BIOTECHNOLOGY AND THE ECONOMICS OF DISCOVERY IN THE PHARMACEUTICAL INDUSTRY

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Helen Simpson is currently a research economist at the Institute for Fiscal Studies and was formerly an economist at the Department of Trade and Industry. However, the opinions expressed here are her own and do not necessarily reflect the views of the IFS or of DTI officials or ministers.

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1 INTRODUCTION

This paper examines the economic aspects of the forces driving the emergence of biotechnology firms, and the implications of this for the organisation of research and development (R&D) and industrial structure in the pharmaceutical industry.

In the early 1970s, two molecular biology breakthroughs – the discovery of a mechanism by which part of a foreign gene could be inserted into another and thereby change its characteristics (recombinant DNA, or rDNA) and techniques for fusing and multiplying cells (hybridomas) – heralded the coming of genetic engineering.[1] 'Biotechnology is used in three different ways in the pharmaceutical industry: i) to produce drugs and vaccines using rDNA technology; ii) to make intelligent screens for new compounds; iii) to apply techniques for rational drug design by understanding molecular structure.'[2]

For the purposes of this paper, the term 'biotechnology firms' is taken to refer to small, research intensive firms that specialise in the drug discovery process. These firms do not necessarily only employ biotechnology methods nor focus exclusively on biopharmaceutical products.

Biotechnology start-ups entered the pharmaceutical industry in the US in the early 1980s. By the mid 1990s, some US biotechnology companies such as Genentech and Amgen were integrated pharmaceutical firms, capable of competing, at least in some therapeutic areas, with large established pharmaceutical firms.

The development of the biotechnology industry in Europe lagged some years behind the US.[3] The UK's most mature biotechnology company, British Biotech, was formed in 1986 and floated on the stock market in 1992. Although there are large numbers of European biotechnology start-ups entering the pharmaceutical industry, their combined scale remains small compared to that of the established pharmaceutical sector. At the end of 1997, the combined market capitalisation of the largest 10 European biotechnology companies was $5.7 billion, compared with the market capitalisation of, for example, $83 billion for Glaxo Wellcome alone at that time.[4]

1 Sharp and Patel (1996) p40.
2 Casper and Matraves (1997) p7.
3 For a detailed discussion of the development of biotechnology in the European pharmaceutical industry, see Sharp and Patel (1996).
4 Ernst & Young International Ltd (1998a).

Figure 1.1 **Growth of the US biotechnology industry, 1986-1997**

	1997	1986
Revenues ($b)	17.4	2.2
R&D spend ($b)	9.0	1.7
Number of companies	1,274	850
Number of employees	140,000	40,000

Sources: Evans (1996); Ernst & Young (1998a).

Figure 1.2 **Biotechnology in the US and Europe**

Public companies	**1997**		**1996**		**1995**		**% change 1995-1997**	
Financial	*Europe*	*US*	*Europe*	*US*	*Europe*	*US*	*Europe*	*US*
Revenues (Ecu m)	648	12,862	433	10,565	297	6,960	118	85
R&D expense (Ecu m)	534	5,145	243	4,226	158	3,440	238	50
Net loss (Ecu m)	347	1,654	73	2,021	73	1,840	375	–10
Industry								
Number of companies	61	317	49	294	28	260	118	22
Employees	8,418	94,000	5,315	73,000	2,958	60,000	185	57

Industry total	**1997**		**1996**		**1995**		**% change 1995-1997**	
Financial	*Europe*	*US*	*Europe*	*US*	*Europe*	*US*	*Europe*	*US*
Revenues (Ecu m)	2,725	15,985	1,721	13,413	1,471	10,160	85	57
R&D expense (Ecu m)	1,910	8,268	1,508	7,258	1,252	6,160	53	34
Net loss (Ecu m)	2,020	3,767	1,113	4,134	1,206	3,680	67	2
Industry								
Number of companies	1,036	1,274	716	1,287	584	1,308	77	–3
Employees	39,045	140,000	27,500	118,000	17,200	108,000	127	30

Sources: Ernst & Young (1998a); Ernst & Young BioBusiness reported in Financial Times 26 November 1996.

The biotechnology industry as a whole is growing fast. Between 1986 and 1997 the industry's revenues and R&D expenditures increased dramatically, as Figure 1.1 shows for the US. In recent years, growth in Europe has just started to outpace that in the US. Figure 1.2 shows that between 1995 and 1997 the number of public biotechnology companies in Europe rose 118 percent from 28 to 61, while employment there rose 185 percent. (Their losses also rose, however). Growth rates in the US, while significant, were much less rapid than this.

Figure 1.3 shows the geographic structure of the European biotechnology industry. The UK leads Europe with approximately 180 firms. Germany comes second with approximately 100, but cannot compete with the UK in terms of firm size. The European industry as a whole is still dwarfed by the US, which has around 1,300 biotechnology companies.

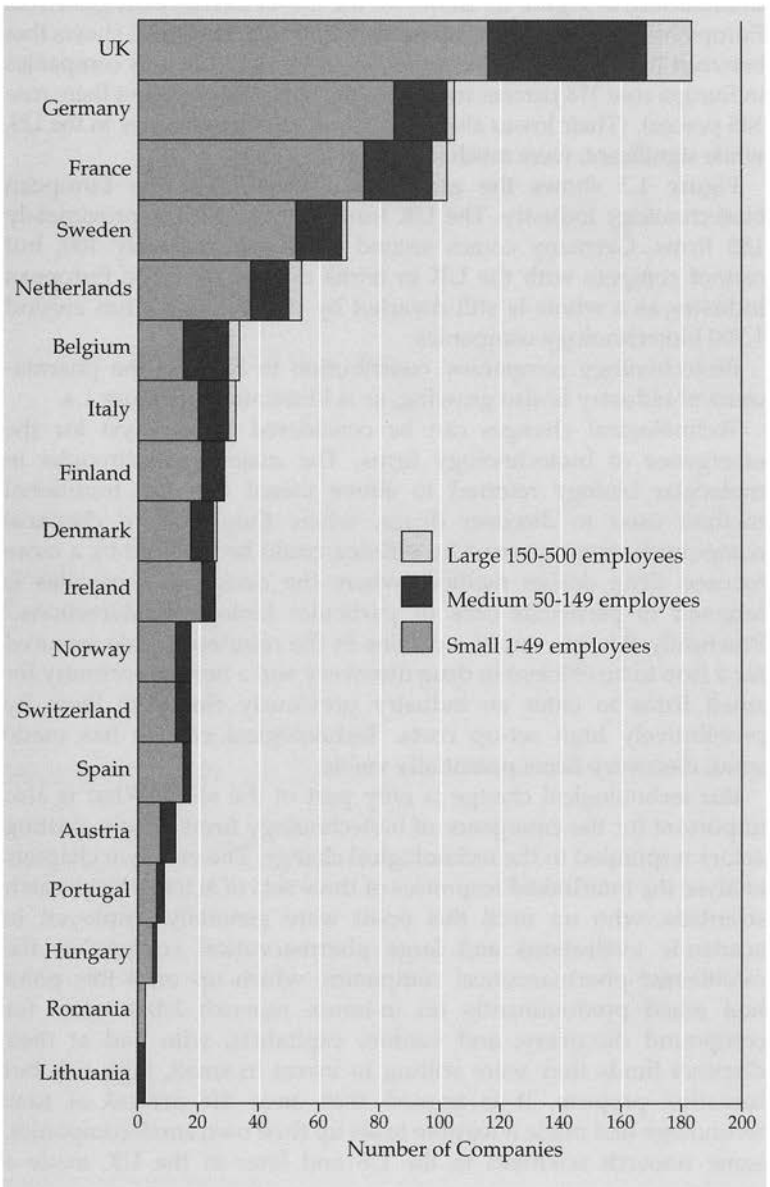
Biotechnology companies' contribution to R&D in the pharmaceutical industry is also growing, as is illustrated by Figure 1.4.

Technological changes can be considered the catalyst for the emergence of biotechnology firms. The major breakthroughs in molecular biology referred to above meant that the traditional method used to discover drugs, where thousands of chemical compounds were screened for efficacy, could be replaced by a more focused drug design method, where the design of molecules is targeted to particular cells or particular biological interactions.[5] Practically this has meant a decline in the minimum scale required for a firm to be efficient in drug discovery and a new opportunity for small firms to enter an industry previously closed to them by prohibitively high set-up costs. Technological change has made small discovery firms potentially viable.

But technological change is only part of the story. What is also important for the emergence of biotechnology firms is how existing actors responded to the technological change. The next two chapters analyse the interlinked responses of three sets of actors: the research scientists, who up until this point were generally employed in academic institutions and large pharmaceutical companies; the established pharmaceutical companies, which up until this point had relied predominantly on in-house research laboratories for compound discovery; and venture capitalists, who had at their disposal funds they were willing to invest in small, high risk but lucrative projects. It is argued that once the arrival of new technology had made it feasible to set up their own small companies, some research scientists in the US and later in the UK made a

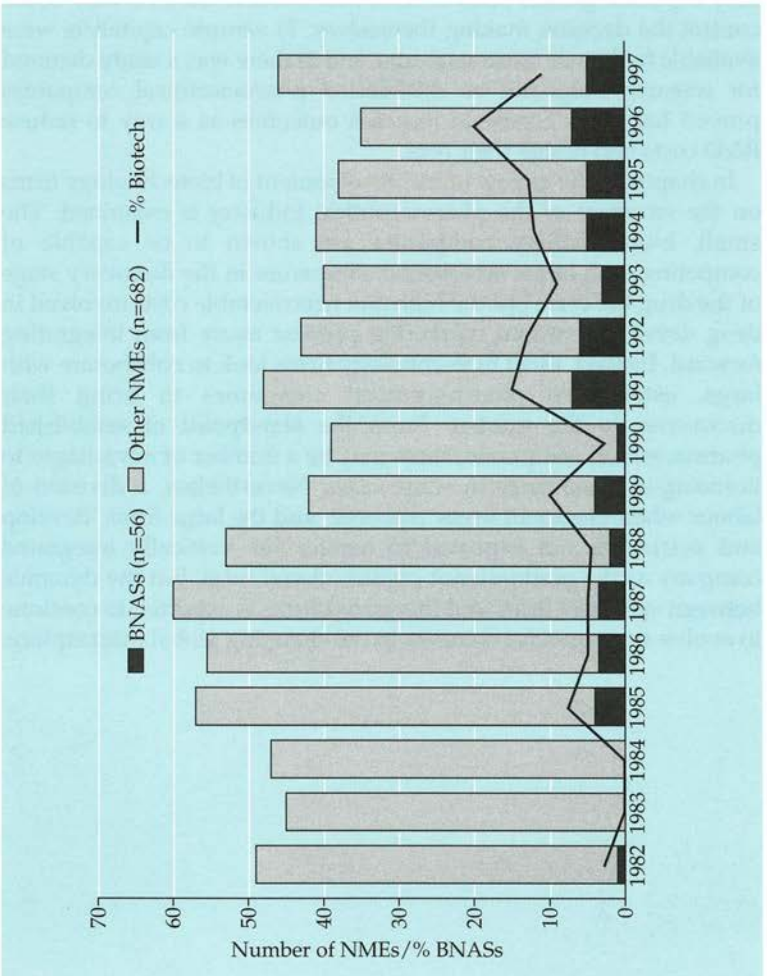
5 Casper and Matraves (1997) p6.

Figure 1.3 **European biotechnology industry by country and company size**



Source: Ernst & Young BioBusiness reported in Financial Times 26 November 1996.

Figure 1.4 **BNASs introduced onto a 20 country market 1982-1997**



BNASs = Biotechnologically-derived New Active Substances (excluding vaccines)
NMEs = New Molecular Entities

Source: CMR International (1998).

decision to take this opportunity. Three reasons are suggested: 1) they expected greater returns from successful research if they could control the decision making themselves; 2) venture capitalists were available to finance these start-ups; and 3) there was a ready demand for research outcomes as established pharmaceutical companies proved happy to license-in research outcomes as a way to reduce R&D costs and hedge their bets.

In chapter 4, the impact of the development of biotechnology firms on the structure of the pharmaceutical industry is examined. The small, biotechnology companies are shown to be capable of competing with large, established companies in the discovery stage of the drug life cycle but the high and irrecoverable costs involved in drug development and marketing prevent many from integrating forward. Instead, most biotechnology firms look to collaborate with large, established pharmaceutical companies to bring their discoveries to the market. From the standpoint of established pharmaceutical companies, there may be a number of advantages to licensing-in discoveries in some cases. Nevertheless, a division of labour where the small firms 'discover' and the large firms 'develop and market' is not expected to replace the vertically integrated company as the predominant organisational form, but the dynamic between specialist firms and integrated firms is expected to continue to evolve as companies compete in the changing global marketplace.

2 THE EMERGENCE OF BIOTECHNOLOGY FIRMS

The emergence of research intensive biotechnology companies in the pharmaceutical industry is the result of a combination of both supply and demand factors. On the supply side:

- technological change;
- entrepreneurial scientists capable of setting up firms;
- availability of external finance;

and on the demand side:

- pharmaceutical companies looking to reduce high R&D costs through collaborations with outside researchers.

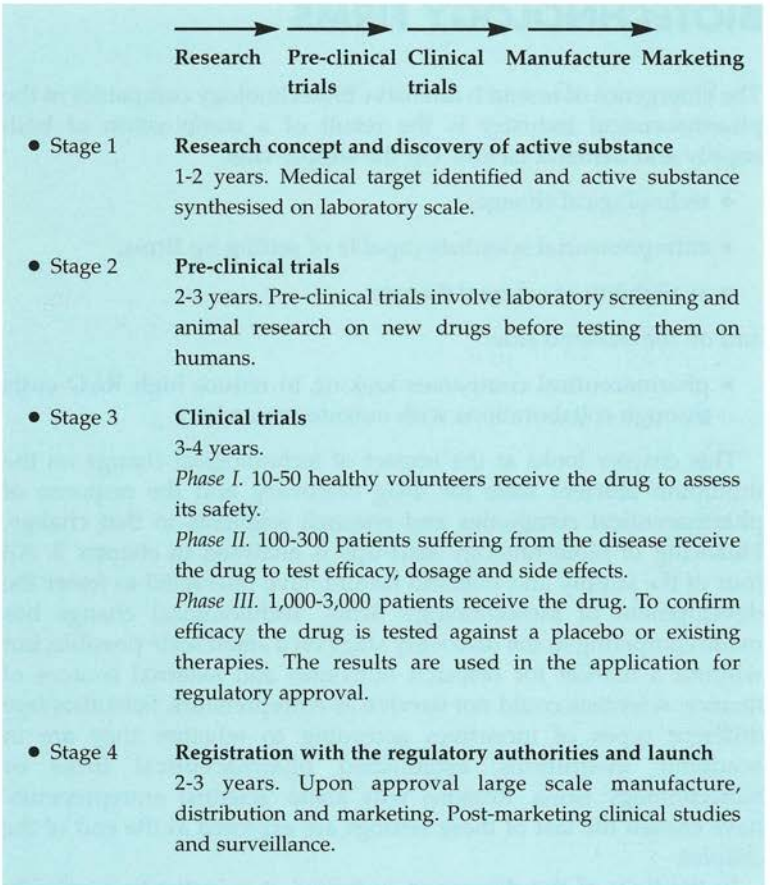
This chapter looks at the impact of technological change on the minimum efficient scale for drug discovery, and the response of pharmaceutical companies and research scientists to that change. Financing of biotechnology start-ups is analysed in chapter 3. All four of the supply and demand factors have interacted to foster the development of biotechnology firms. Technological change has made competing in the discovery stage on a small scale possible, but without a market for research outcomes and external sources of finance, scientists could not survive as entrepreneurs. Scientists face different types of incentives according to whether they are in academic institutions, established pharmaceutical firms or biotechnology firms. Reasons why some 'scientist entrepreneurs' have chosen the last of these settings are explored at the end of the chapter.

In the light of the discussion to follow, it is instructive to begin with a summary of the drug discovery and development process.

To discover and develop a new drug takes 8-12 years and costs up to $600 million according to recent estimates.[6] The development stage of the process, stage 3 in Figure 2.1, is particularly costly. Phases II and III of the clinical trials account for between 57 and 75 percent of total costs.[7] High risk of failure adds to the expense of drug development. Of the drugs entering phase I clinical trials, only 20 to 30 percent will receive regulatory approval.

6 Source: Lehman Brothers (1997).
7 Source: US Food and Drug Administration, cited in Gambardella (1995) p20.

Figure 2.1 **The drug discovery and development process**



It is useful to separate the process into upstream (stages 1 and 2) and downstream (stages 3 and 4) components. The technological change that brought about biotechnology impacts on stages 1 and 2. These are the activities that start-up companies focus on. The question of who completes the development and regulatory stages of bringing a new chemical entity (NCE) to market is analysed in chapter 4, but, until now, financial constraints have tended to prevent biotechnology firms from completing the downstream stages themselves.

2.1 Technological change

Traditionally, barriers to entry in the form of economies of scale may have kept small firms out of the discovery stage of drug R&D. Drug discovery based on traditional, chemical techniques used largely to be a trial and error process, where thousands of candidate compounds were synthesised.[8] Biotechnology provides a more focused approach to drug design, thereby reducing the minimum efficient scale needed to discover drugs. Small companies can now compete more effectively with the established pharmaceutical firms in drug discovery. However, the observation that biotechnology firms are also using traditional drug discovery techniques, suggests that to date biotechnology has been able to produce few commercially viable drugs.[9]

Any caution on the part of large pharmaceutical companies in making substantial investments in biotechnology, left a niche for small companies to fill. Continued collaborations with biotechnology companies even after these established pharmaceutical companies have started to make large investments in the biotechnology field, suggests that small companies may be well suited to this niche and that investments by big and small companies may be complementary.[10]

Any breakdown of entry barriers into research due to technological developments may only have been temporary. New drug discovery technologies: genomics (enabling target selection), combinatorial chemistry (creating possible matching compounds) and high throughput screening (to make the match) are still in their infancy. The large capital resources needed to acquire high throughput screening technology, for example, may, if this becomes essential drug discovery technology, have re-created an entry barrier to research. In that case, new start-ups would now have to enter not as drug discovery companies but even further upstream as specialist technology suppliers, for example of genetic databases.

2.2 The demand for research outcomes

Technological change and a lagged response on the part of large pharmaceutical companies provided an opportunity for small companies to enter the drug discovery industry. But in order to

8 See Gambardella (1995) chapter 2 for a detailed discussion of drug discovery techniques.
9 See, for example, Tapon and Cadsby (1996).
10 Sharp and Patel (1996) p50.

survive, these new companies needed buyers for the outcomes of their research. Existing pharmaceutical firms have provided that demand.

Under increasing pressures from rising R&D costs, on the one hand, and constraints on revenues due to new cost containment health care policies, on the other, large pharmaceutical companies have proved ready to look to external organisations to conduct specific stages of drug development. At the drug discovery stage, existing pharmaceutical companies need to expand their portfolios, introduce new technologies and get products into the clinical pipeline more quickly. As is discussed in detail in chapter 4, there can be advantages to licensing-in some products. Doing so helps firms hedge their bets and allows them to gain access to useful research results and technology, without long-term and expensive investment and employment commitments, especially at a time when the direction of new technologies is uncertain.[11]

Substantial numbers of research scientists have been keen to set up their own companies to supply these new products in an attempt to appropriate more of the returns to their research. As pharmaceutical firms looked to academic institutions to license technology, academic scientists may increasingly have appreciated the commercial potential of their work and the scope for financial reward from setting up their own companies. Biotechnology firms only needed to enter the industry at the research stage, as pharmaceutical firms were willing to complete the development and marketing of the compounds they supplied. A new firm could thus become a sustainable commercial entity without becoming a fully integrated pharmaceutical company, therefore requiring a significantly lower level of start up finance. Collaborations with existing, larger pharmaceutical firms enabled them to begin to generate revenues faster than if they had had to complete drug development in-house. This organisational change in combination with technological advances enabled scientist entrepreneurs to set up their own firms.

2.3 Scientist entrepreneurs

Given the opportunities just described, this section examines what may have induced some scientists to leave academic institutions and the established pharmaceutical companies to become entrepreneurs in their own small biotechnology companies. In order to understand

11 Sharp and Patel (1996) p42.

better the employment choices made by pharmaceutical research scientists, it is helpful first to describe two problematic features of the market for their research. These features are referred to by economists as *the appropriation problem* and *the asymmetric information problem*. These aspects of the market for research outcomes may result in insufficient rewards being realisable by researchers in some circumstances and hence may lead to a level of research effort that is sub-optimal from the standpoint of an industry under pressure to introduce innovative products to the market.

The appropriation problem arises because knowledge is generally *non-excludable*. In other words, once knowledge is in the public domain, agents other than its creator can acquire it costlessly and apply it.[12] In addition, one agent's use of knowledge does not diminish the amount available for use by others. The appropriation problem arises when the knowledge creator cannot practically charge others for the right to use that knowledge. Indeed, even if the creator could charge others it would be difficult to charge them their true valuation of the knowledge. Intellectual property rights (patents) are often used to solve the appropriability problem and provide incentives for research. A research scientist may wish to possess any possible future intellectual property rights associated with his research, if it proves successful, rather than automatically give them over to an employer in return for a regular salary.

The asymmetric information problem arises because suppliers of knowledge may be able to form a better estimate of its value than can potential buyers. This may lead to there being insufficient demand for knowledge, which dampens incentives for knowledge production because researchers may then not recoup sufficient reward for their innovations.

The following describes how these problems play themselves out in different research environments.

Academic institutions

Academic scientists are primarily producers of basic knowledge. Their findings are generally made public. A so-called *priority reward* system exists to motivate academic scientists to conduct research. That is, public disclosure of research findings enables scientists to establish a reputation within the academic community. This helps to solve the appropriation problem for academic research scientists, but

12 Knowledge may sometimes be excludable in part. That is, if other agents cannot apply it without having some specialist background information themselves.

their monetary rewards are not large and not closely linked to individual research projects, at least not in the short run. Academic scientists will be continually competing among themselves for funds, which also provides them with incentives for productive research.

Since there is little reward for coming second in a race to make a breakthrough, there is no incentive for academic scientists to delay knowledge dissemination, (unless doing so would mean that they would lose the rewards expected to result from future knowledge production that builds on the original work). Part of the knowledge that is created in the academic sector is capable of being *codified* but part is likely to be *tacit*, that is it cannot be transferred other than through direct contact with the possessor, for example methods and skills.[13] University alliances with private firms may therefore arise to facilitate the transfer of tacit knowledge. Knowledge which can be codified can be brought more readily into the public domain and hence used by the commercial sector.

Established pharmaceutical firms

Basic research is also carried out in the pharmaceutical industry. Scientists employed in an established pharmaceutical firm may be free to publish papers as in the academic sector and may use this both to build an academic reputation and potentially further their careers within their employing firms. By establishing a reputation through publication, scientists will also increase their value in the external labour market. 'Academic' research may also have long-run, indirect value to the firm, by allowing its scientists to participate in conferences and maintain links with the academic sector[14], as well as any direct value it may have in discovering new drugs.

Monetary incentives for research scientists in the industry will centre on their salaries, as in academia. However, further incentives may be provided by share options and/or performance-related bonuses for successful research teams. Performance may be further enhanced if research teams are in competition for funds from a company's internal capital market. In addition research scientists will face some employment risk, for example due to the possibility of established pharmaceutical firms rationalising their research operations, particularly when involved in a merger.

13 This is discussed in more detail in Dasgupta and David (1994) p493.

14 I thank Paul David for making this point.

Biotechnology firms

In order to set up his own company a scientist requires a good research project and, importantly, an established reputation[15] or links with other reputable scientists.

Employees of any small firm are likely to have a greater sense that 'what they do matters' than have their counterparts in larger companies. The pay of researchers employed by a biotechnology firm may be clearly linked to the firm's performance. They may receive a lower fixed wage than they would in an established company, but at the same time they are likely to hold a significant number of shares and share options. While the firm is loss making, these share options will be heavily geared compared with options held by researchers in pharmaceutical companies. The share price of an established pharmaceutical company will be influenced by its past successes and profits. A biotechnology firm has little history and probably no past profits and hence an employee's research effort can have a far greater impact on the share price. Such incentives are therefore actually likely to weaken once the firm becomes profitable.

A scientist entrepreneur must be willing to bear considerable risk because of the uncertainty and long time scales involved in drug discovery. Unlike in established pharmaceutical companies or academic settings, scientist entrepreneurs in small biotechnology firms can be fairly sure that they will lose their jobs if their projects fail. Furthermore, a second chance may not exist: after a failure, investors will hesitate to commit finances to the same person or team a second time.[16]

Each of the three employment options – academia, established firms and new biotechnology start-ups – offers scientists different prospects for establishing an academic reputation, monetary rewards and freedom to carry out research of their own choice. With the arrival of new technology and the availability of start-up finance, some research scientists may leave both established firms and academic institutions, if they are risk takers and if the opportunity to

15 For example, the Chief Executive of Chiroscience worked at Glaxo as part of the team that developed Zantac, the world's biggest selling drug. Vanguard Medica, which specialises in developing the research of other firms, was founded by a group of eminent scientists including a former Nobel prize winner, a head of R&D at Glaxo, and a former chairman of SmithKline Beecham Research.

16 This is due to attitudes towards bankruptcy. The US has been hugely successful in creating innovative start-up firms. *'If you start a company in London or Paris and go bust, you have just ruined your future. Do it in Silicon Valley, and you have just completed your entrepreneurial training.'* The Economist, 25 January 1997, 'Adventures with Capital' p16.

found or join a biotechnology company means that they expect to receive superior monetary rewards. The less risk averse, or more risk seeking, a scientist is, the more likely are they to choose to become an entrepreneur or seek employment in a biotechnology start-up, where a large proportion of their remuneration will be performance based.

The pharmaceutical industry relies on recruiting talented scientists from academic institutions into commercial research. New technology may enable pharmaceutical research scientists to capitalise on their skills more easily now than when drug discovery was to a greater extent dependent on trial and error. This has led to some originally university-based scientists setting up, or becoming closely involved with, biotechnology firms. Entrepreneurial academic scientists could then see their ideas become commercially successful.

Close contacts with academic institutions provide biotechnology companies with an important advantage in their promotion of new drugs based on new technologies. 'Dedicated biotechnology firms act as intermediaries between the large companies and the academic base. Because of close academic links, they were able quickly to put together the cross disciplinary teams required to develop new products in this new technology whereas big firms with their traditional contacts in chemistry, not biology departments, found it difficult to find the right people'.[17]

Sharp and Patel argue that the US led the way in biotechnology start-ups in part because of generously, publicly-funded leading edge research in natural sciences. 'Many of the dedicated biotechnology firms were spin-offs from academic laboratories, offering researchers both first class facilities in which to pursue their scientific interests and a chance, through stock options, to make themselves considerable wealth when the firm went public and launched its shares on the stock exchange'.[18] The UK's strong science base will certainly have been influential in the UK leading Europe in biotechnology. Biotechnology firms are now clustered around academic institutions such as Oxford and Cambridge with scientists combining their academic and entrepreneurial roles.

On a cautionary note, if the research carried out in academic institutions and private companies converges, it is possible that the academic sector may suffer if individuals have a preference for monetary rewards. There is a long-term danger in this. As Dasgupta

17 Sharp and Patel (1996) p42.
18 Sharp and Patel (1996) p40.

and David (1994) point out, it is important that the academic sector continues to thrive in order to supply the 'for-profit' sector with talented and trained scientists. Allowing academic scientists intellectual property rights and the ability to license their discoveries may improve pecuniary incentives and lessen any outflow of people away from academic science. It may also improve the transfer of knowledge to industry.

3 THE FINANCE OF BIOTECHNOLOGY FIRMS

Changes in technology combined with established pharmaceutical companies' demand for externally supplied research, have created a positive environment for small biotechnology companies. But to transform scientists' skills and ideas into marketable discoveries, finance is needed. Biotechnology start-up firms focus on the research phase of drug discovery and development. They therefore have lower start up costs and face a shorter time scale prior to earning revenues than do integrated pharmaceutical companies which carry out development and marketing in house. But pharmaceutical research is still expensive, drawn out and risky.

One option for the biotechnology firm would be to enter into a collaborative venture with a pharmaceutical firm from the start, from which it would receive an initial up-front payment followed by milestone payments during development. In the US and UK, however, where biotechnology start-ups have enjoyed the most success, companies tend to rely on venture capital to get started. This suggests that 'US/UK' style financial systems may be superior to those on the European continent in supporting risky, but potentially very high growth, innovative enterprises.[19] Start-up firms can obtain external finance from venture capitalists and, later in their development, on the stock market.[20] How this type of financial system benefits the biotechnology firms is examined in this chapter.

The sequence of finance for the company British Biotech is illustrated in Figure 3.1 as an example of how biotechnology firms finance their research. The progression shown, from venture capital to stock market flotation, is typical.

3.1 The role of venture capital

Venture capital financing is suited to the high risk projects of the biotechnology industry. The venture capitalist will invest in a number of small, risky projects. He takes an equity stake in the firm

19 It should be noted that, until recently, biotechnology firms in Germany, for example, were also held back by other national regulations, and not only by greater difficulty in obtaining finance.

20 Of the European public biotechnology companies, approximately 30 are listed on the main London market, a further 10 on the junior markets, and around six on the Paris, Copenhagen and Easdaq markets (Financial Times 15 May 1997).

Figure 3.1 **Financing a biotechnology company**

Year	Financing	£ million net	£ million cumulative
1986	Venture capital	2.5	2.5
1988	Venture capital	8.0	10.5
1989	Private placement	22.7	33.2
1991	Private placement	40.0	73.2
1992	Flotation/IPO	30.0	103.2
1994	Rights issue	48.5	151.7
1996	Warrants	47.5	199.2
1996	Rights issue	148.6	347.8

Venture capital was initially supplied by four specialist venture capital investors, including a venture capital subsidiary of a major pharmaceutical firm. In the second round of venture capital financing new investors included venture capital firms from the US. In 1992, when it started clinical trials for two of its products, British Biotech was simultaneously listed on the London Stock Exchange and quoted on NASDAQ in the US.

Source: British Biotech plc.

and liquidates his holdings when the firm is sold or floated on the stock market, with the expectation that the returns from successful investments will more than outweigh the losses from failed projects.

Features of venture capital contracts

Some standard features of venture capital contracts are:[21]

- The venture capitalist makes his investment in stages. He reserves the right to abandon the project at any stage if he judges performance to be unsatisfactory.
- The venture capitalist buys a significant equity stake in the firm. He receives convertible preferred stock.[22] The entrepreneur also makes an investment and receives common stock.

21 For a comprehensive survey of venture capital contracts see Sahlman (1990).
22 Preferred stock, unlike common stock, does not carry voting/control rights. Holders of preferred stock are entitled to a pre-determined repayment before holders of common stock can be paid dividends. This makes it a senior claim. Convertible preferred stock can be converted to common stock.

- Both parties' compensation is linked to the entrepreneur's performance. Once all rounds of financing are completed, one or both will want to liquidate their holdings. The firm will either be sold to another company or there will be an initial public offering (IPO) and the firm will be floated on the stock market.
- The venture capitalist has the right to provide all future financing. The entrepreneur cannot seek additional finance from a second source without the approval of the existing venture capitalists.
- Venture capitalists may take positions on the company's board of directors and, occasionally, intervene in managerial employment decisions, for example using their contacts to recruit 'star' managers.
- Venture capitalists also provide specialist advice and monitoring services, including access to networks of lawyers, accountants and other professional advisers.

The venture capitalist designs the initial contract to: 1) provide the entrepreneur with the correct incentives; 2) monitor and keep control of the investment process; and 3) guarantee a way to liquidate the investment.

Incentives provision

A firm's financial and governance structure affects an entrepreneur's incentives and the firm's performance. Where there is a separation of ownership and control, the entrepreneur may make decisions that conflict with the investors' goal to maximise the firm's value. Incentives such as stock options, equity stakes and performance related bonuses might be used to bring the entrepreneur's interests in line with those of investors, by linking the former's remuneration with the value of the firm. Complementary to these instruments is monitoring by investors and potential buyers, with the implied threat to the entrepreneur of losing control of the firm if the investors become dissatisfied.

Incentives provision is particularly important under circumstances of *asymmetric information* and *uncertainty*, such as exist in the R&D investment process. The likely success of the project is initially highly uncertain and there may be asymmetric information where by the entrepreneur is better informed about the value or riskiness of their project than is the venture capitalist. This *hidden information* may make it more difficult for the venture capitalist to

target projects for investment. Furthermore, after the investment is made, a *hidden action* problem may exist because the entrepreneur may take actions which are difficult for the venture capitalist to monitor, but which affect the firm's performance, such as the amount of effort actually devoted to research. To circumvent these information asymmetry problems, the venture capitalist scrutinises project proposals carefully before investing and designs a compensation scheme so as to attract entrepreneurs that have an interest in maximising company value. A venture capitalist will typically have enough specialist knowledge to evaluate the projects and abilities of the entrepreneurs seeking finance. Otherwise, they must rely on consultants' evaluations and perhaps other venture capitalists' evaluations and reputations when the company receives financing from more than one venture capitalist.

Despite the existence of a hidden information problem, where the scientist entrepreneurs know more about their projects than do the venture capitalists prior to the contract being agreed between them, the venture capitalists can design contracts and compensation schemes in such a way as to attract the types of projects that they would want to finance. Under a venture capital contract, the scientist entrepreneur will typically receive a lower fixed wage than he would earn as a researcher at an established pharmaceutical company. Additional compensation comes from his own substantial equity stake in the company. If the company is successful, his shares increase in value and he will ultimately receive a substantially higher payoff than in other organisations. Poor performance and project failure will mean that the entrepreneur also loses whatever amount of his own money he put up as start-up capital and will also damage his reputation, which will hinder his ability to obtain external finance in the future. Thus, an entrepreneur will only want to enter into a venture capital contract if he is confident that his project will succeed. The least promising projects will be deterred.

The design of the compensation package is important for selecting profitable projects and for ensuring that once they have the financing the scientist entrepreneurs continue to work towards the goal of value maximisation. At some point in the future the venture capitalist wants to be able to sell his shares at the highest price possible. Because the returns on research projects are unknown at the time that the contract is written, it is impossible to specify how much effort should be devoted to research and in what areas. In addition, as effort is not verifiable, any contract would not be enforceable. To provide incentives to innovate and keep down operating costs, remuneration must be linked to the firm's

performance, so that the entrepreneur shares some of the risk of failure as well as the rewards of success. Allocating shares to the entrepreneur is not the only method for providing incentives. The staging of investment payments is another way to motivate efficient levels of effort. A confident scientist entrepreneur will accept staged payments. If the project is successful and the venture capitalist invests at a higher share price at each subsequent round of financing, staged inputs of finance mean that the entrepreneur will own an increasingly larger proportion of the company than if all the finance had been provided initially at the original share price.[23]

Staged payments are the most potent instrument at the venture capitalist's disposal. Staged finance limits the amount of free cash-flow available to the firm each period and thus imposes a financial constraint on the entrepreneur. If the entrepreneur fails to meet his targets with the capital so far provided, he faces a reduction in his stake in the firm or termination of the entire project. If the venture capitalist is later asked to provide finance above and beyond that specified in the initial contract, he will increase his shareholding correspondingly. Staged finance therefore provides the entrepreneur with incentives for cost containment. It also gives the venture capitalist control over the fate of the project. By refusing to invest in the next stage, he can force termination of the project part way through.

Before each round of finance is supplied the venture capitalist acquires information about entrepreneurial effort and firm performance. As a large shareholder, the venture capitalist has powerful incentives to monitor the firm. Through monitoring, the venture capitalist learns more about the project which allows him to make a more informed decision about what share price to invest at in the next round. The next section examines how staged payments and monitoring can improve the venture capitalist's investment decision and his ability to bear risk.

The search for a new drug: irreversible investment under uncertainty

An investment in a biotechnology start-up has the following characteristics:

- To some extent the investment is irreversible. The full costs of investment can not be recovered if post-investment the firm is liquidated.

23 The higher is the share price at which the venture capitalist invests, the lower is the number of shares he receives for his investment.

- The ultimate pay-off from the investment will be highly uncertain ex ante. However, information may become available after investment begins which, to some extent, reduces this uncertainty.

The uncertainty surrounding a biotechnology investment is largely *project specific*, that is it can only be resolved by commencing the project. If an investment is staged or sequential, the risk of loss is reduced by its incorporation of the *option to abandon* the project in the light of information acquired once the project is under way. The venture capitalist's monitoring and use of staged payments allows him to base his decision whether to invest in the next stage of the R&D project, and to some extent what that next stage should be, on up to date information. This ability to adjust is important when investments are irreversible. The assets of a biotechnology venture in its early stages are likely to be intangible, for example an idea for a new drug, and also firm-specific in that they may have little value if deployed in any other firm. These asset characteristics mean that the firm will have a low liquidation value in its early days and the venture capitalist will not be able to recover his initial investment if the project fails. This argues for frequent milestones, that is short stages, at the start of a pharmaceutical R&D project.

An investment may also involve *technical uncertainty*, 'which relates to the physical difficulty of completing a project'.[24] This means that the cost of a project may be more uncertain than the future revenues. The discovery of a new drug is a lengthy and uncertain process and it may, for example, only become apparent during clinical trials that a drug produces serious side effects and would never gain regulatory approval. Thus the costs of the R&D process, can only be learnt once the R&D is under way. A decision whether or not to continue the investment should therefore be based not only on current information but should also take into account the value of acquiring further information.

Under these particular circumstances, where undertaking the investment reveals information about future costs, which has an indirect value not usually taken into account, it may be optimal to carry on even when the conventionally measured net present value (NPV) of the project is negative. Box 1 sets out a simplified example which explains why this might be so.

24 See Pindyck (1993) p54.

Box 1 **Calculating NPV under technical uncertainty**

Investment in a pharmaceutical R&D project can take place in stages. The first stage requires an investment of £1m. Suppose that with probability 0.5 no further investment will be required, that is the drug can be licensed to a pharmaceutical firm for development. However with probability 0.5 a further £5m will be required before the technology can be licensed.

If the payoff from the project is expected to be £3m, then the expected NPV might appear to be negative, as expected investment costs are £3.5m [1 + (0.5x5)], implying a negative NPV of -£0.5m.

This conventional NPV measure, however, does not incorporate the value of information acquisition and the option to abandon the project, because if it is learned at the end of the first stage of R&D that the extra £5m will be required, then at that point the project can and will be terminated because at that point to continue would require an investment of £5m but would only be expected to yield benefits of £3m.

The appropriate NPV of the project, taking into account information acquisition, is therefore actually positive, namely: (0.5x3) -1 = +£0.5m, so investment in the first stage should proceed.

A venture capitalist will be investing in a portfolio of projects. By using staged finance he can monitor these projects and adjust each investment to new information. By learning early on whether a project should ultimately be profitable, he can minimise his losses from bad projects by ceasing investment and concentrating on the expected winners. As a result, the venture capitalist can accept an initial portfolio which is higher risk than if payments were not staged. Staged venture capital finance is thus a source of finance tailored to biotechnology start-ups.

3.2 Stock market flotation

Venture capitalists specialise in financing start-up firms. Once the firm reaches a certain level of maturity the venture capitalist will liquidate his investment. Experience shows that venture capital financed biotechnology firms have tended to be floated on the stock market at this point:

> 'In..biotechnology,....the proportion of firms that go public is quite high. This may reflect either the relative success of companies in this industry or their need for large capital infusions which an initial public offering (IPO) provides.'[25]

25 Gompers (1995) p1472.

An IPO might provide the venture capitalist with higher returns than would a take-over by another company. For the scientist entrepreneur, retaining control of the firm will be an important consideration. A further reason why a biotechnology firm's stock might be floated rather than sold in one block to another firm is that at the point when the venture capitalist wishes to liquidate his holding, it still represents a risky investment. The level of risk may seem too great to a single potential acquirer, but not for numerous individual shareholders who hold diversified portfolios.

The timing of an IPO is important because the governance structure of the company will change when the financing responsibilities shift from the venture capitalist to the stock market. The firm moves from having one or a few major shareholders to having numerous dispersed shareholders, who individually have less time and incentive to monitor the firm's activities. The firm will be floated on the stock market when the information available about its performance is of a form that can be interpreted by public shareholders.[26]

In 1992, British Biotech became the first UK biotechnology firm to be floated. The move coincided with a change in the rules of the London Stock Exchange to allow scientific research firms which had no trading record to obtain a listing. Biotechnology firms are commonly floated on the stock market before they have profits or even revenues, but usually they have some compounds which have progressed as far as the clinical trial stage.[27] Information about the efficacy, safety and side effects of a drug, which is obtained from clinical trials, provides signals to the shareholders about its prospects for regulatory and commercial success. (Approximately 80 percent of drugs reaching phase III trials eventually gain regulatory approval and so may be marketed).

Shareholders are willing to hold risky biotechnology shares for similar reasons to venture capitalists. Like the venture capitalists, shareholders will move their money between investments when new information becomes available. With less vested interests in any one company, individual shareholders are likely to make more frequent adjustments than venture capitalists. How much they gain or lose by moving funds around depends on the movement of the share price and the fraction of their diversified portfolio that they

26 Investor sentiment towards the biotechnology sector as a whole is also important. A venture capitalist may delay flotation of a biotechnology firm until the sector is buoyant.
27 British Biotech set the standard. It went public when two of its discoveries entered phase I of clinical trials.

have invested in a particular company. The ability to adjust their investment, and hence their exposure to risk, in response to information, enables them to bear that risk.

The change in governance structure at flotation will mean a new monitoring arrangement for the biotechnology company. The shareholders are now responsible for valuing the firm. Investor attitude and the share price move together. Share prices for an individual biotechnology stock fluctuate not only in response to developments in the firm's own clinical trials, but also as a result of news of developments elsewhere in the industry. Some have argued that having dispersed shareholders can result in an insufficient level of monitoring. A minor shareholder who monitors the firm in order to try and influence performance will pay the full costs of monitoring but must share the benefits with all the other shareholders. They may therefore choose not to monitor, but to try and 'free ride' on the monitoring efforts of others. If all try to 'free ride' though, little monitoring will take place. Against this, because the share price is expected to increase dramatically when a biotechnology firm produces a successful drug, investors do clearly have some incentive to monitor performance.

This chapter has shown why financing through venture capital and stock markets is so important to an active biotechnology sector. It has been suggested that the scarcity of information available on a biotechnology firm's performance early on in its life, and the complex nature of such information, make monitoring by a specialised investor necessary. The combination of venture capital and US/UK style capital markets can translate high growth into high returns for the investor. It is this that leads the venture capitalist to bear risk and invest in these firms. A liquid stock market then provides the capital necessary for biotechnology firms to begin to conduct clinical trials.

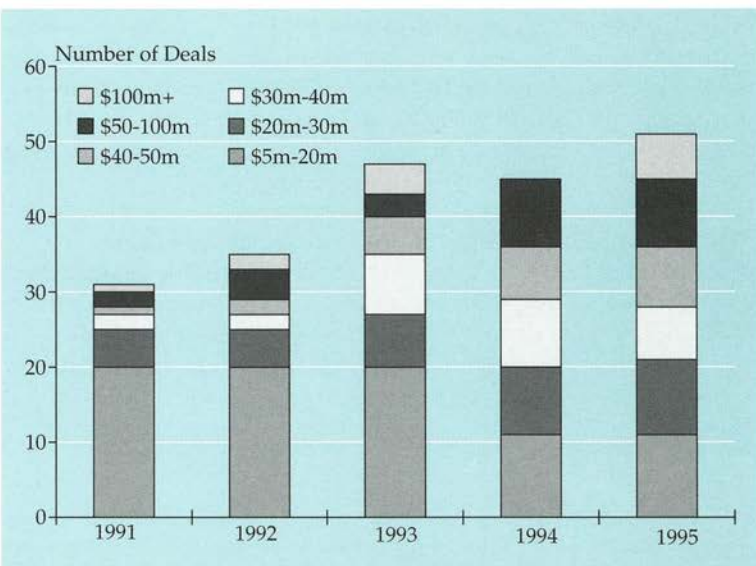
In addition to providing a source of finance, stock markets play an important role in the incentive structure for scientists in the private sector. Stock market flotation allows scientists in biotechnology companies to be paid in shares and share options. This provides potential compensation for their risky employment choice. Remuneration packages comprising share options which are offered by biotechnology firms are also useful in attracting key staff from major pharmaceutical companies, where remuneration may be more salary-centred. Prior to changes in stock market regulations in the UK in 1992, a scientist starting-up a firm to commercialise his own ideas had to hope that he could interest a pharmaceutical company buyer. Stock market flotation allows scientist entrepreneurs to keep

control of their firms, while giving them incentives to align their management and research decisions with the interests of the shareholders.

4 COLLABORATIONS AND THE STRUCTURE OF THE PHARMACEUTICAL INDUSTRY

This chapter investigates whether the pharmaceutical industry is tending towards a division of labour where small firms specialise in the research stage and larger firms specialise in the development and marketing of drug innovations. The effects of changes in the corporate strategies of both established pharmaceutical firms and biotechnology firms on industrial structure are examined. In particular, the costs and benefits, for both parties, of collaborations between biotechnology firms and established pharmaceutical companies are analysed. It is argued that although the number of collaborations is increasing (see Figure 4.1), they should not be expected to replace vertical integration as the predominant organisational form in the pharmaceutical industry.

Figure 4.1 **Biotechnology outlicensing: number and size of deals are increasing**



Source: Windhover's Pharmaceutical Strategic Alliances for the PC and Lehman Brothers.

4.1 The size of innovative firms

The predominance of large firms in the pharmaceutical industry seems to support the arguments of Schumpeter (1942) that only large firms can afford the resources needed for long term R&D investments. According to this argument, large firms are better equipped to finance R&D internally with earnings from existing products. They also face lower costs in obtaining external sources of finance for investment and can use their sizeable marketing infrastructure to appropriate returns to R&D more effectively than small companies. At the discovery stage, when companies use the traditional, trial and error, 'chemical' drug discovery techniques, empirical evidence also suggests that horizontal and dynamic[28] economies of scale may exist. (The technical change wrought by the introduction of biotechnology is, as recorded earlier, potentially changing this). Henderson and Cockburn (1996), examining research productivity in drug discovery, found that large pharmaceutical firms do not have an advantage through economies of scale, but that they do have an advantage in realising economies of scope, by assimilating knowledge spillovers and pursuing diverse research portfolios. DiMasi et al. (1995) found that in the discovery phase, the cost per NCE for large firms was significantly less than for small firms.

An important question is whether the emergence of new technologies makes size less important for drug discovery. The evidence is mixed. On the one hand, there are increasing numbers of successful small biotechnology companies. On the other hand, large costs for technologies such as high throughput screening may mean that scale remains important in some areas.

Arrow (1983) discusses the transmission of information within large and small organisations. He argues that small firms may be well equipped to carry out research but not large scale development. There are two stages in his model of the R&D process. In stage 1, a firm makes a decision about whether to carry out research. Associated with the 'research outcome' is a probability distribution of possible development costs, that is it is uncertain how much it will cost to develop it into a marketable product. In stage 2, a decision is made on how much, if anything, to invest in development. Arrow, assumes that the researchers, who obtain the information which indicates expected development costs and the probability of clinical

28 A firm will have built up a large portfolio of compounds over time.

trials success, are not the same people who are responsible for making the investment decision. In other words, he assumes the research scientists are not managers. As the information is passed by the research scientists to the decision makers, its quality is assumed to degrade. Increased development cost uncertainty results. Arrow assumes, further, that information degradation is greater if the transmission is made across firm boundaries rather than within one firm. Such cross-boundary information transmission is necessary when the research firm seeks external finance.

According to Arrow, the ease of access to finance for large development costs will be a function of firm size. A small, loss-making, firm has to seek project-specific finance from the external capital market, while a large firm is able to finance much of its R&D with retained profits. Furthermore, if they do require any finance from the external capital market, large firms will receive it on more favourable terms than can small firms, because of their performance record, reputation and greater ability to spread risk over many R&D projects. Information degradation would make it difficult for small firms to raise sufficient capital to finance projects with high development costs. In the pharmaceutical industry, therefore, large firms may be the only ones able to cover the high development costs of pharmaceuticals.

Small firms may be better able to cover the research phase, however. The organisational distance between recipients of information and internal decision makers is less in a small firm. This may lead to better decisions about research investment being made within small firms.

If, once the research is complete, the biotechnology firm sells the outcome to a larger company better able to bear the large development costs, then information degradation may be less severe if evaluation is by a specialist firm in the industry, rather than by general capital market investors. A *market for research outcomes*, where potential buyers (pharmaceutical firms) and sellers (biotechnology firms) are active can therefore exist.

In summary, large firms have an advantage where the technology of the R&D process requires large laboratories and extensive research staffs and where large amounts of internal financing are needed, as in development. However, technological change and a growing market for research outcomes, where research-specialising companies can find informed buyers, mean that small firms are now able to afford to carry out drug discovery. In the following section, the circumstances under which large firms may opt to license-in research discoveries, rather than rely on in-house research, are examined.

4.2 The boundaries of the firm: are we moving towards a more efficient organisation of R&D in the industry?

In this section, the property rights theory of the firm[29] is used to consider what determines the boundaries of the firm, and to examine incentives for researchers, specifically in the pharmaceutical and biotechnology sectors, to devote intellectual effort to research under different ownership structures and organisational forms.[30] It is suggested that scientists' incentives to innovate are enhanced when they obtain property rights to their research and can control how it is developed and brought to market, that is whether it is developed in-house or in collaboration with a major pharmaceutical firm.

A pharmaceutical firm striving to maximise returns on R&D, must decide whether to conduct research in-house or to license-in discoveries from independent research, (biotechnology), firms and concentrate solely on the development stages. The two modes of supply of research are associated with different ownership structures:

- *integration.* The pharmaceutical firm obtains the innovation from its in-house laboratory and has the property rights to its researchers' innovation;
- *non-integration.* The researchers in the independent biotechnology firm have property rights to the innovation. The pharmaceutical firm bargains with the biotechnology firm post-discovery over the licence fee.

The property rights theory suggests that the pharmaceutical firm faces a trade off between research effort and control over final returns. Scientists in biotechnology companies have a greater incentive to innovate, because they are in a position to bargain for a greater share of the final return than are in-house scientists within a large company. The pharmaceutical firm must decide how much more it is willing to pay for improved research.

The underlying assumption behind this proposition, is that complete contracts for purchasing the outcomes of research cannot be written prior to the research taking place. In particular, a pharmaceutical firm cannot specify in a contract the amount of

29 Originating in Grossman and Hart (1986).
30 The framework of Aghion and Tirole (1994a,b) is used.

intellectual effort a researcher (either in-house or in a separate firm) must devote to discovering a compound. Effort is non-verifiable, and hence cannot be contracted upon. There will also be uncertainty about the outcome of research. A specific innovation cannot be contracted for *ex-ante* with a potential purchaser. We do not observe competitive bidding to deliver specific innovations. Contracting occurs ex-post, that is after the investment has been made and the research outcome has been produced.

The probability of a successful research discovery depends both on the financial input and the intellectual effort of the researchers. From the researchers' point of view, exerting effort is costly and so to motivate them, they must expect to receive a reward at the end. The problem is that the outcome, and thus the amount of reward, will not be known until after the research is complete, by which point their effort has already been sunk into the project and cannot be withdrawn. One way to motivate researchers at the beginning of the process is to ensure that their bargaining power at the end of the research process will be protected. Their bargaining power will depend on the allocation of property rights.

By the time that a discovery has been made, the researchers' efforts have already been committed. In the *integration* case, the in-house researchers have little bargaining power over their reward at that point and thereafter. At the extreme, if in-house researchers expect to receive no share of the value of the innovation, they will deliver a suboptimal level of effort. This reduces the probability of an innovation ever being made and successfully developed. The pharmaceutical company owners, on the other hand, control all the returns to any successful R&D and so in the integration case do have an ex-ante incentive to provide the right level of financing for the investment.

In the *non-integration* case, the picture is somewhat different. The biotechnology firm has the property rights to any innovation. Once a compound has been discovered, the biotechnology firm bargains with a pharmaceutical firm over their respective shares of expected future returns.[31] The outcome of bargaining is that the pharmaceutical firm pays a licence fee equal to some fraction of the value of the innovation. The researchers' efforts will depend upon the fraction they expect to receive from these negotiations. The

31 At the time when the pharmaceutical and biotechnology companies are bargaining, the revenues from the discovery will actually not be known with any certainty, not least because the drug must still pass through the clinical trials and approval phases.

pharmaceutical company, on the other hand, will expect a smaller share of the returns than in the integration case, and will have less incentive to provide investment finance ex-ante.

Researchers will prefer to hold the property right to the innovation if they get a higher pay-off under non-integration. The pharmaceutical company which purchases the innovation might also receive a higher pay-off under non-integration, even though it has to pay a licence fee, if the researchers' efforts, and therefore the probability of a profitable discovery being made, are greater. This depends, however, on the availability of external investors who are willing to finance the biotechnology firm.

The optimal ownership structure will depend upon the relative importance of researchers' effort and investment. If intellectual effort is a more important research input than finance, then large firms with internal sources of funds may not have the advantage. If the individual biotechnology firms have higher research productivity, pharmaceutical companies can benefit and license-in discoveries.

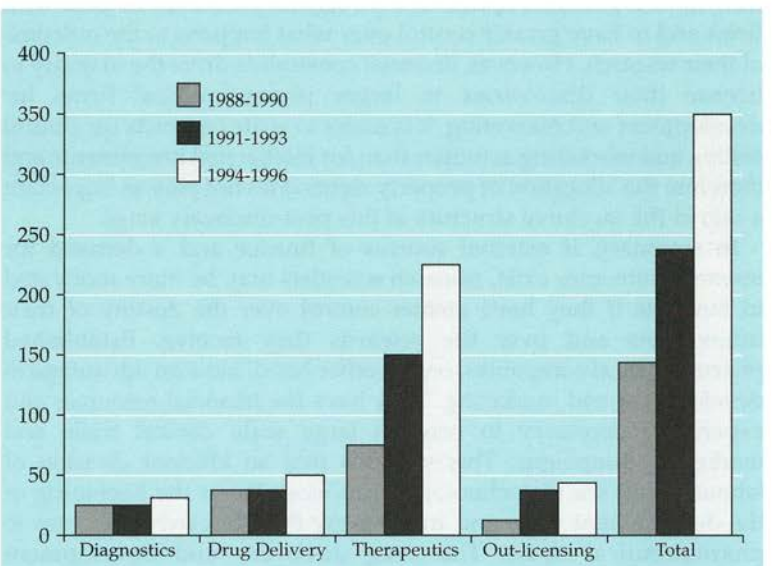
The emergence of biotechnology firms has brought a change in the organisation of research in the pharmaceutical industry. Scientists now have a practical option to own significant stakes in their own firms and to have greater control over what happens to the outcome of their research. However, financial constraints drive the majority to license their discoveries to larger pharmaceutical firms for development and marketing. It is easier to write contracts for clinical testing and marketing activities than for intellectual investments and therefore the allocation of property rights does not play as important a role in the incentive structure at this post-discovery stage.

In summary, if external sources of finance and a demand for research outcomes exist, research scientists may be more motivated to innovate if they have greater control over the destiny of their innovations and over the rewards they receive. Established pharmaceutical companies, on the other hand, have an advantage in development and marketing. They have the financial resources and experience necessary to conduct large scale clinical trials and marketing campaigns. This suggests that an efficient division of labour might see biotechnology firms stopping at the beginning of the development stage and transferring their research outcomes to pharmaceutical firms. The drug discovery and development processes would not then be vertically integrated. However, this can only happen if the market for research outcomes works efficiently, so that both discoverers and potential drug developers can realise the benefits from the trade. The following section therefore examines the nature of this market.

4.3 Collaborations

Between 1994 and 1996 the number of collaborative deals involving the top 20 pharmaceutical companies rose from 117 to 180. Over the same period, the value of these deals more than doubled from $1,187 to $2,842 million.[32] The number and value of collaborative deals involving biotechnology companies specifically have also increased (see Figure 4.1). The collaborations are occurring predominantly in therapeutics and, as was suggested by the discussion in the previous section, principally at the drug discovery stage (see Figures 4.2 and 4.3). A survey of 43 biotechnologically-derived new active substances (BNASs), excluding vaccines, which had reached the market by the end of 1994 found that while 61 percent of them had been originated by either biotechnology companies or research groups, 72 percent were first marketed by larger, traditional, pharmaceutical companies.[33]

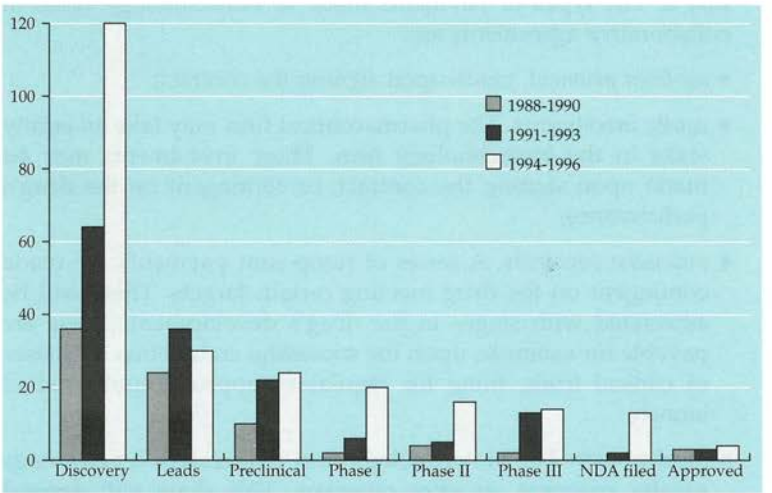
Figure 4.2 **Collaborations by type (top 20 pharmaceutical companies)**



Source: Recombinant Capital and Lehman Brothers.

32 Source: Recombinant Capital and Lehman Brothers.
33 Centre for Medicines Research (1995).

Figure 4.3 **Collaborations by stage of development (top 20 pharmaceutical companies)**



Source: Recombinant Capital and Lehman Brothers.

A development and marketing agreement between a biotechnology firm and a pharmaceutical company typically takes the following form:

1. the biotechnology firm will look for a suitable partner with experience of conducting clinical trials and good marketing ability in the therapeutic area in question;[34]
2. the two parties negotiate the terms of the contract. As the pharmaceutical company's evaluation of the biotechnology company can take up to two years, the latter must initiate the search for a partner before it actually has evidence from phase I clinical trials;
3. once an agreement has been reached, the pharmaceutical firm takes on the full development costs and the biotechnology firm transfers to it some share of the expected return and marketing

34 It is possible that the best match may also be the firm's main rival in that therapeutic area.

rights. The details from an agreement between SmithKline Beecham and Cantab Pharmaceuticals are given as an example in Box 2. The types of payments made to biotechnology firms in collaborative agreements are:

- *up-front payment*, made upon signing the contract;
- *equity investments*. The pharmaceutical firm may take an equity stake in the biotechnology firm. These investments may be made upon signing the contract, or contingent on the drug's performance;
- *milestone payments*. A series of lump-sum payments are made contingent on the drug meeting certain targets. These will be associated with stages in the drug's development. These are payable for example, upon the successful completion of phases of clinical trials, filing for regulatory approval and product launch;
- *royalty share*. The biotechnology firm will receive a percentage royalty payment on sales revenues. This share will depend upon the stage in production process at which the drug is licensed.

The following paragraphs discuss the costs and benefits of collaborations for the established pharmaceutical and new biotechnology firms respectively.

Box 2 **Example of a collaboration**

'Cantab formed a collaboration with SmithKline Beecham Biologicals Manufacturing s.a. (SBBio) to develop and market Cantab's TA-GW vaccine... Under the terms of the agreement Cantab could receive up to £24 million, plus royalties in return for the transfer of world-wide development, manufacturing and marketing rights for TA-GW products to SBBio.... Our choice of SBBio was based on its experience... and its specialised global marketing infrastructure. Cantab received from SBBio an aggregate of £7 million in up-front payments comprising licence fees of £3 million and an equity investment of £4 million... approximately three percent of the company's enlarged share capital.... Cantab may receive up to a further £17 million payable upon the achievement of certain development milestones. In addition, SBBio will also pay Cantab an undisclosed royalty on future product sales.'[35]

35 Source: Cantab Pharmaceuticals plc interim report 1996.

Established pharmaceutical firms

The benefits to established pharmaceutical firms from collaborative agreements arise from:

- risk spreading;
- the ability to redirect R&D resources;
- better access to innovations and innovative technology.

By licensing-in some discoveries, pharmaceutical companies need no longer rely only on in-house R&D for new drugs and can shift some of the risk associated with R&D onto the biotechnology companies. A key question is at what point the company should undertake a collaboration. Pharmaceutical companies can buy 'successful' research outcomes. However they are not acquiring a guaranteed revenue stream. Most collaborations begin before it becomes certain that the discovery will gain market approval (See Figure 4.3). The probability of success increases and risk falls as the drug moves through the stages of clinical trials. But the pharmaceutical company will be able to extract more of a successful drug's value from the biotechnology firm the earlier it takes it on, as the 'purchase price' (comprising milestone payments and a royalty share) will be lower. Thus, the pharmaceutical firm faces a trade off between risk and reward.

There is some debate over how quickly large, incumbent firms can respond and adapt to new technologies. Henderson argues that pharmaceutical firms have the 'ability to foster a high level of specialised knowledge..., while preventing that information from becoming embedded in such a way that it permanently fixes the organisation in the past, unable to respond to an ever changing competitive environment.'[36] This means that although they cannot switch R&D into new areas, or adopt new technologies overnight, they are not left behind for long.[37] Acquisitions, equity stakes and collaborations with biotechnology firms can supplement the direct adoption of new technology and allow new directions for R&D for established pharmaceutical firms.

If a pharmaceutical firm falls behind the leaders in a target therapeutic area, it may decide to acquire a potential compound rather than finance internal R&D in an attempt to catch up. The pharmaceutical firm effectively buys-in information about the new

36 Henderson (1994) p100.
37 See Zucker and Derby (1995).

generation of drugs in this area. It may also decide to acquire a compound from a biotechnology company and then modify it before commencing clinical trials. The pharmaceutical firm saves on the R&D expenditure made by the biotechnology firm, which includes the costs of failed compounds. Licensing-in ideas and technologies allows pharmaceutical firms to concentrate their R&D expenditure on those parts of the drug production process they consider essential to carry out in-house. The benefits of this must be weighed against the costs of licence fees and royalty payments to biotechnology firms which cut into the eventual profit stream, and the transaction costs of negotiation and contracting.

As well as development agreements, collaborations also occur at the research stage. This involves in-licensing of 'platform technologies'. The large number of agreements made at the discovery stage, shown in Figure 4.3, is due to a trend of companies acquiring genetic databases. Pharmaceutical firms can purchase the rights from specialist basic research firms to use genetic information in order to identify disease targets. They can then acquire thousands of potential compounds from a combinatorial chemistry company. The pharmaceutical company can then use its in-house technology and expertise to screen the compounds to try and find a match with the target.

Biotechnology firms

For biotechnology firms, the advantages of collaboration over trying to integrate forward into the clinical trial stages of development include:

- risk pooling;
- earlier revenue flow;
- a quicker process for getting their drugs to the market.

Biotechnology firms must make a fundamental decision whether to license-out their drugs or integrate forward and try to fund the development and marketing processes. If they choose the former option and collaborate with a pharmaceutical firm, they must then decide how far they are going to take development of the drug before licensing.

Integrating forward allows a biotechnology firm to retain all the profits from their products but exposes them to more risk. Development collaborations, on the other hand, mean a new source of finance. By licensing a product to a pharmaceutical company and receiving milestone payments, a biotechnology firm will have some

cash flow to use on new research projects, thus enabling it to widen its portfolio. This will enable it to increase the speed with which it gets products to the licensing stage and also provide back-up if the products it has in clinical trials fail. Entering into a collaborative venture may also have a positive effect on the market value of the biotechnology firm, as it implies approval of their research by an established pharmaceutical firm with a reputation for picking winners. However, it may not be so easy to find a willing partner to collaborate with until the biotechnology firm can provide some information from clinical trials. Pharmaceutical firms may be unwilling to take prospective drugs on board prior to commencement of clinical trials, or only willing to do so by taking a large proportion of any future profits.

A development collaboration involves shifting development risk onto the pharmaceutical firm. The drug still has the same initial probability of failure, but the biotechnology firm no longer has to fund its development. Once the drug has been passed to the pharmaceutical firm for development, the use of milestone payments means the biotechnology firm continues to bear some risk; it is not fully insured against the drug failing. Although the biotechnology firm does not pay the development costs, its remuneration is likely to be linked to the performance of the drug in clinical trials. This co-insurance arrangement helps to overcome a potential asymmetric information problem, in that the biotechnology firm may initially be better informed about the value of the drug, or the probability that it will be successful in clinical trials, than the acquiring pharmaceutical firm. Like the venture capital contract discussed in chapter 3, this form of remuneration should induce some *self-selection*; biotechnology companies will only offer drugs to be licensed which they believe have a positive expected value. A biotechnology firm with a compound it believes will be successful will be willing to continue to bear some risk by entering into such a development agreement. In addition a biotechnology firm which aims to be sustainable on the basis of collaborations will want to develop a reputation for producing successful drugs. The long-run reputational losses from licensing out low quality drugs which subsequently fail[38] should outweigh any short-run financial gains of licence fees from pursuing such a strategy.

If a biotechnology firm chooses to collaborate with a pharmaceutical company on the development of a drug, it must also

38 There will also be losses due to the fall in the company's market valuation.

decide how far it is going to take drug development in-house before licensing it out. A trade-off has been identified between risk and reward which the pharmaceutical company faces when deciding at what stage to in-licence potential drugs. The same trade-off faces the biotechnology company, only in reverse. The further the biotechnology company develops the drug, the more risk it bears but, conditional on the drug progressing through the stages of development, the better is the deal it can get with the partner firm.

The probability, based on past averages, that the drug will gain ultimate regulatory approval increases as the drug progresses through the phases of clinical trials. Perhaps more importantly the information produced on the performance of the drug becomes 'harder' and easier for the pharmaceutical firm to interpret as it progresses though the development process. The biotechnology firm should therefore be able to appropriate more value the later the deal is struck because it is increasingly able to demonstrate the value of its product. Thus, pharmaceutical firms have to pay biotechnology firms significantly more for late stage collaborations.

If, however, a biotechnology firm persistently interprets the information it has available more optimistically than any potential buyer is willing to, in that it views the risk/reward trade-off more favourably, then it may attempt to integrate forward. That is, the biotechnology firm will try to raise finance to enable it to develop the product itself, taking it through clinical trials, and perhaps even to manufacture and market the finished product should it be approved by the regulatory authorities.

A second consideration in whether to collaborate or integrate forward, is the issue of control. The importance of ownership and control rights for incentives has been discussed earlier in this chapter. Problems may arise in agreeing collaborative deals if the scientist entrepreneurs in the biotechnology firm fear too great a loss of control over the process of development of their product.[39] More specifically, the biotechnology firm and the pharmaceutical firm may take different views as to the priority to accord the biotechnology discovery among the larger firm's overall portfolio of products.

Suppose a biotechnology firm licenses its leading compound to a pharmaceutical company for development. The pharmaceutical firm will typically have a portfolio of products in development, many of

39 That is, the scientist entrepreneurs may not wish to place themselves in a position similar to that of a research scientist within a pharmaceutical company, who loses control over what happens to his compound in the development stage – a position which they implicitly rejected when choosing to start up their own biotechnology firm.

which will be the results of their own in-house research, for which some senior managers in the firm may feel a personal responsibility (their career progression may be linked to the success of products they are particularly associated with) and for which the firm does not have to make milestone payments or pay royalties. Thus, from the start, the pharmaceutical firm may demand a higher quality drug for development when it is licensed-in than from an in-house drug, because it has more visibly had to 'pay' the biotechnology firm for it. A further problem arises if what was considered a leading compound for development within the biotechnology firm becomes only a marginal compound for the acquiring pharmaceutical company. If good results are obtained for one of the pharmaceutical company's own, in-house, products, then the company may choose to channel resources to it and away from a licensed-in product. For example they may slow down the trials on the biotechnology firm's drug. The biotechnology firm is faced with the problem of ensuring that the pharmaceutical company commits resources to their product even though it may not be the pharmaceutical company's preferred strategy to do so.

The biotechnology firm may incorporate in the licence contract, time limits for the completion of various stages of the development process, and negotiate buy-back clauses to be implemented if these are not met. However, if it is the case that biotechnology firms are most likely to license-out those discoveries which they can least afford to develop themselves, then to buy them back may not be a credible option as it would leave them in a worse situation than they were originally. The biotechnology firm cannot afford to complete development themselves and so they will need to raise external finance. But the apparent rejection of their discovery by a major pharmaceutical company will send out a negative signal, making it very difficult to find a new partner among other pharmaceutical companies or, indeed, any other source of finance.

Thus, fear of having their discoveries sidelined may discourage biotechnology firms from licensing-out their discoveries to larger pharmaceutical companies, and encourage them to try and integrate forwards instead.

A biotechnology firm will face barriers to entry to development and marketing. Marketing some types of pharmaceuticals, such as medicines aimed mainly at GP prescribing, and those which compete with major existing suppliers, requires a large scale marketing and sales network, which involves a large set-up cost. Whether a biotechnology firm can integrate forward may therefore depend on the type of drug it possesses. For example, British Biotech

has been able to finance all three stages of clinical trials and to set up its marketing infrastructure, but only for some of its drug portfolio. The drugs it has taken forward are those which are prescribed mainly by specialist doctors in hospitals rather than GPs, and therefore require a smaller marketing and sales network.

Thus, collaborations are not a panacea. Both pharmaceutical companies and biotechnology firms may have grounds ultimately to go it alone. It would, therefore, be premature to suggest an end to the predominance of vertically integrated firms in the industry.

4.4 The structure of the pharmaceutical industry[40]

A case has been made for why a small company should, in theory, be able to successfully discover a new drug. Technological change has reduced the minimum efficient scale needed for discovery; venture capital is available to help start-ups cover initial risky investments; there are scientists who want to be entrepreneurs and will be more productive once they control their own innovations; and large pharmaceutical companies are increasingly looking to buy-in research outputs from external sources as a way to cut costs, spread risks and increase their flexibility. However, in order to provide incentives for R&D, it essential that a firm can appropriate the returns to its innovative effort. Discovering a blockbuster drug is not enough for commercial success in this industry. To capture the market share it merits, a drug must be well marketed. The need for firms to build marketing infrastructure to appropriate the returns to their drugs will increase concentration in the industry. Entrants will have to create their own marketing capabilities to compete with the large firms in terms of market share. Any tendency for smaller firms to integrate forward will increase concentration.

Looking at the evolution of the industry, its concentration is determined both by consolidation of existing firms within the industry and by new entry. Consolidation in the form of mergers and acquisitions is driven by the need for firms to acquire technology and to maintain a strong portfolio. Against that, however, the continuing entry of small firms, now encouraged by the advent of biotechnology, lowers concentration.

Start-up companies can be observed following one of three long run strategies: either remaining as research 'boutiques'; or collaborating with pharmaceutical firms at some stage of clinical trials, (referred to as 'proof of principle companies'); or integrating

40 This section draws on the work of Sutton (1995, 1998).

forward. Even those biotechnology firms which integrate forward for some of their products may still engage in licensing agreements and joint research ventures with other firms for other products. Indeed, collaborations, predate the advent of biotechnology. In the past, licensing agreements have not been uncommon between established pharmaceutical firms. But the arrival of biotechnology has increased the number of collaborations.

Finally it should be noted that licensing agreements are not the only form of collaboration occurring in the industry. As well as patented research outcomes and technology, tacit knowledge will also be transferred. There will be research spillovers between the work carried out in firms and academic institutions. This can explain less formal and longer term collaborations between pharmaceutical firms, biotechnology firms and academic institutions. These sectors possess complementary assets, and innovations may come from co-operation between all three, as there is still learning-by-doing occurring in the application of new technology. Research collaborations between biotechnology firms and academic institutions are facilitated by the fact that biotechnology firms tend to cluster around academic institutions.

5 CONCLUSIONS

The combined responses of entrepreneurial research scientists, established pharmaceutical companies and venture capitalists explain the emergence of biotechnology firms in the pharmaceutical industry, given the opportunity provided by technological change. This change has potentially reduced the minimum efficient scale needed for drug discovery, so creating an opportunity for new, small firms to enter the industry. Established pharmaceutical companies have proved willing to purchase biotechnology-based products from such outside sources. These established companies are increasingly looking to license-in drugs at the development stage as a way to reduce costs, spread risks, integrate new technologies and increase flexibility.

The changes in technology and the existence of demand for research outcomes created an opportunity for scientists to pursue a career as entrepreneurs. For some this has proved a more attractive choice than remaining in either an academic or a large firm setting. Reasons have been suggested why these scientist entrepreneurs may expect to earn greater rewards for their research efforts when they control the decision making process. For them the incentives to innovate are greater in small independent firms than in academic institutions or in the research laboratories of established pharmaceutical companies.

Scientist entrepreneurs have been able to take advantage of these changes in the industry because external capital sources existed to finance their new, high-risk, biotechnology start-ups. I have argued that the success of biotechnology start-ups in the US and UK hitherto relative to other countries is linked directly to the greater availability of venture capital and liquid stock markets in these countries. 'Venture capital is important not just as a means of funding, but also as a critical tool that managers of start-ups use to create high-powered incentive structures for employees.'[41]

The incentives for scientists are an important issue both for the emergence of biotechnology firms and for the success of the pharmaceutical industry overall. The outcome of research is as much a function of researchers' effort (and luck) as of finances and scale. Insights from the literature on property rights and corporate governance have been used to show that incentives for scientists matter because they affect a firm's research productivity.

41 Matraves and Casper (1997) p17.

Despite an active market for research outcomes, and the ability of some small start-ups to compete with established firms in the discovery stage of the product life cycle, vertical integration is likely to remain as the predominant organisational form in the pharmaceutical industry. Indeed, some biotechnology firms might themselves become fully integrated pharmaceutical companies that develop and market their own drugs. Collaborations are not universally appropriate. They involve their own costs and risks and so will not suit every circumstance. Although no significant move away from vertical integration is predicted, the number and range of collaborative agreements may well rise. Pharmaceutical firms are identifying what it is essential to do in-house and what can be out-sourced. Companies which specialise in undertaking particular elements of the drug development process, such as clinical trials and marketing approvals, are increasing their presence within the industry.

As they are able to add new value to research projects by implementing new technologies quickly, small start-up ventures play an essential role in the pharmaceutical industry. Research productivity should be enhanced not only as a result of technological change, but also because of the improved incentive structures for entrepreneurial scientists that biotechnology firms provide. The ability of the UK financial system to back these start-ups should ensure them a continuing role in the commercialisation of future scientific advances.

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