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Economics Issues for the U.K. Biotechnology Sector

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Abstract

This paper examines the economic prospects for biotechnology industry, focusing on the U.K. position. We discuss some economic issues relating to the structure of the biotech industry and examine whether these factors can account for the relative success of the biotechnology sector in the U.K. compared to other European countries. We emphasise the importance of the science base, pharmaceutical companies and capital markets in giving Britain an advantage. Looking ahead we argue that prospects are good for the global growth of the industry due to supply and demand side factors. Britain is in a leading position in Europe but faces significant dangers, especially from public towards biotechnology.

Keywords: Biotechnology, policy, R&D

JEL Reference: O3, O5, L6

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1. Introduction

Biotechnology is rarely out of the news. Scientific breakthroughs in finding new drugs, in cloning and in mapping the Human Genome have captured the imagination and fears of the British public in almost equal measure. The sector has seen its ups and downs. In the early 1990s biotechnology was the darling of the London Stock market and venture capital industry, but became eclipsed due to high profile drug failures and by Internet-based start-ups. Now that the Dot.Coms are Dot.Gones biotechnology is enjoying a revival with high valuations and significant numbers of mergers and acquisitions[1].

This paper looks behind these fluctuations to address some of the critical economic issues in biotechnology and their relevance for the U.K. industry. What are the factors that will determine the future of the industry on a global basis and in particular in the U.K.?

There is no commonly accepted definition of a biotechnology `sector'. It is commonly regarded as an enabling technology rather than an industry per se. Roughly speaking, biotechnology is the application of knowledge about living organisms, and their components, to industrial products and processes. The worldwide market for biotech companies reached about £70bn by 2000 and biotechnology dependent sales in the U.K. reached £9bn (about 1.2 per cent of GDP)[2].

In the early 1970s[3], two molecular breakthroughs heralded the coming of genetic engineering:

- Recombinant DNA (rDNA) allowed part of a foreign gene to be inserted into another and thereby change its characteristics
- Hybridomas - techniques for fusing and multiplying cells.

Biotech start-ups entered the U.S. industrial landscape in the early 1980s. By the mid-1990s some US biotech companies (e.g. Genentech, the first real Biotech firm) were integrated pharmaceutical firms, capable of competing with the larger pharma firms, at least in some therapeutic areas. Today, several firms are now fully integrated and approaching the size of "Big Pharma". For example, in December 2001 Amgen paid $16bn for Immunex at the end of 2001. British Biotech was founded in 1986 and floated in 1992. Failure of its key trial drugs resulted in its being overtaken by other rivals, such as Celltech.

The U.K. still leads Europe in biotechnology on almost any measure one chooses. Table 1 looks at a key indicator, the number of drugs in the pipeline (i.e. in clinical or pre-clinical trials). The U.K. has 128 drugs compared to Denmark, its closest rival with only 28 in the pipeline. In terms of total number of firms, Germany has caught up and overtaken the U.K. in recent years (322 firms compared to 281). Yet German firms tend to be smaller, as indicated by the fact that Germany has only 15 listed firms

[1] At the end of 2001 pharmaceutical firms were trading at about 25 times earnings whereas Biotech firms traded at about 60 time earnings. A few years ago Biotech firms traded at a lower price-earnings multiple than pharmaceutical stocks more generally.
[2] *EuropaBio: Benchmarking the Competitiveness of Biotechnology in Europe*, June 1997
[3] For a more detailed historical analysis of the biotech industry see Sharp and Patel (1996)

compared to 48 in the U.K. Furthermore, these firms specialise less in pure drug discovery (as indicated by column (1) of Table 1).

Despite the strong U.K. position within Europe, the U.K. (and the EU) is still a long way behind the U.S., the world leader (see Table 2). Although there are more firms in the E.U. than in the U.S., they remain a lot smaller. The U.S. still dwarfs the E.U. in terms of total revenues, R&D and total employees. Nevertheless, growth has been faster in the EU than the US: in 2001 revenue growth was 38% in Europe and 10% in the US.

The sector has grown rapidly. In 1998 14,000 people were employed in Britain in the sector compared to only 6000 in 1994[4]. Despite rapid growth, the sector remains small relative to the pharmaceutical sector. For example, in 1997, the combined market capitalisation of the largest 10 European biotech companies was $5.7bn compared to $83bn for Glaxo-Wellcome *alone*[5].

The plan of this paper is as follows. In section 2 we sketch the structural features of the industry and in section 3 we explore these in greater economic detail. Section 4 then maps these features to the U.K. economy to see if they shed light on why the U.K. has been relatively successful in biotechnology. In section 5 we cast our gaze forward looking at the prospects for the industry globally and locally in light of the analytical framework developed. Finally section 6 offers some concluding comments. We argue that although there are significant risks, the world-wide growth prospects of the sector are good and there are reasons to expect that the U.K. will share in this growth. To ensure this, however, policies should bolster – or at the least, not undermine - the core competencies that gave us some degree of success in the first place: scientific strength in the universities and equity based financial markets.

2. Features of biotechnology industry

It is useful to begin with a brief description of some of the features of the biotechnology industry from an economic perspective. These features are "structural" in the sense that they are not specific to particular countries and raise questions for the subsequent economic analysis. We state them somewhat baldly and discuss them in more detail in the relevant sections.

1. **Science-based**. Biotechnology is a high R&D (research and development expenditure) intensity, like pharmaceuticals more generally. Whereas traditional pharmaceutical firms used small molecule chemistry, biotechnology firm develop medicines from biological products, such as proteins. Table 3 gives a stylised example of drug development, distinguishing between the different stages between drug discovery and sales. The whole process usually takes between 5-12 years and sometimes longer. The first stage is the research and discovery of the molecule, and the second stage is of laboratory screening and animal research in pre-clinical trials. The next stage is clinical trials on human volunteers (Phases I, II and III). If all three phases in the clinical trials are successful then the drug has

[4] Ernst and Young (1999)
[5] Ernst and Young (1998)

to be registered with the regulatory authorities in different countries and then launched. Biotechnology firms tend to specialise in the first two stages, although a few (mainly US) have attempted to integrate forward and take the drug through to market. Overall, investments projects are of a very long gestation, and highly uncertain: only a few products will actually be successful blockbuster drugs.

2. **Equity-based finance**. Venture capital will be the typical form of early finance followed by a flotation if the company is successful six years or so later. Equity holding by Venture capitalists and initial public offerings comes at a much earlier stage of a biotechnology firm's life than other start-ups.

3. **Low industrial concentration.** There are large numbers of small and medium sized enterprises (SMEs) in biotech. This is unusual relative to other high tech industries, even the technologically related pharmaceutical industry.

4. **Scientist Entrepreneurs.** Entrepreneurs are often scientists from universities

5. **Geographical clustering.** Biotech is an archetypal "agglomerated" industry where activity is heavily concentrated in certain geographical areas. In the USA there are major centres in California, Massachusetts and Maryland. Map 2 shows that this is also true on smaller scale in the U.K. with centres in Cambridge, Oxford, London and Central Scotland. An obvious feature of this geographical pattern is that these areas are clustered around major universities and research centres (see Map 1).

6. **Patents.** Even amongst R&D intensive industries Biotech and pharmaceuticals take out more than the average number of patents. This has exploded in recent years with the controversial attempts to patent genes.

The next section explores the economics behind these six structural features in greater detail.

3. Economic Issues in the Biotechnology Industry

3.1 Universities and the Science Base

The scientist entrepreneur is an important feature of the biotech industry. To understand their role it is important to distinguish two problematic features of the market for research: the appropriation problem and the asymmetric information. The *appropriation* problem derives from the fact that knowledge is partly non-excludable leading to an under-supply of R&D. Private agents will invest in R&D in primarily in order to receive a commercial return. If the value of an innovation is captured by other agents (e.g. other Biotech firms), this chills the initial incentive to invest. In the extreme case where knowledge is a pure public good and there are is no excludability of the knowledge created, the private sector will not invest at all in R&D. *Asymmetric information* arises because suppliers of knowledge may be able to form a better estimate of its value than potential buyers. This may also lead to an under-supply for knowledge relative to the social optimum.

In universities these problems are "solved" by a priority reward system. Academic scientists are rewarded through being first to make a scientific breakthrough. Thus they appropriate the benefits by being first and by sharing the knowledge around as quickly as possible.

Part of the knowledge created is tacit and hard to codify. University alliances are therefore a way of tapping into the tacit knowledge of scientists and researchers. There is an in inevitable conflict, however, between the desire of the scientist to get academic prestige from her discovery and the company's desire to keep knowledge secret (at least until there is a secure patent in place) to ensure appropriability of the innovation's value. In a large pharmaceutical company this problem is compounded by the fact that the scientist may get little direct monetary reward for his/her innovation. Stock options will help, but in a large company the actions of any one individual will have little direct influence on the share price.

In a small biotech company, there is still pressure for commercial secrecy, but there will be a closer link between the actions of the scientist-entrepreneur and the performance of the company. This reduces the problem of moral hazard and increases the incentives of the scientist to increase the productivity of her research. Clearly, however, the downside is that the scientist is bearing more risk compared to an established pharma company and even more so than in a university. Since the individual scientist is more risk averse than a large firm that can hedge its bets, the scientist will under-invest in risky R&D.

Sharp and Patel (1996) argue that the US lead the way in biotechnology start-ups 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 first-class facilities to pursue their scientific interests and a chance … to make themselves considerable wealth" (p.40). The strength of biotech around Oxford, Cambridge and London surely reflects the same phenomenon. Zucker et al (1997) have produced the most convincing work on the scientist-biotech link. Their econometric analysis suggests that the location of U.S. biotech start-ups is strongly influenced by the location of "star scientists" who tend to be located in high prestige research centres (e.g. Stanford in Silicon Valley and the Harvard/MIT cluster around Boston)[6].

3.2 Financing Innovation

There is a large literature on how financial markets may work poorly in supplying finance to high tech industries. Arrow (1962) focuses on "missing markets" for high-risk projects arising from the failure of the market for information. Firms will find it hard to diversify away all the risk arising from R&D projects and will therefore tend to shun expensive and high-risk projects. This is the rationale often given for some government sharing of risk in certain industries such as aerospace. Another implication is that there are likely to be financing constraints for high tech firms,

[6] One caveat over this support for encouraging academics towards the biotech sector comes from Dasgupta and David (1994). There may be a long-term problem for the open platform nature of science if researchers become too profit oriented.

especially small new entrants[7]. These problems may be worse in the U.K. were capital markets are often accused of being "short-termist". Thus, it is surprising that the industry has flourished more in the U.K. than in "long-termist" Germany! We discuss this paradox in the next section.

One partial solution to the problem of risk is through deepening the financial markets. Venture capitalists[8] will typically make their investments in stages, reserving the right to abandon unsuccessful projects. The venture capitalist takes a significant equity stake in the company alongside the entrepreneur. Both parties' compensations are linked to the entrepreneur's performance. The venture capitalist will usually also take a place on the board and provide monitoring and specialist advice. In Silicon Valley the growth of venture capitalism and high tech firms has been symbiotic. A similar phenomenon holds in biotech. For example, in "DNA-Alley" (Interstate 270 outside Washington D.C.) there are two major Venture Capital Funds that invest exclusively in genomics (*Genomics fund.com and Fbr Emerging Tech Partners*).

When the firm has been able to grow to a critical size it will be able to have an IPO (initial public offering). Outside owners of the firm will now participate in sharing the risks and the rewards for the firm's success. This will enable further growth to take place, although there will be some costs in the form of lowering the incentives for the initial entrepreneur whose stake in the company has been diluted.

Prior to the Venture Capital phase, seed corn finance is needed for all start-ups and this usually comes from private resources (e.g. rich individuals - "business angels"). Another important source of seed-corn finance for biotech is corporate venturing from larger pharmaceutical firms. This is relatively unusual in other U.K. industries, although more common in the US (e.g. Microsoft's role in the US software industry)

3.3 The puzzle of high R&D but small firm size

An important distinction between "Big Pharma" and biotech is the role of SMEs. Standard economic wisdom suggests that there are large economies of scale in R&D. This arises because of (a) the desire to diversify risk by holding a portfolio of several drugs "in the pipeline" (as discussed in the previous section), (b) the fixed and sunk costs involved in setting up a research program and (c) complementarities between R&D and other high fixed cost activities such as marketing[9]. The predominance of many small firms seems to demonstrate that the minimum efficient scale for an R&D lab can be quite small in the biotechnology sector. This is partly due to technological changes in the drug discovery process. Drug discovery based on traditional chemical techniques used largely a trial and error process where thousands of candidate compounds were synthesised. Biotechnology provides a more focused approach to drug design and therefore lowers the minimum efficient scale.

[7] There are several econometric studies pointing towards the importance of financial constraints for high tech firms. For the USA see Himmelberg and Peterson (1994) and for the U.K. see Bond, Harhoff and Van Reenen (1999)

[8] See Kortum and Lerner (2000) for econometric evidence for the importance of venture capital in innovation.

[9] See Cohen and Levin (1989) for a more extensive discussion of firm size and innovation.

This reduction of entry barriers may, however, be temporary. New drug discovery techniques are still young - genomics (enabling target selection), combinatorial chemistry (making possible matching compounds) and high throughput screening (to make the match). The latter requires large capital investment and if this became the favoured discovery method then once again the advantages of larger firms to attain efficient scale would arise. In this case the biotech companies may emerge as small very specialised upstream technology suppliers of such things as genetic databases.

In general, the advantages of SMEs are usually seen to be to their higher rates of innovation, R&D productivity and their effect of shaking up incumbents. These facts are disputed[10]. It may be the entry of new firms rather than the existence of small firms that disciplines larger firms. In the U.K. 85% of all R&D is performed by businesses with over 400 employees. From a policy point of view, the disadvantages of SMEs are that their productivity and wages tend to be lower and they have higher levels of exit[11].

There has been a whole raft of policies favourable towards SMEs in recent years and we analyse these in more detail below (section 5).

3.4 Economics of contracts

One of the key developments in modern economics is the analysis of contracts. Aghion and Tirole (1994) formally model the Principal-agent problems arising from the need to share the profits from innovation between the scientist (or inventor) and the financier. The basic trade-off is familiar to those in the biotechnology industry. Assigning control rights over the profits from a successful drug discovery to the small firm/scientist by a larger firm/financial institution may be desirable from an incentives perspective. This is because the scientist will have high incentives to search efficiently for the invention if she is getting a large share of the potential rewards (low "moral hazard"). But the small firm/scientist may not be able to afford the financing on its own due to the capital market problems discussed in sub-section 3.2 above, so an inefficient distribution of control rights may occur. Lerner and Tsai (2000) analyse the performance of 200 agreements entered into by biotechnology firms between 1980 and 1995 and find strong evidence that financing availability does matter. Furthermore, consistent with the Aghion-Tirole theory, agreements signed during periods with little external equity financing that assign the bulk of the control to the corporate partner are significantly less successful than other alliances[12].

3.5 Clusters and Knowledge Spillovers

Apart from the problems of financial market failures discussed above, the main economic justification for intervening in R&D markets is the existence of

[10] Henderson and Cockburn (1996), for example, found that although larger pharmaceutical firms did not have economies of scale advantages in the R&D productivity, they *did* have economies of scope advantages.
[11] See Chennells, Dilnot and Emerson (2000) for a longer discussion.
[12] These agreements are also disproportionately likely to be renegotiated if financial market conditions improve

externalities[13] from knowledge. Innovators do not *appropriate* all the benefits of their innovations so therefore they will invest in a sub-optimal amount of research. There is much empirical evidence supporting the existence of spillovers[14] and this gives another rationale for government subsidies to R&D.

We know of no direct quantitative studies of the extent of spillovers in the biotechnology industry. It is likely that spillovers may be less prevalent in this sector because the patent system operates relatively well in protecting the intellectual property of successful innovators[15]. Despite this, Cockburn and Henderson (1996) do report some evidence of spillovers in pharmaceuticals and there is no econometric evidence that there are significantly less spillovers in drugs than elsewhere.

Clusters are "geographic concentrations of interconnected companies, specialised suppliers, service providers, firms in related industries and associated institutions (for example, universities, standards agencies, and trade associations) in particular fields that compete but also co-operate"[16]. Clustering or "agglomeration" has occurred throughout history as certain areas have comparative advantage through natural resources (e.g. fish processing near harbours). What is more surprising is the clustering which can occur even in high tech industries where one would think distance is no longer so important thanks to telecommunications advances.

New economic geography has stressed the importance of clusters in generating economic growth and innovation (Krugman, 1998). This arises because of various externalities associated with proximity such as transmission of tacit knowledge based on face-to-face interaction or pools of specialised inputs (such as skilled labour). In this view there are geographically localised spillovers[17].

Biotech certainly seems like an agglomerated industry. "DNA Alley" on Interstate 270 in Maryland has the world's largest collection of genome firms – Celera Genomics, Gene Logic, Human Genome Sciences and many start-ups. On a smaller scale in the U.K., Maps 1 and 2 show concentrations of economic activity in Cambridge, Oxford, London and Central Scotland. One of the obvious features of the geographical pattern is that the centres are clustered around major universities and existing pharmaceutical R&D labs.

Once R&D has reached a certain level it may be easier to absorb spillovers from other regions and countries. Under this argument R&D has 'two faces'. In addition to the standard view that R&D stimulates innovation, it also has another function that is to increase the diffusion of new ideas. There is considerable evidence that R&D does have this second, `absorptive capacity' feature[18]. Although there are no studies we

[13] Externalities are benefits from goods that spill over to agents who have not purchased those goods. For example, pollution has negative externalities.
[14] See Griliches (1998) for example
[15] The patent system works better when knowledge can be codified (e.g. the formula of a molecule). In general patents are only one of the means of appropriating knowledge and other mechanisms such as secrecy and lead-time may be more important (See Cohen and Levin, 1989).
[16] Porter (1990)
[17] Analyses of the pattern of patent citations do suggest that "distance matters" in the sense that patents are much more likely to cite other patents of inventors who are geographically "close" to them rather than geographically "distant".
[18] For a recent econometric example see Redding, Griffith and Van Reenen (2000)

know of which specifically relate to the biotech industry, it seems plausible that some part of the R&D spent on biology research has this feature (especially in universities).

3.6 Intellectual Property Rights

Although knowledge spillovers are important, there are various ways that firms can appropriate private value from their innovations. In principle, the patent system is the vehicle by which inventors are given incentives to invest in R&D but in practice patents only offer weak protection in most industries. In software, for example, it is still controversial whether anything can be effectively patented (software firms rely on copyright, secrecy, lead-times, holding on to key employees, etc). In biotech, by contrast successful R&D can be patented to a much more effective degree. A molecule can be specified precisely and patent protection is clearer.

Where things become more intricate is in the area of government regulation over drug compounds. The final revenues achieved for a successful drug is a complex function of negotiations and regulations in many jurisdictions. These regulations pertain not only to the price but also when the compound can be launched. Obviously launch date is affected by the need to be granted approval on safety grounds. But failure to achieve an adequate re-imbursement price from the government will also mean that launches are delayed. These delays are low in the US, but very high in some countries that push for low prices, such as France. This form of regulation is not a formal abrogation of property rights, but it does clearly reduce the value of R&D and will be expected to lower R&D incentives.

In **summary,** the biotechnology industry operates in markets far more complex than those of textbook economic analysis. The critical inputs are very skilled employees who have complicated incentives, the output is knowledge that benefits other firms, there are a large number of inevitable financing problems and profits are heavily influences by the pattern of government regulation of intellectual property and healthcare.

4. Why has the U.K. been successful in biotechnology?

4.1 A U.K. success story?

It is well known that aggregate output per hour in lower in the U.K. relative to our major competitors. This has been recently highlighted by HM Treasury (1999) in their "Productivity Challenge" and by McKinsey Global Institute (1998). One of the reasons for this may be a lower level of innovative activity. It is certainly true that there is a significant gap in total factor productivity between Britain and the US, but this is not so obvious for other European countries. Much of Britain's productivity gap with Germany, for example is explained by the fact that Britain invests less in physical and human capital. One area were Britain has been slipping behind is in

R&D intensity[19]. Analysis of this gap suggests that British R&D is not lower simply because we have fewer high tech industries and firms[20]. Even our high tech industries and firms appear to invest less in R&D than their major competitors.

Given the weakness of the U.K. in high tech areas, the reasons for the U.K.'s relative strength in biotech are obviously an important issue. The observation that the pharmaceutical sector is another very successful high-tech industry is pertinent[21]. Pharmaceuticals are characterised several features common to biotech:

- Operating in the worldwide product market for medicines
- High R&D intensity
- A close linkage of industry with bio-medical research in universities
- A low reliance on engineering skills compared to other high tech areas of manufacturing

4.2 A strong U.K. science base

So one hypothesis is that the U.K. is strong in this sector due to the "core competencies" of a strong U.K. science base, particularly in life sciences. This would underlay success in both pharmaceuticals and biotechnology. These competencies are historically specific and are difficult to replicate, being tied in a "national innovation system". It is well known the U.K. produces 8% of the world's scientific papers and 9% of all cited scientific articles with only 1% of the world's population. This rivals the U.S. and outstrips France and Germany. Britain is also second only to the U.S. in winning science prizes.

Furthermore, if one examines the pattern of specialisation of science (as revealed by citations of scientific papers), Britain is particularly strong in the life sciences relative to physics, engineering and maths. This is illustrated in Table 4 that shows the U.K. particularly strong in citations for scientific papers relating to the spheres of clinical medicine, biology and bio-medical research.

There are two objections to this view. One objection to this core competency view is that Britain is also strong (in absolute terms) physics, but has much weaker presence in physics-based industries. One reason for this could be the poorer quality of engineers and skilled crafts people upon which these industries are more reliant[22]. A more compelling objection is that the strength of British pharmaceuticals could have come from entirely different historical reasons. For example, the stable demand from the NHS, subsidised and high quality clinical trials, and a drug price regulation system that was more favourable to R&D[23] may have been, at least in the past, beneficial to the growth of the pharmaceutical sector.

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[19] Van Reenen, J. (1997)
[20] Bond, Harhoff and Van Reenen (1999)
[21] The U.K. hosts three (now two) of the most important players in the world: Glaxo-Wellcome, Smithkline-Beecham, Astra-Zeneca).
[22] See the extensive set of matched plant studies by the National Institute for Economic and Social Research.
[23] See Bloom and Van Reenen (1998) for a discussion of the Pharmaceutical Price Regulation Scheme (PPRS). The PPRS is voluntary, stable and has resulted in higher drugs prices in the U.K. than in other EU countries such as France, Spain, Portugal and Greece.

Even if the causes of the strength of the British pharmaceutical industry were historical, the very presence of large drugs firms based in the U.K. has positive advantages. Pharmaceutical firms support Biotech through a number of channels – corporate venturing for early stage finance, alliances as the firm grows bigger and more recently, the possibility of buying the biotech firm outright[24]. The presence of much pharmaceutical R&D in the larger firms also creates a healthy labour market that fosters the spread of ideas (this is one of the "clustering" mechanisms).

So, even if one is sceptical about "core competencies" the competitive advantages of the U.K. in Biotech are not completely fragile. Nevertheless, so long as Britain maintains a strong presence in pharmaceuticals, this will be a supporting factor to the biotech industry.

4.3 Deep and liquid equity markets in the U.K.

Over the years there have been numerous complaints regarding the U.K.'s financial systems in providing finance for innovation (especially compared to Germany). The City is seen as "short-termist" relative to Continental Europe and Japan and demands unrealistically high hurdle rates. This, in 1986 Nigel Lawson, U.K. Chancellor of the Exchequer remarked: "The big institutional investors nowadays increasingly react to short-term pressure on investment performance….they are unwilling to countenance long-term investment or sufficient expenditure on R&D".

Given the nature of the biotech industry, however, the U.K. system does have many advantages compared to Continental Europe. Biotech R&D is more uncertain and radical than the more incremental R&D in such industries as engineering that the German financial system is so good at supporting. Biotechnology is more suited to equity-based finance than bank-based finance and the U.K. equity markets have advantages in this regard. U.K. capital markets are deep and liquid and well integrated into global markets with London being one of the top three financial centres in the world. Equity markets provide an exit route for early stage investors in biotech firms and are therefore valuable. The venture capital sector is the largest in Europe so this should also give the U.K. a significant advantage. A caveat to this is little U.K. venture capital goes into early-stage companies (17% compared to nearly 30% in Germany and the US). So there is still an "equity gap" for very early stage finance in the U.K. that remains a problem.

4.4 The U.K. labour market

In the U.S. high-level managers are frequently given share options to encourage them to align their interests with those of the firm. They have a lower base salary but receive a higher average salary (risk is transferred). They also have better incentives to work hard for the firms because they receive a share of its value. These "high powered incentives" are more common in the U.K. than in other parts of Europe.

[24] For example, Bristol Myers recently made a $1bn investment in ImClone, and agreed a further $1bn to co-promote the company's new cancer compound, Erbitux. The deal is currently in trouble as Erbitux failed to win its expected fast track approval from the FDA.

More generally, the U.K. labour market is less regulated than other parts of the EU so it is easier to recruit and retain the talented individuals that the biotech sector relies on. It is easier for scientists to spend time in the private sector than in other European countries. Lower marginal rates of taxation on high earning individuals in the U.K. make it easier to recruit and retain talent.

There is a perception that cultural attitudes towards risk are an important factor in accounting for biotech success. On this view, there is a more "risk-averse" culture in Britain than in the U.S., and, in turn a more risk-averse culture in Continental Europe than in Britain. Although the pattern of start-up firms corroborates this intuition to some extent, it is difficult to know whether these differences are actually due to different patterns of regulation rather than individual preferences. For example, the greater degree of red tape involved in starting up a new company and the more stringent bankruptcy laws may be more important and these regulations are open to government intervention.

In summary, the U.K. scores well on having a good environment for biotechnology on the key features we identified in the previous section. A strong science base and pharmaceutical industry are probably the major factors with capital and labour markets playing a subsidiary role. Two comments need to be made, however. First, we have, however, been implicitly comparing the U.K. to the rest of Europe. Relative to the US, the U.K. is less favourable on all these factors. Second, there is the issue of how stable this position will be in the future. We turn to this in the next section.

5. Biotechnology: Prospects for the future

5.1 Global Prospects

Healthy Growth?

In the drugs biotech sector, the projections are for rapid growth for the sector as a whole in the world. This growth is driven by health expenditure, which has consistently outstripped the growth of national income (drugs are about 10% of total health care expenditure). Health care costs are rising for a variety of reasons. First, as countries grow richer they tend to spend a larger proportion of their incomes on healthcare (it is a superior good, in the economics jargon, like education). Second, the population of the richer countries is ageing and older people have higher demand for medical products.

Compared to the rest of the pharmaceutical industry, biotech also appears very healthy. For example, there are an estimated 1200 drugs in development, 155 of which are in the late stages of clinical trials. This was double the number of 5 years ago. Large pharmaceutical firms have a low pipeline by historical standards with many patents up for expiry over the next year or two[25].

[25] MSD, the largest pharma firm, as well as Bristol Myers have warned that earnings are likely to be flat in 2003. See "Growing Together" Financial Times, 19.12.01.

One caveat to this optimistic picture for biotech is that the regulatory environment of drugs may become more hostile to the pharmaceutical sector as a whole. The US accounts for 40% of the world drugs market and supports higher prices than Europe or Japan. Yet pressure from Health Management Organisations, the Federal and State governments is pushing prices down[26]. In Europe, for example, the European Commission's enforcement of free movement of goods between Member States has meant a large growth in parallel trade pushing down drug price in wealthier countries (like Britain with has higher prices) closer to those in poorer countries (like Greece which has tough price regulation). As government and health insurers seek to contain healthcare and drugs costs there may come increased pressure on pharmaceutical companies to reduce prices and this will have a clear knock-on effect to the biotech sector.

In the food biotech sector the main problems are with public acceptance. EU consumers in particular have become very hostile to GM crops. Despite this the growing population in the world, especially in less developed countries will lead to a continued demand for increasing agricultural productivity.

Trade and Intellectual property: problems ahead?

Like drug regulation, these challenges are essentially global issues. Although the World Trade Organization (WTO) is in some disarray it is still the main locus for keeping the rules of the game in trade. There is increased pressure for compulsory licensing in Developing countries (e.g. AIDS drugs) that could have a negative effect on the incentives to develop certain drug types if this became widespread.

There is ongoing uncertainty over the ability to enforce patent rights over genes. These have been applied for in large numbers and many have been granted, but it is only in litigation that the enforceability of these patent rights will be seen. If they are enforceable then this will give a further incentive to the global growth of the industry, although the ethical implications could further alienate public opinion.

The Impact of the Human Genome Project

In June 2000 President Clinton and Prime Minister Blair proudly (and prematurely) announced the complete mapping of the human genetic code. In February 2001 Celera Genomics (a private company) and the Human Genome Project (a publicly funded research project) simultaneously published their results on the web sites of two leading scientific journals – *Science* and *Nature* respectively.

The huge amount of information revealed in this project will enable a faster rate of drug discovery and undoubtedly be a stimulus to the development of the biotech industry. Furthermore, there are many implications from the fact that a privately funded company (Celera's budget was only $300m compared to HGP's $3bn) almost beat a publicly funded organisation to sequencing the genome and undoubtedly spurred HGP into finishing the job much more quickly. This might cause more government R&D funds to be given directly on the private sector rather than through

[26] Florida and Michigan states both recently passed laws attempting to wrest major cuts in drug prices.

organisations such as the National Institute of Health. This would probably give the US Biotech sector a further boost relative to Europe.

Increasing industrial concentration?

The surprising number of small firms in biotech has been a recurring theme of this paper. But there has been some recent consolidation. In December 2001 there were major deals between Amgen and Immunex, Millenium and Cor Therapeutics and MedImmune and Aviron. The Amgen/Immunex deal created a group valued at $75bn – this is starting to approach the size of "Big Pharma". This may be temporary due to the huge excitement generated by the sequencing of the human genome (and the resulting flood of money that came in to the sector in 2000-2001) or it may signal a maturing of the industry where the need to diversify risk has overcome the advantages of small scale in generating high powered incentives. Analysts sometime refer to the "biopharmaceutical" sector to distinguish such integrated firms from the more R&D intensive loss making smaller biotech firms.

5.2 Local issues: Prospects for the U.K.

Public attitudes to Biotechnology

Overall, our assessment in the last section was that the U.K. biotech industry is still strong relative to other emerging high tech sectors and relative to the rest of the EU.

Perhaps the main problem facing the industry is the public backlash against genetically modified food (GM) and animal testing. The GM crops scare (which closely followed the BSE scandal) raises important issue in terms of managing the risks of environmental damage. The attacks by animal rights activists on Huntington Life Sciences might be lead by a small minority but the inability of the authorities to deal effectively with the attacks and the perception that there is widespread antipathy to animal testing has far reaching implications.

Most observers would argue that the public backlash against GM reveals a very poor perception of risk and low understanding of science. For example, destroying testing centres over the effects of GM crops prevents us even gaining a notion of what might be the true relevant risks. There is a real need to understand how these panics can be managed and how the public perception of science can be improved. Governments and companies are belatedly giving better information about the industry and making a greater attempt to engage with critics. But this should have been done earlier, and there is a serious danger of "knee-jerk" regulation all over the OECD.

Public attitudes in the rest of Europe may not be significantly less hostile. France seems more relaxed on animal testing, but more virulently against GM crops. So the issue may be that the EU loses out to the US. A counter-example is sometimes given of stem-cell research were the regulations on human embryo research are stricter in

the US than in the U.K. But the opposite is true of transplants from animals to people ("xeno-transplantation")[27].

Pharmaceutical Collaboration

In 1998 pharmaceutical companies signed collaborations or licensing deals with biotech firms worth $4bn. By 2000 this had risen to $7bn. There is currently a wave of consolidation in the drugs industry. A Glaxo-Smithkline is a huge player having some 10% of the global market. The company uses some of its funds to buy up biotech firms and certainly will be a major influence in the development of the sector, especially given the multinational's British connections. The merger appears to have gone more smoothly than many observers predicted but it may still lead to a large movement of R&D and activity to the U.S. headquarters. This would certainly mean a waning of support for the U.K. biotech sector.

Competition from Germany and other EU countries

Germany has rapidly growing Biotech sector partially due to extensive aid from the state governments (there are now more German biotech firms than British firms). This is not necessarily a threat to the U.K. If there are large knowledge spillovers then this could be a benefit. Indeed, increased competition could stimulate actually productivity in the U.K. There is also some evidence that German biotech firms are specialising in supplying platform technologies rather than attempting drug discovery directly themselves. The low numbers of German drugs "in the pipeline" would be evidence in favour of this hypothesis. Nevertheless, the success of German biotech does suggest that the "first mover" advantages for the U.K. may be less important than usually imagined.

This also raises the question of how many clusters can be supported within the E.U.? France recently announced "Plan Biotech 2002" which seeks $700m of support for the French Biotech industry[28]. If this passes the state aid rules, it signals that there is a wasteful and uncoordinated policy competition to attract Biotech firms *within* the E.U. As with models of tax competition, this is likely to lead to a very inefficient distribution of Biotech activity.

Regulatory reform of pharmaceutical sector

Pressure to cut drugs bills may mean falling returns for drugs sector in many countries. British regulation is getting tougher with NICE[29] and reformed PPRS[30]. But

[27] For example, ReNeuron, Britain's leading stem-cell company is planning to conduct its trials over a treatment for Huntingdon's disease in the US because of regulatory problems in the U.K. The trials involve injecting brain cells from mice into humans.

[28] The "State Aid and Risk Capital" rules allow state aid for small enterprises and innovation under certain conditions. The $60m for seed-corn funding probably passes this test, but the $90m loan guarantees should not. Given that 70-100% of the cash is informally earmarked for French Biotech, it would seem to be a classic state aid device (*Wall Street Journal*, 3.12.01).

[29] The National Institute for Clinical Medicine regulates the drugs that are available on the NHS using a cost-utility analysis.

[30] The Pharmaceutical Prices Regulation Scheme sets maximum profits levels that can be earned by companies selling drugs to the NHS.

what matters is not really U.K. regulation but changing regulation in world as a whole (US, EU and Japan). Of course U.K. has some influence on these developments, especially within the EU, but this is not huge. Pharmaceutical companies tend to indulge in "sabre-rattling" at any changes (e.g. over NICE) but the main effect is on NHS costs rather than strategy in pharmaceuticals, let alone biotech.

Recent U.K. Policies

There are several policies in the U.K. that are very biotech friendly.

- The R&D tax credit for small firms in being introduced in April 2000. Although small in aggregate (£100m), it is very generous to smaller firms. Although the tax credit would not seem useful to firms without taxable profits, the planned credit is partly refundable. In other words, cash grants can be claimed against R&D spending, making it valuable for biotech companies

- Proposed streamlining of the planning system[31]. This could make it easier for clusters to develop in areas where it is difficult to expand due to land constraints (e.g. Cambridge science park)

- Corporate venturing. The government is making it cheaper for large companies to invest in smaller companies

- Small business corporate tax rate reduction

- The Enterprise Management Incentive Scheme (EMIS) has meant tax privileged share options for key employees in small firms.

- Significant government subsidies have gone into the MIT/Cambridge link-up that will give a boost to the `cluster' around Cambridge.

- Small business services and business LINK have streamlined support for biotech.

These should help small high tech businesses in general and biotech in particular, but only careful evaluation will be able to tell us by how much. The sheer plethora of initiatives could undermine their effectiveness. It is imperative that there are proper quantitative evaluations of these schemes and that resources are set aside to enable policy makers to improve or abandon the programs in the light of evidence.

On the other hand there are also dangers to small firms in general arising from some of the increased regulatory burdens as the government has introduced new labour market policies (Working Families Tax Credit, minimum wage, EU Working hours directive, Stakeholder Pensions, etc). It is unlikely that these will have a large significant effect on Biotech, but again their impact needs to be monitored.

[31] The restrictive planning regulations in the U.K. were identified by McKinsey Global Institute (1998) as a major reason for the U.K.-US productivity gap.

Incentives in universities

Encouraging universities to commercialise more of their research is a priority of public policy. But there is a genuine concern that encouraging the protecting of intellectual property in universities could undermine the "open science" that gives the moral incentives for academics to do pioneering research. University life thrives on open discourse and the lively exchange of ideas and there is a danger of undermining this through secrecy. Additionally, blue skies curiosity-driven research may be replaced by near market R&D. Basic research has higher spillovers than near market research and is least likely to be supplied outside universities. These worries were well articulated by David and Dasgupta (1994). Nevertheless, MIT appears to be able to combine world class basic R&D with a thriving entrepreneurial culture suggesting that the trick can be pulled off.

Relative to Europe (but not to the U.S.) Britain has had a more flexible attitude to university staff working in the private sector[32]. For example, Cambridge University spun-out two companies in 1999 alone: Astex ($38m funding) and Cyclacel ($66m funding)[33]. The increased administrative burdens on academics and their deteriorating labour market position may be undermining this. Furthermore, Europe is catching up. Both France and Germany have recently passed laws allowing university researchers to take up to six years leave to start a company with guarantees of jobs and tenure on return.

In summary the prospects for the growth of the global biotechnology industry are strong. Supply side factors such as breakthroughs in basic science such as the HGP and demand side factors such as escalating healthcare demand are the principle drivers of growth. The U.K.'s position is more precarious. Although there is no sign of the U.K.'s advantages in basic science disappearing, public hostility has become more of an issue. Germany is now a serious competitor within the EU and relocation to the US is an ever-present danger.

6. Conclusions

The biotechnology sector is a small, but rapidly growing sector in the world economy. There is huge potential for growth as the size of the health care sector as a whole gets bigger. The U.K. is well placed to take advantage of this as it already has the strongest presence in the EU, even though it is well behind the US. We would stress the following three points emphasised in this paper.

First, there are significant risks to the growth of the worldwide industry from public hostility. This is most clear in the food-related part of biotech that has suffered due to

[32] For example, the European Molecular Biology Lab (EMBL) is a leading EU funded centre in Heidelberg. Although spin-offs are encouraged (e.g. Cellzome in 2000) they have to be approved by its board consisting of scientists from each of the 16 nations. "The board worries that profit motives will make EMBL researchers like their US counterparts" ("Out of the Lab" by Stephan Herrara, *Red Herring*, December 2001).

[33] Astex specialises in X-ray crystallography and Cyclcel specialises in small molecule, cancer stopping drugs.

the backlash against GM crops and hormone implanted beef. The drugs-related part of the industry is in better shape and some significant breakthroughs could enhance its public image. Nevertheless, engaging in more of a dialogue with the public over fears of biotechnology is extremely important. Social science research has a lot to say about the perception and managing of risk, and this is an area where social and scientific research needs to come together.

Second, what extra support (if any) is needed in terms of U.K. government policy? We have argued that there are already many support mechanisms in place and coming on-line - R&D tax credits, tax breaks for small firms, the small business service, share option breaks (EMIS), increasing university linkages (e.g. Cambridge-MIT), etc. The most important thing is to monitor and properly evaluate how well these new programs deliver added value both for biotech and elsewhere. Perhaps the main priority is fostering the capacity of U.K. life sciences through strong support for basic research and supporting those scientists who become involved in the biotech sector.

Thirdly, can we replicate the success of the industry in other areas? Britain is not traditionally strong in high tech industries, so can we learn lessons from the biotech story? We emphasised the close links between the pharmaceutical industry and biotech. Having a strong pharmaceutical sector has helped British biotech firms tremendously. Elite science in the U.K. is world-class in bio-medical research and the clusters of activity that have developed reflect the presence of world-class universities. Developed capital markets are also a factor. This suggests that other emerging university-linked industries with need for risk capital can also succeed in the U.K.

Finally, it does seem that Europe as a whole is catching up with the U.S. in biotechnology. There are clear advantages of market scale – e.g. in the market for finance and for labour (although the product market is global) – so greater integration of these markets at a European level is important. Excessive and uncoordinated policy interventions breeding competition within Europe for Biotech firms is a real danger. The Commission needs to be scrupulous that support for innovation does not become a new method of "beggar-my neighbour" policies over the location of Biotech firms within the EU.

Bibliography

Aghion, P. and Tirole, J. (1994) The management of innovation **Quarterly Journal of Economics**, 109, 1185-1209

Arrow, K. (1962) Economic Welfare and the allocation of resources for invention in Nelson, R. **The Rate and Direction of inventive activity**, Princeton University Press, Princeton NJ

Bloom, N. and Van Reenen, J. (1998) Pharmaceutical Regulation in the U.K.: Where do we go from here? **Fiscal Studies** 19, 4, 347-374

Bond, S., Harhoff, D. and Van Reenen, J. (1999) Investment, R&D and Financial Constraints in Britain and Germany , Institute for Fiscal Studies Working Paper 99/5 www.ifs.org.U.K./workingpapers/bhvr26.pdf,

Cap Gemini Ernst and Young (2001) **The 15th Biotechnology Industry Annual Report,** Cap Gemini Ernst and Young International, London

Chennells, L., Dilnot, A. and Emerson, K. (2000) **The IFS Green Budget**, London: IFS

Cohen W. and Levin, D. (1989) Empirical studies of innovative activity in R. Schmalensee and Willig (eds) **Handbook of Industrial Organisation,** Amsterdam: Kluwer

Dasgupta, P. and David , P. (1994) Towards a new economics of science **Research Policy** 23(5), 487-521

DTI (1999) **Biotechnology Clusters** A Report lead by Lord Sainsbury, August available at www.dti.gov.U.K./biotechclusters/

Ernst and Young International Limited (1998a) **European Life Sciences 98 - Continental Shift. The fifth annual report on the European life sciences industry**, April 1998, Ernst and Young International, London

Ernst and Young LLP(1998b) **The 12th Biotechnology Industry Annual Report** - *New Direction 98*, Ernst and Young International, London

ESRC (1997) **Uncertain World: genetically modified organisms, food and public attitudes in Britain** Global Environmental Change Programme, London

Gambardella, A. (1995*)* **Science and Innovation: The US Pharmaceutical industry**, Cambridge University Press

Griffith, R., Redding, S. and Van Reenen, J. (2000) Mapping the Two Faces of R&D: Productivity Growth in a panel of OECD industries CEPR Discussion Paper 2457 **www.ifs.org.U.K./workingpapers/wp0002.pdf**

Griliches, Z. (1998) **R&D and Productivity: The econometric evidence**, Chicago: Chicago University Press

Henderson, R. and Cockburn, I. (1996) Scale, Scope and Spillovers: the Determinants of Research in Drug Productivity **Rand Journal of Economics**, 27(1), 32-57

Himmelberg, C. and Peterson, B. (1994) R&D and internal finance: a panel data study of small firms in high tech industries **Review of Economics and Statistics**, 76(1), 38-51

HM Treasury (1999) **Pre Budget Report**, HMSO: London

Kortum, S. and Lerner, J. (2000) Assessing the Contribution of Venture Capital to Innovation **Rand Journal of Economics**, 31(4) 674-692

Krugman, P. (1998) **Peddling Prosperity**, Cambridge: MIT Press

Lerner, J. and Tsai, A. (2000) Do Equity Financing Cycles matter? Evidence from Biotechnology Alliances National Bureau of Economic Research Working Paper No. 7464

McKinsey Global Institute (1998) **Productivity in the United Kingdom,** London: McKinsey&co

Porter, M. (1990) **The competitive advantage of nations**, Cambridge: Harvard University Press

Sharp, M. and Patel, P. (1996) **Europe s Pharmaceutical Industry: an innovation profile** draft prepared for DGXIII, April

Simpson, H. (1998) **Biotechnology and the economics of discovery in the pharmaceutical industry,** London: Office of Health Economics

Van Reenen, J. (1997) Why Has Britain had slower R&D growth? **Research Policy** 26, 493-507

Zucker,L., Darby, M., Brewer, B. (1997) Intellectual Human Capital and the Birth of US Biotechnology enterprises **American Economic Review**, September, 87(4)

Table 1 The Position for European Biotech firms, 2000

	Drugs in Pipeline	Number of Private Biotech firms	Number of Public Biotech Firms
United Kingdom	128	223	48
Denmark	28	61	5
Ireland	23	29	2
Switzerland	20	116	2
France	19	173	8
Sweden	18	158	9
Italy	7	50	2
Germany	6	317	15
Finland	5	81	1
Netherlands	5	77	4
Norway	5	29	3

Source: Cap Gemini Ernst and Young (2001)

Table 2: Growth of Biotechnology Sector in Europe and the US

	1995		1997		2000	
	EU	**US**	**EU**	**US**	**EU**	**US**
Revenues ($bn)	N/a	N/a	N/a	N/a	8	22
Number of firms	28	260	61	317	1615	1040
Employees	2958	60000	8418	94000	N/a	N/a
R&D (ECUm)	158	3440	534	5145	N/a	N/a

Source: 1995 and 1997 data from Ernst and Young (1998), 2000 data from Ernst and Young (2001). There are some inconsistencies over the 1997-2000 period so changes should be interpreted with caution.

Table 3 The Drug Discovery Process		
Stage 1	Research concept and discovery	1-2 years. Medical target identified and active substance synthesised on laboratory scale
Stage 2	Pre-clinical trials	2-3 years. Lab screening and animal research on new drugs
Stage 3	Clinical trials	3-4 years. Human volunteers *Phase I.* 10-50 healthy volunteers to assess safety *Phase II.* 100-300 patients suffering from disease to test efficacy, dosage and side effects) *Phase III.* 1000-3000 patients including testing against a placebo or existing therapies.
Stage 4	Registration with regulatory authorities and launch	2-3 years. Upon approval large-scale manufacture, distribution and marketing. Post-marketing clinical studies and surveillance

Table 4 Specialisation Profiles in Science, 1981-86, Based on Citations

	U.K.	France	Germany	US	Japan
Clinical medicine	1.17	0.78	0.68	1.07	0.72
Biology	1.25	0.64	0.81	0.89	0.95
Chemistry	0.89	1.34	1.58	0.67	1.92
Physics	0.70	1.53	1.55	0.86	1.19
Earth and Space	0.93	0.87	0.71	1.19	0.33
Engineering/technology	0.65	0.82	1.18	0.94	1.86
Mathematics	0.90	1.39	1.16	0.97	0.67

Source: CNR-ISRDS