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The myth of the biotech revolution: An assessment of technological, clinical and organisational change

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Abstract

This paper argues that despite being widely promoted by academics and consultants, the empirical evidence does not support the existence of a biotech revolution. Nor does the data support the widely held expectations that biotechnology is having a revolutionary impact on healthcare or economic development. The revolutionary model is therefore a misleading basis for policy making as it over-estimates the speed and extent of any changes in productivity or the quality of therapeutics. Instead, the evidence suggests biotechnology is following a well-established incremental pattern of technological change and 'creative accumulation' that builds upon, rather than disrupts, previous drug development heuristics.

Keywords: Biotechnology; Revolution; Innovation; Policy

1. Introduction

The aim of this paper is to inform policy by extending previous critiques of the revolutionary model of technological change currently used to understand medicinal biotechnology (e.g. Arundel and Mintzes, 2004; Nightingale and Martin, 2004; Hopkins et al., 2006a).[1] It suggests that a more appropriate framework for policymaking is needed that is more realistic about the incremental nature of major technological changes.

Such a rethink is required because academics, policy makers, consultants and industrialists have promoted a model of technological change in which drug innovation is being revolutionised by biotechnology.[2] The diffusion of this revolutionary model into public thinking has generated widespread, but also very diverse, expectations of biotechnology's impact. These include expectations that biotechnology is transforming pharmaceutical innovation by increasing the number and the effectiveness of

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[1] Biotechnology is defined in this paper, following OTA (1991), as the application of biological organisms, systems and processes to manufacture products or provide services. More specifically, the paper focuses on modern biotechnology i.e. the application of genetic engineering and monoclonal antibodies, e.g., recombinant production of proteins in culture (e.g., insulin) and generation of monoclonal antibodies from mammalian cell hybridomas (e.g., rituxan for treating lymphona).

[2] See for example, Kevles and Hood (1992), OECD (1997, 1998, 2004b), Bell (2003), BIGT (2003), European Commission (2002), and the review at http://www.bio.org/er/biotechtools.asp.

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drugs and diagnostics, and expectations that it is shifting traditional reactive medicine towards more preventative interventions involving increasingly personalised therapies (Bell, 1998; Collins et al., 1998; Lenaghan, 1998; Lindpaintner, 2002; Department of Health, 2003). The biotech revolution is also supposed to be generating significant wealth by improving the productivity of pharmaceutical innovation, and driving a related shift in industrial structure as networks of biotechnology firms, often agglomerated in regional clusters, displace the large drug companies that have previously dominated the sector (DTI, 1999; Enriquez and Goldberg, 2000; Tollman et al., 2001).

These expectations have led to annual investments of tens of billions of dollars of private investment in biotechnology (Ernst and Young, 2004; Gassmann et al., 2004) together with substantial public investment as government agencies at the regional, national and supranational levels attempt to establish a foothold in what is seen as a key part of the Knowledge Economy (DTI, 2001; Dohse, 2000; Giesecke, 2000; Senker et al., 2000). As a result, all OECD members' national and regional development plans and science and technology policies involve biotechnology.[3]

These initiatives take a number of forms, including dedicated research funding programmes, fostering knowledge/technology transfer and networking between university researchers and industry, financial and technical support for start-up firms and regional clusters, R&D tax credits, lower regulatory hurdles, a focus on funding directly applicable research, and changes to the relationship between health services and industry to allow easier clinical trials and earlier access to advanced drugs (DTI, 2001; Senker et al., 2000; Dohse, 2000; Giesecke, 2000; BIGT, 2003).

The questions this paper addresses are: Is there evidence for the revolutionary model of technological change underpinning this transformation of policy? Is the biotech revolution real or is it a myth? And, if it is real, what form is it taking?

The reason that these questions need to be raised is that there are contradictions and inconsistencies in the various expectations of the revolutionary model's impact. While the revolutionary model is widely accepted by social scientists and policy-makers, those in the pharmaceutical industry, in the financial community, and some regulators see a more complex and troubling picture. The FDA, for example, has noted that:

> *Today's revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries that have been made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased. The costs of product development have soared over the last decade*. (FDA, 2004: i).

In this paper, we present a detailed examination of the evidence for a biotechnology-driven revolution in drug innovation by updating and contextualising previous sceptical accounts.[4] In summary, the evidence shows that in moving from the sciences towards the clinic, evidence for a biotechnology revolution rapidly diminishes and the technology increasingly follows a well-established historical pattern of slow and incremental change. The translation of advances in bioscience into new technology is far more difficult, costly and time-consuming than many policy-makers believe. Our analysis will hopefully alert the reader to the deficiencies of the revolutionary model and induce some of its more evangelical proponents to reconsider their positions.

To explore the diverse expectations of biotechnology outlined above, this paper examines evidence from a range of biomedical settings. We begin in Section 2 by placing biotechnology in its historical context. In the following sections, we assess the evidence for a biotechnology revolution in three areas where discussion of revolutionary change has been prevalent. Section 3 analyses advances in drug discovery. Section 4 focuses on changes in drug development. Section 5 surveys changes further downstream, brought about in the clinic as a result of the diffusion of biotechnology-derived drugs. In each section, we explore the empirical evidence for a biotechnology-driven revolution, using both quantitative and qualitative indicators of change, and examine the scope (how different?), scale (how much? how widespread?) and, where relevant, the speed

[3] See, for example, DTI (1999, 2001), on regional policy and OECD (1998, 2004b); for technology policy. For the USA, more specifically see Collins et al. (1998), and for the EU see European Commission (2002). For a review of the various programmes, see http://www.sussex.ac.uk/spru/biotechnology/ebis/.

[4] Particularly, Hopkins et al. (2006a), Nightingale and Martin (2004), Arundel and Mintzes (2004), and Pisano (2006).

(how rapid?) of change. In Section 6, we briefly reflect on structural changes within the industry and the co-evolution of biotechnology and pharmaceutical firms in a period of declining pharmaceutical productivity. In Section 7, we critically assess the evidence and discuss policy implications.

2. Biotechnology: the historical context

New drugs are generated within path-dependent socio-technical systems based on high-level heuristics and hierarchies of interconnected operational principles that structure the way problems are solved (Martin, 1998; Nightingale, 2000). The pharmaceutical industry has relied on a series of heuristics that have been associated with different waves of products over the past two centuries, with each one leading to the development of new social networks (ibid; Galambos and Sewell, 1995; Galambos and Sturchio, 1998; Chandler, 2005; Pavitt, 1984). While the *potential* economic performance of particular heuristics is influenced by the economies of scale and scope that can be generated by the available technologies, organisational structures and social networks, *actual* performance is constrained by managers' abilities to realise those economies (Chandler, 2005). Realising the potential of new technologies therefore typically requires managers to construct new elements and linkages to reconfigure existing socio-technical systems. Consequently, the benefits of new technologies do not come from only possessing firm specific assets or competencies, but instead require the dynamic capability to effectively transform them.

2.1. The extractive heuristic and biological heuristic

During the 19th century the nascent pharmaceutical industry grew using an 'extractive heuristic' based on isolating natural medicinal plant compounds, many of which were supplied by government funded botanical expeditions to the colonies to source new *materia medica* (Goodman and Walsh, 1993).[5] Spurred by the incentive of patent protection on novel preparations (Homberg, 1992), synthetic chemistry began to be used to improve the performance of natural alkaloids, leading to the development of antipyretic drugs such as aspirin, and hypnotics such as chloral hydrate. Importantly, at this time the pill was established as a convenient way to administer a standardised drug dose. A parallel 'biological heuristic' emerged, following research by Koch and others, to develop anti-toxins from serum extracted from animals exposed to bacterium. This provided early treatments for infectious diseases such as diphtheria and typoid. As the biological heuristic drew on germ theory and bacteriology the networks supplying knowledge to industry expanded to encompass academic research from external research laboratories and public health bodies (Martin, 1998). The extractive heuristic was extended and applied by industry to various organs of the body in the early 20th century and provided a stream of new therapies including adrenalin and insulin (Weatherall, 1990). As had occurred with botanical extracts, synthetic analogues of steroids and hormones such as oestrogen began to appear in the inter-war years. Towards the end of this period, expanding search strategies lead to the extraction of antibiotics from bacteria and fungi (e.g., penicillin) (Goodman and Walsh, 1993; Martin, 1998).

2.2. The synthetic organic chemistry heuristic

During the post war period the plant-based extractive and biological traditions waned as a synthetic organic chemistry heuristic provided the pharmaceutical industry with a 'golden age' of productivity driven by random screening of synthetic compounds characterised as 'molecular roulette' (Jolley, 2000; Martin, 1998; Nightingale and Mahdi, 2006).[6] These compounds were often based on natural molecules or synthesised natural products, which avoided the expensive extraction process. Natural products continue to be important today with the anti-viral Oseltamivir (Tamiflu) derived from shikimic acid from the star anise spice (Handwerk, 2005). Within this heuristic firms exploited their capabilities in medicinal chemistry to modify molecular structures and improve the therapeutic properties of drugs. These modifications generated a wealth of new products including synthetic antibiotics, steroids, anti-inflammatory and antipsychotic drugs (Martin, 1998; Nightingale, 2000).

By the 1960s the productivity of 'molecular roulette' began to decline. Pioneers such as James Black realised that improved characterisation of drug receptors (the protein targets on which many drugs act) would allow

[5] Classic examples of drugs produced this way include morphine from opium, and later alkaloids such as quinine, nicotine, and caffeine (Goodman and Walsh, 1993; Swann, 1995).

[6] The emergence of this heuristic can be traced to Ehrlich's synthetic approach to drug research (based on earlier work on dyes), which produced the first synthetic drug, Salvarsan, to treat syphilis in 1910 (Weatherall, 1990).

more directed screening. This would improve productivity by reducing the number of costly experimental cycles (Nightingale, 2000). However, during this golden age pharmacologists had known little about the molecular structure of their targets (OTA, 1991).[7] The 1970s saw a broad-based shift towards generating knowledge about the structural properties of drug–target interactions to guide screening (Nightingale, 2000). This, together with expectations that it might be possible to rationally design drugs, induced a greater focus on biochemical and pharmacological understanding of disease pathways to find proteins that might be suitable drug targets. By working out the structure of these proteins (to which the drug will bind) it was hoped medicinal chemists could understand what types of small molecule would be most drug-like (Nightingale, 2000).[8] It is important to note that this major shift towards a *biology intensive* (rational design) heuristic was established before the emergence of the biotechnology industry.

Pharmaceutical firms continued to work with the academic community to generate insights into biological pathways, often with natural inhibitor molecules providing direction, but a more marked division of labour emerged with therapeutic development increasingly centred on synthetic drug molecules emerging from pharmaceutical firms (Martin, 1998). Captopril, launched in 1981, was designed to fit the active site of its target molecule by Cushman and Ondetti, and provided the proof of concept of the new operational principles. It was quickly followed by a new generation of highly profitable cardio vascular disease (CVD) medicines, the angiotensin-converting enzyme (ACE) inhibitors (Bognor, 1996; Vos, 1991).

With drug discovery increasingly driven by research on drug targets, pharmaceutical companies could now direct their research towards the most lucrative markets and shifted their research portfolios from antibiotics and infectious diseases towards highly profitable chronic diseases.[9] The success of the resulting 'blockbuster' drugs allowed a small number of firms to invest heavily in the marketing and research needed to take advantage of the potential economies of scale and scope opened up by the new rational design heuristic (Nightingale, 2000). The production of the knowledge needed to guide screening has its own distinct technological dynamic, and the experimentation process itself became increasingly industrialised over the 1980s and 1990s.[10] This industrialisation of research created a shift from traditional static economies of scale and scope in production, towards dynamic economies of scale and scope in knowledge (ibid; Chandler, 2005), the organisational implications of which will be addressed in Section 6.

2.3. Revival of the biological heuristic

While pharmaceutical firms used more guided screening and rational design to extend the utility of synthetic heuristic, the development of genetic engineering and monoclonal antibodies in the 1970s revived the biological heuristic by providing new operational principles. Using an expanding toolbox of restriction enzymes, vectors and cell culture methods, molecular biologists learnt how to cut and splice genes, express protein products in scalable volumes and start to generate novel variants (Harris, 1995; OTA, 1991). Similarly hybridoma techniques produced cell cultures capable of producing large volumes of a single form of antibody that could bind specifically to selected targets. This allowed researchers either to study molecules to which labelled antibodies adhered, or to recruit the patient's immune system to destroy cells that antibodies picked out (Harris, 1995; Robbins-Roth, 2000). The ability to generate protein products that had previously only been available in either miniscule quantities or through very costly large-scale extraction processes allowed a range of *existing* biologicals to be produced more economically and safely

[7] Ariens likened medicinal chemistry of the day to a correspondence with a mysterious woman '[the pharmacologist] has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot however claim ever to have seen her, although one day he may do so' (Ariens, 1964: xvi).

[8] It is important to distinguish between small molecule drugs that can be generated through synthetic chemistry and larger molecules that require biological methods of production as they are too structurally complex to be synthesised by other means. Effective small molecule (synthetic chemical) drugs are usually less than 500 Da (Hopkins and Groom, 2002: 730). At this size, small molecule drugs can be made that are structurally similar to natural molecules, mimic their effects and even have new properties, such as being resistant to digestion. Large molecule (biological) drugs may be orders of magnitude bigger. For example, the protein insulin is 5750 DA, but is still small in comparative terms for a protein drug (De Hoffmann and Stroobant, 2001: 7).

[9] The first of these blockbuster drugs (defined as generating sales in excess of $1 billion) was Zantac (ranitidine), launched by Glaxo in 1982. By 1990 the portfolios of large pharmaceutical firms typically included multiple blockbuster drugs such as Tagamet (cimetidine), Vasotec (enalapril) and Mevacor (lovastatin).

[10] It is possible to generate economies of scale, scope and speed in experimentation by automation, reducing the size of technology, speeding up experimentation, running experiments *in silico* and by reapplying knowledge – this has been termed the industrialisation of R&D (Nightingale, 2000).

Subject	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Recombinant DNA					2	0	1	0	1	1	1	1	3	1	4	2	2	1	1	0	11	8	3	2	1
Sequencing DNA					1	0	3	1	1	5	4	10	7	12	9	15	13	25	20	21	14	41	12	13	15
Gene Cloning						1	3	1	3	4	5	15	18	18	16	15	17	18	14	11	16	25	9	9	5
Protein Sequencing							3	0	4	6	4	13	20	21	20	27	27	42	29	38	28	39	11	25	20
Protein Expression							1	0	0	2	0	0	1	3	3	2	2	3	6	10	6	10	2	11	9
Gene Expression									1	2	1	2	8	6	6	11	17	9	25	30	26	28	21	26	21
Sequence Homologies											1	2	6	1	4	2	0	4	5	5	7	6	0	7	4
Transgenic Animals	x	x	x								1	2	0	1	1	2	1	5	5	6	5	7	4	2	2
DNA databases												6	3	5	5	5	6	8	7	12	6	7	5	3	1
Bioinformatics	x	x	x	x	x	x	x	x	x							1	0	2	3	4	4	11	12	10	9
Gene Function																	1	1	3	1	5	2	7	3	1
Genome Mapping																	1	0	1	1	2	4	2	2	1
Gene Knockout	x	x	x	x	x	x	x	x	x	x	x	x	x				1	0	1	2	1	2	1	1	0
Genotyping	x																	2	2	0	2	5	1	2	4
Population genetics																		1	1	1	1	5	0	5	0
Pharmacogenetics																		1	0	1	1	7	2	6	2
Microarray	x	x	x	x															1	0	1	7	4	7	7
Proteomics	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		1	2	9	6	6	6
SNP analysis	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x						1	4	2	4	2
RNA interference	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x					1	0

Fig. 1. The accumulation of research interests related to exploitation of genomics at GSK 1979–2003 (see Footnote 12).

(see Section 5), while their modification opened up new therapeutic possibilities.[11]

The potential of these techniques was rapidly recognised by the academic molecular biologists and venture capitalists who, in the late 1970s and early 1980s, had begun to establish a wave of biotechnology firms to develop recombinant protein or monoclonal antibody-based drugs (mAbs), collectively referred to as biopharmaceuticals (Orsenigo, 1989; Bud, 1993; Robbins-Roth, 2000). While the first biopharmaceutical – recombinant insulin (Humulin, 1982) was the outcome of a joint project between Genentech and Eli Lilly, the majority of the pharmaceutical industry adopted a 'wait and see' approach to these new (potential) sources of innovation (Kenney, 1986) and left the exploitation of the first wave of products to biotechnology companies such as Genentech and Amgen.

In the next two decades, with a few exceptions, most large pharmaceutical firms saw biopharmaceuticals as problematic because of the difficulties of establishing the therapeutic properties of protein drugs, concerns that they were not suitable for oral delivery due to their size and composition (Edgington, 1992) and because of the difficulties of discovering novel proteins that were safe and effective. As a consequence, biotech firms continue to be the main source of these drugs and a large number of new recombinant proteins continue to be second or third generation derivatives of established protein therapies (see Section 4). By comparison, monoclonal antibodies have proved to be an increasingly successful class of therapeutics in recent years, after some initial problems (see Sections 4 and 5). This has stimulated significant investment from the pharmaceutical industry, mainly through strategic alliances and acquisitions, to fill their dwindling product development pipelines. These new operational principles and transformations of socio-technical systems provide the background to the changes in medicinal biotechnology that have been understood in terms of a biotech revolution. In the next sections, we assess the extent of their impact.

3. The impact of biotechnology on drug discovery

3.1. The scope of change in drug discovery

Drug discovery is the process of creating chemical or biological molecules that have the potential to be developed as therapeutic agents, typically because they generate a desired biological effect in an appropriate testing or assay system against a particular molecular (drug) target. Biotechnology has had a profound effect on drug discovery through the development of increasing numbers of research tools for both small-molecule drugs and new biopharmaceuticals. This is depicted in Fig. 1, which illustrates the pattern of publications produced

[11] To illustrate that the early application of biotechnology was for the manufacture of pre-existing products, during the 1980s 15% of clinical projects involved insulin or human growth hormone and by 1988, these were two of only five classes of biotech FDA approved products (Pavlou and Reichert, 2004; Bud, 1993).

by GlaxoSmithKline (GSK) and shows the increasing accumulation of capabilities in biotechnology from 1979 to 2003.[12] The earliest techniques shown in Fig. 1 – molecular cloning, gene and protein sequencing – were used within the synthetic chemistry heuristic as a process innovation to produce recombinant protein receptors for crystallographic modeling and drug screening, and as research tools to enhance understanding of cellular processes (Knight, 1990; Bognor, 1996). Over time, as new biology-based technologies were developed and integrated within large pharmaceutical firms the applications of biotech widened.

The advent of genomics, brought about by the Human Genome Project (HGP) and the availability of high-speed DNA sequencing equipment in the late 1980s and early 1990s further increased the importance of biotechnology. It was expected that the large number of newly discovered genes could provide the basis for tools to generate and validate targets for a new generation of novel small-molecule, blockbuster drugs.

Competencies in key biotechnologies were rapidly developed in large companies throughout the industry through the creation of in-house research groups, as well as external collaborations with academia and firms in the recently created genomics sector (Nightingale and Mahdi, 2006; see Section 6). By the early 1990s improved biotech-based assays led to the development of industrialised high-throughput screening (HTS) platforms, that together with the development of new non-biotech platform technologies, most notably combinatorial chemistry and new informatics systems enabled, the generation and rapid screening of very large chemical libraries against the larger number of new targets emerging from genomics (Nightingale, 2000).[13] This produced an initial move away from theory-driven attempts to rationally design drugs, back towards empirically-driven attempts to direct the screening of large libraries of compounds, that only gradually became increasingly directed by theoretical understanding of 'chemical space' (Nightingale, 2000; Nightingale and Mahdi, 2006).

The focus on empiricism within this emerging industrialised approach meant that the biological role of new targets in disease pathology was often poorly understood. The number of scientific papers associated with each target, for example, fell from 100 in 1990 to eight in 1999 (Booth and Zemmel, 2004). It is therefore not surprising that the failure rate of drugs based on novel targets appears to be 50% greater than for drugs against clinically validated targets (Ma and Zemmel, 2002).

Genomics technologies in drug discovery consequently helped shift the bottleneck in drug innovation from the identification and creation of novel small-molecule drugs against known targets (chemistry) to the biological characterisation and functional validation of large numbers of unknown drug targets (biology) at the molecular, cellular and system levels. This bottleneck has acted as a focusing device for innovation and various new biotech-based techniques for validation have been developed in the last decade. These include the use of more sophisticated animal model systems, gene transfer techniques, gene expression profiling, gene knock out and knock down tools and large genetic databases (e.g. Friedrich, 1996; Shriver et al., 2004; Kramer and Cohen, 2004). As a result, the development of modern therapeutics requires a vast array of new biological techniques to establish and characterise disease correlates. As Section 4 will show this remains a major challenge that is constraining overall productivity improvements.

3.2. The scale of change in drug discovery

The identification and validation of targets has been a major focus for both biotechnology and pharmaceutical firms, based on expectations of rapid and major change. In the mid-1990s the number of molecular targets that all available therapeutics acted on was estimated to be approximately 417, and genomics was expected to raise this by an order of magnitude by providing between 3000

[12] This data is based on keyword citations in publication abstracts and was compiled from the Biosis and CAPLUS databases. Only scientific papers are included in this bibliometric analysis (i.e. editorials, reviews, etc., are excluded). Years where GSK and its constituent predecessors (such as Wellcome and Beecham) published in a field are highlighted in grey, with darker shades indicating higher activity. Where GSK discontinues publishing in a field, that year is unshaded. Unshaded areas indicate publishing activity outside the firm in that field, while an 'X' indicates that the field had yet to emerge and thus there were no publications in the world at large. Publication counts are an indication of internal interest in a field sufficient to generate a peer reviewed paper, rather than a measure of capability. However, absence of evidence (by publication) is not evidence of absence (of capability), and this indicator only indicates research interest, not invention and definitely not innovation. Counts are affected by a number of factors such as the time lag between research and publication, the changing propensity to publish over time within firms or even departments, and changes in the propensity to use the keywords used to classify the data. They are also influenced by potential to publish by field, and should not therefore be used to compare and contrast between fields. Our concern here is indicating (admittedly rather crudely) *variations* by scientific field over time (imperfectly measured by keyword) and the expanding diversity of fields that pharmaceutical firms are interested in.

[13] In a presentation to investment analysts in 2004, GSK highlighted how these new methods had increased the number of compounds each target was tested against from 100,000 in 1996 to 1,050,000 in 2004.

and 10,000 new drug targets within a decade (Drews, 1996). More recent estimates of the number of 'druggable' targets (i.e., the proteins small-molecule drugs bind to in order to moderate disease processes) are a more modest 600–1500.[14] Nonetheless, a single target may be associated with multiple diseases and new biotechnology modalities further expand the range of targets because unlike small molecule drugs they may not depend on competitive binding at relatively small sites on proteins for their mode of action (Hopkins and Groom, 2002). Thus, even though the number of genes in the human genome appears to be 20,000–25,000 rather than 100,000 (Stein, 2004), the number of new therapeutic targets available for exploration in early stage drug discovery has risen substantially in just a few years.

However, in 2002 few firms had taken drugs based on genomics derived targets to the clinic (Van Brunt, 2002) and even at present almost all genomics-derived drug candidates remain in development (Rothman and Kraft, 2006). Nonetheless, the rapid emergence of drug pipelines in 13 of the 22 leading genomics firms (all founded since 1991) suggests genomics-based approaches may produce a substantial number of drug candidates in the future (Rothman and Kraft, 2006).

The current, rather than future, productivity of pharmaceutical drug discovery is typically indicated by the number of new chemical entities (NCEs) approved in a given year divided by total R&D investment (e.g., see Booth and Zemmel, 2004). While the long time lag between investment and yield, the heavily skewed relationship between drugs and profitability; the inclusion of drug development, and quantitative changes in the inputs to R&D make this a poor indicator, this measure is nonetheless widely used and indicates that overall productivity has been falling for the past 30 years (Booth and Zemmel, 2004; Service, 2004; Drews and Ryser, 1997; FDA, 2004). In 2002, FDA approvals of NCEs (17 in total) were the lowest for eight years.[15] Indeed, between 1993 and 2003 the FDA reports an almost continuous decline in submissions for regulatory approval of NCEs (FDA, 2004). This is despite the rise in potential drug targets and the very significant increase in industry and public sector R&D expenditure since the 1970s.[16]

An alternative indicator of changes in productivity with fewer time lags between expenditure on research and performance impact is the number of new-patented drug compounds. Fig. 2 shows changes in the number of patents granted by the US Patent and Trademark Office (USPTO) in patent classes 424 and 514 over the period 1978–2002. These are the main patent classifications for therapeutically active compounds, and can be used as an indicator of the number of molecules considered attractive enough to warrant patent protection, but not necessarily viable enough to enter development. While there was a steady rise in the number of patented molecules between 1978 and 2002, R&D spending in the pharmaceutical industry increased approximately tenfold (Nightingale and Martin, 2004; Hopkins et al., 2006a). Despite the recent rise in patenting after 2000, the data do not suggest patenting activity has done much more than keep pace with expenditure.[17] Nonetheless, the post-2000 rise should not be entirely discounted, and may yet be a genuine indication of productivity improvements. Unfortunately, this indicator (like the NCE indicator) measures quantity without taking into account variations in quality, and does not properly indicate qualitative changes in the difficultly of research process as the industry has sought to address the increasingly complex biology of disease areas such as CNS opened up by improvements in research techniques (see Pisano, 2006 for a managerial analysis of these changes).

3.3. The speed of change in drug discovery

There is no doubt that the revolutionary changes in instrumentation and the volume of scientific knowledge generated by biotechnology and particularly the HGP, have worked to markedly increase the rate of target discovery in just a decade – a very short period of time. New bioinformatics technologies now allow the very rapid discovery of targets *in silico* (sometimes in days rather than years). However, historically, publicly funded research has been required to play the key role in charac-

[14] This is based on the estimated intersection of the set of small molecules with necessary pharmacological properties (such as oral availability) and the set of proteins with suitable sites for these to bind (Hopkins and Groom, 2002).

[15] The numbers of new chemical entities approved annually can be searched using the FDA's Orange Book (available at http://www.fda.gov/cder/ob/ accessed 19/07/06). This excludes biologics, which are recorded separately in the Green Book (available at http://www.fda.gov/cvm/greenbook.html accessed 19/07/06).

[16] As an indication of this, both US pharmaceutical firms' R&D expenditure and NIH (National Institutes of Health) expenditure more than doubled in real terms in the period 1993–2003 (FDA, 2004).

[17] The case for increasing R&D productivity in real terms is further weakened when more global trends such as the increasing propensity to patent in industry are taken into account (OECD, 2004a). Recent interviews suggest firms are now patenting more heavily to protect each potential drug, which suggests the growth in patents may be a less than perfect reflection of productivity changes.

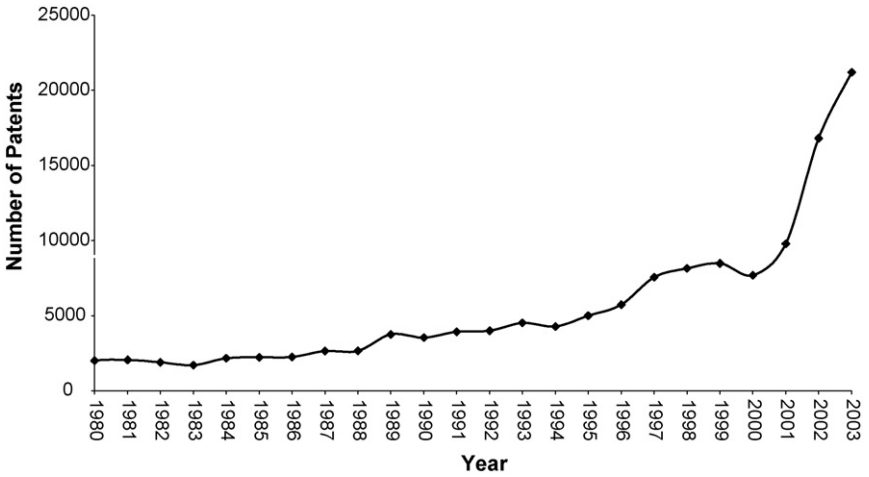

Fig. 2. Patents on therapeutically active compounds at the USPTO.

terizing biological pathways with research often taking decades rather than years. This raises the possibility of a significant lag between investment in genomics and productivity improvements, suggesting these expensive, upfront investment may be making the crisis in productivity worse in the short term (Leheny, 2001).

4. The impact of biotechnology in drug development

4.1. The scope of change in drug development

Drug development is the period of R&D from when a drug prototype enters pre-clinical testing to the time when it is approved by the regulatory authorities (FDA, 2004).[18] It is often characterised as a process of attrition in which 5000–10,000 potential drug candidates are narrowed down to generate a single drug molecule (e.g., Campbell, 2001; Gassmann et al., 2004). Because clinical trials are so expensive, any reductions in failure rates that can be generated during development can produce substantial savings (Nightingale, 2000).[19] Biotechnology-based approaches have the potential to contribute towards these savings by enhancing knowledge of the patient population, its disease, and its interactions with therapeutic molecules. Pharmacogenetics in particular holds out the promise of improving preclinical safety screening, enhancing the effectiveness of early stage trials, streamlining later stage trials, and even rescuing drugs that have failed late stage trials due to lack of efficacy in the whole population (Webster et al., 2004).

From the late 1990s the genetic profiling and targeting of sub-populations in clinical trials was widely expected to reduce the size of trials, improve clinical efficacy and/or safety, and reduce the likelihood of failure in late stage trials by focusing on genetic sub-populations more likely to respond favorably to drugs (Drews and Ryser, 1997; Marshall, 1997; McCarthy, 2000).[20] As a result, pharmacogenetics has been widely adopted and the pharmacogenetics data it provides are feeding into all stages of the R&D process (Webster et al., 2004). However, at present, there is little evidence of widespread benefits (IPTS, 2006).

Similarly, in the early 2000s gene expression studies were promoted as useful toxicological tools for improving candidate selection (Hackett and Lesko, 2003). By removing unsuitable drugs from the pipeline in the preclinical testing stage, or even earlier, it was hoped that

[18] The critical path for drug development moves from pre-clinical, involving the synthesis/purification and testing in animals prior to application for permission to test in humans; then Phase I involving pharmacokinetic studies in from 20 to around 100 patients and healthy volunteers to determine absorption, metabolism, and excretion; then Phase II explores effectiveness and possible side effects in several hundred patients; and then Phase III involving more detailed study of effectiveness and side effects compared to placebo or other treatment, in several hundred to several thousand patients in preparation for submitting to regulators for marketing approval. Once this process is complete post marketing reviews are used to monitor for the emergence of unexpected side effects.

[19] The FDA endorses research suggesting that improvements in predicting which drugs will fail in development by just 10% could save $100 million in the R&D costs of the average drug (FDA, 2004).

[20] This involved ensuring that all drug metabolising enzyme alleles are accurately represented in phase I – so-called balanced trials.

new toxicological and metabolic screens would reduce expensive failures in the clinical phases of development (Booth and Zemmel, 2004; Kola and Landis, 2004). While the majority of large pharmaceutical firms are integrating these technologies into their R&D efforts, it is currently too early to assess their effectiveness (Booth and Zemmel, 2004). One major constraint at present is the lack of agreement on how to validate the gene, protein, or metabolic biomarkers used to distinguish responses and separate patient groups (Hackett and Lesko, 2003; Van Brunt, 2004), which is a vital question for the assessment of biomarkers by regulatory authorities overseeing clinical trials and drug approvals. Without the agreement of regulatory authorities and industry on such issues the potential benefits from these new approaches will be difficult to realise (for example, in clinical trial design).

Moreover, the impact of many new forms of biotech therapies has so far been incremental. Protein drugs were initially expected to be particularly successful in clinical trials because, unlike synthetic drugs, they are endogenous to the human body and thought to be more 'natural,' more potent, and less toxic (Edgington, 1992; Pollack, 2002; Joppi et al., 2005). This has not proved to be the case as large molecular weight biological drugs have poor absorption characteristics, relatively short half-lives in the body, and they have often proved just as toxic and prone to side effects as their small molecule predecessors (Brekke and Sandlie, 2003; Edgington, 1992; Joppi et al., 2005). Treatments that use other new operational principles that biotech has facilitated, such as gene therapy and antisense therapeutics, have not been as successful in clinical trials as was hoped in the 1990s. Although one licensed antisense product (Vitravene) has been approved by the FDA for the treatment of cytomegalovirus retinitis, this is a niche product and few others are in late stage development. Similarly, no gene therapy has been licensed in Europe or North America, and only a handful of products may reach the market in the next few years (Martin and Morrison, 2006). Furthermore, a series of well-publicised and unanticipated complications during clinical trials has dampened investor enthusiasm for some of these technologies.

4.2. The scale of change in drug development

4.2.1. New chemical entities

The scale of the impact of biotechnology on the development of NCEs can be indicated by changes in costs and success rates. Currently, only between 8% and 20% of NCEs entering clinical trials receive final marketing approval (FDA, 2004; Reichert et al., 2005; DiMasi, 2001; Bolten and DeGregorio, 2002).[21] When the price of failed drugs across the industry is taken into account, the cost of bringing a successful NCE to market has been estimated at between $800 million and $1.7 billion (FDA, 2004). Although such figures are often disputed, the upward trend is widely accepted (Dickson and Gagnon, 2004; Booth and Zemmel, 2004) and disproportionately influenced by cost increases in drug development. These have risen from around 40% to around 60% of total R&D expenditure driven by increasing numbers of clinical failures, especially in Phase II (Booth and Zemmel, 2004; FDA, 2004; Hopkins, 2004).[22]

While the decline in R&D productivity predates biotechnology, the application of biotechnology research tools, and in particular genomics, may be making the situation worse (Booth and Zemmel, 2004; Horrobin, 2003; Higgs, 2004). Genomics technologies are generating large numbers of less well characterised new targets that are now being tested in experimental models that are increasingly removed from the intended patients (i.e., from patients, to animals, to cell cultures).[23] Molecules aimed at these novel targets fail more often in the later, more expensive, stages of clinical trials where efficacy is ascertained, increasing the cost of drug R&D (Booth and Zemmel, 2004). The financial risks of 'first in class' drugs therefore tends to be higher (Hopkins, 2004) increasing the relative reward for developing me-too drugs.[24] Although the successful use of biotechnology in drug development may improve productivity in big pharmaceutical firms, there is little publicly available evidence that this is being achieved so far.

4.2.2. Biopharmaceuticals

Data on the relative performance of biopharmaceuticals in clinical trials show that they are more successful in

[21] These broad statistics hide a more nuanced picture. Of the NCEs entering phase I trials in the period 1981–1992, the anti-infectives enjoyed a survival rate of around 30%, while only 12% of respiratory drugs were successful. In oncology, around 16% of molecules passed successfully through trials at the end of the 1990s, although other estimates of 5% have been cited more recently (FDA, 2004).

[22] The FDA (2004) estimates that in real terms development costs have grown from less than $500 million in the late 1990s to almost $1 billion in the early 2000s.

[23] Such models are often regarded with suspicion by those favouring more traditional deductive pharmacological approaches (Higgs, 2004).

[24] They have a 5% survival rate in clinical trials (compared to 8% for established approaches) (Ma and Zemmel, 2002). In recent years 'fast followers' have been more profitable than novel drugs (Ma and Zemmel, 2002) across the industry in both biologicals and small molecules (FDA, 2004).

Table 1
Comparing the approval rates of different therapeutic modes

Drug type	Cohort size	Success rate (%)	Dates of IND filing at FDA	Authors[a]
New chemical entities	671	21	1982–1992	DiMasi (2001)
Recombinant proteins	91	26	1980–1989	Pavlou and Reichert (2004)
Recombinant proteins	120	35	1990–1997	Pavlou and Reichert (2004)
Chimeric Monoclonal antibodies	20	29	1987–1997	Reichert et al. (2005)
Humanised monoclonal antibodies	46	27	1988–1997	Reichert et al. (2005)

Reproduced from Hopkins et al. (2006a) using data from Tufts CSDD.
[a] All data collected by Tufts centre for the study of drug development.

reaching the market (Booth and Zemmel, 2004; Reichert et al., 2005). However, side-by-side comparisons are methodologically problematic as biopharmaceuticals often undergo smaller studies that may not be as effective in revealing side-effects (Horrobin, 2001). Indeed, European regulators have recently highlighted worrying methodological deficiencies in biological marketing approval applications (Joppi et al., 2005).

Furthermore, this apparently high success rate is boosted by an increasing number of 'me-too' drugs that may be little different from established products (Joppi et al., 2005). This may explain the increasing success rate of recombinant protein trials (Table 1) as biotech product portfolios are reshaped to mirror early successes. In particular, this is illustrated by the focus on diabetes and endocrine products maintained by firms after initial success by pioneering biotechs (Pavlou and Reichert, 2004). The continued focus on a narrow range of therapeutic areas (mainly oncology, infection, inflammation/autoimmune, diabetes and endocrinology) is likely to increase competition (Pavlou and Reichert, 2004; Reichert et al., 2005) and cause failure rates, trial sizes and overall costs to rise as drugs have to prove efficacy and safety improvements over existing treatments to achieve commercial success (Booth and Zemmel, 2004).

Table 1 also shows that mAbs have an impressive approval rate in recent years far superior to the initial wave of mAbs entering the clinic in the early 1980s. These early drugs were derived from mouse cell lines and discontinued due to high immunogenicity and a low clinical success rate of 3% (Reichert et al., 2005). Since then monoclonal products have moved from wholly murine-derived antibodies, to chimeric antibodies, then humanised antibodies, and now towards smaller antibody fragment-based approaches, which have reduced immunogenicity, suggesting the recent success of monoclonal therapies may continue (Reichert et al., 2005). Perhaps then after a very long gestation period and some false starts, mAbs are the best indication yet of biotechnology's long-term promise in the development of new products.

Table 2
Changes in drug approval times from the 1970s to the present (in years)

Decade	Preclinical phase	Clinical phase	Approval phase	Total
1970s	(41%)	4.3 (40%)	2.1 (19%)	10.9
1980s	5.3 (38%)	5.9 (42%)	2.8 (20%)	14.0
1990s	5.5 (39%)	6.7 (48%)	1.8 (13%)	14.0
2000s	5.8 (44%)	5.9 (45%)	1.5 (11%)	13.2

Reproduced from Hopkins et al. (2006a) using data from Tufts CSDD 2005.

4.3. The speed of change in drug development

While a number of early protein therapeutics reached the clinic relatively quickly (see Section 5.3), mAbs have taken between 20 and 30 years to emerge as a viable and widely applicable new therapy, and other biological platforms, such as gene therapy and antisense, are yet to provide substantial success in clinical trials. The speed of development of biological drugs also seems to be faster than small molecule drugs (Reichert, 2003). However this may be a transitory effect if the regulatory environment for biologicals tightens.

It is notable too that the development times for NCEs have fallen from 79.5 months (1990–1991) to 63.2 months (2000–2001) while approval times have reduced from 31.3 months to 18.4 months over the same period (Horrobin, 2001; Kaitin and DiMasi, 2000). As Table 2 shows, overall drug development times (including approval times) are beginning to fall for the first time in several decades.[25] This may not necessarily be early evidence of the impact of biotechnology, as the

[25] Development times may vary for a number of specific reasons, such as the speed of patient enrolment (Booth and Zemmel, 2004; Bolten and DeGregorio, 2002). Some diseases require longer treatment times (chronic diseases versus acute). For example, anti-infectives need trials of 50.2 months versus 92.9 months for endocrine disorders. Some decreases in clinical trial times over the 1990s were dramatic – 41% for cancer drugs, 44% for respiratory drugs, but in other areas such as cardiovascular and pain they increased by 12% and 11%, respectively (Booth and Zemmel, 2004; Bolten and DeGregorio, 2002).

regulatory landscape changed in the 1990s due to accelerated approval and fast-tracking (Reichert, 2003) and management practices, especially in large firms, have improved over the same period (Gassmann et al., 2004). In the last decade, the FDA has tried to become an active 'partner in drug development rather than a hurdle' (Booth and Zemmel, 2004: 452), following the FDA Modernization Act of 1997 which introduced the fast track mechanism allowing streamlined NDA submission, and a willingness to accept the use of surrogate end points to determine efficacy in clinical trials (for example, the use of CD4 cell counts and measurement of viral load rather than patient survival for anti-HIV drug approvals). This simplifies effectiveness studies and reduces development time and costs (FDA, 2004; Bolten and DeGregorio, 2002). Such measures indicate that regulators and companies could, together and individually, reap further improvements through organisational changes that could accelerate drug development.

5. The impact of biotechnology on clinical practice

5.1. The scope of change in clinical practice

So far, we have established that while biotechnology has substantially increased the number of drug targets, for the most part these are still being assessed in clinical trials or preclinical testing. Biotechnology, particularly the HGP and Genomics, also promised the rapid development of genetic tests to predict and prevent disease by supporting early interventions, and more optimal or targeted use of therapies (pharmacogenetics) (Cantor, 1992; Gilbert, 1992; Hood, 1992; Department of Health, 1995; Roses, 2000). In previous work (Hopkins et al., 2006b) we have established that the timeframes suggested in many early accounts of pharmacogenetics testing were unrealistic. Many claims remain far from being realised, and the future contribution of genomics to medical practice remains contested (Martin and Morrison, 2006; Royal Society, 2005; Cooper and Psaty, 2003). To produce a substantial impact on mainstream medicine genomics must address prevalent complex disorders, where a number of genes and environmental factors influence disease progression or drug response (Horrobin, 2001). Despite much effort, there is little evidence of major progress in this area (Martin and Morrison, 2006).

Perhaps, the oldest promise of biotechnology for the clinic remains the introduction of new therapies such as recombinant proteins, mAbs, gene therapy, stem cells, and gene silencing technologies such as RNA interference (RNAi). These represent important contributions because traditional pharmaceutical approaches tend to generate antagonists that inhibit biological functions rather than agonists that simulate function (Horrobin, 2001). Many of biotech's greatest successes (see Table 3) have been protein replacement therapies (such as Factor VII for haemophilia) or agonists that promote biological processes (such as the increase in blood cell production generated by erythropoietin for treatment of anaemia). As previously noted only recombinant proteins and mAbs have produced significant numbers of regulatory-approved biological products and our discussion in the next section therefore focuses solely on these.

5.2. The scale of change in clinical practice

Fig. 3 shows that the majority of the products (100 out of 192) being produced by 'biotechnology companies' over the last 20 years are traditional small molecule therapies or biologicals developed using established operational principles rather than new recombinant proteins or monoclonal antibodies. Since almost all drug discovery firms use biotechnology in research and many produce biopharmaceuticals, these "biotech" firms cannot be distinguished from pharmaceutical firms by their products or technology. Many biotech firms producing small-molecule therapies only differ from pharmaceutical firms in their size and would be more accurately described as specialty pharmaceutical companies. The resulting confusion about what is, and what is not, a biotechnology firm or a biotech drug has led to widespread overestimation of the impact of third generation biotechnology in the clinic (for example, compare Arundel and Mintzes, 2004; Arnst, 2005).[26]

Similarly, much of the apparent boom in clinically available biopharmaceuticals is overestimated because their performance is assessed relative to small-molecule drugs. The decline in the numbers of NCEs being approved makes the contribution of biological drugs look higher, even though there has not been an increase in the rate of biological drug approvals (Reichert, 2003). For example, biological drugs increased from 21% of FDA drug approvals in 1998, to 24% in 2001, and 30% in 2002 (Reichert, 2003), but in absolute terms the numbers remain relatively low with only 26 biological drugs

[26] It would seem that firms are often only placed in the 'biotechnology' category because of their size relative to large pharmaceutical firms. With the exception of a small number of biotech firms, an alternative indicator might be a weak financial base. Biotechnology may be more usefully understood as a financial descriptor rather than a term that distinguishes firms' technology or final products.

Table 3
The top 15 biotech-derived therapeutics in 2004

2004 Total global sales ($ billion)	Generic name (brand names)	Companies	Indications
11.8	α and β Erythropoietin (Epogen, Epogin, Procrit, Eprex; NeoRecormon, Aranesp)	Amgen, J&J, Roche, Kirin, Sankyo	Anaemia
6.8	α and β Interferon (PEG Intron, Pegasys Avonex, Rebif, Betaseron)	Schering Plough, Roche Biogen Idec, Serono, Schering AG, Chiron	Hepatitis C, multiple sclerosis
5.6	Human insulin (Novulin, Humalin, Humalog I)	Novo Nordisk, Lilly	Diabetes
3	Granulocytes- colony stimulating factor (Neupogen, Neulasta)	Amgen, Roche, Schering	Granulocytes stimulator
2.8	Rituximab (Rituxan)	Roche	Leukemia, lymphoma
2.6	Etanercept (Enbrel)	Amgen, Wyeth	Rheumatoid arthritis
2.1	Infliximab (Remicade)	J&J	Rheumatoid arthritis
1.3	Trastuzumab (Herceptin)	Roche	Breast Cancer
1.8	Human Growth Hormone (Serostim, Saizen, Humatrope, Protopin, Neutropin)	Serono, Biogen Idec, Roche, Novo Nordisk, Akzo Nobel, Lilly	Dwarfism
0.95	Palivizumab (Synagis)	MedImmune	RSV
0.95	Follicle stimulating hormone (Gonal F, Follistim)	Serono, Akzo Nobel	Infertility
0.88	Glucocerebrosidase (Cerezyme, Ceradase)	Genzyme	Gaucher's disease
0.85	Adalimuzab (Humira)	Abbott	Rheumatoid arthritis
0.76	Factor VII (Novo Seven)	Novo Nordisk	Haemophilia
0.7	Botulin toxin (Botox)	Allergan	Wrinkles
0.55	Bevacizumab (Avastin)	Genentech, Roche	Colon cancer

Reproduced from Hopkins et al. (2006a) using data from Express Pharma Pulse.

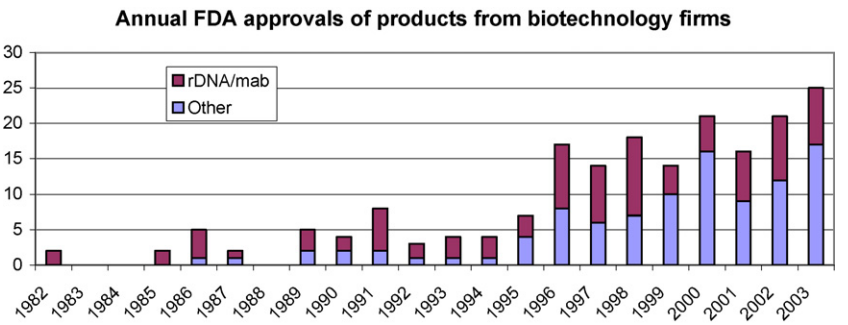

Fig. 3. Annual FDA approvals of products from biotechnology firms. Reproduced from Hopkins et al. (2006a) using data from the Biotechnology Industry Organisation.

approved between 1998 and 2003 (compared with 144 NCEs) (Kneller, 2005). Nonetheless, 33% of the NCEs originated outside traditional pharmaceutical laboratories (Kneller, 2005). This highlights the productivity of the small firm sector, more than biotechnology *per se*.

An indicator of how much biotechnology is used in clinical practice can be found in sales data. At present IMS Health estimates that $55 billion (10%) of global $550 billion pharmaceutical sales are derived from biopharmaceuticals. However, biological drugs are notably more expensive than their traditional pharmaceutical peers (Joppi et al., 2005) and around three-quarters of these sales are generated by the 15 therapeutic product classes in Table 3.[27] Moreover, the therapies listed in Table 3 are often for rare diseases rather than the mass markets of many small molecule drugs. Of the approximately 30 disease groups targeted by biopharmaceuticals, eight are very rare with prevalence rates of less than 1 in 10,000 in the USA and only four have

[27] In 1993, biotechnology-based therapeutics accounted for nearly $3 billion in sales in the USA (>5% of total US therapeutic sales) (Dibner, 1993).

prevalence rates close to or above 1 in 100 (diabetes, stroke, heart attacks, and rheumatoid arthritis) (Arundel and Mintzes, 2004). Of these four disease areas, in three the biopharmaceutical is only approved for use under limited circumstances or as a second-line drug when alternatives fail. Almost all of these therapeutics are used in specialist practice (secondary or tertiary care) rather than in general practice (primary care). The one exception is diabetes, although insulin was already available in the clinic before the emergence of modern biotechnology. As such, biotechnology has had little impact on primary care medicine.[28]

While the majority of products in Table 3 are proteins rather than mAbs, this is likely to change, as 57 mAbs had been launched by mid-2005 and around 200 are in clinical trials (Mitchell, 2005). Furthermore, around 50% of these are predicted to be profitable (compared to only 30% for traditional small-molecule drugs). However, like the protein drugs before them, the monoclonal drugs developed so far are for a relatively narrow range of disease areas – albeit ones with large markets such as cancer and inflammatory diseases.[29] While the early mAbs faced limited competition and targeted the most profitable markets, today 40% of mAbs in clinical development focus on oncology, suggesting future drugs will face greater competition.

There are fewer non-financial metrics available to analyse the scale of the impact of biotechnology on clinical practice. However, some indications are given by reviews of regulatory licensing documentation, and the views of physicians in surveys. Joppi et al. (2005) reviewed EMEA documentation and found that only 15 out of 61 (25%) biologicals approved between 1995 and 2003 (including a number of vaccines) provided efficacy improvements on existing therapies or were targeted in therapeutic areas where effective treatment was unavailable. A further 22 (36%) provided non-therapeutic advantages, such as improved safety, or convenience (e.g., in administration). The largest share, 24 (39%), provided no clinical advance, and were merely 'me-too' applications.

Similarly, data gathered from French physicians by La Revue Prescrire suggests that only 16 of the 48 (33%) biologicals (excluding vaccines) evaluated between January 1986 and June 2004 were better than 'minimal improvements' over pre-existing treatments (Arundel and Mintzes, 2004).[30] This is better than traditional pharmaceuticals, where only one in ten score at this level (i.e. rated as 4- or higher on a 7-point scale). Furthermore, only 24% of the evaluated biologicals were rated as offering no therapeutic advance, compared to the vast majority of other drugs (66%) which achieved this level or lower. This is because many early biological products have been aimed at markets with unmet medical needs (Joppi et al., 2005). However, when the Prescrire data are separated into three time periods, there is an increasing trend towards 'me-too' biological drugs (from 7% between 1986 and 1998 to 40% after 2000), which, for physicians, are less welcome (Arundel and Mintzes, 2004). Furthermore, the proportion of drugs viewed as offering some advance (6 on the scale) or a major advance (the top mark of 7) declined from 39% of the 28 treatments in the period 1986–98 to 13% of the 30 treatments evaluated after 2001.

The work of Joppi et al. (2005) and Arundel and Mintzes (2004) further supports the argument we made in Section 4.2 that the marked rate of advance apparently offered by protein therapeutics and mAbs may not be sustained in the medium to long term. Biopharmaceuticals, like NCEs before them, are increasingly focused on securing economic benefits for developers rather than clinical benefits for patients in areas of unmet medical need.

5.3. The speed of change in clinical practice

The earliest biotechnology drugs reached the clinic in the first half of the 1980s, approximately 10 years after the development of modern biotechnology techniques. They were rapidly followed by innovative protein therapies such as alteplase/tissue plasminogen activator for treatment of pulmonary occlusions following myocardial infarctions (1988), epoietin alfa for treatment of anaemia (1989), and the first monoclonal antibody drug (muromomab-CD3) for treating kidney rejection (1989). These seemingly represented very swift advances, but the targets on which these drugs acted were known prior

[28] Amgen, the largest and most successful biotechnology company in terms of sales has yet to launch a medicine that can be prescribed by family doctors, although such medicines are in development (Bowe, 2006).

[29] They also often need be stored carefully, can only be injected and tend to be delivered in specialist secondary or tertiary care settings. Their use in specialist clinics means a smaller sales force and lower levels of marketing are needed than in the more competitive primary care market where most blockbuster small molecules compete.

[30] The Prescrire data set's collection is funded by journal subscriptions and as such gives the physician respondents' views of the medicinal value of treatments independent of industry or government influences.

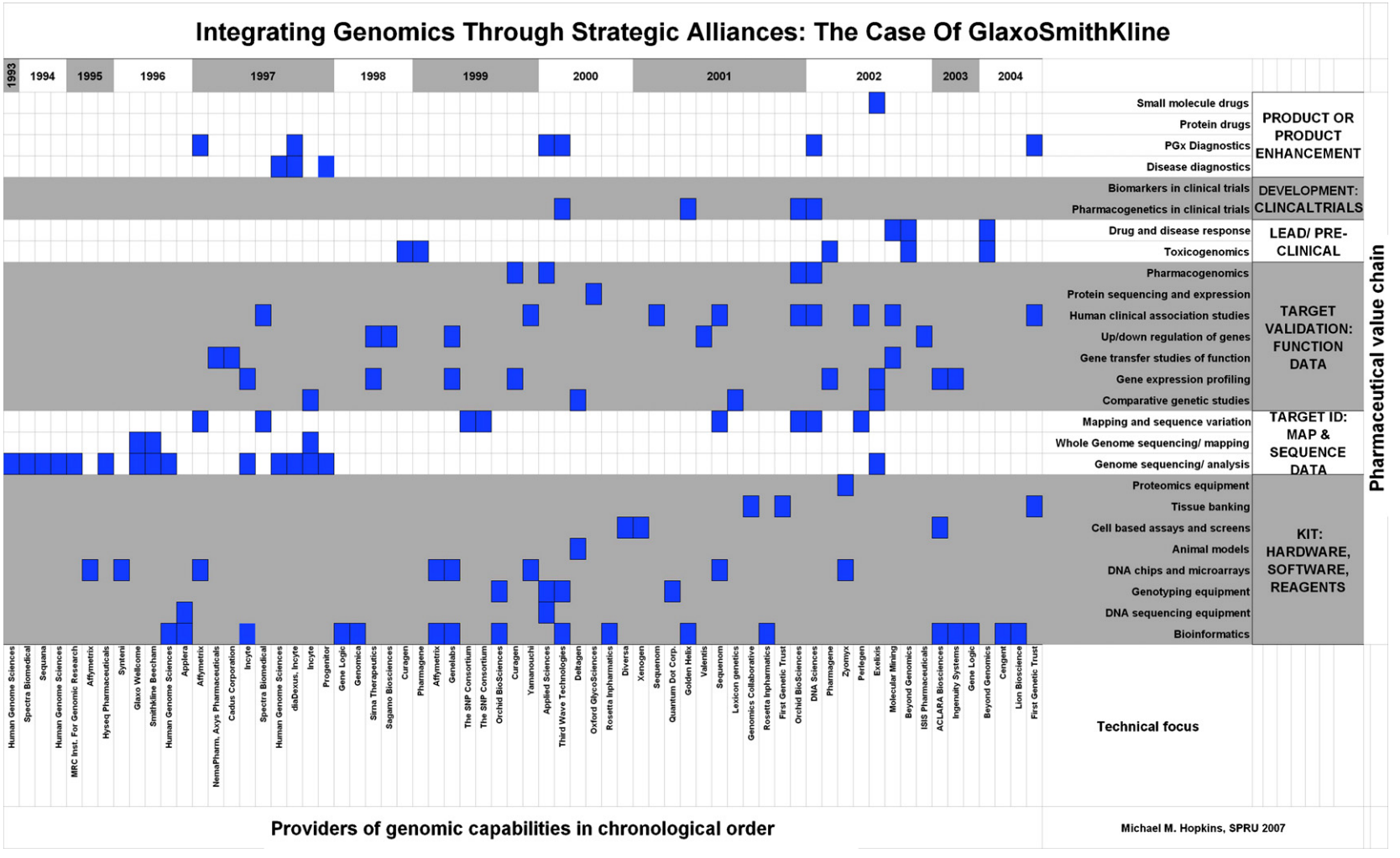

Fig. 4. Integrating genomics through strategic alliances: the case of GlaxoSmithKline. *Source*: Author's original, based on data from www.recap.com and www.newsanalyser.com.

to the development of third-generation biotechnology techniques: insulin and human growth hormone were already in clinical use, alteplase had been isolated and purified in 1964, and epoietin in 1960. Once the genes for the molecules had been cloned, they moved from bench to approval in 5–6 years (Sneader, 2005).

This is not dissimilar to the best-case examples of traditional pharmacological approaches. For example, at the height of HIV/AIDS crises in the 1980s, azidothymidine moved from compound screening in cell cultures to approval on a named patient basis in less than three years. Moreover, biotechnology does not always yield such rapid results: Avastin, the first of the angiogenesis inhibitors, was approved in 2004, 35 years after the angiogenesis research that led to its discovery began (Glassman and Sun, 2004). Yet, even this has been termed a "low hanging fruit" by those in mAb firms (Mitchell, 2005: 906). By comparison some traditional pharmacological approaches have been more rapid, e.g., ACE inhibitors (discovered in 1968, approved for limited use in 1981, with the licence extended in 1985) and statins (from research hypothesis in 1971 to first approval in 1987) (Sneader, 2005). Hence, there is as yet little evidence that biotechnology provides a more rapid route from bench to clinic.

6. The impact of biotechnology on industrial structure

Since the early 1980s a very large and well-financed global biotechnology sector has developed, growing from just a few dozen pioneers in 1980 to nearly 300 biotech firms in the US alone by 1988 (OTA, 1991; Robbins-Roth, 2000). Investor enthusiasm has lead this population to grow to an estimated 4000–5000 businesses globally (Ernst and Young, 2004). The sector raised an estimated $80 billion in the five years to 2004, with $18 billion invested during 2003 in North America and Europe alone (Ernst and Young, 2004).

So far, this paper has described how biotechnology's impact as been evident in upstream pharmaceutical R&D where it has not yet boosted productivity, and in generating new types of drugs that have not yet achieved significant impacts on healthcare. How then are we to understand the changes in the industry which have required such large scale funding for so long?

It is clear that the number of new firms formed represents a radical change in the industrial structure of the pharmaceutical industry (traditionally thought to be closed to new entrants due to high barriers to entry – see Gassmann et al., 2004). While the previous discussion of what is and what is not a biotechnology company suggests care must be taken in interpreting this change, there is no doubt that a 'pure biotech' sector has emerged, developing biopharmaceuticals. Nonetheless, there are other factors at work.

In particular, the potential dynamic economies of scale and scope that have been opened up by recent changes in research technology (which as we noted in Section 3.1 are not all related to biotechnology) have required pharmaceutical firms to continuously build up a range of technological capabilities, as illustrated in Fig. 1. As a result, modern drug development requires a larger and more complex co-ordination of knowledge to establish and characterise disease correlates. Building up capabilities in-house in the 'ever broader range of specialised skills and techniques required for modern drug discovery is [now] beyond the financial capacity of even the largest companies' (SmithKline Beecham, 1992: 17).[31] As a result, large firms are outsourcing more research and building up large numbers of strategic alliances. By the end of the 1990s a new form of heavily networked industrial structure was emerging (Powell et al., 2005) with large companies committing as much as 30% of their R&D budget to technology and product development collaborations with smaller companies (see Gassmann et al., 2004 on increased outsourcing).

Fig. 4 shows the timing and composition of alliances between 1993 and 2004 in which GSK acquired genomics technology from other firms (including in one case a collaborative programme between Glaxo-Wellcome and SmithKline Beecham).[32] Each block represents an element of an alliance. For example, the first alliance undertaken in this area was the purchase of sequence data from Human Genome Sciences, used to identify new drug targets in 1993. The last alliance with First Genetic Trust, concerned the purchase of patient tissue useful for target validation and development of diagnostic tests to identify subpopulations of patients that might benefit from particular drugs (represented as three blocks).[33]

[31] This quote is echoed in company reports and publications throughout the 1990s, although SmithKline Beecham appears to have been early to acknowledge this (for example see Zeneca Annual Report, 1996: 16 and for Pfizer see Rodengen, 1999: 142).

[32] The analysis focuses on alliances with firms, and therefore excludes numerous alliances with public sector organisations which are less reliably reported.

[33] The alliance data in Figs. 4 and 5 was obtained from searches on the RECAP database (www.recap.com). RECAP categorises alliances based on manual indexing (under categories such as bioinformatics, or DNA sequencing) of alliances according to publicly available information such as news coverage in mainstream industry publications. As a result these data are likely to under represent alliances involving

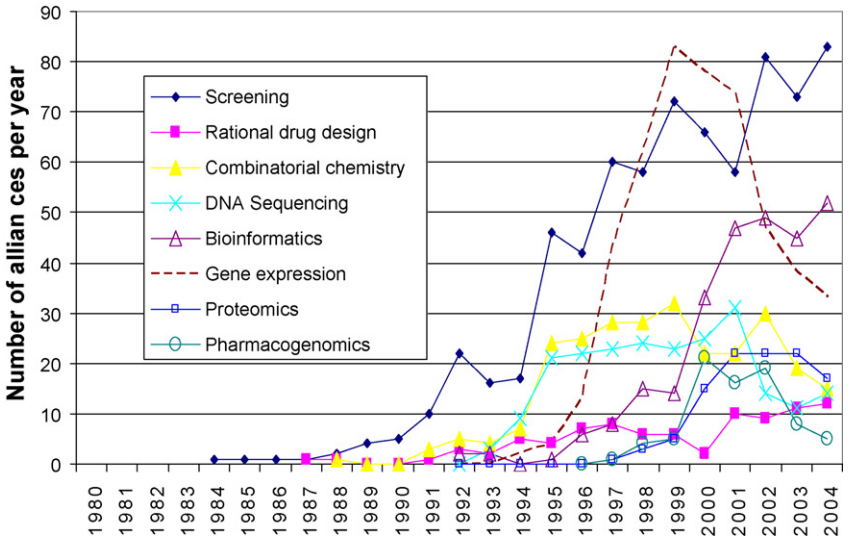

Fig. 5. Successive waves of technology platform alliances between large pharma and biotechs. *Source*: Author's original, based on data from www.recap.com.

The pattern of alliances in Fig. 4 complements the evidence of internal capacity building in Fig. 1. When viewed together they provide further strong evidence of the incremental and continuous creative accumulation of technological capabilities in biotech within large firms. While Figs. 1 and 3 relate to a single firm, Fig. 5 shows how large pharmaceutical firms across the industry as a whole have relied on alliances to develop new internal capabilities that relate to platform technologies (e.g., screening systems, sets of reagents) as opposed to therapeutics. Since the inception of the biotechnology industry additional waves of technologies have emerged which have broadened the range of technological options available over time. In the 1980s, these alliances focused on technologies related to the traditions of the synthetic organic heuristic (such as rational drug design and combinatorial chemistry), but by the early 1990s pharmaceutical firms were purchasing more technologies related to biology (gene expression, proteomics). Fig. 4 depicts how these investments in new technology (bioinformatics software, DNA sequencing equipment, animal models) have facilitated the application of genomics further up the pharmaceutical value chain so that this knowledge now contributes to the start, middle and end of the journey from bench to clinic.

The cost of building capabilities in genomics alone has been estimated at between $100 million and $300 million annually (Gassmann et al., 2004), suggesting that the sort of systems integration model being used by the largest firms is well beyond the means of small/medium sized companies. This indicates that although biotechnology firms may do well at developing a number of therapies in their specialised areas, pharmaceutical firms are better positioned to use platform technologies to industrialise drug discovery and may be able to generate economies of scale and scope unavailable to smaller firms. Since small firms are unable to afford this broad range of platform technologies, they enter into these alliances with different aims – typically offering tools and services relating to drug discovery to the pharmaceutical industry while they survive the lean years awaiting the maturation of their therapeutic pipeline.

This new, networked industrial structure is also being dominated by large firms attempting to reduce the impact of failures on their profitability, whilst increasing the size of their R&D pipelines (see Nightingale and Mahdi, 2006 for a suggested link to changes in finance and the unbundling of risk by institutional investors). Large pharmaceutical firms fill gaps in their R&D pipelines and research portfolios by buying in and co-developing drugs at various stages of development with smaller firms. This is related to a very significant increase in the number of small biotech firms seeking to discover new drugs since

smaller firms with less motivation to publish press releases (e.g., those without publicly traded shares). Fig. 5 uses RECAP's own catagories (as shown in the key to Fig. 5). More detailed analysis of the terms and intended outcomes of alliances were obtained for Fig. 4 by direct reading of these press-releases, available from press release databases at www.recap.com, and www.newsanalyzer.com. Using the RECAP descriptors that make up the subfield for genomics as a whole, alliances were manually searched and classified in the fields shown in Fig. 4.

the 1980s (Hopkins et al., 2006a). This, in turn, is partly explained by sectoral growth, but also by the growth in diversity of biotech firm strategies with some biotech firms choosing not to develop drugs but to develop technology platforms and provide contract research services, although some may opt for dual strategies over time (Rothman and Kraft, 2006). By focusing on the discovery and early stage development of new therapeutic products in an implicit division of labour with larger firms, the genomics sector has seen the number of collaborations relating to the area of target identification and validation grow from zero in 1990 to over 500 by 2000 (Hopkins et al., 2006a). These alliances cover the sale of platforms and data, as well as drug targets and drug candidates. Furthermore, in the early 1990s many biotech firms shifted their strategy towards small-molecule drugs that are more easily absorbed, less likely to be immunogenic, and are orally available and therefore easier to distribute in the body, further blurring the boundary between 'biotech' and small molecule (as discussed above in Section 5).

Together, the emergence of a 'pure biotech' sector, the increasing need for firms of all sizes to build up technological capabilities through external links, and the increased focus on using alliances to buy in drugs, has created a substantial shift in industry structure. Our analysis suggests that rather than biotechnology having its own networked type of organisational structure that has creatively destroyed the older Chandlerian model, we are seeing the emergence of a mixed model in which systems integrators (mainly but not exclusively large pharmaceutical firms) co-ordinate an outsourced knowledge production system.[34] The growth of networks might therefore be simply reflecting a shift towards a Toyota style outsourced supply chain, with large firms at their centre (Pavitt, 1998). Indeed, many of the smaller biotechnology firms are entirely dependent on the pharmaceutical industry to buy their platforms and sell their drugs (Rothman and Kraft, 2006).

7. Conclusions

7.1. Assessing the impact of biotechnology

Having reviewed the data we are now in a position to assess the impact of biotechnology on drug discovery, drug development and clinical practice. The substantial impact of biotechnology on *drug discovery* has to be understood in the context of a number of important industry trends, including changing heuristics, the shift towards blockbuster products, and the ongoing decline in R&D productivity. Molecular biology techniques were initially applied to further extend the existing synthetic chemistry heuristic and implement the rational drug design heuristic. These techniques were steadily integrated with the existing operational principles of discovery programmes during the 1980s. With the advent of genomics, combinatorial chemistry and HTS in the 1990s drug discovery was increasingly industrialised and transformed. Large numbers of new drug targets were identified against which leads could be rapidly generated. However, the validation of these new targets is proving to be slower than expected, which has constrained productivity improvements.

Biotechnology has also led to the creation of new therapeutic modalities including recombinant therapeutic proteins and mAbs. During the 1980s a number of important biopharmaceuticals were produced by first-mover biotechnology firms and some pharmaceutical firms such as Lilly and Johnson & Johnson, but innovation strategies based on these products were not widely adopted. Only in recent years has there been wider interest from large pharma, and this is now starting to feed through into development projects and product approvals.

In traditional small-molecule drug development there is little evidence to date that platform *technologies* such as pharmacogenetics and toxicogenomics have had a significant impact. However, moves to use biotechnology to streamline the drug development process (e.g. the FDAs Critical Path Initiative), as well as to improve development process management and enhance modes of feedback from clinical development to drug discovery, may in the longer term lead to significant improvements in the productivity of development.

Biotechnology has shown more immediate promise in relation to new biological *products*, such as mAbs and therapeutic proteins. Yet even here there is a danger that their shorter approval times and lower attrition rates will decrease over time as the fast-track approval mechanisms and relatively lower regulatory hurdles in areas of unmet medical need give way to familiar 'increases in efficacy' requirements and the commercial pressure to seek profits in more certain markets.

Ultimately, biotechnology may improve the efficiency of development through changes in the discovery and preclinical phases to weed out poorer drug candidates at an earlier stage in the innovation cycle. However, paradoxically, at present it appears that new drugs against the novel targets identified through genomics have a

[34] Before assigning this change solely to biotechnology, it should be noted that all forms of outsourcing have increased in the last decade (Sturgeon, 2002).

lower success rate during development than compounds against well-established targets. In this sense, at least in the short term, biotechnology has exacerbated the problems associated with drug development, rather than led to revolutionary improvements.

If we turn to clinical practice, stories abound in the press about the impact that biotechnology products are already having on the lives of patients (Arnst, 2005; Bergman, 2004). Certainly, there is evidence that biotechnology has provided a number of effective and highly profitable therapies based on novel modalities in areas of unmet clinical need, e.g., Herceptin (Trastuzumab), but even here talk of revolutionary effects are contested (Littlejohn, 2006). The number of these drugs that have been great commercial successes is small ($n < 15$ since 1980) and many are restricted to the treatment of relatively rare conditions. Biotechnology's contribution to clinical practice is accentuated by the dwindling productivity of traditional pharmacological approaches, which ensures that they make up an important and increasing proportion of total therapeutic approvals. Nonetheless, the evidence of clear clinical benefit from more recently developed products based on genomics has yet to emerge.

So, what has been the overall impact of biotechnology on drug innovation? We must start by acknowledging that biotechnology has had a positive impact on the scope of target options available in drug discovery. Furthermore, it has helped the creation of a new industrial sector and has enabled a massive restructuring of the industrial organisation of target identification and validation, drug discovery and the very early stages of development. The increasing outsourcing of these elements of the drug innovation cycle represents a form of vertical disintegration that allows better risk and portfolio management. This new industrial division of labour has resulted in a much greater numbers of drugs (both small molecule and biological) created by biotechnology firms entering the drug development process downstream, where they are managed within large companies.

Despite this shift in the source of new knowledge, within the industry as a whole, overall productivity as measured by drug approvals has continued to decline. This is perhaps unsurprising, as the locus of falling productivity is the development stage and, as highlighted above, this has been largely unaffected by advances in biotechnology. For the advocates of biotechnology this is simply a matter of timing, as in the medium term it is assumed that new innovations will lead to the discovery of greater numbers of high-quality drug candidates entering clinical testing and a streamlining of the assessment and development process. Even though this is not a revolution, to date there is insufficient hard evidence to assess whether even these expectation will become a reality.

7.2. Has biotechnology made any difference?

In arguing that biotechnology has failed to increase productivity in the creation of new therapeutics, we invite an obvious counter-factual question: where would modern drug discovery be without biotechnology? Certainly, the synthetic heuristic that produced spectacular successes in the post-war period was struggling to generate major successes by the 1960s, and in terms of marketed products has increasingly produced me-too drugs in place of truly innovative medicines (Happold, 1967; Angell, 2004). Would this decline have been worse were it not for biotechnology? Answers to such questions must, by necessity, be speculative. However, opinion in industry does not suggest that biotechnology has made a major contribution in lessening the decline as yet.[35] Indeed, some blame the cost of integrating biotechnology into the innovation processes, with the accompanying disruption to the observational approach (i.e., close links from research to the clinic and back), for the decreased productivity and greater co-ordination problems across ever-larger pharmaceutical firms (Booth and Zemmel, 2004; Horrobin, 2003; Higgs, 2004; Chu, 2006). Others note that biotech investment has not even impacted on the decline in the number of drugs pharmaceutical companies have had in trials over the last ten years (Hood and Perlmutter, 2004).

This is not to say that biotechnology cannot and will not contribute in the future by increasing productivity. The evidence in this paper clearly shows that biotechnology is not a fad that will be abandoned by industry in a return to classical methods. The importance of biotechnology to the pharmaceutical industry is supported by the fact that the proportion of large company R&D spent on outsourced activities has continued to increase over the last decade. Although, at present there is no well validated evidence on this phenomenon, it implies that in some instances discovery is being more efficiently carried out in small biotechnology firms than in in-house R&D, within large companies.

[35] Higgs (2004: 727) goes so far as to suggest that: 'the genome sequence has a far greater capacity to mislead than it has to illuminate', whilst noting that in the HTS systems of today, 'optimisation' is often taken to mean 'maximisation' in terms of drug binding. This is in contrast, Higgs (ibid) laments, to the modes of action of previously successful drugs, such as asprin and ibuprofen, that bind so weakly to their targets that they would probably not count as 'hits' today.

In explaining the lack of any major contribution from biotech to solving the productivity crisis, the data would seem to support the suggestion that the infrastructure to exploit biotechnology's data remains immature (Hood and Perlmutter, 2004; cf. Nightingale, 2004). In addition, the increasing complexity of the pathological processes in diseases that are currently being tacked has to be taken into account when assessing qualitative and quantitative improvements in productivity (Nightingale and Martin, 2004; Chu, 2006). *Quantitative declines in productivity may hide very real qualitative improvements*, as the pharmaceutical industry tackles increasingly difficult diseases (ibid). This is intuitive when we consider the nature of the industry's shift from infectious to chronic diseases. Many of the successes of the golden age (such as the sulphonamides, penicillin, and other antibiotics) were drugs that targeted invading (exogenous) organisms. The restoration of balance to a biological system composed of endogenous components or subsystems is an entirely different operational principle (Nightingale and Mahdi, 2006: 78–79). In this context, the historical success of the industry has often been blamed for creating unrealistic expectations in the public mind (Happold, 1967: 2; Porter, 1999: 718; Chu, 2006). At the same time, biotechnology's contribution to chronic disease (a relatively low number of distinct protein replacement therapies) may be 'low hanging fruit' or atypical examples (Nightingale and Mahdi, 2006).

7.3. The idea that biotechnology is bringing about a revolution is misplaced

Given these problems with the revolutionary model, it is hard not to conclude that many of the widely held expectations about the impact of biotechnology are over-optimistic. Given the extensive portfolio of policies (outlined in the introduction) that draw on this revolutionary model, there is clearly a need for a more appropriate basis for policy making (Nightingale and Martin, 2004). One might speculate that such a model might be found within the academic literature that draws on the work of economic historians.[36] This literature highlights how technologies are often initially very primitive when they are first introduced into a narrow range of pre-existing socio-technical systems (typically as new process technologies for producing existing products). Rapid advances in productivity are constrained by bottlenecks elsewhere in the system that limit overall performance and act as focusing devices for further innovation (Rosenberg, 1979). These complementary technical and organisational innovations in surrounding infrastructure can then take decades to be generated which means that new technologies are often subject to large and increasing development costs (von Tunzelmann, 1993: 5).[37]

The evidence presented in this paper suggests that biotechnology may be following a remarkably similar pattern. Biotechnology was first introduced as a process technology for making existing products, and its incremental expansion into wider areas of application has required complementary, and very varied, innovations and organisational changes in drug discovery, drug development and clinical practice. As a consequence, the impact of biotechnology on drug development and in the clinic is far more limited than would be expected from the 'revolutionary' nature of the changes in science. Biotechnology is being used within established heuristics and has broadened the scope of the technological options available to drug developers at a time when the industry is addressing qualitatively more complex medical problems.

This scepticism about the biotechnology revolution needs to be interpreted in the light of its very different types of techniques and procedures and their diverse impact in different areas. It therefore raises questions about the analytical validity of an overarching concept of 'technical change in biotech', rather than technical change in specific areas of application involving particular technologies. This paper has focused on drug innovation, but not other areas of medicinal biotechnology, such as diagnostics, while non-medical applications have not been explored at all. Without further work the 'biotech revolution' cannot be dismissed completely.

Furthermore, the paper has also not examined in detail other changes in the pharmaceutical industry such as the economies of scale and scope in experimentation allowed by automation (Nightingale, 2000) and improvements in innovation management; more efficient 'go/no go' decision making processes; tighter controls on outsourced work undertaken in contract research

[36] See David (1990), Rosenberg (1979, 1982), Crafts (2004), von Tunzelmann (1993, 1978), Freeman (1982), and Freeman and Louca (2002).

[37] Freeman and Louca (2002) highlight how the impact of major innovations can take about 40–60 years. David (1990) has highlighted how it took approximately 40 years for electricity to change productivity, and required changes in factory organisation as electricity allowed a more decentralised form of production than steam power that relied on shafts to distribute power (Devine, 1983). Similarly, von Tunzelmann (1993) positions the impact of steam power in the late 19th century significantly beyond its initial introduction.

organisations; and use of IT based clinical knowledge management systems that may reduce development times and costs (Pisano, 1997; Booth and Zemmel, 2004). Isolating the impact that biotechnology has had on the productivity of large pharmaceutical firms is particularly difficult. Even enthusiastic investors in the technology, such as GSK, attribute increasing R&D productivity to judicious outsourcing and the restructuring of their large internal R&D departments into smaller centres of excellence (Jack, 2006). Similarly firms at the forefront of development efficiencies in clinical trials attribute their success to these organisational approaches rather than to biotechnology (AstraZeneca, 2001). As such, some metrics presented here may substantially over estimate the impact of biotechnology, further strengthening the scepticism in this conclusion.

7.4. The biotechnology revolution: morals of the myth

If the revolutionary model of technological change associated with biotechnology is not supported by empirical evidence, a number of important questions for both policy makers and studies of innovation are raised.

Firstly, what have been the main consequences of adopting an inappropriate model? As mentioned in the introduction, the revolutionary model has underpinned a range of policy initiatives. While many of the goals of these policies are worthy in themselves, our analysis calls into question many assumptions that underpin policy design. In particular, it questions the over-emphasis on biotechnologies, such as genomics, within R&D programmes aimed at improving health. It may well be better to allocate a greater proportion of resources to other activities, which offer more immediate health gains (e.g., the better adoption of existing 'low tech' technologies with a proven track record of safety and efficacy). Our analysis also undermines the idea that the biotech sector will play a key role in economic growth or regional development through the rapid creation of thousands of new, high-technology jobs.

All this underscores the general and pressing need for a more nuanced appraisal of technological change in this area, together with careful assessments of the likely dynamics, impacts and time-scales. These would allow decision makers to be better placed to lend effective support to emerging technologies and industrial sectors in both the short and longer terms. With such appropriate support the benefits of biotechnology are more likely to be realised, and investor backlashes avoided.

Secondly, what would a more realistic model of technological change in medical biotechnology look like? As we have stressed, it would need to include the development of complementary technologies, organisational innovation and new forms of governance. For example, the introduction of many gene and cell based biological drugs will require novel manufacturing technologies, changes in the organisation of clinical work, innovative service models and new regulatory environments. Drawing on ideas from the sociology of technology (Bijker, 1995; Callon, 1986a,b; Martin, 1999) we can think of this as a co-evolutionary process in which scientific, technical, industrial, clinical and regulatory changes enable and shape each other.

In thinking of innovation as a co-evolutionary process, policy-makers should take into account the very particular characteristics of technological change in medicine and specifically the problem of 'translation', where new knowledge and technologies are introduced into routine clinical work. The process of translation is complex and not unidirectional (Vos, 1991) with feedback from clinical experience a vital, but often neglected, element of successful clinical development. Medical innovation is not just the simple application of new scientific knowledge, as new drugs have to show clinical utility in practical, real-world situations. As a result, many kinds of knowledge underpin clinical practice, with important tradeoffs being made during drug development between clinical utility, safety, and the ease with which a new product can be integrated into everyday professional work. From this perspective, it is not easy to separate the process of drug development from the structure and routines of clinical practice. As a consequence, even if it is possible to improve the technical efficiency of drug assessment, it may not be possible to quickly change the process used to demonstrate utility (e.g., clinical trials, and economic assessments by health service providers). Technological change in this domain has not kept pace with up-stream discovery and the assessment process remains costly, time-consuming and uncertain.[38]

Finally, it is worth considering why the myth of the biotechnology revolution has been so prevalent and influential. The key implication of this paper is not the trivial one that biotechnology has been over-hyped. Instead, we wish to make a more subtle point that the creation of

[38] The need to both improve the efficiency of the drug assessment process and stimulate translation is increasing recognised as a key area for public policy (FDA, 2004). However, it must be stressed that even if significant gains can be made in streamlining drug development, this will not bring in an era of revolutionary change, for as we have suggested, there are more fundamental reasons why change in medicine is incremental.

widespread expectations about the impact of biotechnology is an important part of the process of technological change itself. Shared expectations are needed to ensure the co-ordination of the large amounts of resources needed for major innovations. The key message of the paper is that biotechnology is not being hyped because it is a revolutionary technology. If it were revolutionary there would be no need for hype, as people would be too busy making new medicines. Instead, it is being hyped precisely because it is not revolutionary, and shared expectations are needed to co-ordinate the long-term, incremental process of technological accumulation. As such the biotechnology revolution myth might be viewed as a rhetorical device employed to generate the necessary political, social, and financial capital to allow a perceived promise to emerge (see Guice, 1999).

Social scientists studying technological change in biotechnology are not, therefore, passive investigators, but are active co-producers of the expectations that drive the industry (Hedgecoe and Martin, 2003). They have a responsibility to critically engage with the intellectual tools they bring to the exercise. This is important because inappropriate models of innovation have diffused from academia and have led to inappropriate investment and policy decisions. If biotechnology is following the pattern of technological change described by historians rather than the revolutionary model, we would expect it to generate returns over decades rather than years. These timescales may render many current business models unviable, (especially in the small firm sector), and may make some investments uneconomic when the future profits are properly discounted and opportunity costs taken into account. However, by abandoning the revolutionary model as a myth, promoting more realistic public expectations and recognising the incremental, complex nature of major technological changes it may be possible for policy makers to promote the development and adoption of biotechnology, and improve public health through a better informed, more efficient allocation of resources to innovations that can deliver real health gains.

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