Chapter 9

Commercialisation

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Chapter overview

In this Chapter we review the challenges faced in commercialising emerging biotechnologies given the peculiarly long development phase and uncertain outcomes associated with them. We review the experience of the pharmaceutical industry (one area to have made significant attempts to commercialise biotechnology) and the way in which all research, including publicly funded academic research, has become dominated by the expectation of future commercial profit.

Since profit in knowledge-intensive industries depends significantly on the existence of a system for the protection of intellectual property, we describe the current system and its limitations as it applies to emerging biotechnologies and find a tendency for patent protection for emerging biotechnologies to be both too broad and too short to provide the commercial incentive it is intended to provide: by being too broad it discourages creative competition and by being too short it does not secure the prospect of sufficient returns on investment. We examine a number of modifications of the patent system or of regulation which address either the problem of excessive breadth or of inadequate length, and find them useful in certain situations.

We make a distinction between different types of biotechnologies and to show the particular problems attached to intellectual property protection in one of them. In particular, for biotechnologies such as pharmaceuticals and plant breeding which involve intervening in existing biological systems we argue that only radical policy changes can deal with the distortion of commercial incentives that result. These build on the foundations of proposals for health impact funds and value based pricing to offer a new way of paying for drugs and new crop varieties based on the value of *impact* on health and agriculture/environment. For other biotechnologies such as biomanufacturing processes, impact payments are unnecessary and inappropriate: here the necessary incentives will be provided by ecotaxation and similar steering of the market mechanism. In both cases there is a role to be played by social engagement to align commercial incentives with public good.

Introduction

9.1 In biotechnology, as in other science-intensive areas, *commercial exploitation* comes only when the conjunctions between relevant knowledge, practices, products and applications are reasonably well developed. We can therefore expect little experience of commercial exploitation in technologies that are only now emerging, where possible conjunctions are still being explored. The most relevant experience we can hope to find will be of the commercial exploitation of the early (and now 'emerged') biotechnologies, for example in agriculture and pharmaceuticals. However, commercialisation might be given another meaning: the infusion of *commercial purpose* into the assembling of that conjunction from the very first and, indeed, the prominence of commercial values in shaping and selecting biotechnologies. In this Chapter we will consider commercialisation in both of these senses. We will argue that emerging biotechnologies now show a great deal of commercialisation in the second sense.[627]

9.2 The set of principles we set out in Chapter 4 relate to choices and decisions that are in some sense political,[628] to which a good deal of time and care can and should be devoted. Commercial activities, on the other hand, operate within the market mechanism. Since Adam Smith, economists have applauded the market mechanism and the profit motive for coordinating the efforts of many people and organisations in taking a multitude of separate decisions (Smith's 'invisible hand') to produce a globally efficient distribution of resource use. It would be naïve to expect that each of these private, individual decisions will always be taken in accordance with the public virtues we identified in Chapter 4. Instead, in this Chapter, we consider what are the regulatory frameworks and institutional forces that affect commercial or commercialised activities involving emerging biotechnologies, and how a public ethics might bear upon these to produce a better alignment of entrepreneurs' decisions with public good than either the market alone or existing public innovation governance can achieve.

9.3 Regarding commercial exploitation, emerging biotechnologies face very different conditions according to sector. The greatest apparent opportunities for profit have been perceived to be in

[627] The implications of market values 'crowding out' other sources of normativity was made emphatically in a recent book by the political philosopher, Michael Sandel; see: Sandel M (2012) *What money can't buy: the moral limits of markets* (London: Allen Lane). Sandel's prescription in response for this situation is a call for a kind of public ethics.

[628] See paragraphs 4.28 to 4.32.

'biopharma', followed by other areas of health care; here, emerging biotechnologies promise to respond to unmet needs and, if they can do so safely, significant commercial returns can be expected. Indeed, some products, such as monoclonal antibodies, are already successfully generating revenue: the most successful of them, adalimumab ('Humira'®)[629] which emerged during the 1990s from Cambridge Antibody Technology's development of phage display technology was, as of February 2012, expected by some analysts to become the highest-selling drug ever over its lifetime, with $7.9 billion of sales worldwide in 2011 alone.[630]

9.4 Biotechnologies have also started to address unmet needs in industrial chemicals and in plant and animal breeding. The main unmet needs in these sectors are reduction of fossil fuel use, and increases in food production within the constraints of existing resources. Here, the public good to be served by these technologies is currently far from being reflected in prices, and therefore profit. Accordingly we have to treat the different sectors separately to a large extent. However, we begin with two relatively common themes that cut across emerging biotechnologies generally: the framing of emerging biotechnologies in terms of commercial values ('commercialisation' in our second sense), and the effect of intellectual property protections.

The profit motive in biotechnology research

Economic rationality and the pursuit of scientific knowledge

9.5 Established businesses are generally wary of investing in emerging biotechnologies due to the probable high cost and delayed, uncertain outcome of commercial exploitation. In the interests of their shareholders they are probably right to be cautious. There are, however, reasons why businesses may diverge from what is in shareholders' interests (understood as maximising their shareholder value). One is the excitement that may be attached to any new technology that offers exceptional potential for profit, especially technologies that are reported by the media to be making a significant profit for other firms. However, for there to be a mania like the dot-com boom of the late 1990s, one other ingredient is required, namely poor returns on capital for low-risk investments. Financiers then have a strong incentive to persuade their clients (and themselves) that the likely returns in new technologies are expected to be higher – and the risk attached lower – than economic history would suggest. The biotechnology boom was not as marked as the dot-com boom, due to the longer time period needed to get products to market but it showed the same cycle of early investment in the 1990s, in the hope of high returns, followed by disillusion after 2000 when the difficulties became more apparent.[631] Such 'biotech mania' has now subsided.

9.6 The other deviation from economic rationality arises from the inclinations of those who work in the private sector. High quality scientists are needed by businesses in order to develop marketable and saleable products, but such scientists are likely to be interested in 'the science itself' rather than merely sales, profits and incomes. The private sector therefore must accept that some of its employees working in research and development (R&D) will be keen to put their time and energies into advancing research rather than focusing solely on advancing firms' profits. In fact JK Galbraith's concept of the 'technostructure'[632] makes a similar point about whole body of higher-level employees. In the managerial capitalism which developed in large firms in the 1930s and 1940s, such employees collectively freed themselves to a large extent

[629] Adalimumab is used to treat a number of illnesses, including Crohn's disease, several types of arthritis and psoriasis.
[630] Comer B (2012) Brand of the year: Humira *PharmExec* February 1, available at: http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=757392.
[631] A significant sobering moment was the death of Jesse Gelsinger, the first recorded person to die in a gene therapy clinical trial. See: Wilson JM (2009) A history lesson for stem cells *Science* **324**: 727-8. See also Lähteenmäki R and Lawrence S (2007) Public biotech 2006 – the numbers *Nature Biotechnology* **25**: 729-37, for detail on biotechnology financing in the very early years of this century.
[632] Galbraith JK (2007) *The new industrial state* (Princeton, New Jersey: Princeton University Press).

from the close control of shareholders, and could indulge their interest in the growth and survival of their firm as opposed to its profitability.

9.7 Clearly, under managerial capitalism the sectional interest of scientists in carrying out research is more likely to be indulged than under a managerial approach that prioritises profit. During the 1980s a counter-revolution began in the US and the UK to reassert the maximisation of shareholder value as the goal of management. As growth requires profit and profit requires growth, the change is not necessarily obvious. The managerial approach depends on shareholders' understanding of how profit can be made: a venture capitalist may be as motivated by profit as an asset-stripper, but the former aims to make profit through investment in technology, the latter does not. Long-term commercial funding *may* be available for R&D of biotechnologies that are expected to give a good commercial return. Modest funding may also be available for R&D that is not expected to generate large profits, especially where large firms have subscribed to the values of corporate social responsibility. In general, however, the climate requires R&D programmes to carry a realistic prospect of profitability.

Research and profit-seeking in the pharmaceutical sector

9.8 As we have seen, biotechnology can be used in a wide range of sectors, but until now the bulk of research and commercial exploitation has been in health care in general and research-intensive pharmaceuticals.[633]

9.9 Shareholders, naturally, want research to generate profit. The motives of scientists in drug discovery are generally more complex. For example, they may have left academic research in order to get their research funded rather than to enrich themselves financially. Nonetheless, Big Pharmaceutical Firms (BPFs) have been using stock options to motivate senior R&D personnel by aligning their interests with those of shareholders. Some BPFs have recently introduced a system of bonuses for R&D personnel based on the delivery of new drugs to the next stage of the pipeline. Perhaps the most extreme reorganisation is that at GlaxoSmithKline (GSK) where small business units, analogous to in-house biotechnology firms, have to compete with one another for funding, and get it only as long as their projects are successful.[634]

9.10 Shareholder value now appears to demand drastic reductions in the research carried out by in-house R&D in corporations, in favour of increased dependence on university and similar research, packaged in spin-outs. The consensus among BPFs is now to let the dedicated biotechnology firms (DBFs: largely university and industry spin-outs) do much of the most speculative and creative research, such as studying the pathway of disease and working out how to counteract it, as well as carrying out pre-clinical testing of the new active substance (NAS[635]) they produce. At this point, it is possible that a BPF may be prepared to invest in the NAS. One mechanism for the provision of funds is that, when a pre-arranged milestone is reached, sufficient funding is made available for the next stage of the research. The more funds the BPF provides, the larger its stake in the drug. Alternatively, there may be a trade sale of the whole DBF to the BPF. Rarely, an independent DBF may wait until its NAS is ready for market and then licence it to a BPF (if at all).

9.11 Whatever happens to the outputs of the spin-out, there is one inevitable consequence of its existence: those university scientists involved in it will do their scientific work with an eye to the

[633] I.e. non-generic pharmaceuticals.

[634] See, for example, evidence given by Dr Ian Tomlinson, Senior Vice-President - Head of Worldwide Business Development and Biopharmaceuticals R&D at GlaxoSmithKline, to the House of Commons Select Committee on Science and Technology: "Innovation comes from one person having an idea, or a small group having an idea, and prosecuting that idea to some kind of milestone. That is why we have changed dramatically over the last five years. We used to have thousands of people working in R&D. We would throw a load of people at the problem and we would hope to solve it in that way. Now, we have 50-people groups, with a leader fully empowered to prosecute a very specific area of science. If they work, great. If it does not work, that is Darwinian evolution. You have a model where people are accountable for prosecuting a specific area of science." House of Commons Science and Technology Committee (2012) *Bridging the "valley of death": improving the commercialisation of research*, available at: http://www.publications.parliament.uk/pa/cm201012/cmselect/cmsctech/uc1936-i/uc193601.htm.

[635] This term is used in preference to new chemical entities (NCEs) to encompass large molecule drugs (e.g. monoclonal antibodies) as well as small molecules that were the traditional targets of pharmaceutical firms.

profit that it may yield, as will colleagues who may consider following their example. In this they are likely to be encouraged by senior colleagues and managers within the university, since the institution will have a share in the equity and will be able to charge for the use of university facilities (to say nothing of impact studies in the Research Excellence Framework[636]).

9.12 What we have described are the elements of a transformation: 20 to 30 years ago, in pharmaceuticals, the field comprised mainly curiosity-driven scientists in universities and research institutes cooperating with (and partly funded by) scientists in corporate research laboratories, who themselves had licence to 'think long'. Now the latter are driven hard to generate profit and the former are also very interested in it. In other sectors of biotechnology, such as industrial biotechnology, the present situation is similar, with the difference that, in newly emerging industries, there is no corporate golden age to look back to and rather less scope for a DBF to sell to a big firm. Given the importance of profit to the commercial sectors in which biotechnologies are exploited, to understand the market's effect on the social shaping of biotechnologies we must focus squarely on how profit is made in biotechnology, and how far the profit made reflects the value of biotechnology to society.

Patent protection for public goods

9.13 A central activity, for both commercial and non-commercial biotechnology research, is the production of knowledge. Knowledge of any kind is usually considered to be a public good in the weak sense that it is *non-rivalrous* in use but it may also exhibit the characteristic of being *non-excludable*.[637] As such, in emerging biotechnologies as elsewhere, much of the organised generation of scientific knowledge is funded by Government and, in the case of biomedical research, by charities too, because it is assumed that it will be underprovided by commercial organisations who cannot secure sufficient profit from it. It is in this sense that, for example, the Biotechnology and Biological Sciences Research Council refers to 'public-good plant breeding'.[638] (Of course, scientific knowledge may come about as a by-product of commercially-funded research, or indeed through the experience of using technologies, or experimentation with them. The emphasis on academically organised scientific research, in fact, may lead us to neglect the contribution of these other activities both to the fund of scientific knowledge, which may then be taken up as a bridge to further knowledge, and to human welfare more generally.)

9.14 In order to encourage the commercial development of knowledge, enforceable patents or other forms of intellectual property rights (IPR) have been used as a way of making the knowledge generated by research an excludable good. Patenting knowledge also makes it possible for profit to be made from the use or licensing of that knowledge. The nature and effects of IPR are central to the commercialisation of biotechnology, and therefore to this Chapter. In the next section we therefore set out the framework of IPR as they apply to biotechnologies in general and emerging biotechnologies in particular. With those clear, we shall proceed to the problems that arise in ensuring adequate incentives for the commercial development and use of emerging biotechnologies.

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[636] The Research Excellence Framework is the system for assessing the quality of research in UK higher education institutions; assessments against this framework are used by funding bodies to inform the allocation of funding to institutions; see: http://www.ref.ac.uk. See also paragraph 6.38ff.

[637] See paragraph 4.6ff.

[638] See for example, BBSRC (2004) *Review of BBSRC-funded research relevant to crop science*, available at: http://www.bbsrc.ac.uk/web/FILES/Reviews/0404_crop_science.pdf, p6. The BBSRC noted to us: "The BBSRC does not have a standing definition of 'public-good'; instead we work with a shared understanding of its meaning. Public-good research will often address needs that are not currently being met by market-forces. In the context of the crop science review, "public good" refers to (pre-) breeding related work on traits not necessarily of immediate interest to commercial breeders but which would be needed in the longer term to address societal concerns about climate change etc., so called sustainability traits e.g. stress tolerance, resource-use efficiency etc. It is important that there is some benefit to the public and that the research is not solely to the advantage of any specific commercial entity." BBSRC, personal communication, 6 September 2011.

Purpose and operation of the patent system

9.15 The purpose of the patent system, as recently set out by Lord Neuberger in the UK Supreme Court, is

> "…to provide a temporary monopoly as an incentive to innovation, while at the same time facilitating the early dissemination of any such innovation through an early application for a patent, and its subsequent publication. Although this is true in any sector, it has particular force in the pharmaceutical field, where even many of those who are sceptical about the value of intellectual property rights accept that there is a public interest in, and a commercial need for, patent protection."[639]

9.16 The subject matter of the case in which this statement was made was, in fact, a biotechnology product, specifically a therapeutic monoclonal antibody. However, when the patent was applied for, the drug had not yet been made, let alone had its safety and efficacy established. The patent covered the production of this antibody by a gene sequence that the patentee had discovered and that, owing to its similarity to known gene sequences, they believed would be the code for proteins that had a predicted physiological effect. The controversy concerned an issue where emerging biotechnologies present a particular challenge to the patent system: what should be the scope of patent protection for a technology whose *potential* is uncertain? Here the lower courts had, in effect, held the patent to be too speculative validly to cover the monoclonal antibody; the Supreme Court, however, disagreed.[640]

9.17 Patent applications are published within 18 months of their filing or priority date (the date used to establish novelty/obviousness),[641] but cannot be enforced unless and until they are granted. A granted patent confers a monopoly that endures for 20 years from filing of the patent application,[642] although where the patent protects a new drug or agrochemical this can, in the EU and US and some other jurisdictions, be extended to up to 25 years to take account of delay in securing regulatory approval. Patents provide a monopoly over the subject matter of the patent claims in the terms in which they were granted.[643] Unlicensed operation within the scope of such claims exposes those responsible for it to the risk of an award of damages and an injunction against continuing infringement. However, the monopoly conferred by the claims of a granted patent is not absolute; thus, throughout Europe it is not an infringement of a patent to operate within the scope of the claims where this is done for the purposes of research into the claimed invention, even where this is done commercially or for commercial purposes.[644] However, where the patent claims are sufficiently broad to cover any innovation that results

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[639] *Human Genome Sciences Inc v Ely Lilly & Co* [2011] UKSC 51, available at: http://www.supremecourt.gov.uk/decided-cases/docs/UKSC_2010_0047_Judgment.pdf, paragraph 99.

[640] A Technical Board of Appeal of the European Patent Office also came to a similar conclusion as the Supreme Court. See: European Patent Office (21 October 2009) *T 0018/09 (Neutrokine/Human Genome Sciences)*, available at: http://www.epo.org/law-practice/case-law-appeals/recent/t090018eu1.html.

[641] See: IPO (2012) *After you apply*, available at: http://www.ipo.gov.uk/types/patent/p-applying/p-after.htm.

[642] See: Intellectual Property Office (2012) *What is a patent?*, available at: http://www.ipo.gov.uk/types/patent/p-about/p-whatis.htm. In fact, this may be up to 21 years after the very first filing of a patent application if this very first filing is treated as a claim only to priority.

[643] Patent claims as granted are almost invariably narrower, and often *much* narrower, than the claims in the patent application as filed. Much ill-informed and alarmist comment about patents is based on the claims in the application as filed (e.g. in the case of synthetic biology, the patent applications dating from 2005 filed on behalf of Synthetic Genomics Inc. and its associates) when in practice it can often take several years for a patent to be granted, whereupon its true protective scope becomes apparent. There is thus an element of uncertainty in the process, but because a search report identifying relevant prior art is also published at the same time as the patent application it should usually be possible to make an informed assessment as to the likely scope of any patents that might be granted as a result of the application.

[644] The precise expression is "experimental purposes relating to the subject matter of the invention." See: IPO (2008) *The patent research exception: a consultation*, available at: http://www.ipo.gov.uk/consult-patresearch.pdf, p8. Thus, it does not apply to the use of a patented technology as a tool for experimenting on something else. This 'research tool'" issue has given rise to some expressed concerns, notably in academic research settings but there is no evidence that it has thereby restricted research. Much confusion has arisen from the fact that there is no corresponding defence in the US, although the 'Bolar' defence overlaps with it to the extent that the research in issue is directed towards a new therapeutic or diagnostic that will require regulatory approval; see: Cook T (2006) *A European perspective as to the extent to which experimental use, and certain other, defences to patent infringement, apply to differing types of research*, available at: http://www.ipeg.com/_UPLOAD%20BLOG/Experimental%20Use%20for%20IPI%20Chapters%201%20to%209%20Final.pdf.

from that research, they provide a potential barrier to the subsequent commercialisation of such an innovation.[645]

Other relevant kinds of intellectual property protection

Trade secrets

9.18 Patents are one of three main forms of intellectual property protection encountered in biotechnology. In contrast to patents, trade secrets can be protected for so long as they remain confidential, which they would not be once a patent application disclosing the secret is published. Trade secrets can confer effective longer term protection on technology that cannot be reverse engineered from products that are placed on the market, such as technology relating to processes. Fermentation conditions are an example of such process knowledge in biotechnology but the range of possibilities is not wide; this is probably for the best, because secrecy detracts from wider dissemination of the innovation. Trade secrets have a further failing as compared to patents as although most national patent laws provide for "prior user" rights so that someone who can prove that they were secretly using a process that is subsequently patented by a third party can continue to use such process without infringing the third party's patent, their "prior user" rights tend to be narrow in scope in that they do not allow for use in another jurisdiction and often do not cover improvements in the process.

Regulatory data protection

9.19 The third form of intellectual property protection encountered in biotechnology is regulatory data protection: data concerning the safety and efficacy of regulated products such as drugs and agrochemicals as submitted to regulatory bodies is protected for a fixed term against the regulatory authorities cross referring to it for the purposes of granting regulatory approvals to second applicants.[646] Protecting regulatory data clearly provides an incentive to undertake the safety and efficacy studies needed to bring new drugs to market; otherwise second applicants could 'free ride' on the enormous investment in such studies.[647]

Marketing exclusivity

9.20 Yet further forms of protection that offer a targeted incentive exist in biotechnology, such as the marketing exclusivity conferred in the EU and the US on orphan drugs.[648] This gives the first firm to secure regulatory approval for a drug that treats a rare disease a true exclusivity for a number of years as against another person securing a regulatory approval for the same or a similar drug for the same indication, even where the latter has generated a full data package of

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[645] Again, however, the barrier is not absolute, even absent voluntary licensing. This is because throughout Europe the owner of a "dependent patent" that represents an improvement over an earlier "dominant patent" can seek a compulsory licence, although this is in practice rarely done, in part because a separate application for such a licence must be made in each European country. In the US, which lacks a statutory compulsory licensing regime, a similar result is achieved in practice because the Supreme Court has held that the grant of an injunction against a patent infringer is not automatic: *eBay Inc. v. MercExchange, L.L.C.,* 547 U.S. 388 (2006), available at: http://www.supremecourt.gov/opinions/05pdf/05-130.pdf.

[646] Although, like patents, the protection of such regulatory data is internationally mandated by virtue of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), it is much less specific as to how this is to be done than it is for patents, and so for example, unlike patents, does not specify any minimum term. The term differs as between jurisdictions and according to the nature of the regulatory framework and the type of substance being protected. In Europe it is now ten years for the first medicinal product to contain a new active substance, extendable for one further year only if approval of important new indications is secured. See: European Medicines Agency (2012) *European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf , paragraph 35.1.1.

[647] As it is, the term of regulatory data protection is usually keyed to the first authorisation for a particular active substance, so the system does not adequately protect the investment in later studies into new indications.

[648] Ten years in the EU and seven years in the US. See: European Medicines Agency (2012) *Orphan incentives*, available at: http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000393.jsp&mid=WC0b01ac0580024c5a and s.527 Federal Food, Drug, And Cosmetic Act [21 USC 360cc], respectively.

their own.[649] This recognises that patents and regulatory data protection alone are inadequate to provide an incentive for research into some rare diseases, as the possible economic return will be too low.

Limitations of intellectual property for emerging biotechnologies

9.21 Trade secrecy, as we note above,[650] has little obvious relevance to emerging biotechnologies. The same is true of regulatory data protection and marketing exclusivities, since these require a suitable regulatory framework. By their nature, emerging biotechnologies, particularly those that are manifested, at least in their early stages, as enabling technologies[651] rather than specific products, often lack such a well adapted framework.[652]

9.22 This leaves patents as the most important form of intellectual property with the potential to protect emerging biotechnologies.[653] However, for emerging biotechnologies, patents suffer from two main inadequacies. Firstly, their term is likely to be *too short* to recoup investment in the patented subject matter: much, if not all, of the 20 year patent term for those patent applications filed in the early stages of emerging biotechnologies is likely to have been consumed by the time that the technology is commercialised.[654] Secondly, such patents risk, much more than in better developed areas of technology, being *overbroad*. This second tendency may result in patents having a potentially chilling effect on third parties bringing products or processes to market that are within the scope of such patent claims, for so long as the patents remain in effect. Not that research on their subject matter necessarily constitutes infringement,[655] but the commercialisation of its results may require a licence. This, in turn, is likely to have an adverse effect on research directed to such products or processes.

9.23 Patent systems find new types of technology much more of a challenge than existing ones. There are two main reasons. The first is that, institutionally, patent offices that examine patent applications and determine the scope of claims to grant can only effectively do so against a background of relevant prior art. However, in the early years of an emerging biotechnology the most relevant prior art will be in various different areas of technology.[656] This means that relevant prior art may more easily be overlooked and there is thus an even greater risk than usual that patents may be granted with claims that cover, or are obvious in the light of, prior art. Such patents can be challenged in subsequent court proceedings but this is costly and therefore rare. The more they exist in any technical field, the greater the potential chilling effect on third parties looking to commercialise the products of their own research.

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[649] Thus it can protect, in a way in which regulatory data protection does not, investment into later studies into new indications, such as stratified treatments for common complex diseases where the treatment is based, say, on a rare genotype.

[650] See paragraph 9.18.

[651] Patents for enabling technologies can be more difficult to monetise than patents that cover specific products, although there are some exceptions, such as the Cohen-Boyer patent on recombinant DNA technology (US 4237224, available at: http://www.google.com/patents/US4237224) and the suite of patents, originally held by Cetus, on various aspects of the polymerase chain reaction. See, generally, Beardsley T (1984) Biotechnology: Cohen-Boyer patent finally confirmed *Nature* **311**: 3 and Rabinow P (1997) *Making PCR: a story of biotechnology* (Chicago, Illinois: University of Chicago Press).

[652] See paragraph 8.26.

[653] Some commentators challenge from an economic perspective the value of patents in many sectors but still conclude that patents have value to the certain sectors; see, from the perspective of US patent law: Bessen J and Meurer MJ (2008) *Patent failure: how judges, bureaucrats, and lawyers put innovators at risk* (Princeton, New Jersey: Princeton University Press), arguing that from an economic perspective the patent system works substantially best in the chemical and pharmaceutical industries and noting that, despite problems in biotechnology patenting with early stage inventions, patents are probably most important to biotechnology start-ups.

[654] The earliest patents in the field of nanotechnology date from around 1991 and have now expired. The basic patents in RNA interference (RNAi) date from around 2001 and so have less than ten years still to run but as yet no commercial product based on RNAi technology has been authorised. Lundin P (2011) Is silence still golden? Mapping the RNAi patent landscape *Nature Biotechnology* **29**: 493-7.

[655] See footnote 644.

[656] In recognition of this problem the USPTO created in 2004 (nearly 15 years after the earliest patents for it had been filed) patent class 977, dedicated solely to nanotechnology. Class 977 is a secondary classification, which means that patents in that class are also classified in accordance with the more traditional technology to which they relate. For more information on class 977 patents, see: USPTO (2012) *Class 977 nanotechnology cross-reference art collection*, available at: http://www.uspto.gov/patents/resources/classification/class_977_nanotechnology_cross-ref_art_collection.jsp.

9.24 The second difficulty with new technology arises from the fact that patents inevitably include a degree of speculation: the claims as ultimately granted cover not only what the patentee has actually shown to work but also what can, in the light of that demonstration and the state of the art generally, also be expected to work. These ought not, however, to be so broad as to exclude the prospect of non-infringing alternatives that might be commercialised. The judgment as to what degree of speculation is appropriate for coverage by a patent claim, which defines the scope of the patent,[657] is not easy at the best of times; however, it is much more difficult with an entirely new type of technology. This problem is not a new one: the following principle as articulated in the US Supreme Court in 1966 is still apt, in Europe as well as the US, today:

> "This is not to say that … we are blind to the prospect that what now seems without 'use' may tomorrow command the grateful attention of the public. *But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."* [658]

9.25 However the problem is not always readily addressed, as can be seen from the monoclonal antibody case mentioned above.[659] Excessive breadth of patenting is more likely in new fields. But in a new field there is a further danger, that some early patents cover developments that provide the foundations for future inventors and innovators. If those developments are, in effect, unavailable to all but the patent holder, inventive and innovative activity beyond mere research will be severely restricted.

9.26 These various shortcomings are difficult to address, partly because they are to some degree in conflict. As a consequence, in the context of emerging biotechnologies, there is likely to be a combination of what might be an overly short term of protection with the risk of overly broad protection during that short term. We see below that this must limit the sort of commercial support that emerging biotechnologies can attract.

9.27 Short duration may be particularly troublesome for pharmaceuticals, because of the delays forced by the regulatory system; on the other hand, patent duration can be extended for pharmaceutical products from the basic 20 years up to 25 to compensate for this. What longer patent duration cannot compensate for, in pharmaceuticals, is the extra cost of meeting requirements for regulatory approval (such as clinical trials), the additional delay this represents before getting a return on the money already spent, and the possibility that approval will be denied.

The economics of the 'patenting problem'

9.28 In paragraphs 9.15 to 9.17 we examined patenting problems for emerging biotechnologies from a legal perspective. Now we apply economic analysis to show that, in some key areas of emerging biotechnologies, there are other formidable problems which can be expected not only to reduce the rate of investment but to move it away from realising the social value of biotechnologies.

9.29 We have seen that knowledge is intrinsically a non-rivalrous good but can be made excludable by patenting or other IPR. This exclusion allows the market mechanism to apply to the production of knowledge; but the market mechanism can never work really efficiently because of the non-rivalrous aspect. In other words, the necessary incentive for commercial production of knowledge is based on charging for its use (a royalty or a profit margin on top of the cost of producing a medicine or other product) when the use of knowledge in fact incurs no direct cost

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[657] For a discussion of patent claim scope from an economic perspective see: Merges RP and Nelson RR (1990) On the complex economics of patent scope *Columbia Law Review* **90**: 839-916.

[658] *Brenner v. Manson* 383 U.S. 519 (1996), available at: http://supreme.justia.com/cases/federal/us/383/519/case.html. (Emphasis added).

[659] See paragraphs 9.15 to 9.16.

to anyone.[660] So, if a medicine costs 20 cents per dose to produce and distribute but is sold for $2 per dose (in order to pay for the R&D cost of developing it plus trying to develop many other drugs that failed during development), many of those patients who would get it if it were priced at 20 cents per dose, and benefit from it, will not get it. This represents a loss to them and to society overall.

9.30 This restriction of use is a failure of the market mechanism, but it is not the only one. Arguably a worse market failure is that many drugs (and other fruits of knowledge) which should have been developed will not be developed at all. Let us examine with some care what this means. If we knew costs and benefits in advance, we could say that a drug *should* be developed if the cost of development, and any other necessary fixed cost, is less than the net benefit to society that will come from its use. Here we must also recognise that the returns needed to keep pharmaceutical firms at work developing new drugs must include covering the costs not only of developing the drugs that they bring to market but also of the R&D that goes into the large number of those that they do not, that is, those drugs that were abandoned for some reason during development (for example, because of problems with scaling up production, unfavourable clinical trials or a poor financial forecast). In practice there are great uncertainties and most drugs selected for development will fail, but experience suggests that the following scenario is plausibly close to a possible reality for a particular therapeutic area.

- Out of ten drugs chosen for development, nine will fail, costing a total of $900m in R&D spending written off.
- One succeeds, costing $200m to develop. It will be sold for $2 per dose (profit margin over variable costs, $1.80) and, in total (before the patent expires), will sell 500 million doses over its lifetime. It will then make a profit over variable costs of $0.9 billion.
- By itself it then looks like a successful project. But the total development cost of the one successful and nine failing drugs will be $1.1billion, leading to a loss of $0.2 billion.[661] It would then not be in shareholders' interests to proceed with this programme, if such an outcome could be expected.[662]

9.31 Looking at the issue from the point of view of society as a whole, should those ten drugs, the successes and the failures, have been developed? The answer will, very probably, be that they should, because we should take into account not only the producer surplus (i.e. profit) over variable cost, which we calculated at $0.9 billion, but also two blocks of consumer surplus: the difference between what consumers had to pay (or what was paid on their behalf), and what the drug would have been worth to them. The first block of surplus is that for the patients who would get the drug at $2 per dose; the second is that for the extra patients who would have got the drug had it been charged at variable cost of 20 cents per dose. Adding that to the $0.9bn might well have taken the total surplus over the $1.1bn mark.

Innovators versus 'me-toos'

9.32 It is typical in pharmaceuticals that a radically innovative new product will be followed by so-called 'me-toos'. Thus, in drug development, the first NAS to address a particular pathway of disease and therapy – the first statin, say, for cardiovascular therapy, or (in recent biopharma) the first monoclonal antibody which is a beta-lymphocyte stimulator – will be followed by others, developed by rival firms. The early followers may well be would-be radical innovators who lost

[660] Of course, many conditions may need to be satisfied to allow the knowledge to be used, that incur costs and are not necessarily of a generic nature, such as the costs of infrastructure and the cost of training personnel to be able to use the knowledge. These 'sunk' costs account for the immobility of capital even where returns are low, relative to other possible investments, or even negative.

[661] The example is hypothetical but not unrealistic. The generally quoted figure for the cost of developing a drug to the point marketing is $802 million (in 2000-value dollars), which also takes account of the cost of failures. DiMasi JA, Hansen RW and Grabowski HG (2003) The price of innovation: new estimates of drug development costs *Journal of Health Economics* **22**: 151-86.

[662] We have ignored the marketing costs, because they are neither fixed nor an absolutely necessary variable cost. Taking them into account will clearly make the financial outturn even worse. We return to these costs later, at paragraph 9.64.

the race to be first to market; the real me-too drugs, however, are those whose development was initiated in response to the arrival of the innovator. In some cases a me-too drug will turn out to be squarely better than the innovator's; in other cases different drugs will best suit different groups of patients; in others again, the innovative drug will be as good as it gets, and the me-toos will serve no purpose. In all cases, the later comers will get some, probably substantial, share of the market. In one sense this is as it should be: patients will be either better treated, or at least not worse, than if the innovator kept a monopoly.

9.33 Where me-toos are damaging is in what they do to the incentive to innovate, for example, to produce the first statin or beta-lymphocyte stimulator. The innovator, and those rivals who tried to innovate but lost the race, must share the profits to be had from their successful gamble – their commitment of large R&D funding to projects which could be expected to fail – with others who waited until many of the uncertainties had been resolved. Even less of the social value from the innovation will accrue to the innovator; there is even less incentive to fight through the R&D and regulatory jungle, making a path for others to follow.

Intellectual property rights as encountered in emerging biotechnology

9.34 The argument so far has been a general one, but indexed to the specific case of pharmaceuticals. We need therefore to consider how widely it may be applied. At this point we need to make a distinction between three types of biotechnologies:

1 those that are intended to affect biological systems in their natural context (relatively open systems like the environment or relatively closed systems like individual patients receiving medical treatment);
2 those that utilise biological processes or systems in a controlled context to produce outputs for other purposes (e.g. engineered biofuels, bioreactors); and
3 those that provide knowledge or information about biological processes or systems (like gene sequencing or stem cells used in toxicology).

9.35 The two main 'type 1' sectors, (bio)pharmaceuticals and plant breeding, are similar in that there is a separation between the research-intensive firms that innovate and produce patentable knowledge, and the multitude of doctors and farmers who manage the interface with the biological systems (human bodies and agriculture) without, in most cases, doing any formal R&D themselves.[663] This concentration of research upstream, and the risks attached to the letting loose of drugs and new plant varieties in those biological systems, means that an exceptionally high proportion of cost is accounted for by R&D and other fixed costs, and therefore the price of any product that emerges needs to be far above variable costs.[664]

9.36 Another specific feature of the pharmaceutical sector is its exceptional degree of dependence on patents and IPR more generally. The 'me-too problem' largely arises from this: published patents produce a target for inventing round and once that is achieved, it is relatively easy to break into the market that the original innovator has established. The me-too problem may be general in 'type 1', since the original innovator demonstrates with the NAS (or other new product developed) how to intervene in a biological system, and other firms may then follow. We saw this for pharmaceuticals, where the system is human bodies, and the situation seems similar in crop plant breeding, where the system is agricultural.

[663] Of course the development of techniques and biotechnology tools brings some research into the context of use or treatment, for example developing patient-specific genetic tests in clinical conditions. One vision of synthetic biology is of a kind of 'bricolage' by which users can design biological products to address specific needs as they encounter them.
[664] We shall see below that this is at least as true for biopharma as for 'chemopharma'.

9.37 'Type 2' – essentially biomanufacturing[665] – involves a different type of knowledge and learning process, since the core of the task is to manage a closed system. A bioreactor, for example, is a manufacturing plant and so the business of R&D into more advanced bioreactors is bound up with the business of manufacturing. The lead innovator (in the *processes* of the bioreactor) establishes a lead manufacturing capability through its R&D. It then learns by doing (which economises on R&D spend) and may well thereby increase its lead. The task for the follower is more difficult than for the pharmaceutical firm developing a me-too drug. The first mover advantage is greater, because of the learning by doing, and less dependent on IPR – more on secrecy and other assets. This is probably also the case for 'type 3'. Certainly the case of Oxford Nanopore (see Box 9.1) suggests that gene sequencing is free of most of the problems which beset pharmaceuticals.

Box 9.1: Oxford Nanopore

Early attempts at gene sequencing by imaging a single molecule with a scanning probe microscope have proved unsuccessful so far. However, another approach, in which the bases are read out as single molecules of DNA are threaded through a nanoscale pore, has generated significant momentum since the method was first proposed in 1996.[666] This is currently the subject of a significant commercialisation effort by firms such as Oxford Nanopore, exploiting the pore-forming proteins that were introduced as biosensors.[667]

Oxford Nanopore is a UK firm that was set up in 2005 to commercialise this technology. It has been fully funded by "long-term [British] investors".[668] It brought its first product to market in 2012, a product which (if the commentary is to be believed) is a sure-fire commercial success because it offers greater speed for lower cost in a market that has been already developed by others. This product faced few, if any, regulatory barriers. If we suppose that at least some of its patents were filed after 2002, it would have at least ten years of patent-protected production, without allowance for follow-up patents. The apparently smooth translation of scientific knowledge into technology with a broad range of applications, combined with the absence of high regulatory barriers (owing to the fact the product does not directly utilise or impact on biological systems), provide a stark contrast to the experience of firms such as those in the pharmaceutical, biomedical or agricultural biotechnology sectors developing biological or biologically active products.

9.38 We conclude that the market failure in patenting that we are discussing is concentrated in type 1 activities. This failure is important not because (and certainly not only because) it leaves commercial potential unexploited but primarily because of the social value represented by the foregone consumer surplus. Pharmaceuticals and plant breeding differ, of course: thus the regulatory protection of human bodies from damage by drugs is more elaborate – and therefore more expensive for the innovator – than that protecting ecosystems from damage by new varieties of plant (or animal). This may help to account for social resistance (in Europe) to transgenic plant varieties. The result is at least as expensive for the would-be innovator as the requirement for elaborate clinical trials.

9.39 Another variation between pharmaceuticals and plant breeding is in the extent and effectiveness of IPR protection in developing countries. Until recently it was pharmaceuticals whose protection was weaker – indeed non-existent – in many developing countries because (where patents were recognised at all) product patent protection for pharmaceuticals was specifically excluded. Now the general acceptance by developing countries of TRIPS includes pharmaceutical product patents. Meanwhile the development of new plant varieties, largely transgenic, which breed true, makes plant breeders more dependent on IPR than before.[669] While it will usually be possible to identify and pursue pharmaceutical firms in developing countries that produce a patented drug without a licence, to take on a multitude of individual farmers who have transgressed, each using crops grown their own fields, would be a formidable undertaking (see Box 9.2).

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[665] For a discussion of biomanufacturing, see: Morgan S, Colon S, Emerson JA *et al*. (2003) *Biomanufacturing: a state of the technology review*, available at: http://www.che.ncsu.edu/academics/concentrations/documents/Biomanufacturing-AStateofTechRev.pdf.

[666] See: Kasianowicz JJ, Brandin E, Branton D and Deamer DW (1996) Characterization of individual polynucleotide molecules using a membrane channel *Proceedings of the National Academy of Sciences* **93**: 13770-3.

[667] See: Braha O, Walker B, Cheley S *et al.* (1997) Designed protein pores as components for biosensors *Chemistry & Biology* **4**: 497-505.

[668] Cookson C (2012) Oxford Nanopore unveils mini-DNA reader *Financial Times* 16 February, available at: http://www.ft.com/cms/s/2/318a378a-5900-11e1-b118-00144feabdc0.html#axzz252CYKeNP.

[669] Conventionally, seed merchants supply F1 hybrids which do not breed true – that is if the farmer plants seed from the crop it is much less productive than the original seed supplied.

Box 9.2: The limits of patent protection in a global context

We suggested above that intellectual property held in developed countries may obstruct research in less developed ones. However, there is also an opposite risk in such countries, that intellectual property will be ignored altogether. The case of Bt cotton in India offers a striking example. The cotton plant had been engineered to contain a bacterial transgene (from *Bacillus thuringiensis*) for the production of a toxin lethal to a small number of different kinds of insect larvae. Despite opposition from activists concerned about genetically modified (GM) crops, farmers wishing to avoid the costs and dangers of using pesticides were keen to obtain seeds. Seeds disappeared from the test plots that were established in 2002 under authorisation from the Indian Government. By 2005, it was estimated that 2.5 million hectares were under 'unofficial' Bt cotton (twice the area of authorised plantings).[670]

> "The unofficial Bt cotton varieties had been bred, either by firms operating in an ambiguous legal position or by farmers themselves. A veritable cottage industry had sprung up, a state described as 'anarcho-capitalism', whereby small-scale breeders were crossing reliable local varieties with the caterpillar-proof Bt plant…. The world's first GM landraces had arrived, a blend of tradition and science..."[671]

We would not hazard a view on the legality of what the Indian farmers did. At all events, if it had been illegal, we suppose that many would have done it nonetheless, and that the firm that developed the new varieties would have had no success in getting royalties from those who thus used its innovation at one removed.[672] However, the consequence of unchecked 'anarcho-capitalism' of this sort is very likely to be a reduction of the incentive to invent and innovate further technologies that may hold significant and even transformative potential, and, once the ambiguities (highly evident in this case) are worked through, potentially transformative in genuinely beneficial ways for less developed countries.

9.40 'Type 2' emerging biotechnologies suffer from a quite different kind of market failure: the under-pricing of carbon and other environmental 'goods' and 'bads' in relation to their social impact (particularly long term impacts), which should make their competitors considerably less competitive than they in fact are. As systems of industrial production, 'type 2' emerging biotechnologies are mostly in competition with other systems of industrial production, notably those employed in synthetic chemistry. Their key advantage in this competition is their economy in the use of natural resources, particularly energy. The lower their products are priced, the less that advantage tells.

9.41 Plant breeding is also affected by this market failure, but in a subtler manner. A plant might be genetically engineered to thrive when drenched in every kind of fertiliser and pesticide, and irrigated (Variety A); or it might be genetically engineered to do remarkably well in the absence of fertiliser and pesticide, and irrigation (Variety B). So while the bioreactor is squarely *discouraged* by environmental under-pricing, plant breeding is merely *distorted* by it: towards Variety A and away from Variety B. (We see no strong effect of environmental under-pricing on either pharma or 'Type 3' biotechnologies.)

Crossing the 'valley of death'

9.42 In this Chapter we have reviewed the operation of the patent system with regard to emerging biotechnologies, and we have found it does not contribute favourably to the rapid and profitable commercial exploitation of emerging biotechnologies, most notably in pharmaceuticals. The problem of translation, of moving drugs from bench to bedside, has become known as the 'valley of death' at least since the Cooksey report in 2006.[673] While many promising NASs are

[670] Kingsbury N (2009) *Hybrid: the history and science of plant breeding* (Chicago, Illinois: University of Chicago Press), p417.
[671] Ibid.
[672] Where Monsanto does have valid patents, as in North America, it has sued farmers for infringement where the farmers say their seed has been contaminated by patented Monsanto seed grown nearby. For one discussion of a case where a farmer was found to have infringed Monsanto's patents, see: Fox JL (2001) Canadian farmer found guilty of Monsanto canola patent infringement *Nature Biotechnology* **19**: 396-7. Monsanto itself has been sued for "compensatory damages for revenues lost through contamination of organic crops with the companies' GM herbicide-tolerant canola". See: Bouchie A (2002) Organic farmers sue GMO producers *Nature Biotechnology* **20**: 210. For Monsanto's position statement on the matter, see: Monsanto (2012) *Why does Monsanto sue farmers who save seeds?*, available at: http://www.monsanto.com/newsviews/Pages/why-does-monsanto-sue-farmers-who-save-seeds.aspx.
[673] For the Cooksey Report, see: Cooksey D (2006) *A review of UK health research funding*, available at: http://webarchive.nationalarchives.gov.uk/+/http:/www.hm-treasury.gov.uk/d/pbr06_cooksey_final_report_636.pdf. The term 'valley of death' does not appear in the Report itself but "Bridging the 'valley of death'" is the rubric for an inquiry by the UK House of Commons Science & Technology Select Committee which began in December 2011. See: House of Commons

discovered and studied by biotechnology firms, it is a general complaint heard from all sides that there is a gap between the point that biopharmaceutical research can get to on the basis of the public sector grants available, and the point at which the uncertainties have been reduced enough for a BPF to buy in, in the way described at paragraph 9.10.

9.43 This matters, very obviously, not because of the welfare of drug firms and their shareholders, but because of the well being of patients that might be improved: again, the question of opportunity cost must be considered at the broadest level. It is possible, in principle, for venture capital to bridge this gap but it is hard and/or unacceptable in practice, because venture capitalists demand a very large stake in return for their investment. There may be specific reasons for the limitations of venture capital in the UK,[674] but the problem is clearly worldwide.[675] The exorbitant terms of venture capital funding arise from their perception of risk (which depends on their understanding of the technology and the market).[676]

9.44 In the next section we shall examine remedies proposed (some of which are already implemented) for the obstacles to commercialisation discussed above.

Remedies for patenting problems

9.45 There are, in principle, at least two ways of avoiding the dampening effect of excessively broad patents on further invention in a field. One is compulsory licensing, whereby all who wish to use the patented process or make the patented product, may do so in return for payment of a royalty, the level of which would be determined by some kind of regulator. Such systems exist,[677] but they are little used, perhaps because they cost as much as challenging the validity or scope of a patent. That might be altered but to do so risks reducing the incentive and reward to the inventor.

9.46 A second way to avoid the restriction is to avoid patenting in the first place through open access and pre-competitive research. The classic example of the avoidance of patenting is the open source movement in software, revolving around Linux.[678] (Open source licensing in software nevertheless remains dependent on an underpinning of intellectual property, namely copyright, as without this there would be nothing to license.) It is parts-based approaches to synthetic biology that offer the closest case in emerging biotechnologies to computer software. These approaches aim to develop a suite of modules that have been standardised for assembly into products that have characteristics which can be reliably predicted from the nature of their components, allowing rational design of biological systems. To the extent that this can be achieved it will open up the possibility of innovative behaviour to almost everyone who can order components online, akin to software programming in the 1980s.[679] One option is that biological parts, processes and information should circulate in common, so to speak, but could also be

Science and Technology Committee (2012) *Bridging the "valley of death": improving the commercialisation of research*, available at: http://www.publications.parliament.uk/pa/cm201012/cmselect/cmsctech/uc1936-i/uc193601.htm.

674 Smith G, Akram MS, Redpath K and Bains W (2009) Wasting cash – the decline of the British biotech sector *Nature Biotechnology* **27**: 531-7.

675 See, for example: Ernst & Young (14 June 2011) *Despite renewed growth in 2010, biotech industry faces R&D challenges*, available at: https://webforms.ey.com/GL/en/Newsroom/News-releases/Beyond-borders_global-biotechnology-report-2011.

676 Certainly venture capitalists, looking for some scope for an early exit from a project in which they invest, will be much more interested in funding research that is close to market and that can at least identify a tangible end product that can be brought to market whilst there is still a respectably long period of intellectual property protection for it. Venture capitalists do however favour investing in firms that have already filed patent applications and these firms will do better than those that have not. See: Cao JX and Hsu P (2010) *Patent signaling, entrepreneurial performance, and venture capital financing*, available at: http://efmaefm.org/0EFMSYMPOSIUM/Toronto-2011/papers/Hsu.pdf.

677 See, for example, the World Trade Organization's Doha declaration. The declaration allows member states to grant compulsory licences for patented drugs during a public health crisis. World Trade Organization (20 November 2001) *Declaration on the TRIPS agreement and public health*, available at: http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.

678 For contrasting views of progress with open source software, see 'Babbage' (2012) Difference engine: free is too expensive *The Economist* 30 March, available at: http://www.economist.com/blogs/babbage/2012/03/desktop-linux; 'Monitor' (2012) An open-source robo-surgeon *The Economist* 3 March, available at: http://www.economist.com/node/21548489.

679 See: Thambisetty S (2012) *The analytical significance of emergence in the patent system*, available at: www.nuffieldbiothics.org/emerging-biotechnologies-evidence-reviews, p29.

used privately and for exclusionary purposes.[680] An example of such hybrid openness is the 'BioBrick'® public agreement.[681] It can be argued that this combination is an ideal arrangement for commercial organisations, which can 'piggy-back' on advances made by others and then protect their own innovations. One attraction of openness of this kind is that it need not exclude researchers and users in less developed countries, who might otherwise face a 'patent blockade' constructed by firms and others in developed countries. This is not to say that the scientists who have espoused open source in synthetic biology would necessarily accept such a compromise.

9.47 Another means to the same general end is to designate certain areas of research as pre-competitive. There is much current discussion[682] regarding collaborative research as a way of increasing productivity, and such a designation would be an enabling move for this. The idea is that results from research designated as pre-competitive would be placed in the public domain from the start, being disseminated via the internet and published in learned journals, rather than patented. This would then advance the status of the field as a whole and allow the protagonists to compete with one another from a more advanced starting point, increasing the overall chances of success.

The problems of uncertainty and excessive time to market

9.48 In paragraph 9.27, we note that for all pharmaceutical firms the insistence on rigorous and exhaustive clinical trials not only increases the total cost of R&D but, by delaying the point at which the drug can reach the market, reduces the time it can be sold under patent. In any new area like biopharma and, more particularly, emerging biopharma, unexpected difficulties are likely to make for further delays, as well as increasing the uncertainty (poison to venture capitalists and other prospective funders) as to whether the drug will ever be successful. Drug discovery in pharmaceutical and biotechnology firms is a particular case in point where two problems reduce the probability of success and extend the period from patent application to launch: firstly, the lack of truly validated therapeutic targets and secondly, the lack of surrogate endpoints or biomarkers that are accepted by the regulators.

Validated therapeutic targets

9.49 Many drugs fail in the clinical evaluation stage because the predictions of animal experiments carried out early in the discovery process are not realised in human patients. Moreover, experimental medicine studies on human volunteers do not predict the efficacy or lack of efficacy of a treatment in patients. Coupled with this, it has been noted that between 70 and 80 per cent of therapeutic targets are shared across the industry (perhaps not surprising given that medical need is the driver for all the research projects in the first place) so that working together to validate models for some or all of these targets would be mutually beneficial. The amount of information available to work with is increasing exponentially owing to the accumulation of relevant biodata (particularly genomic data) and there is increasing recognition that most diseases need to be approached by studying a network of genes rather than by looking for the effects of a single gene that are disease related.[683] This argues in favour of sharing data and the formation of consortia.

9.50 A number of firms are now making information about problems they wish to solve public via the internet (so called 'crowdsourcing') and may give grants to institutions or individuals who

[680] Ibid, p35.
[681] See: BioBricks Foundation (2012) *The BioBrick™ Public Agreement (BPA)*, available at: http://biobricks.org/bpa.
[682] See, for example, Norman TC, Bountra C, Edwards AM, Yamamoto KR and Friend SH (2011) Leveraging crowdsourcing to facilitate the discovery of new medicines *Science Translational Medicine* **3**: 88mr1.
[683] Chen Y, Zhu J, Lum PY *et al.* (2008) Variations in DNA elucidate molecular networks that cause disease *Nature* **452**: 429-35; Schadt EE (2009) Molecular networks as sensors and drivers of common human diseases *Nature* **461**: 218-23.

express a wish to work on a potential solution but without claiming the intellectual property at this stage.[684]

Box 9.3: Crowdsourcing therapeutic targets

Some pharmaceutical firms have placed information in the public domain in the hope that it will kick-start research by academic groups that will help validate the targets. For example, the release into the public domain by GlaxoSmithKline of 13,000 structures of potential anti-malarial drugs.[685] In other cases it has been achieved by forming public private partnerships (PPP) such as Arch2POCM.[686] The objective of this PPP is to demonstrate in a phase II clinical trial that the mechanism of the selected disease target can be safely and usefully modulated. The consortium includes US, EU and Canadian regulators, pharmaceutical firms, academic institutions, patient advocacy groups and contract research organisations and all data generated will be made public without any patent claims being made.

Surrogate endpoints

9.51 Increasingly, it is necessary to perform pivotal studies in many thousands of patients to get the necessary safety and efficacy data to obtain marketing authorisation for a NAS with a novel mechanism of action. One way of shortening the path to market is to establish a reliable surrogate marker that the regulatory authorities will accept as evidence of efficacy, for example, lowering low-density lipoprotein cholesterol in plasma. Once accepted, the biomarker facilitates the activities of all those wishing to produce drugs in the same therapeutic class. This approach is probably best demonstrated in the cancer field and has already led to a personalised medicine approach for some therapeutic targets.[687] The discovery of biomarkers is approachable through collaborative processes in the same way outlined above for validation of drug targets and may be an integral part of the activity in some cases.[688]

Commercialisation and social value

9.52 All the proposals discussed above may well encourage the commercialisation of emerging biotechnologies, and in the appropriate situations, where they correct or compensate for failings of the patent system, we would support their use. More general actions by Government may also encourage commercialisation, such as the 'patent box' initiative, which guarantees firms a reduction on corporation tax (up to ten per cent) on all profits attributed to qualifying patents.[689] However, the patent system itself, while it endures, remains relatively inflexible, allowing the innovator to obtain all the profit they can for a predetermined period, followed by open competition in which prices are expected to fall towards the marginal cost of production. According to our analysis, this means the social value of innovation is likely to be restricted in the short term and relatively well exploited in the longer term, which is not necessarily an optimum profile (albeit that it coincidentally imposes a gradual and cautious approach to introduction of new products by initially restricting use through affordability). However, our main concern is not to find ways of getting more commercialisation of emerging biotechnologies but to get better commercialisation – to connect it more closely to social value.

9.53 Corporate social responsibility may play a role as a form of soft regulation (discussed in Chapter 8), giving a firm's products a 'soft value' to partners and consumers in addition to their hard economic value, and steering their commercial activities towards socially valuable (or less harmful) outcomes. While there is dispute about whether visible and earnest corporate responsibility may have a positive effect on firms' profits in the long term or compromise the efficiency of markets, standards of corporate social responsibility do provide opportunities for consideration of how innovative measures and technologies may increase sustainability and

[684] Lessl M, Bryans JS, Richards D and Asadullah K (2011) Crowd sourcing in drug discovery *Nature Reviews Drug Discovery* **10**: 241-2.
[685] Cressey D (2011) Traditional drug-discovery model ripe for reform *Nature* **471**: 17-8.
[686] Norman TC, Bountra C, Edwards AM, Yamamoto KR and Friend SH (2011) Leveraging crowdsourcing to facilitate the discovery of new medicines *Science Translational Medicine* **3**: 88mr1.
[687] Million RP (2006) Impact of genetic diagnostics on drug development strategy *Nature Reviews Drug Discovery* **5**: 459-62.
[688] See paragraph 9.49.
[689] See: Intellectual Property Office (2012) *How to use the 'Patent Box' regime to cut your corporation tax*, available at: http://www.ipo.gov.uk/news/newsletters/ipinsight/ipinsight-201207/ipinsight-201207-3.htm.

ameliorate social impact.[690] Despite the limitations of corporate social responsibility information as a form of soft regulation, we believe that the corporate social responsibility movement represents an important way of bringing social values into commercial activities. We therefore recommend that **innovation should be included in corporate social responsibility reports as a separate, specific issue**.

9.54 There may be, however, more direct ways in which to connect innovation with social value. In the next section we focus on proposals squarely designed with this objective. One of these proposals is significantly new.

Intellectual property rights and incentives: addressing the fundamental problems

9.55 The commercial exploitation of biotechnology, in pharmaceuticals and elsewhere, depends heavily on the legal protection of intellectual property. We argued above that there are fundamental difficulties in using a system of intellectual property rights to provide the right incentives for commercial organisations to produce and use new knowledge. It is clear that these problems are all the more acute where technologies are new. We have considered some possible – and actual – modifications of the system to address some of these problems. These show some promise, in particular, in addressing the way over-broad patenting may obstruct the work of subsequent innovators, and in drawing a useful line between, on one hand, scientific and cooperative commercial advance (in the early stages of discovery) and, on the other, the later stages, where it is every firm for itself and patent protection is vital. But the two fundamental problems remain: that patent protection of knowledge restricts its commercial use, and that the market situation to which it leads creates a pattern of incentives and rewards that matches the social value of innovations rather poorly. This situation is indeed becoming less favourable to innovation, in pharmaceuticals at least: the rivals of innovating firms are becoming more efficient at developing me-too drugs, and health organisations under pressure to contain costs are turning at the earliest opportunity to generic alternatives. While this may have short term advantages (more cheap drugs, more quickly) it will not support the long term health of the industry which is necessary if that industry is to be the global engine of therapeutic advance.

9.56 A solution to the problem of the divergence between social value and market value may lie in creating conditions in which the reward for innovation better corresponds to the social value of that innovation. This may be perhaps rather obvious in principle although it is likely to be very challenging in practice, since it involves evaluating the comparative social value of the use of a product and rewarding innovation separately from the price paid for the product. Nevertheless there are conditions in some sectors of biotechnology, and might be in others, that could support such an approach. We therefore recommend that **consideration should be given to state interventions in the market for new biotechnologies to secure the social benefits of innovation through direct reward for socially valued innovations**.

Reflecting the social value of innovation

9.57 It happens that in pharmaceuticals, the UK Government has been something of an innovator in finding an alternative to the simple market mechanism to place a value of certain technologies. The UK's National Institute for Health and Clinical Excellence (NICE) has the responsibility of assessing the therapeutic value of new drugs, in terms such as quality-adjusted life years (QALYs) gained by the patient, and deciding whether (given the price that is proposed) the use of a given drug in the National Health Service (NHS) would be cost-effective, taking into account the drugs and treatments already available, and their prices. The NHS can avoid the use of

[690] For example, ISO 26000 on social responsibility; in common with many standards of private and public 'full cost accounting', contains references to the use of innovative technologies to address social concerns and increase sustainability, although this is currently guidance rather than certifiable standards. See: International Organization for Standardization (2010) *ISO 26000 project overview*, available at: http://www.iso.org/iso/iso_26000_project_overview.pdf.

drugs that are over-priced in relation to their comparative clinical value, and the firm introducing a new drug has an incentive to keep the price below the level that might lead to an adverse judgment by NICE. With an advanced apparatus in place to assess the value of new drugs, the UK Government now plans to go one stage further, and introduce a system of value-based pricing, in which the prices for branded pharmaceuticals that firms are permitted to charge to organisations within the NHS will be worked out on the basis of their value, the assessment of which will involve consideration of "the range of factors through which medicines deliver benefits for patients and society".[691]

9.58 These advances have one fundamental limitation: the price paid for a drug will have to go on performing two functions: to compensate and reward the innovator for the cost and risk they have taken to bring the drug to market, and to guide the user. A new biopharmaceutical product may very well give a big gain in QALYs to one category of patients, a modest gain to another category, and in total be something of a niche product. In that case the first function demands a very high price; however, given the increasing pressures for cost control within the NHS (and all health systems), that price may deny the drug to patients who would have benefited from its prescription. Very simply, "for medicines to be widely accessible, prices need to be low, but low prices do not encourage innovation."[692]

9.59 What is needed, then, is to disconnect the two functions. The clinician should use the drug if its value to the patient exceeds the cost of producing and distributing it, which is usually very modest. The price would need therefore to be set at around that modest level. The compensation and reward to the innovating firm should reflect the social value of its use, which may be high. Clearly it will not get that from the price, so it must receive some kind of supplementary payment. Again this is not a new idea in itself but it has been put forward in a very specific and limited context.[693] However, there are reasons to think that the limitations of such a specific scheme in that context need not apply generally or, pertinently, in the UK.[694]

The idea of a health impact fund

9.60 Under the scheme, a 'Health Impact Fund' (HIF) would be set up to reward pharmaceutical firms that develop drugs mainly for use in developing countries:

> "All pharmaceutical firms worldwide would have the option of registering new medicines with the HIF. By registering, a firm agrees to provide its medicine at a price near the cost of production anywhere it is needed. In exchange, the company will be paid by the HIF annually for 10 years based on the fund's assessment of the actual global health impact of the medicine as a proportion of the global health impact achieved by all products registered with the HIF."[695]

9.61 The HIF proposal has been considered by the World Health Organization (WHO), and the judgment of a Consultative Expert Working Group has been expressed in a recent WHO Report;

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[691] Department of Health (2010) *A new value-based approach to the pricing of branded medicines: a consultation*, available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_122793.pdf.

[692] WHO (2012) *Research and development to meet health needs in developing countries: strengthening global financing and coordination – report of the consultative expert working group on research and development: financing and coordination*, available at: http://www.who.int/phi/CEWG_Report_5_April_2012.pdf, p161.

[693] The proposal is set out in Hollis A and Pogge T (2008) *The Health Impact Fund: making new medicines accessible for all*, available at: http://healthimpactfund.org/hif_book.pdf, with more detail in Incentives for Global Health (2011) *Health impact fund*, available at: http://www.who.int/phi/news/phi_7_cewg_hif_submission_jun2011_en.pdf. A critique of the proposal can be found in Sonderholm J (2010) A reform proposal in need of reform: a critique of Thomas Pogge's proposal for how to incentivize research and development of essential drugs *Public Health Ethics* **3**: 167-77.

[694] The WHO rejected the HIF proposal, largely on the basis of practical difficulties in implementation, in particular, in establishing a measure of health impact in the context of developing countries (see: WHO (2012) *Research and development to meet health needs in developing countries: strengthening global financing and coordination – report of the consultative expert working group on research and development: financing and coordination*, available at: http://www.who.int/phi/CEWG_Report_5_April_2012.pdf.) However the development of QALYs by NICE and the plans for value-based pricing already address many of these substantial difficulties, and the centralised structure of the NHS offers an unusually favourable context for such a scheme. If it will work anywhere, it is likely to work in the UK.

[695] World Health Organization (2012) *Consultative expert working group on research and development: financing and coordination*, available at: http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_24-en.pdf, p150.

after conceding a number of merits in the proposal, the Working Group rejected the proposal in view of practical difficulties in its implementation, in particular, in establishing a measure of health impact in the context of developing countries.[696]

9.62 This criticism is certainly telling, but mainly for developing countries. Since the avowed aim of the HIF is to benefit developing countries, and that was the concern of the Working Group, there was no discussion of its applicability to developed countries. However, with the development of NICE and the plans for value-based pricing,[697] much of the assessment apparatus already exists in the UK, or is being developed. Furthermore, given the centralised structure of the NHS, the circumstances prevailing in the UK appear unusually favourable for getting 'a sufficiently reliable measurement of health impact'.

9.63 As in the proposal for developing countries, so for the UK it would make sense to make participation voluntary, at least in the first instance. The payment rules could be similar: 'based on the… assessment of the actual… health impact of the medicine as a proportion of the… health impact achieved by all products registered with the [UK] HIF.' The total UK HIF moneys to be thus divided up would need to be large enough to ensure that genuinely innovative drugs yielded more profit than they would have done if they had been subjected to the ordinary pricing system (by then, presumably a 'value-based' system). The aim might be ultimately to move to the health impact system – low base pricing plus health impact payment (HIP) – across the board.

Impact on marketing costs

9.64 It is interesting to consider what such a system would do to the marketing activities of innovating firms. (The marketing expenditures of research-intensive big pharmaceutical firms are typically comparable to their R&D spends.[698]) The unethical (and illegal) promotion of off-label prescribing[699] would be simply irrational in this system, assuming that the monitoring system recorded these prescriptions as negative value to patients and therefore reduced the health impact payment accordingly. Once all drugs were subject to the health impact (HI) system, there would be much less to gain from encouraging doctors to prescribe, say, one firm's beta-lymphocyte stimulator rather than another's. The overall payment pot for beta-lymphocyte stimulators as a whole would be maximised by each patient getting the right one for him or her, and for beta-lymphocyte stimulators being prescribed not as widely as possible, but as widely as desirable. According to how the HI system were established, the beta-lymphocyte innovator(s) could get the bulk of the HI payments for this drug class, regardless of the pattern of sales, and me-too followers would get little payment.[700] The total marketing spend of pharmaceutical firms would clearly fall substantially, to public benefit.

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[696] WHO (2012) *Research and development to meet health needs in developing countries: strengthening global financing and coordination – report of the consultative expert working group on research and development: financing and coordination*, available at: http://www.who.int/phi/CEWG_Report_5_April_2012.pdf, p57.

[697] See paragraph 9.57.

[698] A recent study found that pharmaceutical firms spent "almost twice" on promotional expenditures what they spent on R&D, in the US. (Gagnon MA and Lexchin J (2008) The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States *PLoS Medicine* **5**: e1). This study includes as 'promotional' a number of expenditures often excluded: notably promotional meetings and phase IV 'seeding' trials. However, it excludes necessary expenditures on packaging and distribution, which are normally included in 'marketing' expenditure. Given the high prices charged for drugs on the US market, it is reasonable to suppose that promotional expenditures are exceptionally high there, thus our rather cautious judgment.

[699] For example, GlaxoSmithKline (GSK) allegedly promoted its anti-depressant 'Paxil'® to US doctors to use for the treatment of children, when it had not been approved for their use. GSK settled out of court for $3bn, for this and a number of other charges. Economist editorial (2012) The settlers: American prosecutors wring $3 billion from GlaxoSmithKline *The Economist* 7 July, available at: http://www.economist.com/node/21558313.

[700] Of course this would depend on performance, and would not apply when a me-too drug dominated the market due to superior outcomes.

The health impact system and the social shaping of emerging biotechnologies

9.65 Throughout this Report, we have argued that emerging biotechnologies should not, individually, be constrained or favoured but that technological development should, in general, be shaped and steered in the direction of public good by conditions that express a public ethics. A system that rewards innovators for the social value of innovation separately from the market cost of production provides an opportunity for public discourse to contribute to the shaping and steering. True, the most obvious influences will be those of three groups of experts. There will be, as there already are, those in firms who decide which drugs to develop and go on developing; and those in regulatory bodies who decide whether to approve the drugs submitted to them. There will also be a third group who have to work out what the outcomes were of the use of particular drugs or other therapies. However, this third group need not completely control the *valuation* of the outcomes; that can partly be done beforehand. This aspect of valuation is one in which public ethics could and should play a role.

9.66 This valuation might also reflect the judgment that excellent low-tech alternatives to advanced drugs are available; for example, specific and feasible lifestyle changes that might not only cut down the rate of new cases, but go a long way to controlling the condition, perhaps in many cases reversing it. In such a case it might be decided, in comparing the outcomes of new drug treatments with the best previously available alternatives (BPAA), that lifestyle changes be included in the BPAA; pharmaceutical firms might well conclude that there is more money to be made from developing therapies for the many conditions that, on present knowledge, cannot be controlled or reversed by lifestyle changes, or even (to a large extent) prevented. It seems to us that the judgment about what should be treated as part of the best available alternatives to new drugs is one in which public ethics could and should play a role.

The internationalisation of health impact payments

9.67 At paragraphs 9.59 to 9.63, we argued that if a HIP system would work anywhere, it would work in the UK, and that the UK, therefore is an ideal place to start. But if it works in the UK then, in the end, it could work anywhere. Just as it would pay the UK to be a pioneer, because there would be gains in the efficiency of use of drugs, so it would pay other countries with reasonably centralised health systems to follow, possibly saving on the initial cost of the assessment system because that had already been developed. And as one developed country after another joined in, the incentives to firms for innovative drug development of high social value would increase. The better established the HI assessment system, the easier it would be to extend it to at least *some* developing countries, and thus to open the road to the original concept of the HIF.

Impact payments beyond pharma

9.68 Our 'impact' argument has focused on pharmaceuticals thus far because, firstly, the problems we are addressing are much the more pronounced in 'type 1' emerging biotechnologies and, secondly, the impact payment system needs to be managed by a monopoly purchaser, or a state which is able and willing to regulate an industry with large numbers of consumers – for which prices can be set centrally and monitored on a sampling basis. This applies to pharmaceuticals and other medical products but it could also apply to plant breeding. In plant breeding the importance of developing countries is arguably greater. It might well be agreed that plant breeding for developing countries, given climate change and scarcity of (for example) water, deserves a Crop Impact Fund on the lines of the HIF, as originally proposed: a fund financed by aid money and/or carbon credits, which would reward innovative plant breeders (whatever the technology used) according to the social value of the plant variety introduced into developing countries. It would be relatively easy to use satellite photography followed by sampling on the ground to establish the extent to which a new variety of crop plant was used; this would then need to be combined with studies of the agronomic and ecological impact.

9.69 In general, the opposition to transgenic crop varieties is based on predictions of small benefit and large adverse consequences: for example, that farmers will become more dependent on plant breeding firms and on chemicals such as herbicides supplied by them, while not gaining the promised increases in yields. If a plant-breeding firm accepted that it would profit from its investment (if at all) on the basis of (neutral) impact assessment, this opposition might well be

moderated. As with health impact, there is no reason why lay people should not participate in valuing agricultural and ecological impact. The lay people who distrust GM crops might agree with the technologists who enthuse over them to put a high social value on reduction of the need for fertilisers and eutrophication.[701] On the other hand, the impact payments might be reduced where evidence was available that low-technology alternatives (inter-planting with leguminous plants, for example) were available.

Incentivising 'type 2' emerging biotechnologies

9.70 In paragraphs 9.37 to 9.40, we note that 'type 2' biotechnologies appear to face quite different problems in commercialisation from biopharma: general discouragement due to 'environmental under-pricing'. In this case we can express social value in the simplest way: by getting rid of under-pricing through eco-taxation or the equivalent use of 'permits to pollute'. Where a given chemical can be produced either synthetically or in a bioreactor, the relative cost of the latter process will fall. Where, for example, biotechnology produces micro-organisms which can greatly cheapen the production of ethanol from cellulose residues, or of biogas from sewage,[702] a carbon tax will make the biofuel resulting still more competitive with fossil fuels. On the other hand, these expectations may be derailed by hidden complexities or intractabilities. As with an impact payment scheme it is not necessary to know or to take a view on the likelihood of different outcomes, although managers and financiers of biotech firms must do so. If their micro-organism fails, they lose the money they invested. What is necessary is that any firm that makes such an advance should know that it will earn more than would now be the case.

Conclusion

9.71 The goods that biotechnology creates are essentially public goods; paradoxically, emerging biotechnologies are infused with commercial values from the very beginning, from the political stakes placed on the growth prospects of the knowledge economy (as we saw in Chapter 7)[703] to the personal interests of researchers (as we saw in Chapter 6)[704] and the entrepreneurial interests of firms with R&D capacity. (Military and charitable biotechnology development are, for different reasons, less infused with commercialism, although they, too, must interact with commercial contexts.) However, as a dominant tool for the allocation of resources, the market mechanism is poor at meeting social demand for these goods or at generating goods that meet social demand. From an investment perspective, the discourse of high ambition that initially made biotechnologies attractive appears to have fallen victim to the characteristic uncertainties that we identified in Chapter 3. As investors find less uncertain opportunities for investment, those who are institutionally committed to biotechnology – such as pharmaceutical firms – struggle to find business models that make economic sense.

9.72 Nevertheless, the unmet need remains for the benefits that proponents of biotechnology claim it will be able to deliver. The problem is that mechanisms intended to protect market incentives to produce them, principally IPRs, do not function efficiently either to guarantee sufficient reward to innovators or to foster the innovative efforts of competitors. The market value of biotechnology and its social value (or potential market and social values) diverge. We have therefore considered the principle, and one possible practical approach, to separating the reward for innovation from the price paid for products, that is, separating the public goods in which the main value of biotechnologies is invested from the private goods that give them physical form. The reason for putting such a principle into practice would be, in cases in which markets may fail to maximise the social value of innovation, to move away from a situation in which market values determine innovation in biotechnologies towards one in which social values do so. This involves the determination of the social value of biotechnologies through the kind of public

[701] The impact on the ecosystem of response to abnormal levels of artificially introduced nutrients or other substances, for example, bloom of phytoplankton in water or reduction in oxygen levels in the sea impacting on fish populations.
[702] Nuffield Council on Bioethics (2011) *Biofuels: ethical issues*, available at: http://www.nuffieldbioethics.org/biofuels-0.
[703] See paragraph 7.10ff.
[704] See paragraph 6.49ff.

discourse ethics we developed in Chapter 4. The aim in doing so is to restore the proper relationships between markets and society, with markets as tools for distributing resources rather than autonomous forces dictating social organisation and the possible forms that social relations may take: in this sense market determinism is just as corrosive to common social life as the technological determinism discussed in Chapter 4.