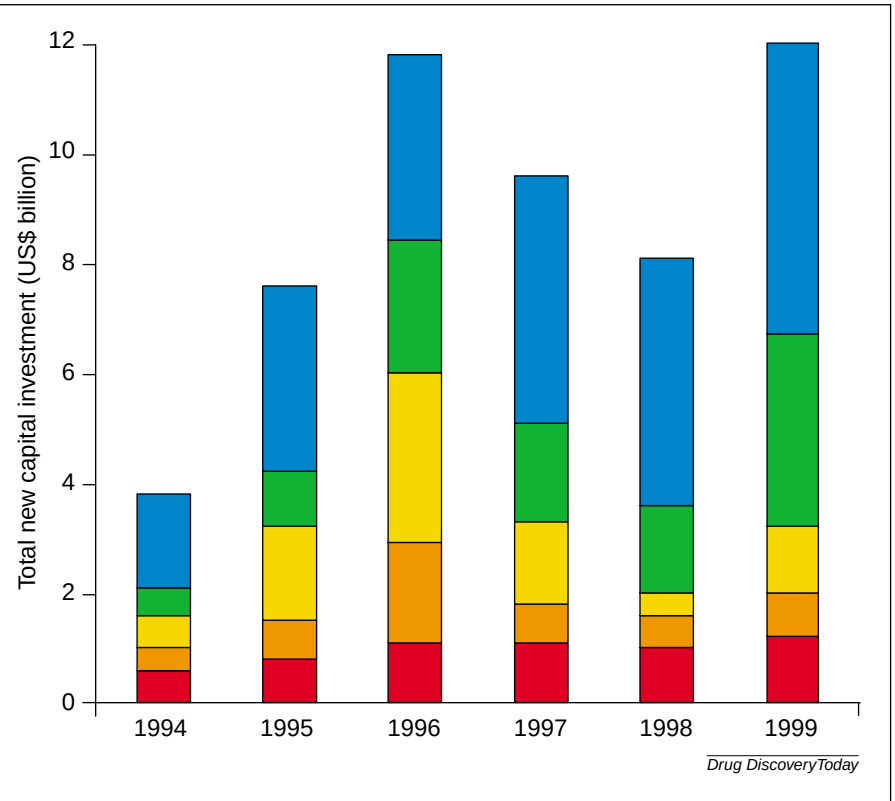

Figure 6. Biotechnology's access to capital: US$20 million deals (blue); private investments in public entities (PIPEs, green); follow-on capital (yellow); initial public offerings (IPOs, orange); venture capital (red). Source: Recombinant Capital.

However, there could be another reason behind the reluctance of large companies to enter into biotechnology collaborations. Between 1994 and 1996 the merger and acquisition of large pharmaceutical companies remained constant and at a high level (Fig. 9). Yet, during the same time period, the deal-making with biotechnology firms increased from US$300 million to almost US$2 billion (Fig. 8). This increase could reflect the enormous scientific achievements in genomics, combinatorial chemistry, cell-based assays and automation that preceded 1997. The pharmaceutical industry had to assimilate a tremendous quantity of information, relevant to drug discovery and development, which came to them largely via biotechnology firms. The drop in the intensity of deal-making during the years following 1996 could reflect some kind of methodological consolidation.

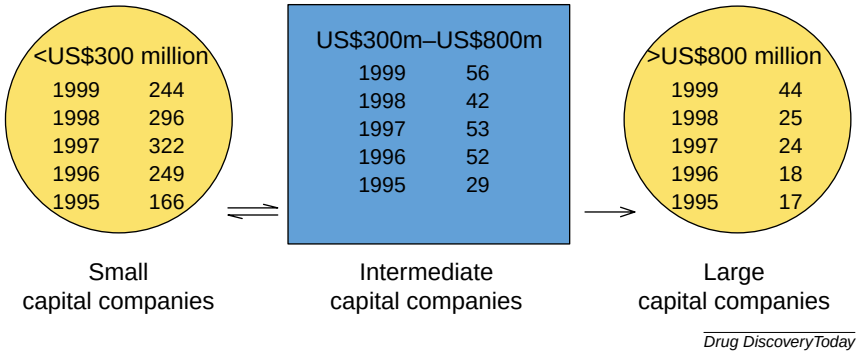

Figure 7. The industry pipeline of public biotechnology companies; intermediate capital companies can reach the top tier, but are subject to relegation to small capital companies in the event of termination of a drug in development. Source: Recombinant Capital.

However, thinking and experimentation never stop. Recent progress in bioinformatics and subsequently in our ability to create meaningful links between chemical, genetic, biochemical and clinical data has not yet been assimilated by large pharmaceutical companies. As the need to embrace these new techniques is inevitable, a new burst of deal-making between large pharmaceutical companies and biotechnology firms, which ride the new technological wave, can certainly be predicted, even if the mergers and acquisitions among the large companies continue.

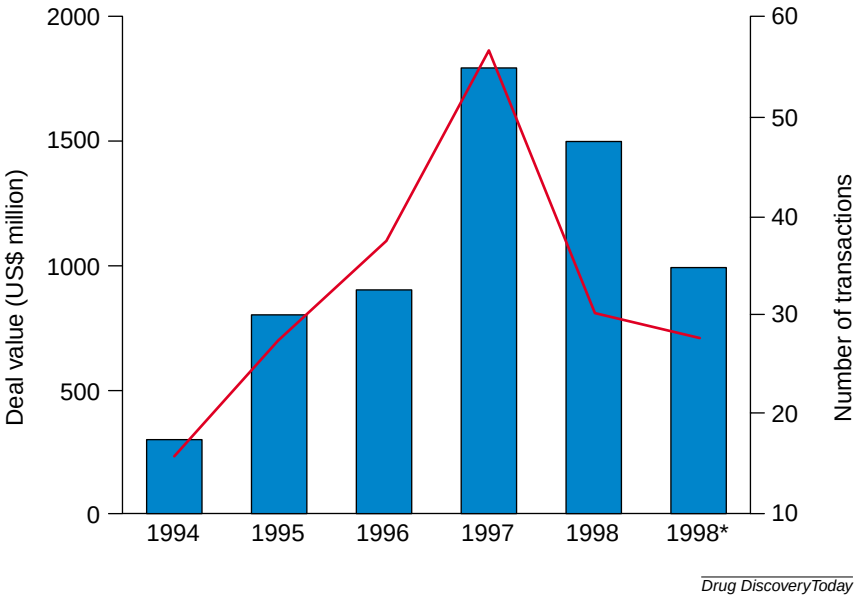

Figure 8. Pharmaceutical deal-making, 1994–1995: drug-oriented deals in genomics, HTS and combinatorial chemistry and molecular diversity. Deal value (US$ million) shown by blue shaded bars; proportion of platform deals, shown by red line.
*Not including: Millennium and Bayer's US$495 million deal; agriculture-focused deals.
Source: Windhover's strategic database (Norwalk, CT, USA, www.windhover.com).

The emergence of a small number of pharmaceutical super-companies gives rise to the following questions:

(1) Does the generation of a handful of globally represented pharmaceutical giants have an influence on the strategies of the biotechnology sector?
(2) Will pharmaceutical consolidation enforce collateral mergers and acquisitions in the biotechnology sector?
(3) What will be the respective role of technology platform companies and product-oriented firms in this new environment?

In addressing the first question, we have to ask whether or not the needs of super-companies will be different from those of traditional large pharmaceutical companies. Although there might not be fundamental differences, some shifts in emphasis can be expected.

First, the very large companies would have an even greater need for new products than smaller pharmaceutical companies. The probability of producing blockbusters is not a linear function of company size, or the size of the R&D organization. The pressure for growth that is commensurate with the revenue base of the merged company will exist from the beginning. Therefore, very large companies will have an increased interest in technology companies, which have created their own pipeline of development products. Second, there will be a greater inclination to acquire comprehensive technological packages rather than fragmented technologies, which brings us the answer to the second question. I would argue that biotechnology companies that offer technologies that identify and validate targets combined with antibody technologies or novel chemical approaches will stand a better chance of attracting the interest of large and very large companies, in contrast to biotechnology firms that have technology to offer but lack the ability to generate their own products. Therefore, a certain degree of consolidation between biotechnology companies concerning the functional requirements of drug

discovery and development would be advantageous.

This leads to the answer to the third question. Do technology platform companies have a chance to become profitable? I think they do, if they succeed in addressing the crucial step of target validation in drug discovery or drug development effectively and exhaustively. Target validation has become the bottleneck of drug discovery[1]. It is relatively easy to make a hypothetical link between a particular gene and disease phenotype, for example, the β_2 adrenoceptor and hypertension or cholesteryl ester transfer protein (CETP) and atherosclerosis.

However, are these gene products really the best targets for drugs? Can it be shown in animal experiments that their modification reverses the associated disease phenotype?

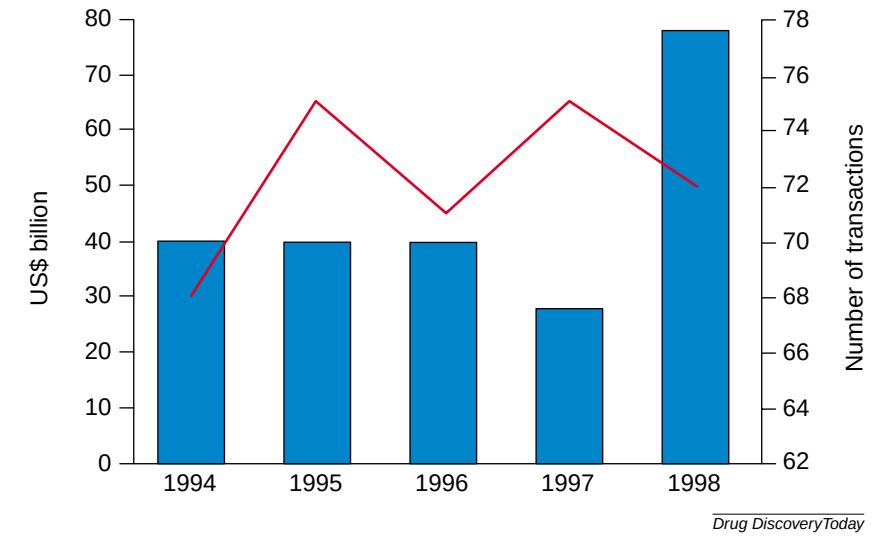

Figure 9. Pharmaceutical mergers and acquisitions (1994–1998). Source: Windhover's strategic database.

Platform companies that deal with these very central questions should be able to approach the problem comprehensively with an array of methods rather than with a single technique. Large companies need comprehensive solutions and are much more likely to deal extensively and seriously with biotechnology firms that can offer such packages, rather than with their peers that can only offer partial solutions. Therefore, in summary, the answer to the third question would be that although technology platform companies continue to play an important role, their success is likely to depend on two factors. First, on the value of their technologies with respect to urgent operational needs in drug discovery and drug development and second, on the comprehensiveness of the approaches taken. A company might play a pioneering role in utilizing a technology such as genomics in target identification and validation or in the identification of secreted proteins. If, along with its technology, it delivers proof that such technology can be used to find and develop products, then credibility is assigned both to the power of the technology and to the sophistication of the products.

Where will biotechnology go from here?

The future of the biotechnology industry cannot be described as an isolated phenomenon. Rather, it must be seen in the context of drug research and development and medicine in general. To look into the future is impossible. Many intelligent people have put themselves into awkward, even ridiculous, positions trying to forecast technical or societal developments in the long term. Only guesses can be made about developments that are imminent. Restricting an assessment of the biotechnology industry to a short-term prospective (5–10 years), I would offer the following perspective. Today the biotechnology industry is

Table 1. Number of profitable biotechnology companies by year of development[a]

Year	Number of profitable companies	Existing or additional biotechnology companies
1986	1	Genentech
1989	2	Amgen
1991	3	Genzyme
1993	4	Chiron
1996	7	Biochem Pharma, Biogen, Medco
1997	10	Biotechnology General, Centocor
1998	13	Agouron, IDEC, MedImmune
1999	17	Immunex, Nabi, NeXstar
2000	22(e)	Ares-Serono, Pathogenesis, Enzon, Celltech, Celgene
2001	36(e)	Millennium Pharmaceuticals, Affymetrix, Gilead, Incyte, Abgenix, Protein Design Labs, Cephalon, SuperGen, Transkaryotic Therapies, Ligand Pharmaceuticals, COR Therapeutics
2002	50(e)	Sangstat, Pharmacyclics, GeneLogic and others

[a]Source, Orbimed advisors.
Abbreviation: e, estimated value.

a stronger industry than ever before. I anticipate that it will continue to drive and exploit cutting-edge research in a much more direct way than the more traditional industries to whom the biotechnology companies have provided their services. The recent increase in the valuation of biotechnology companies, especially of genomic and antibody firms, will have consequences that go far beyond the stock prices that are subject to so much volatility. Biotechnology companies will probably continue to represent the discovery and pre-discovery end of drug research and will position themselves with more self-assurance *vis à vis* pharmaceutical companies and other client industries.

It can also be expected that an increasing number of biotechnology firms will try to build development pipelines of their own and launch novel compounds alone or with the help of other biotechnology companies. Investors might be willing to finance product developments and launches by the biotechnology industry if the medical significance and the originality of the projects promise high returns, at least in a number of cases.

The number of profitable biotechnology firms (24 at the time of writing) is also likely to increase rapidly from now on (Table 1). By the end of the year 2000, there might be 35 biotechnology companies with sustainable profitability, and at the end of 2001, the number is likely to have risen to 45 (S. Isaly and J. Drews, unpublished). Compared with the global number of biotechnology companies, this is still a small proportion of the total industry. However, it should be remembered that this industry is characterized by the continuous generation of new techniques and concepts, and not so much by the optimization of long-established processes and practices. For the investor, profitability must not be a '*conditio sine qua non*' because the increase in value of successful young companies will offer ample opportunities for achieving good returns on investment.

In the future, mature biotechnology companies will probably show an increasing tendency to consolidate. There are two major reasons for this. First, large pharmaceutical companies that are now emerging (Pfizer–Warner Lambert, Glaxo Wellcome–Smithkline Beecham and so on) will be looking for comprehensive support in drug discovery, and biotechnology companies that offer a broad array of methods have a better chance to position themselves for such clients. Second, biotechnology companies might need a completion of their existing methodological spectrum to be able to develop and launch their own products.

Another future prospect is that highly successful biotechnology companies might merge with, or acquire, traditional pharmaceutical companies in order to complete their set of skills and to exploit their technologies and products independently of large pharmaceutical companies. Of course, the reverse will continue to be true: pharmaceutical companies will acquire biotechnology companies. Finally, consolidation will continue to occur among both biotechnology companies and pharmaceutical companies. This multidirectional consolidation will eventually result in extensive changes to the drug industry. Large and globally operating pharmaceutical companies will continue to exist. Their main emphasis will be on development, marketing and sales. New research- and technology-driven companies will arise from mergers between biotechnology companies or between biotechnology and pharmaceutical companies. These new companies, which will include some of the large biotechnology firms of today, are likely to become the powerhouses of drug research. Many of them will be able to develop and utilize the financial potential of their products and technologies independently.

Existing and newly created companies will probably continue to improve drug discovery and development. Structural genomics, molecular modeling, computer simulation, bioinformatics and pharmacogenomics will be among the most attractive areas of the future. The themes and methods of drug research will increasingly be determined by the biotechnology industry rather than by traditional pharmaceutical firms. Furthermore, the rigid tests and trials of drug development that are imposed by governments and regulatory authorities will come under increasing pressure from new pharmacogenomic insights. Again, this change will emanate from biotechnology firms rather than from pharmaceutical companies.

Summary

In summary, the biotechnology industry will probably become the fastest growing industry in the healthcare arena in the future. It will offer a multitude of investment opportunities with high risks but also high and sometimes spectacular returns. However, because this industry is highly heterogeneous, serves other complex processes such as drug research and development, and will constantly absorb new scientific developments, it will remain a difficult arena for the investor. Successful investment in this area requires constant and highly intensive analysis, not only of biotechnology itself, but of the broader issues represented by drug therapy and healthcare as a whole.

Reference

1 Drews, J. (2000) Drug discovery: a historical perspective. *Science* 287, 1960–1964