

Deadly Gaps in the Patent System: An Analysis of Current and Alternative Mechanisms for Incentivising Development of Medical Therapies

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SYNOPSIS

The cost of medicines imposes a significant financial burden on society, with New Zealand spending \$783.6 million between 2012 and 2013 alone. The majority of these costs are due to the monopoly prices charged for new patented drugs. The pharmaceutical industry argues that these high prices are necessary to recover the costs of drug development, which can exceed a billion dollars for a single drug. Because new medicines are relatively cheap to reverse-engineer and manufacture, in absence of a minimum period of exclusivity provided by patents, it is alleged that it would not be commercially viable to develop new medicines.

Most criticisms of the patent system relate to the high prices charged for patented medicines. However, there is another issue which has received limited academic commentary to date, namely, whether the pharmaceutical industry's reliance on patents means that otherwise socially valuable medical therapies are being screened out or ignored, and whether alternative incentive mechanisms are needed to address this problem.

The aim of this thesis is to address this issue. First, the laws applicable to patentability and regulatory approval of new medicines will be discussed, with a focus on New Zealand and the United States. Second, evidence will be provided for the existence of three broad categories of medical therapies which lack private incentives for development under the current patent system: unpatentable therapies, unmonopolisable therapies and unprofitable therapies. Other problems with the reliance on patent monopolies will also be discussed. Third, the process of pharmaceutical reimbursement that is used to determine the price of medicines under the current system will be described, and a set of criteria will be proposed for an ideal incentive system, against which the current system is compared. Fourth, alternative incentive mechanisms for medical therapies comprising exclusivity-based 'pull' incentives, prize-based 'pull' incentives, and publicly funded 'push' incentives, will be analysed and ranked against these ideal criteria. This thesis concludes by proposing two legislative frameworks as part of an optimal incentive system alongside the current patent system, namely, extended regulatory exclusivity for incentivising unpatentable therapies and a prize-based mechanism combined with increased public funding for incentivising unmonopolisable and unprofitable therapies.

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Finally, I would like to dedicate this work to persons close to me affected by chronic illness, without whom none of this would have been written.

STYLE

This thesis has followed the second edition of the *New Zealand Law Style Guide*.¹ Where sources were not covered, citations have been made as consistently as possible with the guide or in accordance with a common citation style for a foreign source in the applicable jurisdiction. This thesis also differs from the guide in that major headings in Chapter Six have been divided into sub-parts 6A, 6B and 6C. Further, in order to condense footnotes and for consistency, authors are referenced by their initials and surname rather than providing names in full.

¹ G McLay, C Murray and J Orpin *New Zealand Law Style Guide* (2nd ed, Thomson Reuters, Wellington, 2011).

I Introduction

A Patenting the Sun: The Problem with Reliance on Patents

[The interviewer] asked Salk, "Who owns the patent on this vaccine?" Salk magnanimously replied: "Well, the people, I would say. There is no patent. Could you patent the sun?"¹

Dr Jonas Salk developed the first safe and effective polio vaccine in 1952.² Since the early 20th century, polio had terrorised the global population (in regular epidemics), including New Zealand.³ In 1952 alone, polio infected nearly 58,000 people in the United States, killing 3,145, and leaving 21,269 people, mostly children, with moderate to disabling paralysis.⁴ However, as a result of the development of the Salk vaccine, after the United States implemented a mass immunisation programme in 1955, polio cases fell to just 5,600 people in 1957.⁵ Overseas countries, including New Zealand,⁶ rapidly adopted equivalent immunisation programmes, which have ultimately reduced the global incidence of polio from "an estimated 350,000 cases in 1988 to a low of 493 cases reported in 2001".⁷ The impact of the Salk vaccine on global disease burden is undeniable. The above quote, from a televised interview in 1955, reinforced the image of Dr Salk as a selfless hero, dismissing the notion of patenting medicine for private gain.

It is unfortunate that, in addition to being somewhat misleading,⁸ the inference that may be drawn from Dr Salk's quote is an anachronism. In the modern era, if "there is no patent", then it usually follows that there is no drug, because new medicines require patent protection to have any chance of receiving the private funding necessary for their development.⁹ It could be said that under the current

¹ G Johnson "Once Again, A Man With A Mission" *The New York Times* (25 November 1990).

² R Singh, AK Monga and S Bais "Polio: A Review" (2013) 4 *Int J of Pharm Sci & Res* 1714 at 1718.

³ G Rice "Epidemics - The polio era, 1920s to 1960s" (20 June 2013) *Te Ara - the Encyclopedia of New Zealand* <www.teara.govt.nz> at 5.

⁴ E Zamula "A New Challenge for Former Polio Patients" (1991) 25 *FDA Consumer* 21 at 23.

⁵ Singh, Monga and Bais, above n 2 at 1718.

⁶ A Day "An American Tragedy". *The Cutter Incident and its Implications for the Salk Polio Vaccine in New Zealand 1955-1960* (2009) *Health and History* 42 at 42.

⁷ O Kew "Reaching the last one per cent: progress and challenges in global polio eradication" (2012) 2(2) *Curr Op in Vir* 188 at 188.

⁸ Commentators have argued that the National Foundation for Infantile Paralysis had attempted to patent the Salk vaccine, but it was deemed unpatentable because of prior disclosures: see R Zwahlen "The Real Reason Why Salk Refused to Patent the Polio Vaccine" (27 January 2012) *Biotechnology Industry Organization* <www.biotech-now.org>. Years later, Dr Salk established a private company that patented an experimental HIV vaccine, although it failed in clinical trials: see Johnson, n 1 above.

⁹ PW Grubb and PR Thomsen *Patents for Chemicals, Pharmaceuticals, and Biotechnology: Fundamentals of Global Law* (5th ed, Oxford University Press, New York, 2010) at 426; BN Roin "Unpatentable drugs and the standards of patentability" (2009) 87 *Tex L Rev* 503 at 504-505; RS Eisenberg "The Problem of New Uses" (2005) 5 *Yale J Health Policy L & Ethics* 717 at 721; H

system, enforceable patent protection is the most important ingredient of a new medicine, with all other considerations being secondary, including medical efficacy and the needs of society at large.

In particular, it is currently estimated to cost over USD 1 billion and take over 10 years to bring a new medicine to market.¹⁰ Further, an experimental medicine has only approximately 20 per cent chance of overcoming the expensive, lengthy but essential clinical trials required to prove safety and efficacy, which allow it to be legally sold to the public.¹¹ Governments and charities do not assume the high costs and risks of drug development, leaving it to the private pharmaceutical industry.¹² For this reason, pharmaceutical companies rely on patents to guarantee a minimum period of exclusivity against competition in order to recover their development costs.¹³ Society ends up indirectly paying for the high costs of drug development, through the estimated USD 500 billion per annum paid in monopoly markups over new drugs.¹⁴

While the high monopoly prices charged for new patented medicines is frequently debated,¹⁵ the reliance on patents to fuel the engine of medical progress has other severe but unseen consequences, which as a result have received little academic commentary to date. In particular, in order for medicines to be patentable, they must satisfy certain strict patentability criteria, which disregards the potentially large social value of ‘unpatentable therapies’. Further, a patent is only useful to the extent that it can be practically enforced against infringers to prevent competition or extract monopoly profits from the sale of a medicine, which means that socially valuable ‘unmonopolisable’ and ‘unprofitable’ therapies are unlikely to receive private

Grabowski “Patents, Innovation and Access to New Pharmaceuticals” (2002) 5(4) J Int Economic Law 849 at 850.

¹⁰ JA DiMasi and HG Grabowski “The cost of biopharmaceutical R&D: is biotech different?” (2007) 28 Managerial and Decision Economics 469 at 475.

¹¹ JA DiMasi and others “Trends in risks associated with new drug development: success rates for investigational drugs” (2010) 87(3) Clin Pharmacol Ther 272 at 272.

¹² While the Salk vaccine’s development was publicly funded through the National Foundation of Infantile Paralysis (known currently as the ‘March of Dimes’), this unprecedented funding drive was only possible because of the pressing and visible nature of the polio threat to the United States. See DJ Wilson *Polio* (Greenwood Publishing Group, California, 2009) at 106.

¹³ See discussion of the process of regulatory approval and generic competition in Chapter Two.

¹⁴ This estimate is calculated on the basis that patented or ‘branded’ drugs are generally 12 times more expensive than off-patent or ‘generic’ drugs, and that global sales of branded drugs were USD 596 billion in 2011. See J Love and T Hubbard “The Big Idea: Prizes to Stimulate R&D for New Medicines” (2007) 82 Chi-Kent L Rev 1519 at 1522; *The Global Use of Medicines: outlook through 2016* (IMS Institute for Healthcare Informatics, July 2012) at 8.

¹⁵ E Rosenthal “The Soaring Cost of a Simple Breath” *New York Times* (online ed, New York, 12 October 2013); D Armstrong “At \$84,000 Gilead Hepatitis C Drug Sets Off Payer Revolt” (28 January 2014) Bloomberg <www.bloomberg.com>; E Torreele and J Bloom “Should Patents on Pharmaceuticals Be Extended to Encourage Innovation?” *Wall Street Journal* (online ed, New York, 23 January 2012).

funding.¹⁶ As a result, such therapies will be screened out from development by pharmaceutical companies, irrespective of social need. This screening occurs at an early stage of development, and the basis for doing so is not publicly disclosed. In addition, the use of patent monopolies creates other inefficiencies in the pharmaceutical industry, such as excessive litigation, price gouging, marketing, potential inhibition of research, and incentives to develop lucrative ‘me-too’ and ‘lifestyle’ drugs with limited health benefits.¹⁷ This thesis will analyse problems with the current incentive system and whether alternative incentive mechanisms would be preferable in order to encourage private investment in a direction that will maximise public health.

B Aim of the Thesis

The aim of the thesis is to identify particular inadequacies in the current patent system¹⁸ for incentivising socially valuable medical therapies and to propose an optimal incentive system to address these issues. This aim will be achieved by satisfying four objectives. The first objective is to provide background information on the legal requirements for patentability and regulatory approval of new medicines and describe in what circumstances exclusivity can be lost. The second objective is to analyse the pharmaceutical industry’s reliance on patent protection for incentivising new medical therapies and the problems with such reliance. The third objective is to consider the determination of rewards under the current incentive system and propose criteria for an ideal incentive system that would address the problems already identified. The fourth objective is to analyse current and alternative incentive systems using these ideal criteria, and propose an optimal incentive framework in light of this analysis.

The thesis will meet these objectives by considering the applicable law regarding patents and drug development, and research by various commentators on gaps in the patent system for medical research, particularly the views of Roin on the lack of incentives to develop unpatentable drugs and second uses of ‘off-patent’ drugs.¹⁹ It will confirm and expand on this analysis by identifying specific factors that cause otherwise socially valuable medicines to become unpatentable, and will rebut the argument that patenting slightly modified drugs or new uses could overcome this problem. The thesis will also define broader categories of ‘unmonopolisable

¹⁶ ‘Unpatentable’, ‘unmonopolisable’ and unprofitable therapies will be defined and discussed in Chapter Three.

¹⁷ See discussion of other problems with patent system in Chapter Three.

¹⁸ The current system refers to the patent system, regulatory environment, and reimbursement mechanisms that incentivise development of new medicines in New Zealand and the United States.

¹⁹ BN Roin, above n 10; BN Roin “Solving the Problem of New Uses” (1 October 2013) Social Science Research Network <www.ssrn.com>.

therapies’ and ‘unprofitable therapies’ which lack private incentives for development. It will consider how the current system determines reimbursement of new patentable medical therapies and the feasibility of various alternative incentive mechanisms in light of proposed ideal criteria.

Finally, the thesis will propose two new incentive mechanisms to optimally incentivise unpatentable, unmonopolisable and unprofitable therapies. It will also make practical suggestions for how these proposed mechanisms should be administered as part of a legal framework, and will analyse them with reference to the ideal criteria.

C Methodology, Scope and Limitations of the Thesis

This thesis will use a sociolegal methodology,²⁰ which includes a broader consideration of the ‘law in action’ having regard to the influence of practical commercial and scientific factors on incentives for drug development, rather than focusing on case law and legislation. The major limitation of the research is the lack of empirical data available on the scale of screening of otherwise socially valuable therapies, due to the high levels of secrecy in the pharmaceutical industry. Therefore, in some cases, the author has had to estimate the level of screening, based on what can be logically inferred from publicly available information.

In order to maintain a manageable size for the thesis, it will focus on New Zealand and the United States, although other jurisdictions will be referred to if useful for comparative purposes. While this thesis will consider incentives to develop a broad range of medical therapies beyond the use of pharmaceuticals, including dietary supplements, diets, and lifestyle interventions, it will not consider the incentive framework for medical devices, as these generally have lower barriers to obtain market entry.²¹ It will also focus the analysis on seven alternative incentive mechanisms, although a large number of alternatives have been proposed.²² Finally, although this thesis will consider existing gaps in protection for medicines under patent law, it will not suggest amendments to lower those patentability standards, as this would be a drastic reform with potential for abusive patenting strategies by

²⁰ M Salter and J Mason *Writing Law Dissertations: an Introduction and Guide to the Conduct of Legal Research* (Pearson Longman, Harlow, 2007) at 119.

²¹ An exception is implantable medical devices, referred to as Class III devices, which require clinical trials in humans in order to be legally sold. See “Overview of Medical Devices and Their Regulatory Pathways” (6 March 2013) Food and Drug Administration <www.fda.gov>.

²² A non exhaustive list of other alternative incentive mechanisms include: Advance Market Commitments and Advance Purchase Commitments, Transferable Exclusivity and Priority Review ‘Wildcard’ Vouchers, Patent Buyouts, and Tax Incentives. An analysis of these alternatives was not included in the thesis because of space constraints and the fact they do not share features with the proposed optimal framework.

pharmaceutical companies and would likely breach international obligations. Rather it will propose alternative incentive mechanisms that can be managed alongside the existing patent and regulatory framework.

D Thesis outline: An Overview of Chapters Two to Eight

Chapter Two provides an overview of the purpose of the patent system. It then discusses the criteria for a patentable medicine in New Zealand and the United States, and the circumstances under which patentability can be excluded. The regulatory framework for obtaining market approval for new medicines is discussed, as well as how this interacts with the patent system to allow a pharmaceutical company to be temporarily protected against competition.

Chapter Three explains the reasons for the high costs and risks of drug development, and how pharmaceutical companies will screen out otherwise promising medicines if they cannot ensure that a monopoly price can be enforced in order to recover these development costs. First, the factors that cause some therapies to be unpatentable are discussed. It is argued that flexibilities in the patent system referred to as ‘evergreening’ are inadequate to restore effective patent protection over such unpatentable therapies. Second, the chapter discusses unmonopolisable therapies, for which the ingredients are readily available from multiple sources. Third, the chapter discusses unprofitable therapies, such as treatments for diseases prevalent in developing countries and antibiotics. Finally, other problems with the patent system are discussed, such as the prevalence of wasteful litigation between pharmaceutical companies and their competitors, gaming of the system to maximise monopoly rents, stifling innovation through an ‘anti-commons’ effect, and incentivising development of profitable ‘me-too’ or ‘lifestyle’ drugs with limited health impact.

Chapter Four discusses the pricing and reimbursement of new medicines under the current system, and the tools of pharmacoeconomic analysis and healthcare metrics used to ensure that the prices paid are cost-effective having regard to the health benefits obtained. It will compare and contrast how prices for medicines are determined by pharmaceutical payers in New Zealand and the United States.

Chapter Five discusses the goals and criteria of the ideal incentive system. First, the chapter addresses applicable international obligations and goals to implement the highest standards of health will be discussed. Next, eight criteria are proposed for the ideal incentive system, which broadly correspond to overcoming the problems identified in Chapter Three. These ideal criteria are then used to rate the current patent system.

Chapter Six considers various alternative incentive mechanisms to provide incentives for medical therapies that have either been implemented or proposed. The chapter is separated into three parts. In Chapter 6A, various exclusivity-based ‘pull’ incentives are discussed and compared against the ideal criteria from Chapter Five. These incentives include patent extensions, regulatory exclusivity mechanisms, and Orphan Drug reforms. The benefits and limitations of each proposal is considered having regard to the ideal criteria. Chapter 6B discusses various prize-based ‘pull’ incentives. Proposals for fixed and flexible prize mechanisms will be compared, as well as their advantages and disadvantages. Finally, Chapter 6C discusses ‘push’ incentives, which involve mechanisms that support medical research during the process of drug development. These include direct public funding via grants and ‘open source’ mechanisms to increase the level of co-operation between medical researchers and the pharmaceutical industry in order to solve common problems.

Chapter Seven proposes two legislative frameworks for an optimal incentive system, having regard to the advantages and disadvantages of the various alternative incentive mechanisms analysed in Chapter Six and with reference to the ideal criteria from Chapter Five. The first proposal involves the use of extended market exclusivity to incentivise unpatentable therapies. The second proposal uses prizes to provide private incentives to prove the efficacy of unmonopolisable and unprofitable therapies in early stage clinical trials, and subsequent public funding to validate those results in larger clinical trials. These proposals are compared against the ideal criteria, and shown to achieve better overall ratings than the alternative incentive mechanisms discussed in Chapter Six.

Chapter Eight concludes the thesis. It discusses the aim of the thesis to analyse problems with the current patent system for incentivising development of medical therapies. It reiterates the research problem and discusses the satisfaction of the four research objectives identified earlier in this chapter. It also considers the need to implement equivalent reforms in major pharmaceutical markets such as the United States and Europe for the optimal incentive system to be a success and highlights the significance of the problem and the need for further debate to highlight this issue and address the current gap in incentives.

E Appendices

Two appendices are attached to this thesis. Appendix One includes the author’s Human Ethics Committee approval notice and survey for collecting quantitative and qualitative data regarding the extent that unpatentable, unmonopolisable, and unprofitable therapies are screened out of development by the pharmaceutical

industry. Although the survey was sent to over 200 members of the pharmaceutical industry in targeted emails, only one partially completed response was received. This confirms the high level of secrecy in the industry, which contributes to the public's lack of awareness of the screening problem. Appendix Two contains an extract of the MODDERN Cures Act of 2013, which is a bill currently before the 113th United States Congress. This bill provides 15 years of regulatory exclusivity to compensate for the lack of private incentives to develop unpatentable therapies.²³ The bill is used as a basis for the extended regulatory exclusivity mechanism proposed in Chapter Seven.

²³ Notably, the legislation refers to these as 'dormant therapies'.

II Patentability and Regulatory Approval of Medicines

A Introduction

Chapter Two will cover the main legal requirements for obtaining patent rights over medicines and regulatory requirements for market entry. First, a general overview of the patent system is provided. Second, the criteria which need to be satisfied to obtain a patent in the jurisdictions of New Zealand and the United States will be discussed, namely, patentable subject matter, novelty, inventive step, and utility. Sufficiency, the major ground for revoking a patent will also be discussed. Third, the main exclusions to patentability under law will be discussed, in particular, inventions contrary to public policy or morality, and methods of medical treatment. Fourth, various judicially-developed inroads into the exclusions for methods of medical treatment under law will be addressed, namely: ‘Swiss-claims’, novel dosage regimens, methods of administration, and novel patient groups. Finally, the chapter will outline the regulatory law applying to the approval of medicines in New Zealand and the United States, including the ‘regulatory exclusivity’ mechanisms that can act as a form of ‘quasi-patent’ protection over new medicines.

The purpose of this chapter is to familiarise the reader with the legal doctrines that govern the patentability and regulation of medicines, and the circumstances by which gaps in protection can occur for otherwise socially valuable medical therapies. Chapter Three will focus on the consequences of these gaps and provide evidence that certain categories of socially valuable therapies are not being developed as a result.

¹

B Overview of the Patent System

Ironically, patent laws conceived of over 400 years ago are still used to incentivise the development of the latest technology.² In particular, the origin of New Zealand patent law dates back to the post-Elizabethan Statute of Monopolies enacted in 1624. Section 6 of the Statute of Monopolies provides that patents will be granted for “...any manner of new manufactures within this realm, to the true and first inventor, and inventors of such manufactures.” Section 6 is incorporated into New Zealand law as part of the definition of invention in section 2 of the Patents Act 1953, and most recently in section 14 of the Patents Act 2013 (Patents Act).

¹ Namely, unpatentable, unmonopolisable, and unprofitable therapies.

² This could be both a criticism of the patent system and an endorsement.

The Statute of Monopolies formalised the process of granting patent monopolies, which had only been possible under royal prerogative.³ Instead, Crown law officers had the right to grant ‘letters patent’ for the disclosure of inventions which fulfilled the requirement of being a ‘manner of new manufacture.’⁴ Thus, the Statute of Monopolies codified minimum patentability standards, which promoted technological development by incentivising the disclosure of new inventions.

Similarly, patent law in the United States has a long history, having been enshrined in article I, section 8(8) of the United States Constitution, which held that its purpose was ‘To Promote the Progress of Science and useful Arts, by securing for limited Times to ... Inventors the exclusive Right to their ... Discoveries.’⁵ The United States is generally viewed as being the most pro-patent jurisdiction in the world, with a specialist appellate patent court⁶ that has led the expansion of the scope of patentable subject matter to life forms, software, and business methods.⁷

Commentators have attempted to justify the establishment of the patent system under various theoretical frameworks. Under ‘contract theory’, society awards an exclusivity right to an inventor for a certain period of time as compensation for the full disclosure of information relating to how to make and perform the invention.⁸ Therefore, theoretically, exclusivity rights discourage inventors from relying on trade secret protection and encourage the exchange of scientific and technological information.⁹ These rights are particularly crucial in the pharmaceutical industry where the costs of discovering new drugs are high and the marginal costs of manufacturing them are low.¹⁰ The importance of this ‘social contract’ or ‘bargain’ for facilitating medical progress is reflected in the more stringent disclosure requirement for pharmaceutical patents, particularly those using biotechnological processes.¹¹

³ See C MacLeod *Inventing the industrial revolution: The English patent system, 1660-1800* (Cambridge University Press, Cambridge, 2002) at 14-19.

⁴ Statute of Monopolies 1624 (UK) 21 Jac 1, c3, s 6. ‘Manner of new manufacture’ as a patent criterion will be discussed in more detail below.

⁵ Constitution of the United States, art I, s 8, cl 8.

⁶ Namely, the United States Court of Appeals for the Federal Circuit.

⁷ Y Kihara “US pro-patent policy: A review of the last 20 years” (2000) 7 CASRIP Newsletter 11 at 15. See discussion of main exclusions to patentability below. The patentability of software and business methods is beyond the scope of this thesis.

⁸ V Denicolò and L Alberto Franzoni “The Contract Theory of Patents” (2004) 23 International Review of Law and Economics 365 at 365.

⁹ S Frankel *Intellectual Property in New Zealand* (2nd ed, Lexis Nexis, Wellington, 2011) at 392.

¹⁰ The high costs of drug development as well as adverse consequences of the pharmaceutical industry’s reliance on patent exclusivity will be discussed in Chapter Three.

¹¹ DL Burk and MA Lemley “Is patent law technology-specific” (2002) 17 Berkeley Tech LJ 1155 at 1155. See further discussion under ‘Sufficiency’ subheading below.

Every patent has various common features, whether issued in New Zealand, the United States, or other jurisdictions. Information regarding how to make and perform the invention is contained within a document called a ‘specification’, which is typically supported by drawings. The most important part of the specification is the claims, which describe the boundaries of the invention and scope of monopoly granted.¹² A claim is a carefully-worded sentence which describes the various features or ‘integers’ comprising an invention. In order for a product or process to infringe a patent claim, every single integer must be present. Therefore, in general, narrow patent claims have more integers and broad patent claims have fewer integers. A patent owner has exclusive rights to make, use, sell, and import any invention covered by the claims and may seek injunctive relief or damages from the Courts against anyone who would infringe those rights.¹³

In order to provide adequate protection for medicines, claims must cover a commercially relevant product or process and must be sufficiently broad so that they cannot be ‘designed around’ by competitors, which means manufacturing or selling a medicine in a way that does not infringe the patent. For medicines such as new drugs, the most valuable claims are known as ‘composition of matter’ claims, which describe the chemical structure of the drug. It is also possible to claim chemical structures in a broad manner, covering a core functional group or ‘active ingredient’ with millions of variations of optional chemical groups. These are known as ‘Markush’ claims in the United States.¹⁴

Further, it is possible to claim a method of using a known chemical to treat a particular disease, which is called a ‘method-of-use’ claim. However, ‘composition of matter’ claims are the most valuable, because they prevent the drug from being manufactured for any medical use whatsoever.¹⁵ With strategic use of patents, an applicant can secure market exclusivity over a new drug, assuming claims fulfill the requirements for patentability as at the filing date, which is also referred to as the ‘priority date.’

¹² Formal claims must be submitted with a ‘complete specification’. It is possible for an applicant to file a ‘provisional’ specification without formal claims, provided that they submit a complete specification within 12 months of filing.

¹³ Patents Act 2013, s18. For a discussion of the principles relevant to injunctive relief see *Klissers Farmhouse Bakeries Ltd v Harvest Bakeries Ltd* [1985] 2 NZLR 129 (HC) at 142 and for a discussion of damages remedy in New Zealand see generally *Acquaculture Corporation v New Zealand Green Mussel Co Ltd* [1990] 3 NZLR 299. Damages are significantly higher in the United States because the Courts can grant triple damages for patent infringement: see 35 USC § 284.

¹⁴ See PW Grubb and PR Thomsen *Patents for Chemicals, Pharmaceuticals, and Biotechnology: Fundamentals of Global Law* (5th ed, Oxford University Press, New York, 2010) at 379-380.

¹⁵ Method of use patents can sometimes be used to effectively extend patent protection after a composition of matter patent has expired, if used in a strategic manner. These patent ‘evergreening’ strategies will be discussed in Chapter Three.

Patent rights are in force for 20 years from the priority date, unless the patent is challenged and revoked before expiry.¹⁶ According to ‘prospect theory’, introduced in a seminal paper by Edmund Kitch, the granting of monopoly rights from the priority date helps incentivise investment in development of an invention by preventing wasteful races to commercialisation.¹⁷ However, the downside of an early priority date is that it reduces the effective length of patent exclusivity when the product is ready to be commercialised. This is particularly relevant to the pharmaceutical industry, where drug development can take over a dozen years and cost more than a billion dollars in up-front investment.¹⁸

The priority date of a patent application is also important because that is the date from which the patentability criteria are formally examined. These criteria, which have now been standardised pursuant to international agreements, will now be discussed.

1 Minimum standards of patentability under TRIPS

The standards of patentability of medical therapies are the same as the patentability of other inventions, subject to some specific exclusions.¹⁹ These standards are now relatively consistent in World Trade Organization (WTO) member countries pursuant to the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), which was signed in 1994.²⁰ Part 5 of TRIPS (Articles 27 to 34) requires all WTO signatories to impose certain minimum standards of patent protection.

In accordance with international obligations under TRIPS, a patent must be allowable for any product (for example, a medicine) or process (for example, a method for producing a medicine) which fulfills the requirements of patentability. In particular, under Article 27.1 an invention must be novel,²¹ involve an inventive step - also referred to as ‘non-obviousness’ in the United States,²² and be capable of industrial application - also referred to as ‘utility’.²³

¹⁶ The grounds for revoking a patent will be discussed below in this chapter.

¹⁷ EW Kitch “The nature and function of the patent system” (1977) *Journal of Law and Economics* 265 at 278.

¹⁸ The implications of long development times and high costs on the ability of patents to provide adequate incentives for pharmaceutical research and development (R&D) will be discussed in Chapter Three.

¹⁹ See discussion under the sub-heading ‘Exclusions from Patentability’.

²⁰ Agreement on Trade-Related Aspects of Intellectual Property Rights 1869 UNTS 299 (opened for signature 15 April 1994, entered into force 1 January 1995) [TRIPS].

²¹ See discussion of the ‘novelty’ criterion below.

²² See discussion of the ‘inventive step’ criterion below.

²³ See discussion of the utility criterion below.

While TRIPS specified minimum standards of patentability, it did not define how those standards were to be applied. Therefore, WTO member countries have interpreted these standards in different ways, which has resulted in medical therapies being held patentable in some jurisdictions but not in others.²⁴ These patentability standards are also applied by patent examiners in accordance with policy decisions of regional intellectual property offices, such as the in the Intellectual Property Office of New Zealand (IPONZ) and the United States Patent and Trademark Office (USPTO).²⁵

In some cases, a WTO member country may be arguably non-compliant with TRIPS. For example, under the former Patents Act 1953, a New Zealand patent examiner could only examine a new patent specification for novelty.²⁶ However, under the new Patents Act, New Zealand is now TRIPS compliant because novelty, inventive step, and utility are formally examined.²⁷ New Zealand has also adopted a standard of ‘absolute novelty’ which means that the scope of knowledge used to determine the novelty or obviousness of an invention - referred to as the ‘prior art base’ - comprises all available knowledge, whether located in New Zealand or overseas.²⁸

²⁴ For example, in the decision of the United States Federal Circuit, *Amgen Inc v Hoechst Marion Roussel, Inc* 65 USPQ 2d (BNA) 1385, a claim over a biologic drug erythropoietin produced using a novel method was upheld, on the basis that it could not be made without human involvement, even though it was known how the drug could be extracted from urine. However, in the United Kingdom, the House of Lords in *Kirin-Amgen, Inc v Hoechst Marion Roussel Ltd* [2004] UKHL 46 rejected this type of claim (known as a product-by-process claim), whereby a product may still be novel if it is produced by a novel method.

²⁵ The decisions of examiners can be appealed to tribunals in the regional intellectual property [IP] offices. For example, at the Intellectual Property Office of New Zealand [IPONZ] the Commissioner of Patents appoints a panel of Hearings Officers to give decisions on matters referred to a hearing. The decisions of Hearing Officers can be appealed to the High Court. In the United States, decisions of the examiner of the United States Patent and Trademark Office [USPTO] can be appealed to the Patent Trial and Appeal Board [PTAB], formerly the Board of Patent Appeals and Interferences [BPAI], which is an administrative tribunal within the USPTO. Because of the often highly technical subject matter of patents, specialist courts have been established to hear appeals from decisions of the regional IP offices. The United States Court of Appeals for the Federal Circuit [CAFC] is an example of such a specialist court. Decisions from the CAFC can only be appealed to the Supreme Court of the United States.

²⁶ Patents Act 1953, s 13.

²⁷ Patents Act 2013, s 65(1)(a)(iii). Under this section, the Commissioner will determine on the balance of probabilities whether ‘the invention, so far as claimed, is a patentable invention under section 14’. Under section 14 a patentable invention must be a manner of manufacture within the meaning of s 6 of the Statute of Monopolies, and must novel, inventive, and useful.

²⁸ Patents Act 2013, s 8. Under the Patents Act 1953, New Zealand applied a ‘local novelty’ standard, meaning that novelty was assessed against what was known in New Zealand. However, in *Sutton v Bay Masonry Limited* HC Tauranga CIV-2003-470-000260, 28 May 2004, Williams J held that the scope of knowledge would include anything available on-line in New Zealand. The term ‘prior art base’ is synonymous with the term ‘prior art’, which will be discussed below regarding the novelty and inventive step patentability criteria.

Another source of variation between jurisdictions is the applicability of exclusions from patentability. TRIPS allows member countries to exclude from patentability “inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality”.²⁹ TRIPS also allows “diagnostic, therapeutic and surgical methods for the treatment of humans or animals” to be excluded from patentability.³⁰ However, there have been certain inroads into the exclusion of methods of medical treatment due to judicial acceptance of certain types of claim language which are interpreted as falling outside those exclusions.³¹

The following sections will highlight how the criteria for patentability are applied to secure monopoly rights over medicines.

C *Criteria for Patentability of Medical Therapies*

In this part, the main criteria for patentability of a medical therapy will be discussed. It is notable that in addition to the ‘novelty’, ‘inventive step’ and ‘utility’ patentability criteria required under TRIPS, there is another criterion, which is not defined by TRIPS. This concerns the definition of invention, which is required to be either ‘patentable subject matter’ or a ‘manner of manufacture’. In particular, the definition of invention has been broadened from a ‘vendible product’³² to include any intervention which creates an ‘artificial state of affairs’.³³ However, this can be contrasted with the ‘discovery’ of a natural principle or ‘abstract idea’ which does not fall within the definition of invention.³⁴ These four criteria will be analysed with reference to applicable law in New Zealand and the United States.

In New Zealand, the applicable law is set out in the Patents Act, which is the first major reform of its patent system since 1953. When the Patents Act enters into force,³⁵ inventions will be formally examined against four patentability criteria, namely, (a) manner of new manufacture, (b) novelty, (c) inventive step and (d)

²⁹ TRIPS, art 27.2.

³⁰ TRIPS, art 27.3(a).

³¹ See discussion of ‘Swiss claims’, and claims over second medical uses, dosing regimens, and novel patient groups below. However, as will be noted in Chapter Three, the difficulty with detecting infringement of such method claims can significantly reduce their practical value.

³² See discussion of *GEC’s Application* [1943] RPC 1 below.

³³ See discussion of *National Research Development Corporation v Commissioner of Patents* [1959] HCA 67 below.

³⁴ See discussion of *Pfizer Inc v Commissioner of Patents* [2005] 1 NZLR 362 (CA) and *Bilski v Kappos* 130 S Ct 3218 (2010) below.

³⁵ The Patents Act 2013 enters into force on 12 September 2014.

utility.³⁶ Similarly, in the United States, the Patents Act is codified under Title 35 of the United States Code (USC),³⁷ which has equivalent patentability criteria.³⁸

While there are some differences between the patentability criteria between New Zealand, the United States, and other jurisdictions, an in-depth analysis of other jurisdictions is not necessary to understand the argument in the thesis, namely, that the current patent system fails to incentivise otherwise viable medical therapies which do not fulfill the patentability criteria or where it is not possible to enforce a monopoly price. The chapter will now turn to those patentability criteria.

1 Patentable subject matter

The first patentability criterion requires that an invention is patentable subject matter. As noted above, the question hinges on the definition of invention. However, this question also overlaps with exclusions from patentability, discussed separately below, because of greater relevance of policy considerations to these issues. Accordingly, the appropriate scope of patentable subject matter is usually subject to controversy.³⁹ What is currently deemed patentable subject matter in New Zealand and the United States will now be discussed.

(a) New Zealand

In order to be patentable, New Zealand law requires that an invention must be a ‘manner of manufacture.’ The definition of manner of manufacture was considered in the Australian case, *National Research Development Corporation v Commissioner of Patents (NRDC)*,⁴⁰ which considered whether a method of applying herbicide to weeds could be patentable. Previously, under the English case *GEC’s Application*,⁴¹ a ‘manner of manufacture’ could only include methods or processes that produce, improve or restore a ‘vendible product’ or protect it against deterioration. *NRDC* broadened the definition of manner of new manufacture to include any ‘artificial state

³⁶ Patents Act 2013, s 14.

³⁷ With the passage of the America Invents Act of 2011 [AIA], United States patent law has undergone one of its most significant reforms. The most salient aspect of those reforms is the change from a ‘first-to-invent’ to a ‘first-to-file’ system for determining the priority date, which brings the United States in line with other jurisdictions. See generally, “AIA Implementation” United States Patent and Trademark Office <www.uspto.gov>.

³⁸ See 35 USC § 101-103.

³⁹ For example, the patentability of genes, software and business methods is subject to considerable debate by policy makers and academics. However, only the former is relevant to this thesis.

⁴⁰ *National Research Development Corporation v Commissioner of Patents* [1959] HCA 67 [NRDC].

⁴¹ *GEC’s Application* [1943] RPC 1 at 4.

of affairs’.⁴² This approach was followed in New Zealand,⁴³ and eventually the definition of invention was extended to include manufacturing a known drug for a new use.⁴⁴

By contrast, naturally occurring products, pure discoveries, abstract ideas, and mere schemes, are not considered a patentable ‘manner of manufacture’ under common law.⁴⁵ However, it is arguable that isolated and purified biological material – including genetic material - should be patentable on the basis that it would be an ‘artificial state of affairs’ that would not spontaneously occur in nature.⁴⁶ Patents over genetic material for use in diagnostic tests have been granted in New Zealand, although it is uncertain whether they would be upheld if challenged.⁴⁷

(b) United States

The United States has an equivalent patentability criterion to ‘manner of manufacture’, referred to as ‘statutory subject matter.’ Under 35 USC § 101, for an invention to comprise statutory subject matter, it must fall within one of four categories: a process, machine, manufacture, or composition of matter.⁴⁸ According to the Supreme Court of the United States, “laws of nature, natural phenomena, and abstract ideas” are judicially excluded from these four categories, and therefore cannot be subject matter for a valid patent.⁴⁹

The unpatentability of abstract ideas can be relevant to medical inventions that involve ‘mental steps’. For example, in *Prometheus Laboratories v Mayo*

⁴² *NRDC*, above n 40 at para [25].

⁴³ *Swift & Co v Commissioner of Patents* [1960] NZLR 775 (SC).

⁴⁴ See *Pharmaceutical Management Agency Ltd v Commissioner of Patents* [2002] 2 NZLR 529 (CA) allowing ‘Swiss claims’, as will be discussed in this chapter below. Compare *Pfizer Inc v Commissioner of Patents* [2005] 1 NZLR 362 (CA), denying patentability to methods of medical treatment.

⁴⁵ See *Pfizer* at [103]-[106] per Hammond J citing *Swift’s Application* [1962] RPC 37 and *International Business Machines Corporation’s Application* [1980] FSR 564. See also Ian Finch (ed) *James & Wells Intellectual Property Law in New Zealand* (Thomson Brookers, Auckland, 2007) at 20; Frankel, above n 9, at 404; Paul Sumpter *Intellectual Property Law: Principles in Practice* (CCH New Zealand, Auckland, 2006) at 234.

⁴⁶ See T Cleary “Gene Patents: Should New Zealand Let the Gene Genie Out of the Patent Bottle?” (LLB (Hons) Dissertation, University of Otago, 2011) at 22.

⁴⁷ For example, a controversial patent of Myriad Genetics covering a diagnostic test for the BRCA breast cancer gene was been granted by IPONZ as NZ Patent No. 326525. The patentability of the Myriad BRCA genes was recently challenged and upheld by the Australian Federal Court in *Cancer Voices Australia v Myriad Genetics Inc* [2013] FCA 65.

⁴⁸ 35 USC § 101. See generally, Manual of Patent Examining Procedure [MPEP] § 2106, I, The Four Categories of Statutory Subject Matter.

⁴⁹ See *Bilski v Kappos* 561 US__ (2010) at 39 citing *Diamond v Diehr* 450 US 175 (1981) at 185. See also MPEP § 2106, II, Judicial Exceptions to the Four Categories.

Collaborative Services (Prometheus),⁵⁰ the Supreme Court of the United States recently considered the patentability of a method to determine the correct therapeutic dose of an immunosuppressant in patients with inflammatory bowel disease.⁵¹ The Court denied patentability, stating that the claims merely “inform a relevant audience about certain laws of nature ... any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community”.⁵²

The ‘natural phenomena’ exemption also has implications for the patentability of medicines that are based on naturally occurring biological materials. Generally, as in New Zealand, the isolation and purification of biological material can be patentable if it requires human manipulation to achieve that state.⁵³ This means that a biological extract found in nature, such as a herbal medicine or dietary supplement, may be patentable. However, the Supreme Court of the United States recently decided that isolating genes found in nature cannot make them patentable.⁵⁴ Although medicines do not tend to use genetic material *per se* as their active ingredient,⁵⁵ it is uncertain whether this decision may impact the patentability of medicines based on naturally occurring products.

2 Novelty

The second patentability criterion is that an invention must be novel. Mere prior publication or public use of a potentially safe and effective medicine before the priority date will destroy its patentability. For a medical therapy to be patentable, it must claim novel subject matter in respect of anything that was published or used before the filing date of the patent application. If all the features of a claim are present

⁵⁰ *Prometheus Laboratories v Mayo Collaborative Services* 566 US__ (2012).

⁵¹ The patent disclosed a method of determining the correct dosage of a drug for a patient by (1) administering a drug to a patient, (2) measuring the level of metabolites of the drug and (3) changing the administered dose by comparing the level of metabolites with a certain threshold level.

⁵² At 11.

⁵³ *Parke-Davis & Co v H K Mulford & Co* 189 F 95 (CCSD NY 1911). See also RS Gipstein “The Isolation and Purification Exception to the General Unpatentability of Products of Nature” (2003) 4 *Colum Sci & Tech L Rev* 1 at 4.

⁵⁴ See *Association for Molecular Pathology v Myriad Genetics* 569 US__ (2013) at 14 [*Myriad*]. Notably, the Supreme Court allowed the patentability of ‘man-made’ cDNA, which is created by removing the non-coding ‘introns’ from a DNA strand. The *Myriad* decision has been criticised by patent attorneys as destabilising the diagnostics industry and disincentivising new innovations in this area. See KE Noonan “Mayo Collaborative Services v Prometheus Laboratories -- What the Court’s Decision Means” (22 March 2012) Patent Docs <www.patentdocs.org>.

⁵⁵ One exception is antisense DNA, which is genetic material that can be used as a potential ‘drug’ to ‘silence’ gene expression. See JL Ryan “Unlikely Splicing: The Myriad Decision, the Genomic Research and Accessibility Act, Orphan Diseases, and the Future of Antisense Drugs” (2011) 28 *J Contemp Health L & Poly* 144 at 144.

in a single ‘prior art’ reference,⁵⁶ it is not novel, which is known as ‘anticipation’ of the claim. The applicable law in the New Zealand and the United States will now be discussed in turn.

(a) New Zealand

In New Zealand, novelty requires that an invention does not form part of the prior art base.⁵⁷ Section 8(1) of the Patents Act defines the ‘prior art base’ as information about a product or process or anything else that has been “made available to the public (whether in New Zealand or elsewhere) by written or oral description, by use, or in any other way.”⁵⁸ A patent can either be anticipated by prior publication or prior use.

(i) Prior publication

An invention can be ‘anticipated’ by a prior publication if it is available before the priority date.⁵⁹ The Patents Act does not define ‘publication’. Under section 2 of the Patents Act 1953, ‘published’ means a document that “can be inspected as of right at any place in New Zealand”.⁶⁰

Patent applications are commonly cited as prior art documents as they are published within 18 months of the filing date, which, as noted above, is also the priority date.⁶¹ Notably, a patent application which is *published* after the priority date of an invention can still anticipate an invention, if it was *filed* before the priority date of the invention being examined.⁶²

Research articles or technical publications are also a source of novelty-destroying prior art. An ironic consequence of the prior publication rule is that a researcher can invalidate their chance of obtaining a patent over a viable medicine by

⁵⁶ It is not possible to combine features from different prior art references for the purpose of assessing novelty. However, combinations are possible when assessing inventive step, if it would have been obvious to do so. The assessment of inventive step is more complex and uncertain than novelty, as will be discussed in the next section below.

⁵⁷ Patents Act 2013, s 6.

⁵⁸ Patents Act 2013, s 8(1).

⁵⁹ As noted above, the priority date is the date the patent application is filed. A patent can have multiple priority dates if subsequent applications are filed which rely on subject matter disclosed in the ‘parent’ application.

⁶⁰ Patents Act 1953, s 2.

⁶¹ Patents Act 2013, s 76. See also Rule 48.3 Patent Co-operation Treaty [PCT]: PCT applications published 18 months from earliest priority date. However, provisional patent applications which do not proceeded with as ‘complete applications’ are not published.

⁶² Patents Act 2013, s 8(2).

publishing their own research prematurely.⁶³ For the same reason, pharmaceutical companies make ‘defensive publications’ to prevent competitors from obtaining patents in a therapeutic area.⁶⁴

Moreover, a ‘publication’ is not limited to written documents. An oral disclosure forms part of the prior art base. For example, disclosure to a single member of the public not under a duty of confidentiality will be novelty destroying.⁶⁵ The relevant test for such oral ‘publication’ is that ‘the information [had] been communicated to any member of the public who was free in law or equity to use it as he pleased.’⁶⁶

In *Peterson Portable Sawing Systems Ltd (in liq) v Lucas (Lucas)*⁶⁷ the New Zealand Supreme Court confirmed the applicable test for prior publication or ‘anticipation’ from *General Tire & Rubber Co v Firestone Tyre & Rubber Co*.⁶⁸ The latter case established the ‘reverse infringement test’, which is satisfied if “carrying out the directions contained in the prior inventor’s publication will inevitably result in something being made or done which, if the patentee’s patent were valid, would constitute an infringement of the patentee’s claim.”⁶⁹

Therefore, when considering this test, it is necessary to consider the test for patent infringement. In particular, infringement requires the court to interpret or ‘construct’ the meaning of each ‘integer’ in the claims. The principles of ‘claim construction’ for the purpose of determining the scope of a claim are complex and can vary between jurisdictions. While a detailed analysis of claim construction is beyond the scope of this thesis, in general, claims are provided a ‘purposive construction,’ which includes ‘variants’ that would obviously not affect how an invention works, provided that a person skilled in the art would not have expected that strict literal

⁶³ However, as will be discussed below, a ‘grace period’ applies in the United States and some other jurisdictions.

⁶⁴ See B Barret “Defensive use of publications in an intellectual property strategy” (2002) 20(2) *Nature Biotechnology* 191 at 191.

⁶⁵ *Bristol-Myers Co’s Application* [1969] RPC 146 (QB);

⁶⁶ *Forlong & Maisey Ltd v Prima Technologies Ltd & Simcro Tech Ltd* P01/2004 at 16 citing *Humpherson v Syer* [1887] RPC 407 (CA).

⁶⁷ *Peterson Portable Sawing Systems Ltd (in liq) v Lucas* [2006] NZSC 20, [2006] 3 NZLR 721 at [3] [Lucas].

⁶⁸ *General Tire & Rubber Co v Firestone Tyre & Rubber Co* [1972] RPC 457 (CA) [*General Tyre*].

⁶⁹ At 485-486 per Sachs, Buckley and Orr LJ. A similar reverse-infringement test is was endorsed by Aickin J of the High Court of Australia in *Meyers Taylor Pty Ltd v Vicarr Industries Ltd* (1977) CLR 228 at 235 and Gibson J of the Canadian Federal Court in *Reeves Brothers Inc v Toronto Quilting & Embroidery Ltd* (1978), 43 CPR (2d) 145 (FCTD) at 157.

compliance with the language of the claim was necessary.⁷⁰ However, a purposive construction will not extend beyond the clear meaning of the words in the claim.⁷¹

When applying the ‘reverse infringement test’ from *General Tyre*, the question is whether the patent claims ‘read on’ the prior art. For example, if a research article published before the priority date contained “clear and unmistakable directions”⁷² for making a drug compound that would have infringed the claims of a latter filed patent application, this would destroy the patentability of those claims. The crucial issue is the amount of information required to be disclosed in the prior art document in order to constitute ‘anticipation’.

In the leading English case *Synthon BV v Smithkline Beecham Plc*,⁷³ the House of Lords considered two well-known authorities on what would constitute anticipatory disclosure: *General Tyre*⁷⁴ and *Hill v Evans*.⁷⁵ While *Synthon* has not been applied in New Zealand, it was considered in Finch’s Intellectual Property Law in New Zealand.⁷⁶ Lord Hoffman held that there were actually two parts to the test for anticipation, namely, (1) disclosure and (2) enablement. Firstly, the prior art document must ‘disclose’ the subject matter of the patent, which if performed would only result in the infringement of the patent. For this requirement, no amount of experimentation is allowed.⁷⁷ Secondly, there must be ‘enablement’ so that a prior art document would allow a person ‘skilled person in the art’ to be able to perform the invention with a minimum degree of experimentation.⁷⁸

In *Synthon* it was held that a specification which incorrectly described how to make a drug could still invalidate a subsequent patent, because it could be made by a

⁷⁰ *Catnic Components Ltd. v. Hill & Smith Ltd* (1982) RPC 183 at 243 per Lord Diplock.

⁷¹ *Portable Sawing Systems Ltd (in liq) v Lucas* [2006] NZSC 20, [2006] 3 NZLR 721 at [28].

⁷² *General Tyre*, above n 68 at 486 per Sachs LJ.

⁷³ *Synthon BV v Smithkline Beecham Plc* [2005] UKHL 59.

⁷⁴ *General Tyre*, above n 68.

⁷⁵ *Hill v Evans* (1862) 31 LJ Ch (NS) 457 at 463: ‘I apprehend the principle is correctly thus expressed: the antecedent statement must be such that a person of ordinary knowledge of the subject would at once perceive, understand and be able practically to apply the discovery without the necessity of making further experiments...’. A similar test for novelty/anticipation has been adopted in Australia: see *Nicarco Holdings Pty Ltd v Martin Engineering Co* (1990) 91 ALR 513 at 530 per Gummow J; See also *H Lundbeck A/S v Alphapharm Pty Ltd* (2009) 177 FCR 151 at 173 per Bennett J.

⁷⁶ Finch, above n 45, at 60-62.

⁷⁷ *Synthon*, above n 73, at [34]-[37].

⁷⁸ At [38]-[55]. The two-part test for anticipation was also applied by the Supreme Court of Canada in *Apotex Inc v Sanofi Synthelabo Canada Inc* [2008] 3 SCR 265. The Canadian Supreme Court (at [33]) held that the test for enablement requires that these experiments do not constitute an ‘undue burden’. It also held (at [37]) that prolonged trial and error experiments were deemed an ‘undue burden’ while ‘routine’ trials were not. Notably, the test for ‘enablement’ is equivalent to the test for the ‘sufficiency’, which will be discussed in this chapter below.

‘skilled person’ with a minimum of experimentation.⁷⁹ The House of Lords also stated that ‘disclosure’ and ‘enablement’ are distinct tests that should not be confused.⁸⁰

Synthon also addressed the important doctrine of ‘inherent anticipation.’ This doctrine seemingly contradicts the ‘enablement’ requirement, because it allows an invention to be anticipated despite the fact that it was not known to exist in the prior art. The House of Lords considered their previous decision in the case *Merrell Dow Pharmaceuticals v H N Norton & Co Ltd (Merrell Dow)*.⁸¹ This case involved an attempt to patent a metabolite of terafibine (a known hayfever drug), which was produced in the liver of the person who took terafibine. Lord Hoffman held that the patent specification for terafibine anticipated the subsequent metabolite via ‘disclosure,’ because it described a process that would have infringed the new claims for the metabolite patent. This enabled a “skilled reader to work the invention” even though nobody realised they were producing it.⁸²

Synthon and *Merrell Dow* illustrate that even if a prior publication does not disclose full scientific details of how a particular medicine works, it may still comprise novelty-destroying prior art with respect to aspects of the invention that were unknown at the time.

Because the number of prior publications is vast and increasing significantly over time,⁸³ an important question is whether specific medically useful compounds that have been disclosed within a broader class can still be patented. In particular, it is possible to obtain a patent in respect of one or more ‘species’ within a narrow class which have already been disclosed as part of a broader ‘genus’ as long as that choice of ‘subgenus’ or ‘species’ has a specific advantage which has not been previously disclosed. This is referred to as a ‘selection invention’.

In *Beecham Group Ltd v Bristol-Myers Company (No 2)*⁸⁴ (*Beecham*), Barker J applied the general test for selection inventions from the English case *IG*

⁷⁹ *Synthon*, above n 73 at [27] and [51]-[55] per Lord Hoffman. By way of background, *Synthon* had filed a patent which had incorrectly described technical values for manufacturing a drug. It was held that because, according to an expert deposed, the drug could be made by a person skilled in the art using *Synthon*’s description with a minimum of experimentation, this satisfied the ‘enablement’ requirement.

⁸⁰ At [30] per Lord Hoffman.

⁸¹ *Merrell Dow Pharmaceuticals v H N Norton & Co Ltd* [1996] RPC 76.

⁸² At [33]. Lord Hoffman proposed the following test: ‘The question is whether the specification conveyed sufficient information to enable the skilled reader to work the invention.’

⁸³ See R Van Noorden “Global Scientific output doubles every nine years” (7 May 2014) Nature News Blog <www.blogs.nature.com>.

⁸⁴ *Beecham Group Ltd v Bristol-Myers Company (No 2)* [1980] 1 NZLR 192 at 240.

Farbenindustrie AG's Patents (IG Farbenindustrie).⁸⁵ The three-part test was described as follows:⁸⁶

First, a selection patent to be valid must be based on some substantial advantage to be secured by the use of the selected members. (The phrase will be understood to include the case of a substantial disadvantage to be thereby avoided.) Secondly, the whole of the selected members must possess the advantage in question. Thirdly, the selection must be in respect of a quality of a special character which can fairly be said to be peculiar to the selected group.

In *Beecham*, a derivative version of penicillin was held to be patentable, despite the fact that its chemical formula was disclosed in a previous patent application, because the specific version had “new and unexpected qualities.”⁸⁷

Thus, selection inventions can mitigate the harsh novelty-destroying effect of a broad prior publications containing many potentially viable drug compounds, by potentially allowing patentability over drug ‘species’ which have previously unknown and substantial advantages.⁸⁸

(ii) Prior use

Prior use of the subject matter claimed by an invention will also destroy novelty in New Zealand. According to the Commissioner of Patents at IPONZ,⁸⁹ in order to establish prior use it must be established:

- [1] that the instance of prior use was not secret use;
- [2] what was used and by whom;
- [3] where and when use occurred; and
- [4] whether any apparatus still in existence can be inspected by the Court.

The prior use doctrine was applied in *Merrel Dow*, which held that ‘information about what was being done should have been made available to the public.’⁹⁰

⁸⁵ *IG Farbenindustrie AG's Patents* (1930) 47 RPC 289.

⁸⁶ At 322-323 per Maugham J.

⁸⁷ *Beecham*, above n 84, at 250.

⁸⁸ Chapter Three will discuss whether it is possible to ‘rescue’ patentability of valuable medicines using selection inventions and other so-called patent ‘evergreening’ techniques.

⁸⁹ IPONZ Practice Note, 76, Patent Office Journal 714 (Issue No 1287, July 1986).

⁹⁰ *Merrel Dow*, above n 84, at 84. This case was influenced by Article 54(2) of the European Patent Convention [EPC] which provides that ‘[t]he state of the art [i.e the prior art] shall be held to comprise everything made available to the public....by use, or in any other way, before the date of filing of the European patent application.’

However, interestingly, ‘commercial use’ will invalidate a patent even if under conditions of confidentiality, such as taking a confidential order for goods.⁹¹ For example, this could occur when a biotechnology company enters a license agreement regarding the commercial development of its confidential in-house library of drug-like compounds.

(b) United States

In the United States, prior publication or prior use of an invention will also destroy patentability.

(i) Prior publication

Under USC 35 § 102(a), a person shall be entitled to a patent unless “the claimed invention was ... described in a printed publication ... before the effective filing date of the claimed invention.”⁹² A ‘printed publication’ requires “a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.”⁹³

Publications can still invalidate a patent, even if available for a short period of time. In the case *In re Klopfenstein*,⁹⁴ the Federal Circuit held that posters which could be viewed for three days at a conference “were sufficiently publicly accessible to count as a “printed publication””.⁹⁵ Further, as with New Zealand, patent applications are frequently cited as prior art because they are usually published 18 months after filing.⁹⁶ An earlier filed patent can be cited against a subsequently filed patent, even if the former was published after the latter was filed.⁹⁷

Anticipation requires that the invention is disclosed within one prior art reference. This is known as the ‘single source anticipation rule’.⁹⁸ The United States

⁹¹ *Wheatley’s Application* [1985] RPC 91.

⁹² 35 USC § 102(a)(1).

⁹³ *In re Wyer* 655 F 2d 221 (CCPA 1981) at 226. See generally, MPEP § 2128. Publication includes information available in an on-line database.

⁹⁴ *In re Klopfenstein* 380 F 3d 1345 (Fed Cir 2004).

⁹⁵ At 1352.

⁹⁶ 35 USC § 122(b)(1). Europe also requires publication after 18 months from filing. see Article 93 EPC.

⁹⁷ 35 USC § 102(a)(2). The position in Europe is similar: see EPC Article 54(3).

⁹⁸ *Verdegaal Bros v Union Oil Co of California* 814 F2d 628 (Fed Cir 1987) at 631; *Metabolite Laboratories Inc v Laboratory Corp of America Holdings* 370 F 3d 1354 (Fed Cir 2004); *Continental Can Co USA v Monsanto Co* 948 F 2d 1264 (Fed Cir 1991). By contrast, the test for inventive

also requires a prior publication to comprise an ‘enabled disclosure’, although this has a lower threshold for ‘enablement’ than New Zealand.⁹⁹ Anticipation can even occur if “after disclosing an invention, the reference then disparages it.”¹⁰⁰ This contributes to what has been described as a “hair-trigger approach” to novelty in the United States.¹⁰¹

Inherent anticipation was considered by the United States Federal Circuit in the case *Schering v Geneva (Schering)*, which held that anything ‘inherent’ in a document is included in the prior art, including a product that is inherently produced by a disclosed method.¹⁰² The case involved similar material facts to *Merrell Dow*.¹⁰³ *Schering* was a significant departure from previous caselaw,¹⁰⁴ and broadened the application of the ‘inherent anticipation’ doctrine to situations where the “person of ordinary skill in the art” would not have recognised the inherent trait in the prior art.¹⁰⁵

While commentators have noted the potential for the inherent anticipation doctrine to “endanger innovation” by preventing the patenting of metabolites,¹⁰⁶ the public policy justification of the doctrine is to prevent the undue extension of patent protection by claiming metabolites of a drug, without substantially contributing to scientific knowledge.¹⁰⁷ Such unjustifiable attempts to lengthen the effective period of patent protection over drugs are referred to as patent ‘evergreening’, which will be discussed in Chapter Three.

step/obviousness allows the combination of prior art documents in some circumstances, as discussed below.

⁹⁹ See MPEP § 2131.01. Unlike New Zealand, the standard for ‘enabled disclosure’ for the purpose of anticipation is not equivalent to the requirement for ‘sufficiency’ under 35 USC § 112. See discussion of the sufficiency requirement below.

¹⁰⁰ BN Roin “Unpatentable drugs and the standards of patentability” (2008) 87 Tex L Rev 503 at 524 citing *Bristol-Myers Squibb Co v Ben Venue Laboratories, Inc* 246 F 3d 1368 (Fed Cir 2001) at 1378 and *Celeritas Techs Ltd v Rockwell Int’l Corp* 150 F 3d 1354 (Fed Cir 1998) at 1361.

¹⁰¹ Roin, at 560.

¹⁰² *Schering v Geneva* 339 F 3d 1373 (CAFC 2003) at 1377.

¹⁰³ In particular, after the patent for loratidine (an anti-histamine) expired, an attempt was made to patent desloratidine, a metabolite of loratidine produced in the body.

¹⁰⁴ *Continental Can Co*, above n 98.

¹⁰⁵ *Schering*, above n 102, at 1377. See also A De La Rosa “A Hard Pill To Swallow: Does *Schering v Geneva* Endanger Innovation Within The Pharmaceutical Industry?” (2007) 8 Colum Sci & Tech L Rev 37 at 43. The European Union has not yet adopted the ‘inherent anticipation’ doctrine, although anything ‘implicit’ within the content of a prior document, ‘in the sense that, in carrying out the teaching of the prior document, the skilled person would inevitably arrive at a result falling within the terms of the claim’, would anticipate the claim. See European Patent Office [EPO] Guidelines for Examination 2010 – Part G, Chapter VI, Para 6.

¹⁰⁶ De La Rosa, at 37.

¹⁰⁷ De La Rosa, at 48: ‘The Federal Circuit’s concern [in the *Schering* case] is that permitting the consecutive patenting of pharmaceuticals and their in vivo biological by-products would substantially lengthen the patent protection of the pharmaceutical without substantially advancing the present frontiers of science.’

The United States also permits patenting of a selection of a narrow species with distinct characteristics over the broad genus disclosed, although this is not referred to as a ‘selection invention’, as under New Zealand jurisprudence. The question asked is in what circumstances the disclosure of a broad genus may anticipate a claim to a species.¹⁰⁸ This is a question of fact and depends on the circumstances of the case.¹⁰⁹ However, disclosure of a species will always anticipate a genus.¹¹⁰ This means that broad genus claims covering millions of drug variations can be risky,¹¹¹ because if any member of the group is deemed to cover a species disclosed in the prior art, the entire group is anticipated.

Some reforms have alleviated the harsh consequences of prior disclosure by the inventor on patentability. In particular, the United States has a ‘grace period’, which allows prior publications by an inventor not to be cited as prior art against them if they file a patent application within 12 months.¹¹² The length of grace periods varies depending on the jurisdiction.¹¹³ Notably, New Zealand and Europe does not have a grace period.¹¹⁴ This means that even an inadvertent publication of research will destroy the chance of obtaining a patent in those jurisdictions.

(ii) Prior use

The United States has a similar test to New Zealand regarding public use of an invention. Prior to the Leahy-Smith America Invents Act of 2011 (AIA), only public use within the United States was relevant prior art. This qualification no longer applies and public use anywhere in the world will destroy novelty.¹¹⁵

The United States test for public use is whether the purported use (1) was accessible to the public, or (2) was commercially exploited.¹¹⁶ There will be commercial exploitation where the invention is (1) the subject of a commercial offer

¹⁰⁸ See MPEP § 2131.02.

¹⁰⁹ See *Sanofi-Synthelabo v Apotex, Inc* 550 F 3d 1075 (Fed Cir 2008) at 1083: ‘[W]hether a generic disclosure necessarily anticipates everything within the genus ... depends on the factual aspects of the specific disclosure and the particular products at issue.’ See also *Atofina v Great Lakes Chemical Corp* 441 F 3d 991 (Fed Cir 2006) and *In re Baird* 16 F 3d 380 (Fed Cir 1994) at 382.

¹¹⁰ *In re Slayter* 276 F 2d 408 (CCPA 1960) at 411: ‘A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus.’

¹¹¹ For example, refer to discussion of ‘Markush’ claims above.

¹¹² 35 USC § 102 (b).

¹¹³ For example, Canada, Australia, Brazil, South Korea, Argentina, Malaysia, and Mexico have a 12-month grace period; Japan, Russian Federation, Eurasia, and Taiwan have a 6-month grace period.

¹¹⁴ However, there is a limited exemption in respect of prior disclosure or use an invention at certain gazetted ‘international exhibitions’ or prior disclosure or use made of an invention by a third party without the consent of the inventor, provided that a patent is filed within 6 months. Patents Act 2013, s 9(1)(d); For Europe, see EPC, art 55.

¹¹⁵ 35 USC § 102(a).

¹¹⁶ *Invitrogen Corp v Biocrest Manufacturing LP* 424 F3d 1374 (Fed Cir 2005).

for sale not primarily for experimental purposes and (2) ready for patenting.¹¹⁷ In addition, if invention is put on public display then this is public use even when the workings of the invention are hidden.¹¹⁸ This demonstrates the ease by which patentability can be lost over a medicine by allowing the public to access it on display.

Notably, however, the explicit reference to “public use” in section 102(a) of the AIA has been interpreted by the USPTO as meaning that secret use of an invention will not constitute prior art.¹¹⁹ This would mean that commercial exploitation of a secret process for manufacturing a drug may no longer constitute prior art against a subsequently filed patent.

Summary

A medicine will no longer be patentable if it has either been published, used or on public display prior to filing a patent. Anticipation occurs if a prior art document teaches something which either infringes or inevitably would lead to infringement of the claims of a patent. For example, if a claimed pharmaceutical drug has a different chemical structure to what was disclosed, then it is not anticipated. However, ‘intrinsic’ properties of a medicine are automatically disclosed, even if not known to the public at the time. This means it is not possible to claim a drug metabolite.

Further, the disclosure of a particular species of drug within a class will always anticipate a genus claim over the broader chemical class. Conversely, it may be possible to patent certain selected members of a previously disclosed broader class, provided that the prior art did not disclose the advantages of making that selection.

The legal tests for novelty are relatively objective, using the principles of ‘reverse infringement’. However, even if a medicine fulfils the novel criterion, patentability is not assured. We now turn to the more complex and subjective tests of inventive step.

¹¹⁷ *Pfaff v Wells Elecs, Inc* 525 US 55 (1998) at 67.

¹¹⁸ *In re Blaisdell* 242 F 2d 779 (CCPA 1957) at 783; *Hall v Macneale* 107 US 90 (1882) at 96-97; *Ex parte Kuklo* 25 USPQ2d 1387 (BPAI 1992) at 1390.

¹¹⁹ MPEP § 2132: ‘...a secret use of the process coupled with the sale of the product does not result in a public use of the process unless the public could learn the claimed process by examining the product’. This interpretation arguably overrides the ‘forfeiture doctrine’ in *Metallizing Engineering Co v Kenyon Bearing and Auto Parts* 153 F 2d 516 (2d Cir 1946) which requires an inventor to choose between exploitation of a trade secret or patent protection. But see P Morgan “The Ambiguity in Section 102(a)(1) of the Leahy-Smith America Invents Act” (2011) *Patently-O Patent Law Review* 29 at 31.

3 *Inventive step*

The most onerous hurdle for patentability of medicines is the requirement that inventions must possess an inventive step with respect to the prior art. Due to the large number of chemicals or compounds that could be potentially viable medicines, the question of whether a medicine is ‘obvious’, and therefore unpatentable, is a particularly difficult question to determine in advance, with multiple relevant factors to consider. This lack of clarity has created significant uncertainty for pharmaceutical innovators - particularly in the United States - who risk spending hundreds of millions of dollars on clinical trials, only to have their patents challenged and invalidated on the basis of obviousness. The following sections will discuss the legal tests for inventive step in New Zealand and the United States.

(a) New Zealand

Section 7 of the Patents Act defines an invention as having an inventive step “if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the prior art base.”¹²⁰ New Zealand applies a four-part test for inventive step.¹²¹ The test was set out by the English Court of Appeal in *Windsurfing International Inc v Tabur Marine (GB) Ltd*.¹²²

[1] The first is to identify the inventive concept embodied in the patent in suit.

[2] Thereafter, the court has to assume the mantle of the normally skilled but unimaginative addressee in the art at the priority date and to impute to him what was, at that date, common general knowledge in the art in question.

[3] The third step is to identify what, if any, differences exist between the matter cited as being 'known or used' and the alleged invention.

[4] Finally, the court has to ask itself whether, viewed without any knowledge of the alleged invention, those differences constitute steps which would have been obvious to the skilled man or whether they require any degree of invention.

¹²⁰ Patents Act 2013, s 7.

¹²¹ *Portable Sawing Systems Ltd (in liq) v Lucas* [2006] NZSC 20, [2006] 3 NZLR 721 at [54]. See also *Ancare NZ Ltd v Cyanamid of NZ Ltd* [2000] 3 NZLR 299 (CA) at 309.

¹²² *Windsurfing International Inc v Tabur Marine (GB) Ltd* [1985] RPC 59 per Oliver LJ at 73-74.

The Supreme Court in *Peterson Portable Sawing Systems Ltd (in liq) v Lucas*¹²³ also endorsed the decision of the English Court of Appeal in *Mölnlycke AB v Procter & Gamble Ltd (No 5)*¹²⁴ which provides that various secondary considerations can be relevant to the determination of inventive step, namely: “the failure of others to hit on the alleged obvious invention, commercial success and the circumstances of particular individuals in the field.”¹²⁵

In applying the *Windsurfing* test, the most crucial aspect is to identify the ‘person skilled in the art’ and the ‘relevant common general knowledge of that person’. The ‘person skilled in the art’ is a judicially created entity. In *Inglis v Mayson*¹²⁶ Prichard J approved the dicta of Lord Reid in *Technograph Printed Circuits Ltd v Mills and Rockley (Electronics) Ltd*,¹²⁷ who described the person skilled in the art as a “skilled technician ... who has carefully read the relevant literature”, but is “incapable of a scintilla of invention.”¹²⁸

Therefore, when examining pharmaceutical inventions, the person skilled in the art would likely be a medicinal chemist, albeit one with no inventive capacity. A determination of the common general knowledge of the person skilled in the art involves a consideration of the kind of documentation in the prior art they would be familiar with in practice. For example, the common general knowledge of a medicinal chemist would likely include known and routine methods of modifying a drug to improve its safety and efficacy, and any documents that they would have been likely to consider when being faced with the problem solved by the alleged invention. Such consideration includes all prior art documents that would have been available, not just those that would have been discovered by a “diligent searcher”.¹²⁹

By contrast to the novelty criterion, it is possible to combine prior art documents when assessing inventive step. However, for the invention to be obvious, those documents must be deemed to fall within the common general knowledge of the person skilled in the art. It is difficult to apply the test in practice.¹³⁰ Importantly,

¹²³ *Peterson Portable Sawing Systems Ltd (in liq) v Lucas* [2006] NZSC 20, [2006] 3 NZLR 721.

¹²⁴ *Mölnlycke AB v Procter & Gamble Ltd (No 5)* [1994] RPC 49 (CA).

¹²⁵ At 113.

¹²⁶ *Inglis v Mayson* (1983) 3 IPR 588 at 600.

¹²⁷ *Technograph Printed Circuits Ltd v Mills and Rockley (Electronics) Ltd* [1972] RPC 346.

¹²⁸ At 355 per Lord Reid.

¹²⁹ *Ancare*, above n 121, at [43]; *Cool 123 Limited v Vodafone New Zealand Limited and Ors* HC Wellington CIV 2006-485-698, 29 August 2007.

¹³⁰ For example, in applying the test, a single prior art reference that includes most of the features of the claim can be considered first. Subsequently, it is asked whether it would have been obvious for a skilled person to combine the closest prior art reference with other references that include the missing features from the claim being considered or otherwise modify the closest reference to include those features. If so, the claim is obvious and therefore unpatentable.

there is a rule against hindsight when considering multiple prior art references.¹³¹ However, as noted by Lord Reid in the *Technograph* case, “it is permissible to make a ‘mosaic’ out of the relevant documents, but it must be a mosaic which can be put together by an unimaginative man with no inventive capacity.”¹³² Moreover, combining features that are present in the prior art would only comprise an inventive step if that combination were not a “mere collocation”.¹³³ For example, it would not be possible to patent a drug combination or formulation where the features are known and there are no ‘unexpected’ synergistic effects from the combination.¹³⁴ Nevertheless, the Supreme Court has acknowledged that combining known features without a synergistic effect may be inventive in “rare cases”.¹³⁵

Another useful tool for determining the obviousness question is the ‘obvious to try’ test. This test asks whether it would have been obvious for a person skilled in the art to try a particular step in order to solve the problem requiring an alleged inventive step. In the leading English case, *Johns-Manville Corporation's Patent*,¹³⁶ an invention is deemed obvious if “[i]t is enough that the person versed in the art would assess the likelihood of success as sufficient to warrant actual trial.”¹³⁷ New Zealand had also endorsed this approach in *Ancare*.¹³⁸

¹³¹ See *Lucas v Peterson Portable Sawing Systems Ltd* [2003] 3 NZLR 361 (HC) per Fisher J at 369: ‘The Court must also avoid the danger of falling into ex post facto analysis. It must put out of its mind developments since the invention and view the question of obviousness from the perspective of persons skilled in the art immediately before the priority date.’ Other jurisdictions also apply this rule against hindsight: see the decision of the EPO Board of Appeals in *GENENTECH, INC/Expression in yeast* T 455/91 [1995] OJ EPO 684 stating that aim was to answer, objectively and avoiding any ex post facto analysis, the question whether it would be obvious to the skilled person to make given changes in a structure or procedure. For the position in Australia, see *Minnesota Mining & Manufacturing Co v Tyco Electronics Pty Ltd* (2002) 56 IPR 248 (FCA) at 45; *Pac Mining v Esco Corp* [2009] FCAFC 18.

¹³² *Technograph*, above n 127, at 355.

¹³³ See *Assa Abloy New Zealand Ltd v Aluminium Systems NZ Ltd* HC Wellington CIV-2010-485-2, 7 March 2011. The rule against the patentability of a ‘mere collocation’ has also been applied in Australia: see *WM Wrigley JR Co v Cadbury Schweppes Pty Ltd* [2005] FCA 1035, (2005) 66 IPR 298; *Nutrasweet Australia Pty Ltd v Ajinomoto Co Inc* (2006) 67 IPR 381 (FCA). See also *International Paint Co Ltd's Application* [1982] RPC 247] at 275: ‘There is no invention from a ‘mere collocation of integers’ where however juxtaposed to the other ingredients of the mixture or parts of the article, each part performs its own function and would do so even in the absence of the other parts.’ For the European position, see EPO Guidelines for Examination 2012, G-VII, 7.

¹³⁴ Lucas, above n 123, at [56].

¹³⁵ At [61].

¹³⁶ *Johns-Manville Corporation's Patent* [1967] RPC 479.

¹³⁷ At 495 per Lord Diplock. For a discussion of the obvious to try test by the House of Lords, see *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49. The Canadian Supreme Court also endorsed the obvious to try test in *Sanofi-Synthelabo Canada Inc v Apotex Inc* (2008) SCC 61. However, the Australian High Court rejected the obvious to try test in the *Alphapharm* case.

¹³⁸ *Ancare* above at [43].

Ultimately, applying these tests to the same material facts can result in inconsistent outcomes for patent validity in different jurisdictions.¹³⁹ This highlights the uncertainty faced by innovators that must rely on patents to recover their costs.

(b) United States

The inventive step criterion is referred to as ‘non-obviousness’ in the United States. A finding of non-obviousness also involves a construing of the “person having ordinary skill in the art”,¹⁴⁰ whether the differences between the alleged invention and the prior art are obvious to that person, and finally whether any ‘secondary considerations’ may be relevant. These so-called ‘Graham factors’ are taken from the case *Graham v John Deere Co. of Kansas City*:¹⁴¹

... the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long-felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Under the previous leading cases, there was a caution against hindsight or “ex-post facto” analysis,¹⁴² and a requirement of some teaching, suggestion or motivation to combine prior art documents in a manner which anticipates the claims.¹⁴³ The mere fact that a combination of documents was “obvious to try” suggested the invention was obvious; a “reasonable expectation of success” was required.¹⁴⁴ The Supreme

¹³⁹ For example, in *Aktiebolaget Hassle v Alphapharm Pty* [2002] HCA 59, the High Court of Australia held that a three-layered drug formulation was inventive, comprising a known antacid (omeprazole) with an inert buffer between the external acidic enteric coating, which allowed breakdown of the drug in the upper small intestine not the stomach. The New Zealand Court of Appeal reached the same conclusion in equivalent proceedings: *Novartis New Zealand Ltd v Aktiebolaget Hassle* [2004] 2 NZLR 721 (CA) per Blanchard J at [3]-[4]. However, compare *Cairnstores Limited, Generics (UK) Limited v Aktiebolaget Hässle* [2002] EWHC 309 (Ch), where Laddie J (at [1]-[2]) reached the opposite conclusion with respect to the same drug.

¹⁴⁰ 35 USC § 103.

¹⁴¹ *Graham v John Deere Co of Kansas City* 383 US 1 (1966) at 17-18.

¹⁴² *In re Kahn* 441 F 3d 977 (CA Fed Cir 2006) at 986. See also *Ortho-McNeil Pharm Inc v Mylan Labs* 520 F 3d 1358 (Fed Cir 2008) at 1364.

¹⁴³ *Winner Int'l Royalty Corp v Wang* 202 F 3d 1340 (Fed Cir 2000) at 1348. Compare the New Zealand position, above n 131. See also EPO Guidelines for Examination 2012, G-VII, 5.3, 6. The European test requires some ‘implicit prompting or implicitly recognisable incentive’ to combine the elements from the prior art.

¹⁴⁴ *In re O'Farrell* 853 F 2d 894 (Fed Cir 1988) at 904.

Court of the United States in *KSR International Co v Teleflex Inc (KSR)*¹⁴⁵ has since raised the hurdle for non-obviousness. The Supreme Court approved the Graham factors analysis, but rejected the ‘teaching, suggestion or motivation test’, as well as the ‘obvious to try’ test, stating:¹⁴⁶

When there is a design need or market pressure to solve a problem and there are *a finite number of identified, predictable solutions*, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. ... Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it.

In supporting a more flexible ‘common-sense’ approach in *KSR*, the Supreme Court stated that “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton”.¹⁴⁷ There was a concern by various commentators that the higher non-obviousness threshold and legal uncertainty post-*KSR* would result in a detrimental effect on pharmaceutical patent protection.¹⁴⁸ However, the consensus has been that this has not occurred yet,¹⁴⁹ with several challenges to lucrative pharmaceutical patents being successfully defended after the *KSR* decision.¹⁵⁰

According to the United States Manual of Patent Examining Procedure (MPEP), failure to satisfy the above-referenced tests supports a *prima facie* determination of obviousness by the examiner.¹⁵¹ Moreover, a combination of ingredients having a known purpose will also generally be *prima facie* obvious.¹⁵²

¹⁴⁵ *KSR International Co v Teleflex Inc* 550 US 398 (2007) [*KSR*].

¹⁴⁶ At 421 (emphasis added).

¹⁴⁷ At 421.

¹⁴⁸ R Teitelbaum and M Cohen “Obviousness, hindsight and perspective: the impact of *KSR v Teleflex* on biotech and pharmaceutical patents” (2007) 25(10) *Nature Biotechnology* 1105 at 1105.

¹⁴⁹ KJ Bernier “Obviating the Obvious? An Appraisal of Pharmaceutical Patents” (2010) 10 *J High Tech L* 208 at 236; MJ Sweet “The Patentability of Chiral Drugs Post-*KSR*: The more things change, the more they stay the same” (2009) 24(1) *Berkeley Technology Law Journal* 129 at 147; J M Spenner “Obvious-to-Try Obviousness of Chemical Enantiomers in View of Pre- and Post-*KSR* Analysis”(2008) 90 *J Pat & Trademark Off Soc'y* 476 at 478-479; AV Trask “Obvious to Try’: A Proper Patentability Standard in the Pharmaceutical Arts?” (2008) 76(5) *Fordham Law Review* 2625 at 2629.

¹⁵⁰ For examples of unsuccessful legal challenges brought by generic drug companies against patents subsequent to the decision in *KSR v Teleflex* see *Takeda Chem Indus, Ltd v Alphapharm Pty Ltd* 492 F 3d 1350 (Fed Cir 2007); *Eisai Co v Dr Reddy's Laboratories* 533 F 3d 1353 (Fed Cir 2008); *Ortho-McNeil*, above n 142 at 1360.

¹⁵¹ See generally, MPEP § 2143: Examples of Basic Requirements of a *Prima Facie* Case of Obviousness.

¹⁵² See MPEP § 2144.06: ‘It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art’: *In re Kerkhoven* 626 F 2d 846 (CCPA 1980) at 850.

However, ‘secondary considerations’ such as commercial success of the invention can help rebut this *prima facie* presumption.¹⁵³

Another important factor to rebut the *prima facie* finding of obviousness is whether the prior art teaches away from or discloses a technical prejudice against the invention, such as an expectation that a drug would not work.¹⁵⁴ However, the fact that a drug possesses a benefit that was not recognised until later by a patent applicant is not in itself sufficient to make the compound distinct from the prior art.¹⁵⁵

It is also problematic, however, that the tests for determining obviousness tend to conflict with the modern process of drug development. For example, this process typically involves selection of a ‘lead compound’ on the basis of structural similarity to another compound with known therapeutically beneficial properties, which is part of the modern ‘rational’ drug discovery approach.¹⁵⁶ This can be contrasted with ‘trial-and-error’ screening using animals.¹⁵⁷ However, structural similarity increases the likelihood of finding obviousness.¹⁵⁸ In the case *In re Payne*,¹⁵⁹ the United States Court of Customs and Patent Appeals noted that “[a]n obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.”

Nevertheless, the high level of unpredictability in medicinal chemistry can create a “firewall” to protect a drug candidate against a finding of obviousness.¹⁶⁰ For example, a *prima facie* case of obviousness based on structural similarity can be rebutted by evidence of unexpected advantage or superior properties of the claimed compounds.¹⁶¹ Further, in the case *In re Baird* the Federal Circuit held “the fact that a

¹⁵³ *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal*, 231 F.3d 1339 (Fed. Cir. 2000). See generally, MPEP § 2145. Compare *Mölnlycke*, above n 124, at 113: ‘there may be commercial reasons for this success unrelated to whether this invention was or was not obvious in the past’.

¹⁵⁴ For example, in *Novartis Pharmaceuticals Corporation v Teva Pharmaceuticals USA Inc* No 05 Civ 1887 (D NJ Sept 6, 2007), the patentability for a drug was considered obvious because prior art as a whole did not teach away from producing the compound and the greater number of references considered it would have powerful therapeutic properties. See also *Pozzoli Spa v BDMO SA* [2007] FSR 37 (CA) at [27]-[29] per Jacob LJ: ‘[a] patentee who contributes something new by showing that, contrary to the mistaken prejudice, the idea will work or is practical has shown something new.’

¹⁵⁵ *In re Dillon* 919 F 2d 688 (Fed Cir 1991).

¹⁵⁶ S Mandal, M Moudgil and SK Mandal “Rational drug design” (2009) 625(1) *European Journal of Pharmacology* 90 at 92.

¹⁵⁷ This is also referred to as phenotypic screening.

¹⁵⁸ MPEP § 2144.09: ‘A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities.’

¹⁵⁹ *In re Payne* 606 F 2d 303 (CCPA 1979) at 313.

¹⁶⁰ Sweet, above n 149, at 147.

¹⁶¹ *In re Papesch* 315 F 2d 381 (CCPA 1963) at 386-387; see also *In re Wiechert*, 370 F 2d 927 (CCPA 1967) at 933; *Pfizer Inc v Apotex Inc* 480 F 3d 1348 (Fed Cir 2007) at 1369.

claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.”¹⁶²

Therefore, it is the unexpected therapeutic effects of a medicine that provides the most support to a finding of non-obviousness. However, this highlights the pernicious effect of relying on patents to incentivise drug development: as improvements in technology allow the medicinal effects of experimental drugs to be predicted with greater accuracy, the non-obviousness criterion will tend to block the patentability of an even greater number of therapeutically valuable compounds.¹⁶³

Summary

The tests for obviousness in New Zealand and the United States have many principles in common. In both cases, the relevant person skilled in the art must compare the differences between the alleged invention and the prior art. Structural and functional similarity to a prior art compound will support a finding of obviousness, and there must not be a suggestion in the prior art for a skilled person to make modifications or changes to the prior art compound to create the medicine being claimed. However, the unpredictable nature of drug development means that even minor changes can have unexpected results, which can support a finding of patentability, despite structural similarity to a lead compound. Additional factors supporting a finding of inventive step are the prior art teaching away from the claimed invention and the absence of a reasonable expectation of success. Finally, secondary considerations such as commercial success or solving a long-felt need are relevant.

The requirement to take numerous indeterminate factors into account makes it difficult for innovator companies to predict whether a medicine will be likely to satisfy the obviousness criterion at the time of filing a patent application. Further, as technological advances make the therapeutic effects of new medicines less unexpected, it will also become more difficult to secure patent protection over new medicines.

¹⁶² *In re Baird* 16 F 3d 380 (Fed Cir 1994) at 382. See also MPEP § 2144.09.

¹⁶³ Roin, above n 100, at 542. Examples of such technological improvements include computer modeling techniques, biomarkers, and animal models, which are used as part of pre-clinical testing to predict a drug’s safety and efficacy in humans.

4 Utility

The fourth patentability criterion requires that an invention is ‘useful’, in the sense that it can achieve a practical result.¹⁶⁴ In contrast to the novelty and inventive step criteria, ‘utility’ generally focuses on the contents of the specification rather than external subject matter such as prior art.

Satisfaction of the utility criterion is often a significant hurdle for biopharmaceutical inventions, because it requires evidence that a medicine has therapeutic value at the time of filing. However, this is usually unknown because the medicine has typically not yet been tested in humans at the time of filing.¹⁶⁵ Accordingly, there is a tension between the advantages of being the first to file, which secures priority over competitors in respect of a potentially lucrative medicine, and conducting enough laboratory tests to adequately satisfy the utility criterion. The applicable law in New Zealand and the United States will now be described.

(a) New Zealand

Under section 10 of the Patents Act, an invention must have a specific, credible and substantial use.¹⁶⁶ In *Smale v North Sails*¹⁶⁷ the High Court approved the test for utility from the English case, *Lane Fox v Kensington & Knightsbridge Electric Lighting Co Ltd*.¹⁶⁸ In *Lane Fox* it was held that that utility does not depend on obtaining results necessary for commercial success, but whether the effects that the patentee seeks can be obtained and whether the end result is practically useful in terms of the objects indicated by the patentee.¹⁶⁹

There is a dearth of applicable caselaw in New Zealand considering the utility criterion, although it was unsuccessfully argued in the High Court case *Hammar Maskin AB v Steelbro New Zealand Ltd*.¹⁷⁰ It remains to be seen how the New Zealand courts will interpret the utility standard under the new Patents Act. The

¹⁶⁴ The terms ‘useful’, ‘utility’ and ‘industrial applicability’ can be used interchangeably in different jurisdictions to refer to the same criterion.

¹⁶⁵ This evidence is typically provided in the form of results from *in vitro* and *in vivo* pre-clinical tests, as will be discussed below.

¹⁶⁶ Patents Act 2013, s 10.

¹⁶⁷ *Smale v North Sails* [1991] 3 NZLR 19.

¹⁶⁸ *Lane Fox v Kensington & Knightsbridge Electric Lighting Co Ltd* (1892) 9 RPC 411. The general test for utility is also taken from *Fawcett v Homan* [1896] RPC 398 (CA) at 405: ‘If an invention does what it is intended by the patentee to do and the end attained is itself useful, the invention is a useful invention.’

¹⁶⁹ At 417.

¹⁷⁰ *Hammar Maskin AB v Steelbro New Zealand Ltd* HC Christchurch CIV-2006-409-977, 8 October 2008. Leave for the defendant to appeal to the Supreme Court on the grounds of inutility was also declined: see *Steelbro New Zealand Ltd v Hammar Maskin AB* [2010] NZSC 65.

requirement for a specific, credible and substantial use is very similar to the test in the United States¹⁷¹ and Australia,¹⁷² which means that case law in those jurisdictions is likely to be influential.

(b) United States

Under 35 USC § 101 an invention must be useful to be granted a patent.¹⁷³ As with New Zealand, the United States does not require actual evidence of commercial success, which means a patent can be granted over a medicine at an early stage of clinical development.¹⁷⁴

The leading case on utility is the Supreme Court case of *Brenner v Manson*.¹⁷⁵ This case involved the attempt to patent a steroid with no known utility - although related compounds had known utilities - and a method of producing the steroid. The majority of the Supreme Court denied patentability, holding that the applicant was required to show a ‘specific’ and ‘substantial’ utility to the claims for the steroid and the method for producing the same.¹⁷⁶ A ‘specific’ utility means that the subject matter of the claim can “provide a well-defined and particular benefit to the public”¹⁷⁷ and ‘substantial’ utility requires the disclosure of “real world” value that would provide “some immediate benefit”.¹⁷⁸

However, Federal Circuit case *In re Brana*¹⁷⁹ departed from this strict standard. The case involved an attempt to patent anti-tumour compounds, where the applicant had submitted laboratory evidence from *in vitro* and *in vivo* tests in support of utility.¹⁸⁰ The Court confirmed that proving utility did not require the full extent of clinical tests in humans required for regulatory approval, but that evidence from pre-clinical tests, such as testing on animals, would be acceptable.¹⁸¹

¹⁷¹ See *Brenner v Manson* 383 US 519 (1966), discussed below.

¹⁷² Patents Act 1990 (Cth), s 7A, s 18(1)(c).

¹⁷³ 35 USC § 101.

¹⁷⁴ *Studiengesellschaft Kohle v Eastman Kodak* 616 F 2d 1315 (5th Cir 1980) at 1339.

¹⁷⁵ *Brenner*, n 171.

¹⁷⁶ At 534.

¹⁷⁷ *In re Fisher* 421 F 3d 1365 (Fed Cir 2005) at 1371.

¹⁷⁸ *Nelson v Bowler* 626 F 2d 853 (CCPA 1980) at 856.

¹⁷⁹ *In re Brana* 51 F 3d 1560 (Fed Cir 1995).

¹⁸⁰ An *in vitro* test refers to evidence obtained from outside a living organism such as from a test-tube or Petri dish. By contrast, *in vivo* tests refer to evidence obtained from use in a living organism.

¹⁸¹ At 1568. The legal requirements for regulatory approval of a new drug will be discussed in this chapter below.

Therefore, pre-clinical laboratory results will usually be sufficient to establish utility for a pharmaceutical compound.¹⁸² Notably, *in vitro* tests may only demonstrate that the compound binds a target protein, which is far removed from proving that the compound is a safe and effective treatment in humans. In addition, the Federal Circuit has allowed supporting evidence from pre-clinical tests to be provided *after* the filing date of the invention, in order to “substantiate doubts as to the asserted utility since this pertains to the accuracy of a statement already in a specification”.¹⁸³

However, a specification must contain “more than respectable guesses as to the likelihood of ... success”.¹⁸⁴ Moreover, if a particular disease etiology is not well-understood there may not be any target proteins or animal models that can be used to generate such pre-clinical evidence of utility.¹⁸⁵ For example, this is the case with mental disorders that have unknown cause, such as schizophrenia.

Finally, it is notable that a patent over a medicine which is denied for lack of utility due to inadequate pre-clinical evidence can still anticipate a subsequently filed patent application over the same medicine.¹⁸⁶ The potentially adverse effect of this on private incentives for drug development will be discussed further in Chapter Three.

Summary

The patent system requires an inventor to create *useful* information. Accordingly, it is not possible to simply patent the discovery of a chemical or protein *per se* without disclosing its utility or functionality. This helps incentivise innovators to find and disclose practical uses for new discoveries.

¹⁸² See generally, MPEP § 2107 Guidelines for Examination of Applications for Compliance with the Utility Requirement.

¹⁸³ *Eli Lilly and Co v Actavis Elizabeth LLC et al* No 2010-1500 (Fed Cir July 29, 2011) at 16 citing *In re Brana* at 1567. Contrast *Janssen Pharmaceutica NV v Teva pharmaceuticals USA Inc* 583 F 3d 1317 (Fed Cir 2009) and *Rasmusson v SmithKline Beecham Corp* 413 F 3d 1318 (Fed Cir 2005)[*Rasmusson*]. For a discussion of the EPO position regarding after-filed evidence, see Nina L White “Time waits for no man: deciding when to file a patent application in Europe” (2007) 25 *Nature Biotechnology* 639.

¹⁸⁴ *Rasmusson* at 1325.

¹⁸⁵ See CM Holman “Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation” (2011) 76 *Mo L Rev* 645 at 660 citing *Eli Lilly & Co v Actavis Elizabeth LLC* 731 F Supp 2d 348 (DNJ 2010) at 352.

¹⁸⁶ See Roin, above n 100, at 522 citing *In re Hafner* 410 F 2d 1403 (CCPA 1969) at 1405: “a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim.”

However, because of the commercial pressure to file a patent application before information supporting the actual usefulness of a medicine is available, patents are often susceptible to attack on the basis of lack of utility. Further, this pressure to file early also widens the scope of prior art which can subsequently be used to destroy novelty of medicines, even if evidence of utility was insufficient at the time.

Notably, even if a new medicine has been deemed to satisfy the novelty, inventive step, and utility criteria and a patent has been allowed, it is still be susceptible to revocation on other grounds.

D Grounds for Revocation

While there are various grounds for revocation of a patent after grant,¹⁸⁷ this thesis will focus on the requirement that a patent specification have adequate sufficiency. Like utility, sufficiency is frequently raised as grounds to invalidate a pharmaceutical patent due to the pressure to file a patent application early in clinical development.

1 Sufficiency

The concept of sufficiency is at the heart of the social ‘contract’ between the inventor and society.¹⁸⁸ That is, a patent monopoly is granted in exchange for sufficient disclosure of information to allow a person skilled in the art to ‘perform’ the invention. With insufficient disclosure, society cannot benefit. There is a tendency to confuse the concepts of sufficiency and utility, because in order to obtain a useful result, the specification must also provide enough detail for a person skilled in the art to perform the invention.¹⁸⁹ The next sections will discuss the applicable law in New Zealand and the United States.

(a) New Zealand

Section 39(2)(c) of the Patents Act provides that the contents of a complete specification must include claims which are “supported by the matter disclosed in the

¹⁸⁷ Patents Act 2013, s 112. See also 35 USC § 282(b)(2) or (3). These include grounds such as obtaining the invention from the true inventor or providing fraudulent information to the patent office.

¹⁸⁸ See Denicolò and Franzoni, above n 8.

¹⁸⁹ This distinction was addressed by the English Court of Appeal in *Tetra Molectric Ltd’s Application* [1977] RPC 290 (CA) at 297: ‘If you cannot achieve the promised result because of deficiencies in the information given in the specification, there is insufficiency. But, if following that information and having achieved mechanically that which the specification promises you will achieve by so following, the end product will not of itself achieve that promise, then that is inutility.’

complete specification.”¹⁹⁰ If the claims refer to subject matter which is not “broadly described” in the specification, the claims are deemed not “fairly based upon the disclosure”.¹⁹¹ Although sufficiency does not fall within the formally examined patentability criteria, it is possible for the Commissioner to refuse to proceed with a patent application which is insufficient.¹⁹²

The test for sufficiency in New Zealand requires that a skilled person would be able to perform the invention by following the specification without applying some further invention on their part.¹⁹³ Notably, the test is the same for ‘enablement’, which is the second part of the two-part test for ‘anticipation’ specified in the *Synthon* case above.¹⁹⁴ It is a question of fact whether the skilled person can ‘carry out’ the invention as claimed, from the wording of the specification.¹⁹⁵ The high level of unpredictability in drug development would raise the level of disclosure required for pharmaceutical inventions.

Sufficiency also requires that the entire scope of a claim is supported by the specification. In particular, the Court of Appeal in *Beecham Group Limited v Bristol-Myers Company* held that a patentee cannot claim more than they have invented.¹⁹⁶ For example, in *Biogen Inc v Medeva* it was held that a ‘composition of matter’ claim for a drug product will fail for insufficiency if the specification only discloses one way of making the drug but “the claims cover other ways in which [the drug] might be delivered”.¹⁹⁷ The literal application of the ‘*Biogen* sufficiency’ doctrine can threaten any ‘composition of matter’ claim over a drug that could be manufactured by different processes. However, the House of Lords distinguished *Biogen* in *Generics (UK) Limited & Ors v H Lundbeck A/S*, holding that where the method of making a drug is novel and inventive, and the specification sufficiently describes how to make it, the claim for the drug product is not invalid.¹⁹⁸ Although the Assistant

¹⁹⁰ Compare section 10(3)(a) of the Patents Act 1953, which stated that a complete patent specification must ‘particularly describe the invention and the method by which it is to be performed’.

¹⁹¹ *Mond Nickel Company Ltd's Application* (1956) RPC 189 at 194.

¹⁹² *Standard Brand Inc's Patent (No 2)* [1981] RPC 499 (CA) at 530-531, cited with approval by *Synthon BV v Smithkline Beecham Plc* IPO P15/2007, 11 June 2007 at 24.

¹⁹³ *Noton New Zealand Ltd v Alister Bevin Ltd* (1999) 1 NZIPR 236 at 238.

¹⁹⁴ *Synthon*, above n 78, at [38]-[55].

¹⁹⁵ See *International Business Machines Corporation's Application*, above n 45, at 542; *Edison and Swan Electric Co v Holland* [1889] RPC 243 (CA) at 280.

¹⁹⁶ *Beecham Group Limited v Bristol-Myers Company* [1981] NZLR 600 at 612.

¹⁹⁷ *Biogen Inc v Medeva* [1996] UKHL 18; [1997] RPC 1 at [70] per Lord Hoffman.

¹⁹⁸ *Generics (UK) Limited & Ors v H Lundbeck A/S* [2009] UKHL 12. *Biogen* was distinguished in that it was a part product and process claim. Lord Neuberger stated [at 83] that a product claim, provided it was novel and inventive, would also provide a monopoly over the ‘technical contribution’ which was the product itself regardless of the method of producing the product. Lord Hoffman stated [at 46] that ‘is too late to have regrets about the breadth of the monopoly which such [product] claims confer.’

Commissioner of Patents has followed *Biogen* without reference to *Lunbeck*,¹⁹⁹ it is unclear to what extent ‘*Biogen* insufficiency’ would apply in New Zealand.

(b) United States

The United States has a ‘sufficiency’ requirement,²⁰⁰ although it is defined in terms of the related concepts of ‘enablement’ and ‘written description.’²⁰¹ If a patent is determined to lack ‘enablement’ or ‘written description’, then it will not be granted.²⁰² ‘Enablement’ requires a person skilled in the art to make the invention without “undue experimentation”.²⁰³ The ‘written description’ requirement is satisfied if the invention is conveyed with reasonable clarity such that a person having ordinary skill in the art can reasonably conclude that the applicant had ‘possession’ of the invention at the time of filing.²⁰⁴ Again, the high level of unpredictability for pharmaceutical inventions means that the sufficiency hurdle is more difficult to satisfy.

By way of example, it is not possible to claim a therapeutic method without disclosing specific compounds which can be used,²⁰⁵ or to broadly claim a chemical ‘genus’ without disclosing a representative number of ‘species’ so that a person skilled in the art can implement any member of the claimed ‘genus’.²⁰⁶ Attempts to

¹⁹⁹ *Malik M Hasan v Ministry Of Health, Accident Compensation Corporation, Southern Cross Medical Care Society and Telecom New Zealand Limited* [2012] NZIPOPAT 2 (9 February 2012) at [188]-[208].

²⁰⁰ 35 USC § 112(a) ‘The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.’

²⁰¹ See MPEP § 2161 - Three Separate Requirements for Specification Under 35 USC 112(a) or Pre-AIA 35 USC 112, First Paragraph.

²⁰² See MPEP § 2163 for examination guidelines regarding an objection based on lack of ‘written description’ and MPEP § 2164 for a rejection based on lack of ‘enablement’.

²⁰³ *Re Wands* 858 F 2d 731 (Fed Cir 1988) at 736: ‘The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art.’

²⁰⁴ *Vas-Cath Inc v Mahurkar* 935 F 2d 1555 (Fed Cir 1991) at 1563-1564; See generally MPEP § 2161-2163.

²⁰⁵ For example, in *University of Rochester v G D Searle & Co Inc* 358 F 3d 916 (Fed Cir 2004), a method for inhibiting COX-2 activity by administering a non-steroidal drug which inhibits COX-2 was claimed, however, no compounds were disclosed. It was held there was a lack of written description.

²⁰⁶ *In re Alonso* 545 F 3d 1015 (Fed Cir 2008), considered a claimed method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotype to the neurofibrosarcoma. It was held there was a lack of written description as the specification only disclosed a single antibody to an antigen and there were no fully characterised antigens disclosed, with a large variability in possible antigens and antibodies.

file broad claims over medicines without an adequate number of working examples will invalidate a patent.²⁰⁷

It is black letter law that enablement for a claimed drug does not require disclosure of all possible formulations or methods of use for that drug, although there is still large amount of uncertainty in this area.²⁰⁸ While there is still a requirement to disclose the “best mode” of performing the invention,²⁰⁹ changes under the AIA mean this is no longer a ground for revocation of a patent.²¹⁰ As a result, pharmaceutical companies will not have to disclose all known uses or ‘indications’ for a drug upon filing.²¹¹ However, the lack of ‘bright line rules’ makes it difficult for pharmaceutical companies to know whether their patents may be revoked for insufficiency.²¹²

Summary

The requirement for sufficiency is a difficult and risky hurdle for an applicant seeking patent protection for a pharmaceutical invention. In general, merely disclosing the composition of a drug without providing its function will mean the patent will be invalid for insufficiency. Pharmaceutical companies must decide whether to file a patent application disclosing their lead compounds at an early stage, and risk a claim of insufficiency, or delay filing until they have more data.²¹³

Like utility, the more stringent disclosure requirement also increases the scope of subject matter available as prior art to invalidate patentability of subsequent medicines. Further, while the ‘unpredictability’ of medicinal research can assist to overcome novelty and obviousness objections, it also makes the sufficiency hurdle more difficult to overcome. The result is a constant threat that a pharmaceutical innovator must be vigilant against when attempting to secure patent protection.

²⁰⁷ In *Ariad Pharmaceuticals Inc v Eli Lilly and Co* 598 F 3d 1336 (Fed Cir 2010), a method of binding NF-KB was claimed, which is a protein that regulates gene expression in human cells. Invalidating the patent for insufficiency and overturning a USD 65.2 million verdict for patent infringement, the Federal Circuit held [at 1357-1358] that while the applicant disclosed three categories of inhibitors of NF-KB, they provided no ‘working or prophetic’ examples or evidence of functionality.

²⁰⁸ Holman, above n 185, at 662.

²⁰⁹ 35 USC § 112(a).

²¹⁰ 35 USC § 282(b)(3)(A).

²¹¹ This may facilitate patent ‘evergreening’ by allowing claims over new uses for a drug after the original patent is nearing expiry. The effectiveness (or lack thereof) of patent ‘evergreening’ techniques will be discussed in more detail in Chapter Three.

²¹² Holman, above n 185, at 648.

²¹³ At 657-663.

While this chapter has so far considered the major legal requirements for obtaining patent protection over medical therapies, it will now discuss the circumstances where such therapies may be excluded from patentability under law.

E Exclusions from Patentability

In addition to the requirements for patentability, there are various specific exclusions under law which relate to medical therapies. Notably, the United States has few exclusions, being a relatively ‘pro-patent’ jurisdiction.²¹⁴ Therefore, the following sections will mainly discuss the law as it applies to New Zealand, although the United States position will also be referenced where applicable. Under section 15 of the Patents Act, an invention is excluded from patentability if its commercial exploitation would be contrary to public order or morality.²¹⁵ Section 16 of the Act includes additional exclusions, namely: (1) humans, the biological processes involved in their generation, and (2) methods of treatment of human beings by surgery or therapy.²¹⁶ These exclusions will be discussed in turn.

1 Section 15: Inventions contrary to public order or morality

Article 27 of TRIPS provides that “[m]embers may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality.” The commentary to section 15 of the Patents Act includes several examples of inventions which are deemed contrary to public order or morality, such as processes of cloning human beings, modifying the germ line genetic identity of human beings, using human embryos for industrial or commercial purposes, and modifying the genetic identity of animals in a manner which is likely to cause them suffering without any substantial medical benefit to humans.²¹⁷ Notably, the United States does not have a public order or morality exception to patentability.

²¹⁴ Interestingly, in the recent *Prometheus* and *Myriad* decisions [discussed above n 50 and n 54, respectively], the Supreme Court of the United States has reversed the global trend of expanding patent rights.

²¹⁵ Patents Act 2013, s 15.

²¹⁶ Section 16 of the Patents Act 2013 contains other exclusions: section 16(3) denies patentability to methods of diagnosis practiced on human beings, and section 16(4) denies patentability of plant varieties. These exclusions are not directly related to the commercialisation of medical therapies, and will not be considered further.

²¹⁷ This reflects the position already taken by IPONZ under the Patents Act 1953. See IPONZ Guidelines, 5.1 “Contrary to morality: Raising objections under section 17(1)” (8 December 2012) <www.iponz.govt.nz>.

Only some of these examples are relevant to the commercialisation of medical therapies. Human cloning is subject to legal prohibitions,²¹⁸ which would interfere with any commercial application, apart from any patentability issues.²¹⁹ However, human embryos can be used in the production of stem cells,²²⁰ which can be used as medicines. The patentability of human stem cells is somewhat controversial,²²¹ and while the United States currently grants patents over stem cells, the position may change in the future.²²² The effect of patentability issues on private incentives to develop stem cell therapies will be considered in Chapter Three.

Genetically modified animals are also used in drug development. Since the landmark case of *Diamond v Chakrabarty*²²³ which allowed patents for micro-organisms, the patentability of higher forms of life has been upheld in various jurisdictions. For example, the USPTO has allowed patents over the Harvard oncomouse, which is genetically engineered to develop cancer, and therefore is very useful for screening cancer drugs.²²⁴ IPONZ has also granted the oncomouse patent in New Zealand.²²⁵ It is likely that the current Patents Act will not change the ability to patent genetically modified animals, provided that it does not cause them suffering without substantial medical benefit to humans.²²⁶

²¹⁸ See Human Assisted Reproductive Technology Act 2004, s 8, sch 1. Human cloning is also banned in 15 states in the United States: see “Human Cloning Laws” (January 2008) National Conference of State Legislatures <www.ncsl.org>.

²¹⁹ A consideration of the ethics of commercially exploiting human cloning is beyond the scope of this thesis.

²²⁰ Stem cells are ‘pluripotent’, which means they can transform into any cell in a body. For this reason, stem cells are being actively researched as a therapeutic means of regenerating body parts damaged by disease. Notably, recent breakthroughs may allow the generation of stem cells without use of human embryos: see LJ Schroth “Researchers create embryonic stem cells without embryo” *Harvard Gazette* (online ed, Cambridge (Mass), 29 January 2014).

²²¹ See TA Caulfield “From human genes to stem cells: new challenges for patent law?” (2003) 21(3) *Trends in Biotechnology* 101 at 101-102; Gerard Porter and others “The patentability of human embryonic stem cells in Europe” (2006) 24 *Nature Biotechnology* 653 at 653;

²²² U Storz “The Limits of Patentability: Stem Cells” In A Hübel, U Storz and A Hüttermann *Limits of Patentability: Plant Sciences, Stem Cells and Nucleic Acids* (Springer, Berlin, 2013) 9 at 21-22.

²²³ *Diamond v Chakrabarty* 447 US 303 (1980). In this case, the Supreme Court held [at 308] that “Congress intended statutory subject matter to ‘include anything under the sun that is made by man’”.

²²⁴ US Patent No. 4,736,866 claimed ‘a transgenic non-human mammal whose germ cells and somatic cells contain a re-combinant activated oncogene sequence introduced into said mammal’. Patent No. 5,087,571 claimed a method of producing a cell culture from the oncomouse. Patent No 5,925,803 claimed a method of testing a substance suspected to be a carcinogen on the oncomouse. The validity of these patents were not challenged in the United States, and they are deemed to have expired as of 2005.

²²⁵ New Zealand Patent No 243908. Compare in *Harvard College v Canada (Commissioner of Patents)* [2002] 4 SCR 45, 2002 SCC 76, where the Supreme Court of Canada denied patentability of the oncomouse.

²²⁶ A related issue, although outside the scope of this thesis, is whether the patenting of living organisms may be objected to as offensive to Māori. See Patents Act 2013, ss 225-228, which provide for the appointment of a Māori Advisory Committee, whose advice the Commissioner must consider before granting a patent.

2 *Section 16: Other exclusions*

- (a) Patentability of humans, human cloning, and the biological processes involved in their generation.

Under section 16(1) of the Patents Act “[h]uman beings, and biological processes for their generation, are not patentable inventions.” As noted above, patents for human cloning are also excluded under the grounds of public order or morality. In addition, pursuant to Section 33(a) of the AIA, human beings are not patentable in the United States.²²⁷

- (b) Methods of medical treatment by surgery or therapy

The patentability of methods of medical treatments by surgery or therapy is controversial, as it is argued they could interfere with a doctor’s freedom to provide the best treatment to their patients due to the fear of infringement.²²⁸ Under Article 27(3)(a) of TRIPS, WTO member countries are permitted to exclude methods of medical treatment from patentability.²²⁹

Section 16(2) of the Patents Act specifically excludes methods of medical treatment by surgery or therapy practised on human beings from the definition of patentable invention,²³⁰ which reflects the position at common law.²³¹ Under *Pfizer Inc v The Commissioner of Patents*²³² the Court of Appeal held that methods of medical treatment are not patentable inventions, due to being “generally inconvenient”²³³ in terms of the so-called ‘proviso’ in section 6 of the Statute of

²²⁷ Leahy-Smith America Invents Act, s 33(a): ‘Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism.’ See also MPEP § 2105.

²²⁸ See O Mitnovetski and D Nicol “Are patents for methods of medical treatment contrary to the *ordre public* and morality or ‘generally inconvenient’?” (2004) 30 *Journal of Medical Ethics* 470 at 473. It should be noted that patents over medicines also impact on a doctor’s choice of treatment, by preventing access to cheap medicines where the patient or government cannot afford the monopoly price.

²²⁹ TRIPS, art 27(3).

²³⁰ Patents Act 2013, s 16(2).

²³¹ *Pfizer Inc v The Commissioner of Patents* [2005] NZLR 362 at [7]. Compare the position in Australia, which allows patents over methods of medical treatment at common law. See *Anaesthetic Supplies Pty Ltd v Rescare Ltd (Rescare)* (1994) 50 FCR 1.

²³² *Pfizer* at [7].

²³³ At [7] per Anderson P: ‘...this Court once more unanimously holds that in terms of the present law, methods of medical treatment of humans are not patentable. Such methods may be inventions, but in terms of longstanding authority it is generally inconvenient to protect them with letters patent or grants of privilege.’

Monopolies.²³⁴ Notably, medical treatments which are deemed ‘non therapeutic’, such as cosmetic treatments, are still patentable in New Zealand.²³⁵

In the United States, claims over methods of medical treatment have been permitted since 1954.²³⁶ Nonetheless, under 35 USC § 287(c), there is a specific exclusion in the definition of patent infringement for medical practitioners that perform ‘medical activity’ on a human or animal. This exclusion is limited to ‘purely’ surgical or diagnostic methods which do not involve the use of a patented device, medicine or biotechnology process.²³⁷

Summary

As noted above, there are various categories of invention related to medical therapies that are excluded from patentability. Although patents over methods of medical treatment by therapy are permitted in the United States, patents over methods of medical treatment by surgery are unavailable and unenforceable, in New Zealand and the United States respectively. The possible effect of these exclusions on private incentives for development of socially valuable medical therapies will be discussed further in Chapter Three.

In recognition of the adverse policy implications of patentability exclusions to methods of medical treatment on private incentives for medical research, there has been a development of judicial inroads that overcome these exclusions in New Zealand. This will be discussed in the next section.

F Judicial Inroads into Exclusions of Methods of Medical Treatment

Judicial commentators have noted how excluding patents over methods of medical treatment may disincentivise medical research.²³⁸ The following sections will discuss various exceptions that have developed to overcome the exclusions of methods of

²³⁴ Statute of Monopolies 1623, s 6. The proviso reads: “so they be not contrary to the Law, nor mischievous to the State, by raising prices of commodities at home, or hurt of trade, or generally inconvenient.” See also Frankel, above n 9, at 405-407 and 409-412.

²³⁵ *Re Handleman’s Application* PO P02/1993, 23 February 1993. See also *Joos v Commissioner of Patents* [1973] RPC 59.

²³⁶ *Ex Parte Scherer* 103 USPQ (BNA) 107 (Pat Off Bd App 1954) at 109.

²³⁷ 35 USC S 287(c)(2)(A).

²³⁸ See dicta of Jacob J in *Merck & Co Inc’s Patents* [2003] FSR 29 at [80]: ‘I conclude that the claim is in substance to a method of treatment of the human body by therapy. I do so with regret. For patents are provided to encourage research. If new and non-obvious improved methods of administration of known drugs for known diseases are not patentable in principle...there will be less of a research incentive to find such methods.’

medical treatment from patentability, namely, ‘Swiss’ claims, novel dosage regimens, methods of administration, and patient groups.

1 ‘Swiss’ claims

Because methods of medical treatment *per se* are not patentable in most Commonwealth and European jurisdictions, a dilemma arose in respect of known compounds for treating a different or new disease. If a compound was known, it would be unpatentable for lack of novelty under the *General Tyre* test for anticipation. In addition, the ‘use’ of a known compound to treat a disease would be an unpatentable method of medical treatment.

This dilemma was overcome in the landmark case, *ESAI/Second medical indication* G0005/83, when the Enlarged Board of Appeal of the European Patent Office (EPO) first allowed so-called ‘Swiss claims’.²³⁹ Swiss claims are directed to the ‘manufacture of a medicament’, a substance used for a particular treatment, which avoids a claim over the method of treatment itself.²⁴⁰ Such claims allow the patent holder to sue a pharmaceutical company that manufactures a drug for an infringing use, but preserves the exemption for the doctor or pharmacist who prescribes the drug for that use.²⁴¹

The patentability of ‘Swiss’ claims was upheld in New Zealand pursuant to the landmark decision of the Court of Appeal in *Pharmaceutical Management Agency Ltd v Commissioner of Patents*.²⁴² There is a subtle difference between Swiss claims and second medical use claims,²⁴³ whereby the latter may be interpreted as having a slightly broader scope of coverage.²⁴⁴ Despite this, second medical use claims are deemed an unpatentable method of medical treatment in New Zealand.²⁴⁵ By contrast,

²³⁹ *ESAI/Second medical indication* G 0005/83 [1985] OJ EPO 64. ‘Swiss claims’ originated from the practice of the Swiss Intellectual Property Office to allow claims over the use of a known compound ‘in the manufacture of a medicament’ for a novel and inventive therapeutic use. The terms ‘Swiss claims’ and ‘Swiss-type’ claims are used interchangeably.

²⁴⁰ An example of a Swiss claim format is as follows: ‘Use of [drug X] in the manufacture of a medicament for the treatment of [disease Y].’

²⁴¹ In any case, the difficulty with enforcing a patent against doctors or pharmacists is a characteristic of an unmonopolisable therapy, as will be discussed in Chapter Three.

²⁴² *Pharmaceutical Management Agency Ltd v Commissioner of Patents* [2000] 2 NZLR 529 [PHARMAC].

²⁴³ An example of a second medical use claim format is as follows: ‘Use of [drug X] for the treatment of [disease Y].’

²⁴⁴ See *ESAI/Second medical indication*, above n 238. Notably, the European Union has now approved second medical use claims pursuant to amendments to article 52(4) and article 53(c) under the EPC 2000. The EPO will no longer accept claims in the ‘Swiss-type’ format: see *ABBOTT RESPIRATORY/Dosage regime* G 02/08 [2010] OJ EPO 456.

²⁴⁵ See *Pfizer Inc v The Commissioner of Patents* [2005] 1 NZLR 362 at [7]. See also discussion of s 16(2) Patents Act 2013, above n 229.

in the United States, under 35 USC § 100(b) specifically allows a patentable ‘process’ to include “a new use of a known process”.²⁴⁶

2 *Novel dosage regimen, methods of administration, and patient groups*

After a new drug is developed, it is often discovered that novel and inventive dosing regimen²⁴⁷ or methods of administering a drug²⁴⁸ have better outcomes for particular patient groups due to their unique genetic or physiological profile. This is an active area of research that falls within the promising field of ‘personalised medicine’. Claims over such innovations use the same language as Swiss claims. However, unlike Swiss claims, it is possible to claim a novel method of using the known drug for its original disease rather than a new disease.

Despite the prohibition against patenting methods of medical treatment, these types of claims have been allowed in New Zealand. For example, in the IPONZ hearings *Merck & Co v Arrow Pharmaceuticals*²⁴⁹ and *Genentech’s Application*,²⁵⁰ the Commissioner of Patents approved Swiss-type claims where novelty and inventiveness resided in a novel dosing regimen. The Commissioner has also allowed claims drafted in the Swiss-type format for treatment of a group of patients with early-stage breast cancer with a drug that was originally used to treat patients with advanced-stage breast cancer.²⁵¹ IPONZ have issued new guidelines supporting the patentability of such claims.²⁵² However, commentators have questioned whether it is appropriate for IPONZ to make this determination rather than Parliament.²⁵³ It is also unclear how the courts will treat this issue in light of the specific exclusion of methods of medical treatment under s 16(2).

The patentability of dosing regimens in the United States is also uncertain. While dosing regimens fall within the scope of method claims, such claims may be excluded as non-statutory abstract ideas, as already discussed above with reference to the *Prometheus* case.²⁵⁴

²⁴⁶ 35 USC § 100(b).

²⁴⁷ For example, dosing a medicine at particular time intervals and at particular concentrations.

²⁴⁸ For example, administering a medicine to a patients via different routes, including intravenous, oral, vaporised, inhaled, topical, and sublingual.

²⁴⁹ *Merck & Co v Arrow Pharmaceuticals* P3/2006.

²⁵⁰ *Genentech’s Application* P1/2007.

²⁵¹ *AstraZeneca AB’s Application 533106* P23/2007 and *AstraZeneca AB’s Application 539603* P24/2007.

²⁵² See IPONZ Guidelines 5.2 “Guidelines for the examination of Swiss-type claims” (8 December 2012) <www.iponz.govt.nz>.

²⁵³ S Frankel “Lord Cooke and Patents: The Scope of Invention” (2008) 39 VUWLR 73 at 94.

²⁵⁴ See *Prometheus*, above n 50.

Further, as will also be discussed in the regulatory law section below and in Chapter Three, the commercial value of ‘Swiss’ claims and second medical use claims is doubtful. Generic drug companies can manufacture ‘off-patent’ or ‘generic’ drugs when the original patents expire, and are able to ‘carve out’ any patented second uses from their labels and sell them to the market, thereby avoiding claim of infringement.²⁵⁵ This is referred to as ‘skinny labeling’. Case law from various jurisdictions shows how difficult it is for innovator companies to prove infringement of such claims, as they must usually show that the generic manufacturers supplying the generic drugs to the market knew the drugs would be used in an infringing manner.²⁵⁶ An innovator drug company would also be unlikely to sue individual doctors or pharmacists who supply the generic drug for a patented use, as this would be uneconomic and impractical.²⁵⁷

Summary

Despite the difficulties with obtaining and enforcing Swiss claims and second medical use claims, the fact that pharmaceutical companies are actively prosecuting such patents before the courts demonstrates that they must provide some incentives for drug development. However, there is a lack of evidence that the absence of such claims would have an adverse effect on incentives for research.²⁵⁸ Further, as will be discussed in Chapter Three, it is difficult or impossible to enforce such claims where a drug is available on the market for a non-infringing use.

The previous sections have discussed the major patentability requirements and exclusions from patentability. While obtaining adequate patent protection is a critical step in the process of drug development, the requirement to obtain regulatory approval is much more onerous, and like a patent, has the ability to exclude competitors from the market for a certain period of time. This regulatory environment will now be discussed.

²⁵⁵ See A Rai “Use Patents, Carve-Outs, and Incentives - A New Battle in the Drug-Patent Wars” (2012) 367(6) *New England Journal of Medicine* 491 at 491.

²⁵⁶ See *Bristol-Myers Squibb v Shalala* 91 F 3d 1493 (DC Cir 1996); *Actavis v Merck* [2008] RPC 26 at para [10]; *Grimme Landmaschinenfabrik GmbH & Co KG v Derek Scott (trading as Scotts Potato Machinery)* [2010] EWCA Civ 1110 at [131]; compare the decision of the High Court of Australia in *Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd v (No. 2)* [2012] FCAFC 102 which found infringement of a method of medical use claim for a generic drug which was listed for use in a related indication to the patented use.

²⁵⁷ Second uses of generic drugs fall within the category of ‘unmonopolisable therapies’, which will be discussed in Chapter Three.

²⁵⁸ Frankel, n 9 above, at 412.

G Regulatory Environment

Compared to other industries, the pharmaceutical industry has a complex and onerous regulatory environment, which requires pharmaceutical companies to undertake significant costs before launching a new product. An important consideration to note for the purpose of this thesis is that obtaining a patent and obtaining regulatory approval to market a drug are entirely separate events, with the former typically preceding the latter by five or more years.²⁵⁹

The requirement to obtain regulatory approval has an important public health function. In particular, a medicine must be demonstrated as safe and effective in clinical trials before it can be marketed for sale.²⁶⁰ This section of the chapter will describe the process for obtaining regulatory approval of a drug from the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) and the United States Food and Drug Administration (FDA).

While the stringency of requirements differ between New Zealand and the United States - with the latter perceived as the most stringent in the world - both regulatory agencies require evidence of safety and efficacy from clinical trials in humans. These clinical trials are divided into Phase I, Phase II, and Phase III,²⁶¹ with technical requirements having been standardised internationally pursuant to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.²⁶²

Regulatory agencies separate medicines into two groups: small molecule drugs and biologics. The former are ‘standard’ drugs which are chemically synthesised, and usually taken in a pill form, and the latter are a new class of drugs, usually injected, which comprise proteins created through a biological process such as recombinant DNA technology.²⁶³ The main function of regulatory agencies is the oversight of

²⁵⁹ JA DiMasi, RW Hansen and HG Grabowski “The price of innovation: new estimates of drug development costs” (2003) 22(2) *Journal of Health Economics* 151 at 164 and 166. The adverse consequence of this gap on private incentives to develop unpatentable therapies will be explored further in Chapter Three.

²⁶⁰ By contrast, dietary supplements do not have to be proven as safe and effective before being sold on the market. The lack of regulatory oversight over supplements has consequences for private incentives to conduct clinical trials that will be discussed in Chapter Three.

²⁶¹ Phase I clinical trials administer the medicine on up to 100 volunteers in order to test the safety of the drug at various dosing levels. Phase II trials test therapeutic efficacy on between 100-300 patients. Phase III trials test safety and efficacy on 1000 or more patients. Medicines can fail at any stage of clinical trials, although Phase II is the most difficult hurdle, as will be discussed in Chapter Three.

²⁶² *ICH Guidelines* (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, November 2005).

²⁶³ Recombinant DNA technology involves genetically modifying bacteria to produce novel proteins, which are subsequently extracted and purified into a biologic drug.

small molecule drugs, biologics, and any other substances over which therapeutic claims are made and are sold to the public.²⁶⁴

1 *Generic competition*

Another important function of regulatory agencies is to facilitate entry of cheaper medicines when a drug goes ‘off-patent.’ As mentioned above, ‘off-patent’ drugs are also referred to as ‘generic drugs’. An innovator’s drugs which are still ‘on-patent’ are referred to as ‘branded drugs’.²⁶⁵ Generic drug manufacturers do not have to conduct the same Phase I-III clinical testing, but only have to prove their generic drug has an equivalent structure to a ‘branded’ drug.²⁶⁶ This means they can quickly and cheaply launch their generic drug on the market once the innovator’s patent protection expires. This is known as the ‘patent cliff’, because of the steep decline in the innovator’s profits due to generic entry after patent expiry.²⁶⁷ Generic drug companies also have specific defences to patent infringement that allow them to prepare to launch the drug prior to patent expiry.²⁶⁸

Because they are more cost effective, generic drug prescriptions have grown to almost 80 per cent of total prescriptions in the United States by 2010.²⁶⁹ It is notable, however, that sales of expensive ‘branded’ medicines still comprised over 74 per cent of the total spending on pharmaceuticals during the same period.²⁷⁰ According to the Congressional Budget Office, generic competition saved the United States

²⁶⁴ As will be discussed in Chapter Three, any substances can be subject to regulatory oversight, including dietary supplements, if they are advertised as having a therapeutic effect, although certain specified health claims can be made.

²⁶⁵ Notably, however, some highly profitable ‘branded’ drugs are off-patent, such as Aspirin, which is a brand name owned by Bayer, and has the generic name of acetylsalicylic acid. In the context of this thesis, ‘branded’ drugs will refer to patented drugs, and ‘innovators’ will refer to biopharmaceutical companies which develop new patented drugs as part of their business model. This can be contrasted with generic drug companies whose business model involves relying on clinical trial data generated by innovators.

²⁶⁶ As will be discussed below at n 303, it is cheaper to obtain generic approval for small molecule drugs as opposed to biologics, because the latter are manufactured according to biological processes that are difficult to replicate consistently without significant investment.

²⁶⁷ B Hirschler “Drugmakers face \$140 bln patent ‘cliff’ – report” (1 May 2007) Reuters <www.reuters.com>.

²⁶⁸ In particular, it is a defence to patent infringement to manufacture a patented drug for the purpose of obtaining regulatory approval. These defenses are known as ‘Bolar exemptions’ after the decision of the United States Federal Circuit in *Roche Products, Inc v Bolar Pharmaceutical Co* 733 F 2d 858 (Fed Cir 1984). New Zealand has a similar exemption to infringement under s 145 of the Patents Act 2013, along with most other countries.

²⁶⁹ *The Use of Medicines in the United States: Review of 2010* (IMS Institute for Healthcare Informatics, April 2011) at 3.

²⁷⁰ At 6. In particular, in 2010 the United States spent USD 229 billion on ‘branded’ drugs in 2010 out of total spending of USD 307 billion on medicines.

government USD 33 billion in 2007.²⁷¹ Another report by the Generic Pharmaceutical Association estimated that generic drugs resulted in over USD 1 trillion in savings between the year 2002 and 2011.²⁷²

Despite the social benefits of such cost savings, generic competition significantly reduces the ability of an innovator to profit from new ‘branded’ drugs. For this reason, regulatory agencies do not approve generic drugs for a minimum period, so that the innovator can use this ‘regulatory exclusivity’ to recoup their development costs. The importance of protecting the clinical trial data of innovators against “unfair” generic competition has been recognised in TRIPS.²⁷³ However, as will be discussed below, regulatory exclusivity is shorter and weaker than the protection provided by patents. In absence of such protection, it is unlikely that drug companies would develop new medicines, the consequences of which will be explored in Chapter Three.

The process whereby regulatory agencies manage the regulatory approval of new medicines by innovators and provide regulatory exclusivity against generic competition will now be discussed with reference to New Zealand and the United States.

2 *Regulation of medicines by Medsafe*

In New Zealand, the regulation of medicines is overseen by Medsafe in accordance with the Medicines Act 1981 and Medicines Regulations 1984. In order to obtain regulatory approval, the innovator drug company must file a “new medicine application” with the Minister of Health or their delegate, and include clinical trial data that demonstrates quality, safety and efficacy of the new medicine.²⁷⁴ The Minister will refer this information to the Medicines Assessment Advisory Committee for a recommendation,²⁷⁵ and will not provide consent to regulatory approval under s 20 of the Medicines Act 1981, unless “he or she is satisfied that the likely therapeutic

²⁷¹ *Effects of using generic drugs on Medicare’s prescription drug spending* (Congressional Budget Office, September 2010) at 7.

²⁷² Generic Pharmaceutical Association “New Study finds Generic Prescription Drugs Saved Consumers and the US Health Care System \$1 Trillion over Past Decade” (press release, 21 September 2011). Similarly, in Europe, lower prices due to generic competition were estimated to save EUR 30 billion per annum for small molecule drugs and EUR 1.4 billion per annum for biologics. See *Vision 2015: The EGA’s Thoughts on how to Improve the Legal and Regulatory Framework for Generic and Biosimilar Medicines* (European Generic Medicines Association, October 2010) at 3.

²⁷³ TRIPS, art 39.3 provides for protection of clinical trial data submitted to obtain regulatory approval against ‘unfair commercial use’.

²⁷⁴ Medicines Act 1981, s 21(1)-(2). See also *New Zealand Regulatory Guidelines for Medicines - Part B* (Edn 6.15, Medsafe, November 2011) at 3.

²⁷⁵ s 22(2).

value of the medicine outweighs the risk”.²⁷⁶ The approval process is similar for small molecule and biologic drugs.²⁷⁷

New Zealand currently provides five years of ‘data exclusivity’ for clinical trial data submitted in an innovative medicine application which have achieved regulatory approval.²⁷⁸ Data exclusivity means that generic drug companies cannot rely on an innovator’s clinical trial data in order to obtain regulatory approval for their generic drug. New Zealand does not provide additional data exclusivity for new indications or formulations of approved medicines, unlike the FDA. This will be discussed in more detail in the next section.

After expiry of patent protection and data exclusivity, generic drugs can obtain regulatory approval if they can demonstrate ‘bioequivalence’ with the New Zealand Reference Product, which is normally the innovator’s ‘branded’ drug.²⁷⁹

The Medicines Act 1981 also permits the ‘off-label’ use of medicines by doctors.²⁸⁰ An off-label use of a medicine means that it has been prescribed to treat a disease for which it has not received regulatory approval.²⁸¹ Off-label use is relatively widespread in the medical profession, with New Zealand hospitals prescribing medicines off-label in up to 40% of adult and 90% of paediatric patients.²⁸² Potential competition through off-label use is relevant to the lack of private incentives to develop new uses for generic drugs, an issue which will be discussed further in Chapter Three.

3 *Regulation of medicines by the FDA*

The process of obtaining regulatory approval for a new drug in the United States is overseen by the FDA. Once Phase I-III clinical trials are performed, the innovator will file a New Drug Application to seek approval for a small molecule drug²⁸³ or a

²⁷⁶ Medicines Act 1981, s 20A.

²⁷⁷ *New Zealand Regulatory Guidelines for Medicine – Part B*, at 3.

²⁷⁸ Medicines Act 1981, s 23B.

²⁷⁹ *New Zealand Regulatory Guidelines for Medicines - Part D* (ed 6.15, Medsafe, November 2011) at 11.

²⁸⁰ Medicines Act 1981, s 25. See also “Regulatory Issues - Use of Unapproved Medicines and Unapproved uses of Medicines” (April 2012) Medsafe <www.medsafe.govt.nz>.

²⁸⁰ Medicines Act 1981, s 25(1)(b).

²⁸¹ An example would be the use of a painkiller drug for treating depression when it only has regulatory approval to treat pain.

²⁸² R Newson “Take care when prescribing unapproved and off-label medicines” *Pharmacy Today* (online ed, Auckland, 18 October 2012).

²⁸³ Federal Food Drug and Cosmetics Act, s 505(b).

Biologic License Application to seek approval for a biologic drug.²⁸⁴ These different approval pathways will be discussed in turn.

(a) New Drug Application (NDA)

In order for an NDA for a small molecule drug to be approved, the sponsor must submit “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use”.²⁸⁵ The Abbreviated New Drug Application (ANDA) generic approval process was enacted pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act).²⁸⁶ The purpose of the Hatch-Waxman Act was to facilitate generic competition while balancing the rights of innovators by providing minimum periods of data exclusivity.²⁸⁷ In particular, under the Hatch-Waxman Act, for a small molecule drug that is deemed a New Chemical Entity (NCE), it is not possible to submit an ANDA until five years from the date of regulatory approval.²⁸⁸ An NCE is a drug with an active ingredient that has not previously received regulatory approval. For modifications or new uses of a previously approved NCE, the Hatch-Waxman Act also provides three years data exclusivity.²⁸⁹

In order for a generic drug company to obtain regulatory approval it only need show that its drug is “bioequivalent” to the innovator’s drug, the latter referred to as the Reference Listed Drug (RLD), without the generic company having to provide data from human clinical trials.²⁹⁰ Bioequivalent drugs are provided an ‘A’ therapeutic equivalence code, which means they may be automatically substituted for the RLD under state reimbursement schemes or substitution laws.²⁹¹ As will be discussed in Chapter Three, automatic substitution of a branded drug with a cheaper generic is also relevant to the lack of private incentives to develop new uses for generic drugs.

²⁸⁴ Public Health Service Act, s 351.

²⁸⁵ 21 USC § 355(b)(1)(A).

²⁸⁶ Federal Food Drug and Cosmetics Act, s 505(j)(2).

²⁸⁷ 21 USC § 355(c)(3)(E). See also AB Mehl “The Hatch-Waxman Act and Market Exclusivity for Generic Drug Manufacturers: an entitlement or an incentive?” (2006) 81 Chicago-Kent Law Review 649 at 653-654.

²⁸⁸ Federal Food Drug and Cosmetics Act, ss 505(c)(3)(D)(ii) and (j)(5)(D)(ii); 21 USC § 355(c)(3)(D)(ii) and (j)(5)(D)(ii).

²⁸⁹ 21 CFR § 314.108(a). Allowable modifications include new or amended formulations, indications, dosing regimens, patient populations, salts, or other label changes.

²⁹⁰ 21 CFR § 320.1(e). In particular, bioequivalence of a generic drug must be between 80% and 125% of the innovator’s reference listed drug, having regard to its pharmacokinetic properties. See *Approved Drug Products with Therapeutic Equivalence Evaluations* (“Orange Book”) (34th ed, Food and Drug Administration, 16 May 2014) at Preface.

²⁹¹ See HG Grabowski and JM Vernon “Substitution Laws and Innovation in the Pharmaceutical Industry” (1979) *Law and Contemporary Problems* 43 at 49.

Notably, these data exclusivity provisions do not prevent a generic drug company from generating their own clinical data to file an NDA or ANDA during the exclusivity period. In practice, however, a generic drug company is unlikely to do this because the expense would negate their competitive advantage, although they may be willing to do so for a highly lucrative drug.

Generic drug companies are also prevented from filing an ANDA until expiry of any patents which may cover the RLD. These patents along with their relevant RLDs are listed in an FDA publication: the Approved Drug Products with Therapeutic Equivalence Evaluations ('Orange Book').²⁹² Therefore, in the United States, approval of generic small molecule drugs is linked to patent expiry.²⁹³

In particular, a generic drug company that wishes to apply for an ANDA before patent expiry can file a so-called 'paragraph IV' certification within 4 years of the NDA, alleging that the generic will not infringe any valid patent covering the RLD.²⁹⁴ If the innovator's patent is invalidated, the generic company will gain a 180-day period of exclusivity,²⁹⁵ which provides a strong incentive for generic companies to challenge an innovator's weak patents. However, provided that the patent owner files a patent infringement lawsuit within 45 days of the generic's paragraph IV certification, the approval of the ANDA will be delayed for 30 months, unless the Court determines that the patent is either invalid or not infringed at an earlier date. This 30-month delay of ANDA approval means that the innovator company gets an effective exclusivity period of up to 7.5 years.²⁹⁶ Notably, until reforms were implemented in 2003 which abolished the practice, innovator companies could list new patents on the Orange Book which they alleged covered their drugs in order to obtain multiple 30-month delays.²⁹⁷

Another important point is that where an innovator company only has patent protection covering a second use or indication of a medicine, and the patent over the original use of the drug has expired, a generic company may file a so-called 'section viii' statement under the ANDA procedure to approve a 'skinny labeled' version of

²⁹² 21 CFR § 314.53.

²⁹³ These are referred to as 'patent linkage' provisions.

²⁹⁴ 21 USC § 355(j)(2).

²⁹⁵ Federal Food Drug and Cosmetics Act § 505(j)(5)(B)(iv).

²⁹⁶ 21 USC § 355(j)(5)(B)(iii).

²⁹⁷ See 21 USC § 355 (j)(2) and (5), as amended pursuant to the Medicare Prescription Drug Improvement and Modernisation Act 2003. See also *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (Federal Trade Commission, 2002) at 40. This practice is referred to as 'linkage evergreening'. See TA Faunce and J Lexchin "'Linkage' pharmaceutical evergreening in Canada and Australia" (2007) 4(1) *Australia and New Zealand Health Policy* 8 at 8.

the generic drug that ‘carves out’ the protected use.²⁹⁸ However, this does not allow the generic company to benefit from the 180-day period of exclusivity. It will be argued in Chapter Three that such ‘skinny labeling’ also reduces incentives for finding new uses for drugs once initial patent protection has expired, particularly as the FDA does not restrict ‘off-label’ prescription by doctors,²⁹⁹ who are also unlikely to be sued for infringement by the innovator.

(b) Biologic License Application (BLA)

Obtaining regulatory approval for a biologic drug requires a BLA, which is regulated by section 351(k) of the Public Health Service Act. As with the NDA approval process, a BLA also requires submission of full clinical trial data demonstrating safety and efficacy of the biologic drug for treating a particular disease.³⁰⁰

There was no generic approval process for biologics in the United States until the enactment of the Biologics Price Competition and Innovation Act of 2009 (‘BPCI’) as part of Title VII of the Patient Protection and Affordable Care Act.³⁰¹ The BPCI created an abbreviated pathway for generic approval of ‘biosimilar’ generics,³⁰² which allows at least partial reliance on the safety and efficacy data of the innovator’s “reference brand product” after the expiry of a 12-year period of data exclusivity for the innovator.³⁰³

Unlike small molecule drugs, due to the inherent variability of biologics, the establishment of ‘biosimilarity’ requires evidence from clinical studies.³⁰⁴ Accordingly, biosimilar approval is much more expensive than small molecule generic drugs, which reduces the likelihood of biosimilar competition upon patent

²⁹⁸ 21 USC § 355(j)(2)(A)(viii); 21 CFR § 314.94(a)(12)(iii)(A).

²⁹⁹ *Federal Trade Commission v Simeon Mgmt Corp* 391 F Supp 697 (ND Cal 1975) at 706-707.

³⁰⁰ 21 CFR § 601.2(a).

³⁰¹ Patient Protection and Affordable Care Act, Title VII.

³⁰² Section 351 of the Public Health Service Act defines a ‘biosimilar’ or ‘biosimilarity’ to mean that ‘the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,’ and that ‘there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.’

³⁰³ 42 USC § 262(k)(7)(A).

³⁰⁴ 42 USC § 262(k)(2)(A)(i).

expiry.³⁰⁵ Notably, at the date of writing, no biosimilars have been approved in the United States under the BPCI.³⁰⁶

If a biosimilar can be deemed ‘interchangeable’, this means that it can be substituted with the innovator’s biologic drug without any change in clinical result.³⁰⁷ This is a higher standard than ‘biosimilarity’, therefore, interchangeable biologics are granted one year of exclusivity or an increased exclusivity period (18 months or 42 months) if the applicant is sued for patent infringement and the action is dismissed.³⁰⁸

Under the BPCI provisions, a drug company may file an application to market a biosimilar version of the innovator’s biologic within four years of regulatory approval.³⁰⁹ This triggers a formal negotiation and dispute resolution process which is mandated before initiating patent litigation.³¹⁰ The aim of these provisions is to clarify and resolve any patent related disputes by the time the 12-years data exclusivity period has expired.³¹¹

The BPCI also includes an ‘anti-evergreening’ provision which provides that an additional 12-years of data exclusivity is not available for a “new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength”, or new structural modifications that do not “result in a change in safety, purity, or potency”.³¹² This helps reduce opportunities for gaming by innovators, who may otherwise obtain a new 12-year period of data protection by making minor modifications to their biologic drug.³¹³

³⁰⁵ In particular, seeking regulatory approval for a generic small molecule drugs costs approximately USD 2 million while biosimilar approval is estimated to cost USD 100-150 million due to the need for specialised equipment: see “Big generic pharma” *The Economist* (online ed, New York, 28 July 2005); L Burger “Battle over Biosimilar Drugs is Only for the Brave” (2 July 2010) Reuters <www.uk.reuters.com>; Roin, above n 100 at 511.

³⁰⁶ However, Novartis recently filed the first Biologic License Application at the FDA: see D Garde “FDA opens the door for a Novartis biosimilar of Amgen’s Neupogen” (24 July 2014) Fierce Biotech <www.fiercebiotech.com>. Further, sixteen biosimilars have been approved in Europe and four biologics have been approved in the United States under the previous ‘generic’ pathway: see EA Blackstone and JP Fuhr “Innovation and Competition: Will Biosimilars Succeed?” (2012) 9(1) *Biotechnology Healthcare* 24 at 24.

³⁰⁷ 42 USC § 262(k)(4).

³⁰⁸ 42 USC § 262(k)(6).

³⁰⁹ 42 USC § 262(k)(7)(B).

³¹⁰ 42 USC § 262(l).

³¹¹ H Grabowski, G Long and R Mortimer “Implementation of the Biosimilar Pathway: Economic and Policy Issues” (2011) 41 *Seton Hall Law Review* 511 at 554.

³¹² 42 USC § 262(k)(7)(C).

³¹³ As will be discussed in Chapter Five, it is important that optimal incentive mechanisms reduce such opportunities for gaming.

H Conclusion

As has been demonstrated in this chapter, there are significant hurdles to obtain patent protection and regulatory approval for a new medicine. New Zealand and the United States provide for periods of data exclusivity to incentivise drug companies to overcome these regulatory hurdles, however, data exclusivity is weaker than patent protection as it does not prevent competitors from conducting their own clinical trials and it is shorter in length, particularly for small molecule drugs.

In the next chapter it will be argued that the pharmaceutical industry relies primarily on patent protection to recover the high costs of drug development, and will discuss the significant problems with such reliance.

III The Problem with the Pharmaceutical Industry's Reliance on Patents

A Introduction

Chapter Three will analyse whether reliance on the patent system by the pharmaceutical industry, as currently designed, causes a lack of private incentives to develop certain categories of socially valuable medical therapies. First, it will be argued that the high costs and high risks of drug development cause pharmaceutical companies to screen out ‘unpatentable therapies’ with insufficient patent protection. Second, the impact of five ‘unpatentability factors’ on the risk of creating an unpatentable therapy will be considered, namely: (1) lack of novelty, (2) lack of inventive step, (3) lack of utility/sufficiency, (4) insufficient patent length, and (5) unpatentability under law. Third, it will be considered whether so-called ‘patent evergreening’ strategies can be used successfully by pharmaceutical companies to ‘regain’ patentability over an unpatentable therapy. Fourth, the chapter will provide evidence of ‘unmonopolisable therapies’, which lack private incentives for development because market exclusivity cannot be practically enforced. Fifth, a catch-all category of ‘unprofitable therapies’ that lack a profitable market will be discussed. Finally, the chapter will outline several other problems with the current patent system in the context of the pharmaceutical industry.

B Deadly Gaps in the Patent System

It is widely-recognised that the patent system plays an essential role in motivating drug development.¹ Accordingly, the pharmaceutical industry has been described as the ‘poster child’ for a strong patent system,² with each new small molecule and

¹ See PW Grubb and PR Thomsen *Patents for Chemicals, Pharmaceuticals, and Biotechnology: Fundamentals of Global Law* (5th ed, Oxford University Press, New York, 2010) at 426; BN Roin “Unpatentable drugs and the standards of patentability” (2009) 87 Tex L Rev 503 at 504; RS Eisenberg “The Problem of New Uses” (2005) 5 Yale J Health Policy L & Ethics 717 at 721; H Grabowski “Patents, Innovation and Access to New Pharmaceuticals” (2002) 5(4) J Int Economic Law 849 at 850.

² LL Ouellette “How Many Patents Does It Take To Make a Drug? Follow-On Pharmaceutical Patents and University Licensing” (2010) 17 Mich Telecomm Tech L Rev 299 at 300 citing WM Landes and RA Posner *The Economic Structure of Intellectual Property Law* (Harvard University Press, Cambridge (Mass), 2009) at 316; S Basheer “The Invention of an Investment Incentive for Pharmaceutical Innovation” (2012) 15(5-6) The Journal of World Intellectual Property 305 at 305; J Bessen and MJ Meurer *Patent failure: How judges, bureaucrats, and lawyers put innovators at risk* (Princeton University Press, Princeton, 2008) at 27; compare generally, M Boldrin and DK Levine *Against Intellectual Monopoly* (Cambridge University Press, Cambridge, 2008) at Chapter 9.

biologic drug brought to market protected by several patents on average.³ Pharmaceutical companies rely on patents so they can recover their development costs. However, the consequences of this may be severe; pharmaceutical companies will screen out medicines which they consider to have insufficient patent protection or commercial viability irrespective of whether they might have been lifesaving treatments or even cures.

The next sections will discuss how the high costs and risks of drug development combined with the low marginal costs of production encourage the screening of ‘unpatentable therapies’ by pharmaceutical companies.

1 High Costs of Drug Development

Various studies have supported the fact that the costs of developing new medicines are extremely high. One of the most oft-cited is a 2003 study by DiMasi, Hansen and Grabowski,⁴ which estimated the cost of developing a new small molecule drug⁵ at USD 802 million. A subsequent 2007 study by DiMasi and Grabowski⁶ estimated costs of USD 1.241 billion to develop a new biologic drug⁷ versus USD 1.318 billion for a new small molecule drug. Notably, however, approximately half of these estimates relate to costs of obtaining long-term finance⁸ over a nine to 12 year average development time.⁹ For example, excluding the costs of obtaining long-term finance provides an out-of-pocket expense estimate of USD 559 million per biologic drug and USD 672 million per small molecule drug.¹⁰ These estimates also factor in the cost of failed drugs.¹¹ The majority of development costs are spent on clinical trials,¹² rather than pre-clinical studies.¹³

³ Ouellette, above, at 300. A notable exception is paclitaxel (brand name Taxol), an anti-cancer drug developed mostly from public funds without patent protection. However, the innovator company relied on 5-year data exclusivity in the FDA, subsequently filed patents, and controversial settlements with generic drug companies in order to prevent competition: see K Garber “Battle Over Generic Taxol Concludes, But Controversy Continues” (2002) 94(5) J Natl Cancer Inst 324 at 324.

⁴ JA DiMasi, RW Hansen and HG Grabowski “The price of innovation: new estimates of drug development costs” (2003) 22(2) Journal of Health Economics 151 at 151.

⁵ As discussed in Chapter Two under Regulatory Environment, small molecule drugs are ‘standard’ pharmaceutical drugs, which are chemically synthesised.

⁶ JA DiMasi, HG Grabowski “The Cost of Biopharmaceutical R&D: Is Biotech Different?” (2007) 28 Manage Decis Econ 469 at 475.

⁷ As discussed in Chapter Two under Regulatory Environment, biologic drugs are newer drugs based on proteins, which manufactured from genetically modified cells using recombinant DNA technology.

⁸ This is referred to as the ‘cost-of-capital’, which is the opportunity cost of not investing in other areas for the period that a medicine is in development. DiMasi used a relatively conservative ‘cost of capital’ figure of 11 per cent: see Dimasi, Hansen and Grabowski, above n 4, at 164.

⁹ M Dickson and JP Gagnon “The cost of new drug discovery and development” (2009) 4(22) Discovery Medicine 172 at 172.

¹⁰ At 469.

¹¹ DiMasi and Grabowski, above n 6, at 470.

Other commentators have supported these high cost estimates,¹⁴ which are often cited by the pharmaceutical industry to justify the multi-billion dollar revenues earned from so-called ‘blockbuster’ drugs.¹⁵ However, the estimates have also been strongly criticised by various commentators, mainly because of alleged conflicts of interest due to the studies being partially funded by the industry and because pharmaceutical companies have not released their actual development costs for public auditing.¹⁶ For example, an opposing study by Light and Warburton estimated expenditure at a median cost of USD 43 million to develop a new drug.¹⁷ It is arguable, however, that the Light estimates are misleading because they do not take into account the cost of finance and failed drugs. Despite valid points made on both sides, in the absence of publicly audited data on drug development expenditure, it is unlikely that any study can be relied on as a “gold standard”.¹⁸

Nevertheless, determining the precise development cost per new drug is not required to support the central argument of this thesis. As long as an innovator’s initial development costs are significantly greater than the ‘reverse engineering’ costs of achieving regulatory approval for a generic small molecule drug¹⁹ or biosimilar biologic,²⁰ it will be uneconomic for an innovator to develop new medical therapies, without means of recovering their costs using a patent or some alternative incentive mechanism.

¹² Clinical studies refer to the Phase I-III human studies required for regulatory approval of a new medicine, as discussed in Chapter Two under Regulatory Environment.

¹³ See DiMasi and Grabowski, above n 6 at 476, Figures 3 and 4. Pre-clinical studies are studies performed before clinical trials, such as animal testing and ‘high-throughput screening’ that are used to determine which molecules are the best drug candidates and optimise them.

¹⁴ SM Paul and others “How to improve R&D productivity: the pharmaceutical industry’s grand challenge” (2010) 9 *Nature Reviews Drug Discovery* 203; see also CP Adams and VV Brantner “Estimating The Cost Of New Drug Development: Is It Really \$802 Million?” (2006) 25(2) *Health Affairs* 420; M Herper “The Truly Staggering Cost Of Inventing New Drugs” *Forbes* (online ed, 10 February 2012).

¹⁵ A ‘blockbuster’ drug is a term used by the pharmaceutical industry to refer to a drug that earns more than USD 1 billion per annum in sales.

¹⁶ See DW Light and RWarburton “Demythologizing the high costs of pharmaceutical research” (2011) 6(1) *BioSocieties* 34 at 34; *Rx R&D Myths: The Case Against the Drug Industry’s R&D ‘Scare Card’* (Public Citizen, Washington DC, 2001); M Goozner *The \$800 Million Pill: The Truth Behind the Cost of New Drugs* (University of California Press, Berkeley, 2004); R Collier “Drug development cost estimates hard to swallow” (2009) 180(3) *CMAJ* 279;

¹⁷ Light and Warburton, at 47.

¹⁸ S Morgan and others “The cost of drug development: A systematic review” (2011) 100(1) *Health Policy* 4 at 4.

¹⁹ As noted in Chapter Two, achieving regulatory approval for a generic drug is estimated at a few million dollars: see “Big generic pharma” *The Economist* (online ed, New York, July 28, 2005); see also Roin, above n 1, at 511.

²⁰ As noted in Chapter Two, it can cost between USD 100-150 million to develop a ‘biosimilar’ drug: see L Burger “Battle over Biosimilar Drugs is Only for the Brave” (2 July 2010) Reuters <www.uk.reuters.com>.

It is also notable that due to increasing costs under the current system, the pharmaceutical industry is facing a productivity crisis. A report by the United States Government Accountability Office (GAO) highlighted an overall decline of FDA submissions for new drugs since 1995, despite the fact that inflation-adjusted research and development (R&D) costs have increased by 147 per cent between 1993 and 2004.²¹ Another study by Scannell estimated that the number of new drugs developed per USD 1 billion spent on R&D is halving every 9 years.²² Various commentators have recognised this decline in productivity as a threat to the sustainability of the pharmaceutical industry as a whole.²³

2 *High Risks of Drug Development*

As discussed above, the estimated costs of developing a new drug take into account the drugs that failed to achieve regulatory approval. It is practically impossible to predict whether a new drug will be safe and effective in advance of expensive clinical trials. Therefore, regulatory hurdles, while arguably serving to protect the public from potentially dangerous drugs, significantly increase the financial risks of undertaking drug development.

According to a 2010 study by DiMasi, success rates for drugs which entered clinical trials between 1993 and 2009 were at 13 per cent for small molecule drug versus 32 per cent for biologics, with a success rate of 19 per cent overall.²⁴ Amongst disease types, cancer drugs have the lowest chance of approval at 11 per cent.²⁵

²¹ *New Drug Development: Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts* (Government Accountability Office, November 2006) at 4.

²² See JW Scannell and others “Diagnosing the decline in pharmaceutical R&D efficiency” (2012) 11(3) *Nature Reviews Drug Discovery* 191 at 191, Figure 1. This steady decline in productivity of pharmaceutical R&D has been coined ‘Eroom’s Law’, which is an anadrome of the more familiar ‘Moore’s Law’, the latter being the observation that the processing speed of computer circuits is doubling approximately every two years.

²³ Paul and others, above n 14, at 203; F Pammolli, L Magazzini and M Riccaboni “The productivity crisis in pharmaceutical R&D” (2011) 10(6) *Nature Reviews Drug Discovery* 428 at 428; Grubb and Thomsen, above n 1, at 425; but see EF Schmid and DA Smith “Keynote review: Is declining innovation in the pharmaceutical industry a myth?” (2005) 10(15) *Drug Discov Today* 1031 at 1031.

²⁴ JA DiMasi and others “Trends in risks associated with new drug development: success rates for investigational drugs” (2010) 87(3) *Clin Pharmacol Ther* 272 at 272.

²⁵ M Hay and others “BIO / BioMedTracker Clinical Trial Success Rates Study” (paper presented to BIO CEO & Investor Conference, New York, 15 February 2011) at 7.

Figure 1: R&D model showing costs (in millions) to successfully develop and launch a single new molecular entity at each phase in pre-clinical and clinical development²⁶

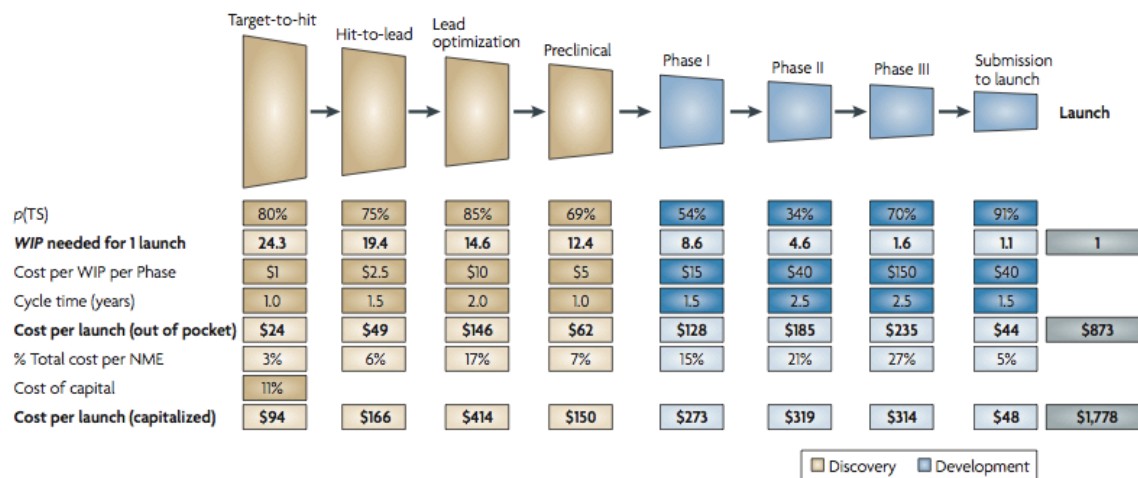


Figure 1 is a useful illustration of the ‘attrition rate’²⁷ and expenditure requirements at each stage of drug development, from pre-clinical (brown) to Phase I-III clinical trials (blue). According to Paul and others, of approximately 24 drug candidates²⁸ that generate a ‘hit’ on the drug target in the pre-clinical phase,²⁹ just over 8 are tested in humans at Phase I,³⁰ and only one passes Phase III to achieve regulatory approval. The most difficult hurdle for drug approvals is Phase II which has only a 34 per cent chance of success, compared to 54 per cent for Phase I and 70 per cent for Phase III.³¹ Notably, while Phase III trials have the greatest chance of success, the financial consequences of failure at this stage are the most severe, often causing hundreds of millions of dollars in losses.³² Many clinical trials are also abandoned due to “strategic reasons”, unrelated to a drug’s safety or efficacy.³³

In addition to the risk of failure, there is a significant risk that the drug will not achieve commercial success after regulatory approval. For example, according to a 2002 study by Grabowski, Vernon, and DiMasi, only a third of drugs launched

²⁶ Paul and others, above n 14, Figure 2. Costs are in USD.

²⁷ See Figure 1: the ‘attrition rate’ is expressed as a percentage next to the symbol p(TS), which shows the percentage chance that a particular drug candidate will pass into the next development phase.

²⁸ Referred to as ‘Work-in-process’ or ‘WIP’ in Figure 1 above.

²⁹ In the context of drug development, a ‘hit’ refers to a compound that increases or decreases the activity of a therapeutically relevant protein target.

³⁰ See Paul, above n 14, Figure 2.

³¹ At Figure 2. Other studies have shown even lower rates of success for Phase II trials: see J Arrowsmith “Trial watch: Phase II failures: 2008-2010” (2011) 10 Nat Rev Drug Discov 328 at 328, showing that Phase II success rates dropped from 28 per cent in 2006-2007 to 18 per cent in 2008-2009.

³² For example, Pfizer’s cholesterol drug torcetrapib failed in Phase III after USD 800 million was spent on development: see M Martino, LJ Hollis and E Teichert “Torcetrapib - Pharma's Biggest Flops” (18 October 2010) Fierce Pharma <www.fiercepharma.com>.

³³ Arrowsmith, above n 31, at 328. As will be discussed below, this may be indirect evidence of late-stage patentability screening.

between 1990 and 1994 matched or exceeded their USD 500 million average R&D costs.³⁴ Notably, however, the highest earning ‘blockbuster’ drugs earned over 5 times the R&D cost on average.³⁵ This finding suggests that the pharmaceutical industry relies on ‘blockbuster’ drugs³⁶ to compensate for failed or commercially unsuccessful drugs.

Summary

The high costs and risks of drug development combined with the relatively low marginal costs of production means that patents - or some form of exclusivity or alternative incentive mechanisms - are the *sine qua non* for incentivising pharmaceutical R&D.³⁷ As a result, it is arguable that pharmaceutical companies will screen out potentially socially valuable therapies with insufficient patent protection irrespective of medical value or social need.

3 *‘Patentability screening’ of socially valuable therapies*

The ability to guarantee market exclusivity using patents is less critical in industries outside the pharmaceutical industry. For example, other industries are not required to conduct expensive clinical trials before market entry.³⁸ Other industries also tend to rely on a ‘first-mover’ advantage, because of the ease in which competitors can design around patents.³⁹

By contrast, as discussed in Chapter Two, innovators in the pharmaceutical industry rely on monopoly rights to recover the costs of obtaining regulatory approval, with generic competitors being prevented from entering the market until the patent over the drug is invalidated or expires, subject to any applicable ‘regulatory exclusivity’. Consequently, innovators will routinely screen medicines for patentability at all stages of drug development. For example, according to industry sources, such ‘patentability screening’ occurs at least twice during pre-clinical trials,

³⁴ H Grabowski, J Vernon and J DiMasi “Returns on Research and Development for 1990s New Drug Introductions” (2002) 20 *Pharmacoeconomics* 11 at 17-18.

³⁵ At 17-18.

³⁶ See above n 15.

³⁷ AJ Devlin “Systemic Bias in Patent Law” (2012) 61 *DePaul Law Review* 57 at 57, 59.

³⁸ For example, a new software or electronic product can be put on the market without having to spend hundreds of millions of dollars to obtain regulatory approval.

³⁹ MB Lieberman and DB Montgomery “First-mover advantages” (1988) 9 *Strategic Management Journal* 41 at 43.

and once again as a “gate-keeping event” before significant funds are committed towards Phase I clinical trials.⁴⁰

Roin summarised this previously uncharacterised phenomenon in his 2009 article, “Unpatentable Drugs and the Standards of Patentability”.⁴¹

Despite the seemingly great magnitude of this injury, [the screening of socially valuable unpatentable drugs] has gone largely unnoticed by the public because of the early stage at which most un-patentable drugs are screened out of development. Pharmaceutical companies do not announce the drug candidates that they choose not to develop, including the ones dropped on account of a prior disclosure that undermined their patent protection. While industry insiders acknowledge that many such drugs exist, the decisions to discard them are made behind closed doors.

Unfortunately, the high level of secrecy in the industry has made it difficult or impossible to empirically verify these claims.⁴² Nevertheless, even if the proportion of therapies screened or abandoned due to patentability issues is relatively low, it represents a lost opportunity, given the above-mentioned decline in productivity levels for pharmaceutical R&D,⁴³ and the fact the therapeutic value of a drug is mostly irrelevant to patentability.⁴⁴

Given that up to 90 per cent of clinical trials are funded by the for-profit pharmaceutical industry,⁴⁵ it is arguable that an inefficient private funding bias exists

⁴⁰ Roin, above n 1, at 546-547. Patentability screening would typically involve a ‘prior art search’ in the academic literature, the Chemical Abstracts Registry, and previous patent applications by a pharmaceutical company’s in-house legal counsel or external patent attorney. A ‘freedom-to-operate’ search will also be performed to determine whether a drug candidate is subject to an in-force patent held by a competitor. In both circumstances, an unfavourable report would mean that a drug candidate would be likely to be screened irrespective of potential or actual therapeutic efficacy.

⁴¹ At 552.

⁴² The author attempted to obtain empirical data on this issue by sending out over 200 targeted emails to researchers, patent attorneys, and pharmaceutical industry executives requesting participation in an anonymous survey on the level of patentability screening which occurs, however, unfortunately, only one response was received. The author had also made a separate online appeal for participants, to no avail: see S Barazza “Dormant and unmonopolisable therapies: can you help: Part One/Part Two” (6 June 2013) The IPKat <www.ipkitten.blogspot.com>. Human Ethics Committee approval and related documentation has been attached to this thesis as Appendix One.

⁴³ See BN Roin “Solving the Problem of New Uses” (1 October 2013) Social Science Research Network <www.ssrn.com> at 50.

⁴⁴ For example, as discussed in Chapter Two under Criteria for Patentability of Medical Therapies, only the utility criterion requires some nominal evidence of potential clinical benefit, whereas the potential or actual clinical benefit of a drug is not relevant to the tests for novelty or inventive step.

⁴⁵ O Vragovic “Developing Budgets for Research Projects with a Focus on Phase III Clinical Trials” (seminar presented at OCR Seminar Series Presentations: Boston University Medical Campus, Boston, 17 June 2009) at 5. For example, the largest public funders of clinical research in the United States (National Institutes of Health, Department of Defense, and the Department of Veterans Affairs) have an annual spend of approximately USD 2.9 billion on clinical trials versus USD 26 billion by the

towards ‘highly excludable’ therapies where a monopoly price can be enforced using patents, and an underfunding of other categories of therapies that could be of significantly greater social value.⁴⁶

Summary

Due to the high costs and risks of drug development, it is alleged that the pharmaceutical industry will regularly screen promising medical therapies due to insufficient patent protection. Evidence of this ‘patentability screening’ is difficult to observe due to the high level of secrecy in the industry and the fact that such therapies are typically screened at the pre-clinical stage of development. The consequences of this screening on public health could be severe, as will be demonstrated further below.

The next section will analyse such ‘unpatentable therapies’, and how they are created as a result of the presence of five ‘unpatentability factors,’ namely: (1) lack of novelty, (2) lack of inventive step, (3) lack of utility/sufficiency, (4) insufficient patent length, and (5) unpatentability under law.

C The impact of ‘Unpatentability Factors’ on the Problem of ‘Unpatentable Therapies’

In this section, it will be argued that due to the impact of certain ‘unpatentability factors’, otherwise viable medicines can become ‘unpatentable therapies’ that lack private incentives for development. The following analysis will focus on examples from the United States, because entry into the United States market is essential for the overall commercial viability of a medicine.⁴⁷ Accordingly, the presence of unpatentability factors in the United States will significantly increase the likelihood that a medicine will be screened during development, regardless of where an innovator company is located.

private industry. See also T Bodenheimer “Uneasy alliance: Clinical investigators and the pharmaceutical industry” (2000) 342 *New England Journal of Medicine* 1539 at 1539 which quotes the figure at 70 per cent private funding of clinical trials; See also Roin, above n 43, at 25.

⁴⁶ A Kapczynski and T Syed “The Continuum of Excludability and the Limits of Patents” (2013) 122(7) *Yale Law Journal* 1900 at 1942.

⁴⁷ T Bartfai and GV Lees *Drug Discovery from Bedside to Wall Street* (Elsevier, Burlington, 2006) at 138: ‘...unless the American marketing arm of a multinational company says: ‘It will be marketed in the States,’ there is no real point even to make the drug.’

1 *Lack of novelty*

As discussed in Chapter Two, in most cases, the mere disclosure of a potential medicine's chemical formula prevents a 'composition of matter' claim over that medicine. It may be possible to patent a narrower 'species', derivative version, or new uses of a known chemical⁴⁸ in order to distinguish a claim from the prior art. However, if claims are so narrow that they can be easily 'designed around' by generic drug companies, the patent might as well be non-existent. Further, disclosure of a 'species' will anticipate any subsequent attempt to patent a broader 'genus' class of drugs.⁴⁹ Some common causes of a lack of novelty now will be discussed.

(a) Prior publications by the pharmaceutical industry

The major cause of a lack of novelty are previously filed broad patent applications by the innovators themselves. For example, in the case *In re Metoprolol Succinate Patent Litigation*,⁵⁰ the Federal Circuit invalidated a patent claiming a hypertension drug in light of an earlier patent application filed by the innovator which claimed nine drug formulations with two 'slow release' layers.⁵¹ While only one of the formulations in the prior art included the subsequently claimed chemical formula, it was enough to invalidate the claim that could have prevented generic competition.⁵²

In other cases, obscure references in patent applications can destroy patentability when discovered many years later. Roin used the example of Ultracet, a combination of tramadol and paracetamol – the latter known as acetaminophen in the United States - which was launched in 2001 by Othro-McNeil Pharmaceutical Inc.⁵³ Othro-McNeil had initially obtained a broad patent over the drug combination.⁵⁴ However, a few years after launch, it was discovered that a patent specification filed in 1972 disclosed the drug combination in a ratio of 1:10, although the 1972 specification did not state that the combination would work synergistically for pain relief.⁵⁵ It is likely the prior art specification was not discovered during patentability screening or examination at the USPTO because it used an "obscure synonym" for

⁴⁸ For example, as discussed in Chapter Two under Judicial Inroads into Exclusions of Methods of Medical Treatment, the United States allows a claim over the second use of a known drug. It is also possible to use 'Swiss' claim language in New Zealand.

⁴⁹ *In re Slayter* 276 F 2d 408 (CCPA 1960) at 411. Broad claims may be commercially necessary to prevent the dilution of monopoly profits from 'me-too' drugs which act on a similar drug target. The problem of 'me-too' drugs will be discussed below.

⁵⁰ *In re Metoprolol Succinate Patent Litigation* 494 F 3d 1011 (Fed Cir 2007).

⁵¹ US Patent No 4,780,318.

⁵² *In re Metoprolol Succinate Patent Litigation* at 1020-1021; see Roin 2009 at 523, n 102.

⁵³ Roin, above n 1, at 521.

⁵⁴ US Patent No 5,336,691.

⁵⁵ US Patent No 3,652,589.

acetaminophen: “p-acetamino phenal”.⁵⁶ Ortho-McNeil ‘reissued’ their patent,⁵⁷ claiming a narrower drug combination in a ratio of “about 1:5”, in order to distinguish it from the ratio of 1:10 disclosed in the obscure prior art reference.⁵⁸ However, in *Ortho-McNeil Pharm, Inc v Caraco Pharm Labs, Ltd*,⁵⁹ the Federal Circuit held that the reissued patent could not block a generic drug launched by Caraco Pharmaceuticals which contained the drug combination in a ratio of 1:8.67.⁶⁰ By contrast, in *Ortho-McNeil Pharmaceutical, Inc v Kali Laboratories, Inc*,⁶¹ the reissued patent claims were at least partially effective in preventing generic competition, blocking a generic drug launched by Kali Laboratories, which had a drug combination ratio of 1:6.41.⁶²

Roin’s Ultracet example was critiqued by Outterson, who argued the prior publication did not prevent the drug from getting to market.⁶³ However, Ultracet may be the exception to the rule; a rare example of a prior art reference that escaped detection by Ortho-McNeil’s patent attorneys and the USPTO examiner. It is also difficult to determine the public harm that has resulted from the screening of medicines due to prior art disclosures, because that would require making an inference based on medicines which do not exist - or only exist on a laboratory bench. While unlikely that prior art would prevent all claims from issuing, a very narrow claim that avoids the prior art could have the same value as no patent at all if it would not prevent competition – as noted above. Ultimately, the decision by pharmaceutical executives whether to launch a drug requires a consideration of multiple uncertain factors, such as: the scope of enforceable claims, the likelihood of generic competitors being able to ‘design around’ those claims, and the drug’s commercial potential having regard to other drugs on the market or in development. Unfortunately, there is no public record of these commercially sensitive decisions, which means that any evidence of the extent of patentability screening would have to be indirect.

Nevertheless, USPTO tribunal decisions of the Board of Patent Appeals and Interferences (BPAI)⁶⁴ provide some evidence of patent claims invalidated at an early stage of development. For example, in *Ex parte Feldmann*⁶⁵, the inventor claimed a

⁵⁶ Roin, above n 1, at 521.

⁵⁷ US Reissue Patent No RE39221E.

⁵⁸ Above, claim 6.

⁵⁹ *Ortho-McNeil Pharm, Inc v Caraco Pharm Labs, Ltd* 476 F 3d 1321(Fed Cir 2007).

⁶⁰ At 1328–1329.

⁶¹ *Ortho-McNeil Pharmaceutical, Inc v Kali Laboratories, Inc* 482 F Supp 2d 478 (D NJ 2007).

⁶² At 497 per Lifland DJ. In particular, the ratio of ‘about 1:5’ was construed to encompass ‘ratios up to and including 1:7.1 and ratios down to and including 1:3.6.’

⁶³ K Outterson “Death from the Public Domain?” (2009) 87 Texas Law Review 45 at 48.

⁶⁴ The BPAI has now changed its name to Patent Trial and Appeal Board (PTAB) as part of reforms under the America Invents Act of 2011.

⁶⁵ *Ex parte Feldmann* No 2002-0253 (BPAI Mar 21, 2003).

method of treating rheumatoid arthritis using a combination of a tumour necrosis factor antagonist and cyclosporin, an immunosuppressant.⁶⁶ The BPAI held that this was anticipated by a prior patent application,⁶⁷ which disclosed the claimed compounds among a number of drug combinations.⁶⁸ In particular, the claims were held invalid as they “read on” disclosures in the prior patent.⁶⁹

Another source of prior art is that innovators may deliberately publish their research findings in order to prevent competitors from obtaining patents where they do not wish to pursue research. These are referred to as “defensive publications”.⁷⁰

(b) Prior publications in academia

Academic publications by medical researchers are another major source of prior art. For example, in *SmithKline Beecham Corp v Copley Pharmaceutical, Inc*,⁷¹ the Federal Circuit had invalidated patent claims over the drug nabumetone pursuant to a ‘paragraph iv’ challenge by a generic drug company, Copley Pharmaceutical.⁷² The prior art was a 1973 research publication, Chatterjea & Prasad, which disclosed the compound and a method for its synthesis in a liquid form, but did not disclose the solid form of the drug or its medicinal use.⁷³

There is other evidence that academic publications can contribute to ‘unpatentability factors’ that may reduce levels of private investment.⁷⁴ A survey of universities with large medical-research programs found that 82 per cent could not secure a patent in the previous year and 71 per cent were unable to find a commercial partner because “research outcomes were already published”.⁷⁵ Lack of novelty caused by academic publications may have a dire effect on medical progress because of the fundamental contribution of academic research to the development of

⁶⁶ At 2-4. In medicinal chemistry, an antagonist is a compound which inhibits the activity of the drug target protein. This can be contrasted with an agonist compound, which increases the activity of the drug target.

⁶⁷ US Patent No 5,672,347.

⁶⁸ At 6.

⁶⁹ At 7. The concept of claims ‘reading on’ the prior art is equivalent to the *General Tyre* ‘reverse infringement’ test which applies in New Zealand.

⁷⁰ See G Parchomovsky “Publish or perish” (2000) Michigan Law Review 926 at 928-929.

⁷¹ *SmithKline Beecham Corp v Copley Pharmaceutical, Inc* No 01-1611 (Fed Cir Aug 15 2002).

⁷² As discussed in Chapter Two under Regulatory Environment, a ‘paragraph IV’ challenge is filed by a generic drug company alleging that the innovator’s patent claims over their drug are invalid.

⁷³ *SmithKline Beecham Corp v Copley Pharmaceutical, Inc*, at 1-2.

⁷⁴ Roin, above n 1, at 527.

⁷⁵ At at 528, n 125 citing EG Campbell and E Bendavid “Data-sharing and data-withholding in genetics and the life sciences: Results of a national survey of technology transfer officers” (2002) 6 J Health Care L & Policy 241.

medicines.⁷⁶ For example, 72 of 478 drugs approved in the United States between 1988 and 2005 had academic inventors.⁷⁷ Another study analysing all 478 drugs approved in the same period, concluded that over half involved publicly-funded academic research, including two thirds of drugs that received “priority review” status.⁷⁸

However, it could be argued that lack of novelty is not a true unpatentability factor if it is avoidable. In particular, academic centres can ensure that they file patents before disclosing their research. This argument can be rebutted on several grounds.

Firstly, it is established there has been a significant increase in patenting by universities in the United States, from 390 per annum in 1980 to 3088 in 2009, as a result of the Baye-Dole Act of 1980,⁷⁹ which allowed the patenting of taxpayer-funded research in order to encourage its commercialisation by private industry.⁸⁰ However, increased patenting requires up-front financial commitments, and not all universities have well-funded technology transfer offices (TTOs) that can afford to file patents over all medical research with therapeutic potential.⁸¹ Therefore, TTOs may not file many patents due to funding priorities.

Secondly, TTOs must make decisions about which research to patent before its commercial potential may be known by the academic researchers themselves. The selection of potentially viable drug candidates has been described as “part science and part art”,⁸² with frequent mistakes made both by scientists and pharmaceutical industry executives.⁸³ Accordingly, any potentially lifesaving medicines mistakenly overlooked by TTOs, become unpatentable therapies upon publication.⁸⁴

⁷⁶ AJ Stevens and others “The role of public-sector research in the discovery of drugs and vaccines” (2011) 364(6) *New England Journal of Medicine* 535 at 537.

⁷⁷ BN Sampat “Academic patents and access to medicines in developing countries” (2009) 99(1) *American Journal of Public Health* 9 at 11.

⁷⁸ BN Sampat and FR Lichtenberg “What are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation?” (2011) 30(2) *Health Affairs* 332 at 332. Priority review of a drug allows an accelerated regulatory approval for drugs deemed the most innovative and which address unmet medical needs.

⁷⁹ Baye-Dole Act 35 USC § 200-212.

⁸⁰ WH Schacht *The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology* (Congressional Research Service, 3 December 2012) at 8-9.

⁸¹ A notable exception is Stanford University’s Office of Technology Licensing, which generated USD 87 million in gross licensing royalties in 2012-2013: see “Research Facts” (23 April 2014) Stanford University <www.facts.stanford.edu>.

⁸² Bartfai and Lees, above n 45, at 258.

⁸³ Roin, above n 1, at 530, n 137, citing GA Showell and JS Mills “Chemistry Challenges in Lead Optimization: Silicon Isosteres in Drug Discovery” (2003) 8 *Drug Discovery Today* 551 at 551.

⁸⁴ As will also be discussed below, even if a patent is filed, before publication, patent length runs from the date of filing, and the patent might have insufficient length by the time it is ready to achieve regulatory approval.

Thirdly, the almost exponential increase in research publications over time,⁸⁵ along with scientific norms encouraging early publication and open sharing of data, increases the chance of a discovery being unpatentable due to a prior academic publication. Moreover, academia tends to reward the publication of research results rather than the number of patents filed, and there is a corresponding pressure to publish results as soon as possible.⁸⁶

(c) Inherent anticipation

The doctrine of ‘inherent anticipation’ is another example of how lack of novelty may be unavoidable. As discussed in Chapter Two, the fact that a compound possesses an inherent property or benefit that was not recognised until later, is not in itself sufficient to make the compound distinct from the prior art.⁸⁷

For example, in *Abbott Laboratories v Baxter Pharmaceutical Products Inc*,⁸⁸ the Federal Circuit invalidated a patent for an inhalation anaesthetic that was found to have lower toxicity in storage when combined with water. A prior art reference described combining the drug with water to remove impurities. However, at the time, it was not realised that this would result in lower toxicity. Despite the acknowledgment by the Federal Circuit that “knowledge of the beneficial nature of a water-sevoflurane mix was wholly lacking”, it was held that “a [prior art] reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time.”⁸⁹

Similarly, the case *SmithKline Beecham Corp v Apotex Corp*⁹⁰ involved the invalidation of a patent for a blockbuster antidepressant, Paxil, which was produced in undetected trace amounts during the manufacture of an older version of the drug. The Federal Circuit held that “inherent anticipation does not require a person of ordinary skill in the art to recognize the inherent disclosure in the prior art at the time the prior art is created.”⁹¹

⁸⁵ M Pautasso “Publication growth in biological sub-fields: patterns, predictability and sustainability” (2012) 4(12) Sustainability 3234 at 3237-3238.

⁸⁶ Roin, above n 1, at 527.

⁸⁷ *In re Dillon*, 919 F 2d 688 (Fed Cir 1991); *Schering v Geneva* 339 F 3d 1373 (CAFC 2003) at 1377; see also *Merrell Dow Pharmaceuticals v H N Norton & Co Ltd* [1996] RPC 76.

⁸⁸ *Abbott Laboratories v Baxter Pharmaceutical Products Inc* 471 F 3d 1363 (Fed Cir 2006).

⁸⁹ At 1365-1367.

⁹⁰ *SmithKline Beecham Corp v Apotex Corp* 403 F 3d 1331 (Fed Cir 2005).

⁹¹ At 1343-1345.

In *Ex parte Levin*,⁹² the BPAI considered the validity of a claim over a method of administering an artificial sweetener, tagatose, in order to raise the level of high-density lipoprotein to promote cardiovascular health.⁹³ The BPAI stated this was inherently anticipated by a published specification that disclosed a method of administering of tagatose to a mouse to try and slow the aging process.⁹⁴ It was held to be irrelevant that the cardiovascular benefits of administering tagatose would have been unappreciated by a person skilled in the art at the time.⁹⁵

As discussed in Chapter Two, commentators have noted the inherent anticipation doctrine's potential to stifle incentives for drug development, particularly by removing the ability to patent useful drug metabolites.⁹⁶

(d) Prior use

Lack of novelty due to prior use can also be an unpatentability factor. For example, in *Dey, LP v Sunovion Pharmaceuticals, Inc.*,⁹⁷ it was argued that a clinical trial where participants could take the medicine without signing a confidentiality agreement constituted public prior use. However, an application for summary judgement was reversed by the Federal Circuit on the basis that while no formal secrecy obligation was imposed, "the study was conducted with a reasonable expectation of confidentiality as to the nature of the formulations being tested."⁹⁸ Therefore, arguably, a clinical trial where confidentiality is not reasonably expected, such as one sponsored by an academic investigator, would constitute invalidating public use.

Summary

In general, prior publication through previous patent applications or academic research is a major contributor to the lack of novelty unpatentability factor. While anticipation by prior art may be overcome by redrafting narrower claims, these may

⁹² *Ex parte Levin* No 2004-1391 (BPAI Jan 1, 2004).

⁹³ High-density lipoprotein (HDL) is referred to as 'good cholesterol', because it clears low-density lipoprotein, or 'bad cholesterol' from the cardiovascular system.

⁹⁴ At 7. The prior art reference was US Patent No 5,356,879 (Zehner).

⁹⁵ At 7, citing *Schering v Geneva*.

⁹⁶ A De La Rosa "A Hard Pill To Swallow: Does Schering v Geneva Endanger Innovation Within The Pharmaceutical Industry" (2008) 8 Colum Sci & Tech L Rev 37 at 42 citing *Eli Lilly & Co v Barr Labs, Inc* 251 F 3d 955 (Fed Cir 2001) at 976 per Judge Newman: '[E]very biological property is a natural and inherent result of the chemical structure from which it arises, whether or not it has been discovered. To negate the patentability of a discovery of biological activity because it is 'the natural result' of the chemical compound can have powerful consequences for the patentability of biological inventions.'

⁹⁷ *Dey, LP v Sunovion Pharmaceuticals, Inc* No 12-1428 (Fed Cir May 20, 2013).

⁹⁸ At 1439.

not effectively prevent competition. It may also not be possible to avoid lack of novelty by filing patents before disclosure. Academic centres have insufficient funding and expertise to file patents over every potentially valuable medicine, and the doctrine of inherent anticipation means that medicinal properties that were unrecognised in the prior art can still invalidate subsequent patentability. Prior use of medicines in experimental clinical trials may be a further source of lack of novelty.

Finally, even if it were possible to modify claims to avoid direct anticipation, the aforementioned prior art would still contribute to the most significant ‘unpatentability factor’: lack of inventive step.

2 *Lack of inventive step*

Lack of inventive step is an ‘unpatentability factor’ with far greater impact on the patentability of medicines compared to lack of novelty because it allows the combination of multiple prior art references to invalidate a patent. Moreover, as technology progresses and it becomes easier to predict the effects of new drugs, lack of inventive step becomes a more difficult hurdle to overcome.⁹⁹ For example, many pharmaceutical companies already use computer-modelling techniques to ‘virtually’ screen drug compounds to predict efficacy against a target molecule even before they are synthesised.¹⁰⁰

(a) Denying patentability of medicines with predictable effects

According to Roin, one of the stated reasons that the patent system does not allow patents for inventions which lack an inventive step, is because it is assumed that obvious inventions do not have significant development costs.¹⁰¹ However, this assumption is misplaced in the context of the pharmaceutical industry. Medicines with ‘obvious’ therapeutic potential will still have to undertake expensive clinical trials ‘post-invention’ in order to reach the market, and innovators will not assume those costs without an enforceable patent.

As noted in Chapter Two, the leading decision of the Supreme Court of the United States in *KSR v Teleflex* denies patentability to inventions created “according

⁹⁹ Roin, above n 1, at 543.

¹⁰⁰ This process is referred to as ‘rational drug design’. See Soma Mandala, Mee'nal Moudgila and S K Mandal “Rational drug design” (2009) 625 *European Journal of Pharmacology* 90 at 91.

¹⁰¹ Roin, above n 1, at 533. It is assumed that the public already has ‘possession’ of inventions which lack novelty, and therefore do not require a monopoly right as incentive.

to known methods... [that] yield predictable results.”¹⁰² Commentators have argued that this test is in conflict with the scientific method, which involves using known techniques to make predictions, and will ultimately reduce incentives to innovate.¹⁰³

In addition, the test for non-obviousness lacks bright line rules that would allow simple determination of patentability *ex ante*. When billions of dollars in sales can hinge on the opinion of a patent examiner or judge as to whether the therapeutic effect of a drug is ‘unexpected’ enough to a ‘person skilled in the art’ prior to commencement of clinical trials,¹⁰⁴ the existence of any similar prior art may be enough to dissuade investment in otherwise socially valuable medicines.

(b) ‘Composition of matter’ claims and the relevance of structural similarity

As mentioned in Chapter Two, ‘composition of matter’ claims are perceived as the most valuable as they can restrict the manufacture of a medicine for any medical use. Another reason that composition of matter claims are sought-after is because they are perceived as less susceptible to invalidity challenges than so-called ‘secondary patents’ over derivatives, formulations, combinations, or methods of use of medicines. However, this assumption may not be justified. For example, a recent Federal Court case *Bristol-Myers Squibb Company v Teva Pharmaceuticals USA, Inc*¹⁰⁵ was notable for invalidating a composition of matter patent over Bristol-Myers Squibb’s hepatitis B drug, entecavir. There was a finding of obviousness due to the fact that entecavir only differed from the prior art ‘lead compound’ 2'-CDG by the addition of a single carbon atom.¹⁰⁶ Traditionally, generic entry is delayed until ‘composition of matter’ patents expire, and this case may cause a change in the industry’s perception.¹⁰⁷

Structural similarity to a prior art compound was also a cause of obviousness in the case *In re Merck & Co.*¹⁰⁸ The Federal Circuit denied patentability over amitriptyline to treat depression, due to its ‘close structural similarity’ to imipramine,

¹⁰² *KSR International Co v Teleflex Inc* 550 US 398 (2007) at 416; see also *Portable Sawing Systems Ltd (in liq) v Lucas* [2006] 3 NZLR 721 at [54]; *Windsurfing International Inc v Tabur Marine (GB) Ltd* [1985] RPC 59.

¹⁰³ R Greendyke “No Patent for You: How KSR v Teleflex’s Nonobviousness Test Conflicts with the Scientific Method and Removes the Incentive to Innovate” (2010) 35 U Dayton L Rev 413 at 430.

¹⁰⁴ Roin, above n 1, at 539.

¹⁰⁵ *Bristol-Myers Squibb Company v Teva Pharmaceuticals USA, Inc* No 2013-1306 (Fed Cir June 12, 2014).

¹⁰⁶ At 13.

¹⁰⁷ E Silverman “Not So Obvious: A Bristol-Myers Patent Defeat May Change Wall Street Views” *Forbes* (online ed, New York, 12 February 2013).

¹⁰⁸ *In re Merck & Co* 800 F 2d 1091 (Fed Cir 1986).

a known anti-depressant.¹⁰⁹ Despite the fact that anti-depressant properties of amitriptyline were not disclosed in the prior art, the Court held:¹¹⁰

...one of ordinary skill in the medicinal chemical arts, possessed of the knowledge of the investigative techniques used in the field of drug design and pharmacological predictability, would have expected amitriptyline to resemble imipramine in the alleviation of depression in humans.

Accordingly drug companies may be less willing to develop a promising drug where its molecular structure is very close to a prior art compound.

(c) Examples of lack of inventive step invalidating patent claims over medicines

As noted above with regard to lack of novelty, it is difficult to observe evidence of drugs which may have got to market, but for lack of inventive step. Again, records of BPAI decisions at the USPTO contain some examples of claims over medical therapies that were deemed to lack inventive step, resulting in narrower claims that may have been unable to effectively prevent competition.

In *Ex parte Williams*,¹¹¹ there was an attempt to claim a method of treating HIV using leflunomide combined with a pyrimidine compound. The BPAI cited prior art which suggested it would be beneficial to combine leflunomide with antiviral agents, which included pyrimidine compounds. The patent proceeded to grant, but only with a narrower claim combining leflunomide with a pyrimidine compound “without antiviral activity”.¹¹² There are no records of this treatment receiving regulatory approval.¹¹³

Ex parte Linnenbach,¹¹⁴ involved a cancer vaccine targeting GA733-2, which is a protein expressed in various human cancers. The original broadest claim comprised a truncated protein GA733-2E, which was a suitable ‘antigen’ used to stimulate a patient’s own immune system to target cancer cells expressing GA733-2. However, the BPAI denied patentability for obviousness in light of a combination of

¹⁰⁹ At [42].

¹¹⁰ At [42].

¹¹¹ *Ex parte Williams* No 2005-0902 (BPAI June 22, 2005).

¹¹² US Patent No 7,691,890, Claim 11.

¹¹³ However, it is difficult to draw any inferences on the impact of narrower claims on the decision not to commercialise the treatment, as perhaps it was not commercially viable for other reasons, such as lack of efficacy or a small market size.

¹¹⁴ *Ex parte Linnenbach* No 2001-1258 (BPAI Jan 1, 2004).

four prior art references: Szala,¹¹⁵ Bumol,¹¹⁶ Hussey,¹¹⁷ and Johnson.¹¹⁸ In particular, Szala taught the production of the full-length GA733-2 protein, but not a truncated sequence,¹¹⁹ Bumol disclosed a truncated version necessary to facilitate production in bacteria,¹²⁰ and Hussey and Johnson taught producing a truncated protein in animal cells, but not GA733-2E specifically. The BPAI held that it would have been obvious to a person skilled in the art to combine the prior art to produce a truncated version of GA733-2 in animal cells.¹²¹ In the patent that was granted, the broadest claim combined the GA733-2E antigen with least one other cancer treating compound in a pharmaceutically acceptable carrier.¹²² There are no records of this vaccine achieving regulatory approval.¹²³ It is conceivable that narrower claims may have had a role. For example, a generic drug company could avoid infringement by manufacturing a vaccine containing the GA733-2E antigen but omitting the combination with a cancer treating compound.

In *Ex parte Childers*,¹²⁴ patent claims 1-3 over neuroprotective serotonin receptor-binding compounds were rejected as being obvious in light of a previously filed patent by Abou-Gharbia and others. The BPAI held: “[h]ere, the applied prior art establishes that one of ordinary skill in the art would have reasonably expected the compounds of Abou-Gharbia having the ethyl bridging moiety modified by a phenyl group would continue to exhibit the property of binding to the [serotonin] receptor”.¹²⁵ Although a patent with narrower claims was granted in 2004,¹²⁶ it has since lapsed due to non-payment of fees.¹²⁷ There are no records of this neuroprotective compound being developed as a drug.¹²⁸

¹¹⁵ S Szala and others “Molecular cloning of cDNA for the carcinoma-associated antigen GA733-2” (1990) 87 Proc Natl Acad Sci Vol 3542.

¹¹⁶ European Patent Application No 0 326 423.

¹¹⁷ RE Hussey “A soluble CD4 protein selectively inhibits HIV replication and syncytium formation cells” (1988) 311 Nature 79.

¹¹⁸ PW Johnson “Synthesis of soluble myelin-associated glycoprotein in insect and mammalian cells” (1989) 77 Gene 287.

¹¹⁹ *Ex parte Linnenbach*, at 4.

¹²⁰ At 5. In particular, the sequence in Bumol was missing the first 81 amino acids.

¹²¹ At 8-12.

¹²² US Patent No 6,645,498.

¹²³ This was verified by the author by accessing Cortellis by Thomson Reuters. Cortellis is a proprietary database that holds patent and clinical trial data for new drugs. From Cortellis records (accessed 27 January 2014), OncoVax-CL containing the GA733-2E antigen was developed by Jenner Biotherapies Inc but failed to achieve regulatory approval.

¹²⁴ *Ex parte Childers* No 2003-0890 (BPAI Dec 22, 2003).

¹²⁵ At 7.

¹²⁶ US Patent No 6,831,084.

¹²⁷ The author confirmed this by accessing USPTO ‘Public Pair’ records on 30 January 2014.

¹²⁸ According to Cortellis records (accessed 27 January 2014), the drug was ultimately not developed by Pfizer [originally owned by Wyeth and American Home Products].

Roin provided many other examples of BPAI decisions which were invalidated for lack of non-obviousness,¹²⁹ including claims covering potentially viable drugs for cancer,¹³⁰ tuberculosis,¹³¹ HIV,¹³² hypertension,¹³³ and diabetes.¹³⁴ Such drugs could have had significant social value, however, a drug company would be unlikely to pursue development without strong patent claims that can prevent generic competition. Further, a narrower valid patent claim may mean that only a medicine having a certain chemical structure covered by that claim will be developed, which may be worse than the version that was covered by an invalidated patent claim. In other words, under the current system, ‘patentable’ medicines may not be the most safe or effective medicines.

Summary

Lack of inventive step is a significant hurdle for drug development. Paradoxically, society loses medicines that would be predicted to have superior benefits,¹³⁵ even if they are the only treatment for a disease. Society also loses medicines that would have performed unexpectedly better during clinical trials but had insufficient patentability to attract private funding. Lastly, ‘patentable’ medicines will be developed that may be worse than the ‘public domain’ versions, which lack private incentives for development.

3 *Lack of utility and sufficiency*

As discussed in Chapter Two, lack of utility and sufficiency relate to the level of disclosure in a patent application, and are frequently used as grounds for challenging a patent over a medicine because the pressure to file a patent early in development can

¹²⁹ Roin, above n1, at 552, n 262. For example see *Ex parte Selzer* No 2006-0760 (BPAI Feb 28, 2007) at 4; *Ex parte Arbiser* No 2007-0091 (BPAI Feb.6, 2007) at 1; *Ex parte Skurkovich* No 2006-0624 (BPAI Jan 1, 2006) at 1; *Ex parte Gormley* No 2004-0543 (BPAI Dec 29, 2004) at 4; *Ex parte Lapeurta* No 2003-1745 (BPAI Jan. 1, 2004) at 2; *Ex parte Bodmer* No 2001-1044 (BPAI Jan 1, 2004) at 3.

¹³⁰ Roin, above n 1, at 544, n 215: *Ex parte Cuthbertson* No 2007-1140 (BPAI May 24, 2007) at 2; *Ex parte Rajopadhye* No 2007-0856 (BPAI May 21, 2007) at 1; *Ex parte Chen* No 2006-3290 (BPAI Mar 16, 2007) at 1; *Ex parte Barbera-Guillem* No 2006-2466 (BPAI Nov 30, 2006) at 1; *Ex parte Shawver* No 2004-0005 (BPAI Mar 4, 2004) at 2; *Ex parte Rosenblatt* No 2004-1505 (BPAI Jan 1, 2004) at 1; *Ex parte Bianco* No 1996-0756 (BPAI Jan 1, 1996) at 1.

¹³¹ *Ex parte Horwitz* No 2002-1740 (BPAI June 19, 2003) at 5-7.

¹³² *Ex parte Maury* No 2007-1621 (BPAI July 24, 2007) at 2-7; *Ex parte Stapleton* No 2005-1797 (BPAI Jan 1, 2006) at 3-6; *Ex parte Williams* No 2005-0902 (BPAI June 22, 2005) at 4-6.

¹³³ *Ex parte Pershadsingh* No 95-0885 (BPAI Oct 14, 1997) at 2-5. All but one of the claims was rejected on obviousness grounds.

¹³⁴ *Ex parte Schmitke* No 2007-0854 (BPAI July 24, 2007) at 5-6.

¹³⁵ Roin, above n 1, at 540. See also T Syed “Should a Prize System for Pharmaceuticals Require Patent Protection for Eligibility?” (IGH Discussion Paper No 2, Incentives for Global Health, June 10, 2009) at 4.

make it vulnerable to attack on this basis. As such, lack of utility and sufficiency may comprise major unpatentability factors. Commentators have noted that uncertainty regarding satisfaction of the utility and sufficiency requirement “disincentivizes investment and thereby hampers innovation.”¹³⁶

One problem is that if particular disease aetiology is not well-understood there may not be any target proteins or animal models that can be used to generate the pre-clinical evidence necessary to satisfy utility.¹³⁷ As mentioned in Chapter Two, this is particularly the case for mental disorders, which often have unknown causes. Advantageously, however, the United States allows the applicant to supply more clinical evidence after filing to support utility, if necessary.¹³⁸ Therefore, it might be argued that lack of utility can be easily overcome by filing more evidence when it becomes available in order to overcome these objections.

Regardless, there is another problem that can frustrate the strategy of filing more evidence when it becomes available. It is well-settled United States case law that a disclosure within a specification may anticipate an invention, while at the same time having insufficient written description or sufficiency to be granted a patent.¹³⁹ While a more stringent ‘enablement’ requirement in New Zealand¹⁴⁰ may alleviate this effect somewhat, the United States is the crucial market for deciding whether to fund a new drug.¹⁴¹ This means that lack of utility and insufficiency overlap with the previous two unpatentability factors in the United States.

Roin has provided several examples of this phenomenon.¹⁴² The case *Rasmusson v SmithKline Beecham Corp*,¹⁴³ involved a patent for the use of the hair-loss drug, finasteride, for the treatment for prostate cancer. In that case, it was held that although an earlier attempt to patent the use had “failed to demonstrate the effects of finasteride in treating prostate cancer”, this nonetheless invalidated a subsequent attempt to patent its use for treating prostate cancer once more data became available.¹⁴⁴ In *Bristol-Myers Squibb Co v Ben Venue Laboratories, Inc*,¹⁴⁵ patents for

¹³⁶ CM Holman “Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation” (2011) 76 Mo L Rev 645 at 657.

¹³⁷ At 660 discussing *Eli Lilly & Co v Actavis Elizabeth LLC* 731 F Supp 2d 348 (DNJ 2010) at 352.

¹³⁸ See *Eli Lilly & Co v Actavis Elizabeth LLC*, No 2010-1500 (Fed Cir 2011).

¹³⁹ Roin, above n 1, at 522 citing *In re Hafner* 410 F 2d 1403 (CCPA 1969) at 1405; *In re Schoenwald*, 964 F 2d 1122 (Fed Cir 1992) at 1123-1124; *In re Samour* 571 F 2d 559 (CCPA 1978) at 563-564.

¹⁴⁰ For example, the *Synthon* case which requires ‘disclosure’ and ‘enablement’ for anticipation.

¹⁴¹ Bartfai and Lees, above n 45, at 138.

¹⁴² Roin 2009 above at 522-524.

¹⁴³ *Rasmusson v SmithKline Beecham Corp* 413 F 3d 1318 (Fed Cir 2005).

¹⁴⁴ At 1322. See also Roin, above n 1, at 523, n 101.

¹⁴⁵ *Bristol-Myers Squibb Co v Ben Venue Laboratories, Inc* 246 F 3d 1368 (Fed Cir 2001).

a chemotherapy drug were invalidated in light of prior publications which discussed the patented uses, but described them as being ineffective.¹⁴⁶

Insufficiency also can prevent claims over ‘downstream’ innovations, which are known as ‘reach-through’ claims, such as claiming any drugs which may bind to a particular receptor. These usually also fail on the enablement or written description requirement, particularly where ‘undue experimentation’ is required to achieve a practical result.¹⁴⁷ Further, as will be discussed below, such ‘upstream’ patent claims may stifle innovation by creating ‘patent thickets.’¹⁴⁸

Summary

Due to the commercial pressure to file a patent before competitors, lack of utility and sufficiency is a gap that many socially valuable drugs can fall through and become ‘unpatentable therapies’. Further, in the United States, a patent application which is deemed to lack utility or sufficiency can still invalidate a subsequent attempt to patent the same medicine.

The pressure to file a patent early in the development stage can increase the likelihood that there is insufficient patent length to justify the time and expenditure required for clinical trials. The consequences of insufficient patent length will now be discussed.

4 Insufficient patent length

The ‘translation’ of basic research from discovery to a clinically effective treatment can take an average of 17 years.¹⁴⁹ Patent applications are usually filed before the commencement of clinical trials in humans, which typically last at least 7 to 14 years from patent filing until regulatory approval.¹⁵⁰ A 2012 study by Hemphill and Sampat indicated that medicines enjoy market exclusivity for an average of 12.2 years until generic drug entry.¹⁵¹ This is consistent with reports that a period of at least 10 years

¹⁴⁶ At 1377–81. See also *Astra Akteibolag v Andrx Pharmaceuticals, Inc.* 222 F Supp 2d (SDNY 2002) at 596–598.

¹⁴⁷ See *University of Rochester v GD Searle & Co* 358 F 3d 916 (Fed Cir 2004); *In re Fisher* 421 F 3d 1365 (Fed Cir 2005).

¹⁴⁸ M Heller *The gridlock economy: How too much ownership wrecks markets, stops innovation, and costs lives* (Basic Books, New York, 2008) at 4–6.

¹⁴⁹ R Pozen and H Kline “Defining success for translational research organizations” (2011) 3(94) *Sci Transl Med* 1 at 1.

¹⁵⁰ Grubb and Thomsen, above n 1, at 424–425; KI Kaitin “Deconstructing the drug development process: the new face of innovation” (2010) 87(3) *Clinical Pharmacology and Therapeutics* 356, Figure 1. See also DiMasi and Grabowski, above n 6, at 475.

¹⁵¹ Scott C Hemphill and BN Sampat “Evergreening, patent challenges, and effective market life in pharmaceuticals” (2012) 31(2) *Journal of Health Economics* 327 at 330; see also H Grabowski, G Long

of exclusivity is required to justify investment in a new drug.¹⁵² Therefore, having less than 10 years of patent life remaining could be viewed as a major ‘unpatentability factor’ that will disincentivise development of many new drugs.¹⁵³ The public will not be aware of such drugs if they are abandoned before development commences.

Abramowicz recognised the problem of diminishing incentives to develop an invention as a patent’s length runs out, particularly for biotechnological inventions with long development times.¹⁵⁴ Accordingly, pharmaceutical companies try to minimise clinical trial development times in order to maximise the length of patent exclusivity remaining after market approval.¹⁵⁵

Unfortunately, a number of factors can increase development times, which are outside the control of pharmaceutical companies. Firstly, the inherent unpredictability of drug development means that a medicine may initially be tested for the wrong disease indication or dosage during pre-clinical or clinical trials. These largely unavoidable errors can take several years off the life of a patent. Secondly, it may not be possible to manufacture a drug in bulk due to technological limitations. This was an issue for dozens of medically useful proteins that were patented in the mid-1980s, but for which the patents have now expired.¹⁵⁶ By the time these manufacturing issues are resolved, useful drugs may have insufficient patent duration left. Thirdly, some medicines require long clinical trial development times, such as treatments for chronic diseases with gradual increases in morbidity. For example, this includes Alzheimer’s disease, multiple sclerosis, or early interventions in cancer. This could skew private funding towards medicines with shorter development times, but which may have less of an impact on disease burden. A recent paper by Budish, Roin and Williams showed that this funding bias could have a major impact on public health.¹⁵⁷

and R Mortimer “Recent trends in brand-name and generic drug competition” (2013) 17(3) *Journal of Medical Economics* 207 at 207, which found the average period of market exclusivity to be 12.9 years overall.

¹⁵² Roin, above n 1, at 557, n 290 citing Anonymous Director of Intellectual Property at a mid-sized pharmaceutical company.

¹⁵³ It may be possible to effectively ‘extend’ patent protection over a medicine using patent ‘evergreening’ techniques however, the ‘strength’ of such ‘secondary patents’ is weaker, as will be discussed in the next section.

¹⁵⁴ M Abramowicz “The Danger of Underdeveloped Patent Prospects” (2007) 92 *Cornell L Rev* 1065 at 1097: ‘[O]ne danger of granting patents in gene sequences is that, by the time researchers see a therapeutic use on the horizon, the patent term might have expired or too little patent term will remain to make the research financially worthwhile.’

¹⁵⁵ Paul and others, above n 14, at 210.

¹⁵⁶ S Lyman “Rescuing Patent-Less Proteins from the Drug Development Dustbin” (November 6, 2012) *Xconomy* <www.xconomy.com>. Lyman describes 37 known interleukins, growth factors, chemokines and various receptor agonists and antagonists patented by the biotechnology industry between 1985 and 1995. Most ‘composition of matter’ and ‘method of use’ patents over these useful proteins have now expired.

¹⁵⁷ See E Budish, BN Roin and H Williams “Do fixed patent terms distort innovation? Evidence from cancer clinical trials” (NBER Working Paper No 19430, September 2013) at 5. By analysing United

Another factor which can reduce effective patent length is a judge-made legal doctrine unique to the United States called ‘non-statutory obviousness-type double-patenting.’ The doctrine applies where “claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent”.¹⁵⁸ Typically, a pharmaceutical company will file several patents over small improvements at each stage of a drug development life cycle, which can be cited as prior art upon publication. For example, in *Ex parte Picard*,¹⁵⁹ various patent claims filed in 1993 over promising novel sulfonyl urea compounds for the lowering of blood cholesterol,¹⁶⁰ were deemed unpatentable due to obvious-type double-patenting in light of an earlier patent filed in 1991 by the same inventor.¹⁶¹

In the United States, an objection for non-statutory obviousness-type double-patenting can be overcome by filing a ‘terminal disclaimer’, which is an acknowledgement by the applicant that the subsequently filed patents will expire 20-years from the priority date of the first patent application filed.¹⁶² For example, in *Ex parte Picard*, filing a terminal disclaimer would have resulted in a shortening of patent protection by two years.¹⁶³

As with other ‘unpatentability factors’ it is difficult to empirically verify the numbers of drugs abandoned before completion of clinical trials due to insufficient patent length as opposed to lack of safety or efficacy. However, it may be possible to make some inferences from the proportion of clinical trials abandoned due to undisclosed strategic or commercial reasons.¹⁶⁴ For example, a 2011 study by Arrowsmith analysed the reasons for 108 Phase II failures between 2008 and 2010, and found that 29 per cent were for ‘strategic reasons’ and 19 per cent, were for unreported reasons.¹⁶⁵ Similarly, a 2001 study by DiMasi stated that 33.8 per cent of R&D terminations between 1987 and 1992 were for economic reasons, for example, because the “commercial market [is] too limited” or there is “insufficient return on

States cancer patients who were diagnosed in 2003, this paper found that distortions in R&D incentives due to fixed term patents have resulted in approximately 890,000 lost life years, with a social cost of approximately USD 89 billion per annum.

¹⁵⁸ *Eli Lilly & Co v Barr Labs*, above n 94, at 967-968. See also 35 USC 102(a)(2) and 102(b)(2)(C).

¹⁵⁹ *Ex parte Picard* No 95-2879 (BPAI Jan 1, 1995).

¹⁶⁰ US Patent No. 5981595.

¹⁶¹ US Patent No 5,254,589.

¹⁶² See Manual of Patent Examining Procedure § 804.

¹⁶³ A similar process can occur in New Zealand whereby an applicant can file a ‘patent of addition’ with improvements that lack inventive step in light of their previously filed patent, but the latter patent of addition is limited to the length of the ‘parent’ patent. However, it is necessary that both patents have common ownership. See Patents Act 2013, s 106.

¹⁶⁴ For example, the drug might be less cost-effective than other drugs already on the market, or other drugs in the same class are further advanced in development or comparatively better.

¹⁶⁵ Arrowsmith, above n 31, at 328.

investment.”¹⁶⁶ It is arguable that some of these terminations may have been due to insufficient patent length. Notably, however, termination due to insufficient patent length at the clinical trial stage may be rare, given that most ‘patentability screening’ occurs at the pre-clinical trial stage.

Summary

Insufficient patent length may be an important ‘unpatentability factor’ which can discourage private incentives to develop useful medicines. Insufficient patent length may be unavoidable for various reasons, including unpredictable and long clinical trials, manufacturing issues, and earlier filed patents. The optimal length of exclusivity is outside the scope of this thesis, although it is likely that at least 10 years is required to be an adequate incentive. Extensions to patent and regulatory exclusivity periods as alternative incentives for medical therapies will be discussed in Chapter 6A. The next section will consider the scenario where patentability over a medical therapy is excluded by law.

5 *Unpatentability under law*

The final ‘unpatentability factor’, unpatentability under law, has limited overlap with the previous unpatentability factors. As discussed in Chapter Two, there are various categories of medical therapies that include features which could make them unpatentable under law.

First, medical therapies are excluded from the definition of patentable subject matter if they consist of naturally occurring products, pure discoveries, or abstract ideas.¹⁶⁷ For example, medical therapies that involve mental steps, such as a method for determining the appropriate dose of a medicine, may be deemed abstract ideas.¹⁶⁸ There is also potential uncertainty regarding the patentability of genes to the extent they are identical to that which exists in nature, which may impact on patentability of medicines isolated from natural products. However, it is arguable that isolated and purified biological material will remain patentable, provided that it is not naturally occurring.¹⁶⁹

¹⁶⁶ JA DiMasi “Risks in new drug development: approval success rates for investigational drugs” (2001) 69(5) *Clinical Pharmacology and Therapeutics* 297 at 304.

¹⁶⁷ See discussion in Chapter Two regarding the first patentability criterion, ‘Patentable Subject Matter’.

¹⁶⁸ See Chapter Two discussion of *Prometheus Laboratories v Mayo Collaborative Services* 132 S Ct 1289 (2012).

¹⁶⁹ See generally, RS Gipstein “The Isolation and Purification Exception to the General Unpatentability of Products of Nature” (2003) 4 *Colum Sci & Tech L Rev* 1 at 1. But compare *Association for*

Second, certain medical inventions may be excluded on the basis of public order or morality.¹⁷⁰ For example, patents over genetically modified animals that model disease processes can be denied where the animal may suffer without substantial medical benefit to humans.¹⁷¹ Commentators have also noted the uncertain position on patent protection for stem cells.¹⁷² This is particularly the case in New Zealand, which prevents the use of human embryos for commercial purposes¹⁷³ and biological processes for generation of humans,¹⁷⁴ both of which relate to potential therapeutic applications of stem cells.

However, despite the uncertainty around patentability, the first stem cell therapy, Remestemcel-L, was recently approved in New Zealand and Canada as a treatment for steroid refractory graft-versus-host disease using mesenchymal stem cells as the active ingredient.¹⁷⁵ According to the developer, Osiris Therapeutics, Inc, the therapy has over 50 US and 156 foreign patents as well as 10 years regulatory exclusivity as an Orphan Drug in the European Union.¹⁷⁶ Arguably, however, this reliance on regulatory exclusivity and a large portfolio of patents reflects the uncertain legal position behind the patentability of stem cells. This may deter private investment into many promising applications of stem cells,¹⁷⁷ which will have an adverse effect on public health.

Third, as discussed in Chapter Two, patents over surgical methods are excluded from patentability in New Zealand.¹⁷⁸ There is also a statutory defence to

Molecular Pathology v Myriad Genetics 569 US__ (2013) denying patentability to isolated DNA because it is not distinct from how it is found in nature.

¹⁷⁰ Notably, the United States does not have a morality exclusion.

¹⁷¹ However, this would only be to the extent that suffering of an animal was not justified on the basis of substantial medical benefit to society. Patents Act 2013, s 15(1). See discussion in Chapter Two.

¹⁷² M Little, W Hall, and A Orlandi “Delivering on the promise of human stem-cell research. What are the real barriers?” (2006) 7(12) EMBO Reports 1188 at 1191.

¹⁷³ Patents Act 2013, s 15.

¹⁷⁴ Patents Act 2013, s 16.

¹⁷⁵ see “Summary Basis of Decision (SBD) for PROCHYMAL®” (10 May 2012) Health Canada, Office of Regulatory Affairs <www.hc-sc.gc.ca>; see Medsafe Data Sheet “Prochymasol” (1 June 2012) Medsafe <www.medsafe.govt.nz>.

¹⁷⁶ Osiris Therapeutics, Inc “Osiris Therapeutics Receives Title of European Orphan Drug Designation for Prochymal” (press release, 19 February 2013). Orphan Drug exclusivity will be discussed under regulatory exclusivity mechanisms in Chapter 6A.

¹⁷⁷ For example, hematopoietic stem cell transplantation (HCT) has the potential to permanently cure various autoimmune disorders, which otherwise require a lifetime of immunosuppressant medications and outpatient care: see Keith M Sullivan, Paolo Muraro and Alan Tyndall “Hematopoietic cell transplantation for autoimmune disease: updates from Europe and the United States” (2010) 16(1) *Biology of Blood and Marrow Transplantation* S48 at S48.

¹⁷⁸ Patents Act 2013, s 16(2).

infringement in the United States.¹⁷⁹ Despite this, there are many innovative surgical methods which could address unmet medical needs, including circumcision for preventing transmission of HIV,¹⁸⁰ gastric bypass surgery for reversing Type II diabetes,¹⁸¹ and increasing blood outflow from the brain for treatment of multiple sclerosis.¹⁸² In the latter case, larger clinical trials¹⁸³ would not have occurred without extensive media coverage and political pressure.¹⁸⁴ This could be interpreted as evidence of the lack of private incentives to develop therapies based on surgical methods because they are unpatentable under law.

Lastly, in New Zealand, the recently-enacted section 16(2) of the Patents Act and the *Pfizer* decision deny patentability to methods of medical treatment. Further, with legal uncertainty regarding the public policy justification of ‘Swiss’ claims,¹⁸⁵ there is arguably an unpatentability factor present for methods of medical treatment in New Zealand.¹⁸⁶ The inability to protect new uses over known drugs may reduce private incentives to obtain regulatory approval for medicines when a composition of matter patent has expired.¹⁸⁷ However, methods of medical treatment are patentable in the United States.¹⁸⁸ Due to the small size of the New Zealand pharmaceutical market, this unpatentability factor is unlikely to have a significant effect on private incentives to develop medical therapies, although enforceability issues are more problematic in both jurisdictions, as will be discussed below.

¹⁷⁹ See 35 USC § 287(c). It also may be arguable that surgical methods are ‘unmonopolisable therapies’ due to the difficulties for detecting infringement. ‘Unmonopolisable therapies’ will be discussed in this chapter below.

¹⁸⁰ RC Bailey and others “Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial” (2007) 369(9562) *The Lancet* 643 at 643.

¹⁸¹ SA Brethauer and others “Can Diabetes Be Surgically Cured? Long-Term Metabolic Effects of Bariatric Surgery in Obese Patients with Type 2 Diabetes Mellitus” (2013) 258(4) *Annals of Surgery* 628 at 628.

¹⁸² P Zamboni and others “Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis” (2009) 80(4) *J Neurol Neurosurg Psychiatr* 392 at 392.

¹⁸³ AH Siddiqui and others “Percutaneous transluminal venous angioplasty (PTVA) is ineffective in correcting chronic cerebrospinal venous insufficiency (CCSVI) and may increase multiple sclerosis (MS) disease activity in the short term: Safety and efficacy results of the 6-month, double-blinded, sham-controlled, prospective, randomized endovascular therapy in ms (PREMiSe) trial” (paper presented to 65th Annual Meeting of American Academy of Neurology, San Diego, CA, 20 March 2013).

¹⁸⁴ See D Pullman, A Zarzeczny and A Picard “Media, politics and science policy: MS and evidence from the CCSVI Trenches” (2013) 14(6) *BMC Medical Ethics* 1 at 1

¹⁸⁵ S Frankel “Lord Cooke and Patents: The Scope of Invention” (2008) 39 *VUWLR* 73 at 78-79.

¹⁸⁶ Refer to discussion of ‘Swiss-claims’, ‘Swiss-type claims’ and other Legal Doctrines to Overcome Exclusions for Methods of Medical Treatment in Chapter Two.

¹⁸⁷ This problem will be discussed further in the next section on evergreening.

¹⁸⁸ *Ex Parte Scherer* 103 USPQ (BNA) 107, 109 (Pat Off Bd App 1954).

Summary

The lack of patentability under law can be a significant unpatentability factor, particularly for surgical methods. For other therapies such as second uses for known drugs, flexibilities within patent law may allow innovator companies to work around any relevant exclusions to obtain patent protection over their medicines. However, it may not be possible to overcome the other unpatentability factors so easily.

An important question therefore arises: whether existing patent law can be leveraged to ‘rescue’ unpatentable therapies, for example, by patenting minor modifications to drugs, selection inventions, or methods of medical treatment, in order to overcome the unpatentability factors based on lack of novelty or inventive step.

D Can ‘Unpatentable Therapies’ be ‘Rescued’ using Patent ‘Evergreening’ Techniques?

Despite the presence of ‘unpatentability factors’ described above, it could be argued that pharmaceutical companies could still utilise creative patent claiming strategies to ‘rescue’ patentability over socially valuable unpatentable therapies. In this context, ‘rescue’ means to file a new patent that can block competition from generic drug companies and allow a monopoly price to be enforced. The next sections will discuss these so-called ‘patent evergreening’ techniques, and the circumstances in which they may be ineffective or effective.

1 What is patent evergreening?

The core implication behind the concept of ‘patent evergreening’ is that it is possible to effectively ‘extend’ patent protection by filing narrower claims over a drug, such as a new formulation or method of use. This term is frequently used by critics of the pharmaceutical industry, which allegedly uses such techniques to unjustifiably obtain a new period of patent protection over their medicines.¹⁸⁹ Accordingly, if ‘evergreening’ works, it could allow patentability over a formerly unpatentable therapy to be regained. For example, Outterson argues¹⁹⁰ that companies can re-patent unpatentable therapies that have fallen into the public domain by using evergreening

¹⁸⁹ Grubb and Thomsen, above n 1, at 428; G Dwivedi, S Hallihosur and L Rangan “Evergreening: A deceptive device in patent rights” (2010) 32(4) *Technology in Society* 324 at 324.

¹⁹⁰ Outterson, above n 63 at 50.

techniques, such as ‘method-of-use’ patents,¹⁹¹ patenting formulations,¹⁹² and patenting drug combinations.

However, it has been argued that patent evergreening is a misnomer.¹⁹³ Specifically, it is not possible to extend the length of a patent claim.¹⁹⁴ For example, assume that a patent having a ‘composition of matter’ claim over a drug, comprising active ingredient A¹⁹⁵ plus an inactive ingredient B¹⁹⁶ (A + B), is about to expire. A pharmaceutical company can subsequently obtain a patent over a new formulation of a drug which includes a composition of matter claim having the same active ingredient plus a slightly modified inactive compound B’ (A + B’), assuming that the new formulation is novel and non-obvious. Whilst the latter patent can prevent a generic company from manufacturing the new formulation (A + B’), it cannot prevent manufacture of the original ‘off-patent’ drug (A + B), which has the same active ingredient. This means that, assuming the original drug has regulatory approval, patenting a new formulation cannot extend the effective period of market exclusivity against generic competition, because a generic drug company is free to manufacture the original version - although it can be prevented from manufacturing the new formulation.¹⁹⁷ The impact of this on incentives to find second uses for generic drugs will be discussed in the next section on ‘unmonopolisable therapies’.

By contrast, if a drug candidate has not yet achieved regulatory approval, then ‘evergreening’ can effectively extend the effective period of market exclusivity against generic competition for the duration of the new patent. In particular, as discussed in Chapter Two, a generic drug must be ‘bioequivalent’ to the formulation which has obtained regulatory approval.¹⁹⁸ This essentially means that it must have

¹⁹¹ For example, new uses of known drugs, dosing regimens, and new methods of drug delivery and administration. See discussion in Chapter Two.

¹⁹² Section 3(d) of the Indian Patents Act 1970 provides a useful description of new drug formulations typically used for ‘patent evergreening’: ‘salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance[s].’ Due to a strong local generics industry, India restricts the patentability of new formulations. A consideration of the effect of this ‘anti-evergreening’ legislation on incentives for drug development is outside the scope of this thesis.

¹⁹³ See JJ Darrow “Debunking the Evergreening Patents Myth” (2010) 131(6) Harvard Law Record 6 at 6.

¹⁹⁴ Other than patent extensions provided for by law under applicable legislation, which will be discussed in Chapter 6A.

¹⁹⁵ The active ingredient of a drug is the part that modifies the activity of the target protein and is responsible for its therapeutic effect.

¹⁹⁶ Inactive ingredients combined with the active ingredients of a drug are referred to as ‘excipients’. Excipients can help stabilise the drug or help more of the active ingredient reach its protein target. Excipients may also be used to make the manufacturing process more efficient.

¹⁹⁷ Assuming the new formulation patent will not be successfully challenged, an issue which will be discussed in the next section.

¹⁹⁸ 21 CFR § 320.1(e); see also *New Zealand Regulatory Guidelines for Medicines - Part D* (ed 6.15, Medsafe, November 2011).

the same chemical formula. Therefore, an enforceable composition of matter claim over a new formulation (A + B'), could prevent generic competition because the generic drug company can only obtain regulatory approval using the same chemical formula, which means it cannot 'design around' the new patent claim. Similarly, a recently-filed method of use claim over a known composition can prevent generic competition if the branded drug has not yet obtained regulatory approval, because a generic drug company could only obtain regulatory approval for the same use.¹⁹⁹

Therefore, arguably, it may be possible to use evergreening to prevent generic competition over unpatentable therapies by claiming new formulations or methods of use, particularly where the medicine has not yet obtained regulatory approval. For example, study of 1304 listed patents in the FDA's 'Orange Book'²⁰⁰ between 1988 and 2005 found that new formulation patents added an average of 6.5 years of patent life, and new method of use patents added 7.4 years, "at least nominally".²⁰¹

2 *When is patent evergreening ineffective?*

Although evergreening may be effective in some circumstances, as mentioned above, and discussed in more detail below, this section will provide several reasons why patent evergreening is largely ineffective.

Firstly, patents used in evergreening such as new formulations and new methods of use are referred to as "secondary" or "second-generation" patents, due to an increased likelihood of successful obviousness challenges.²⁰² For example, new formulations or derivative drugs are unpatentable for obviousness if their therapeutic properties were not unexpected to the relevant person skilled in the art.²⁰³ The combination of an active ingredient with a new inactive substance, but with known properties, is unlikely to be patentable unless there was some unexpected synergy.²⁰⁴

¹⁹⁹ Technically, the generic drug company could obtain regulatory approval by submitting its own clinical trial data supporting a new indication. However, as discussed above, this defeats the competitive advantage of the generic drug company.

²⁰⁰ The FDA's Orange Book is an informal publication listing each medicine that has received regulatory approval in the United States and any in-force patents over them. See discussion in Chapter Two.

²⁰¹ A Kapczynski, C Park, BN Sampat "Polymorphs and Prodrugs and Salts (Oh My!): an Empirical Analysis of 'Secondary' Pharmaceutical patents" (2012) 7(12) PLoS One 1 at 1.

²⁰² See T Cook "How IPRs, like Nature, Abhor a Vacuum, and What Can Happen When They Fill it - Lacunae and Overlaps in Intellectual Property" (2012) 17 JIPR 296 at 299; Grubb and Thomsen, above n 1, at 427.

²⁰³ See discussion of tests for inventive step in Chapter Two: *KSR International Co v Teleflex Inc* 550 US 398 (2007) at 421; *Portable Sawing Systems Ltd (in liq) v Lucas* [2006] NZSC 20 at [54].

²⁰⁴ *In re Kerkhoven* 626 F 2d 846 (CCPA 1980) at 850. See also *Assa Abloy New Zealand Ltd v Aluminium Systems NZ Ltd* HC Wellington CIV-2010-485-2, 7 March 2011 at [38].

Research has shown that secondary patents that do not claim a composition of matter are more likely to be challenged by generic drug companies.²⁰⁵ These patent challenges are particularly common for ‘blockbuster’ drugs because of the potential to take a share of the highly-profitable market.²⁰⁶ For example according to a study by the United States Federal Trade Commission, 73 per cent of patent challenges that go to trial are determined in favour of generic drug companies.²⁰⁷ Therefore, investors may be unwilling to develop a medicine that can only be protected with ‘secondary patents’.

*Pfizer, Inc v Apotex, Inc*²⁰⁸ illustrates the above point. Apotex successfully invalidated a patent over Pfizer’s lucrative hypertension drug, amlodipine besylate.²⁰⁹ A previous patent filed by Pfizer was cited as prior art,²¹⁰ because it disclosed amlodipine maleate, a different ‘salt’ formulation of amlodipine.²¹¹ The Court suggested it would be obvious to combine that patent with an academic publication which disclosed, *inter alia*, benzene sulphonate, which could be used to make amlodipine besylate.²¹² Pfizer argued that there was no motivation for a skilled person to combine the prior art citations because benzene sulphonate was rarely used.²¹³ However, the Federal Circuit held that “Pfizer has simply failed to prove that the results are unexpected” and “engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts”.²¹⁴

In *Alza Corp v Mylan Labs, Inc*,²¹⁵ the Federal Circuit invalidated a patent over a new controlled-release formulation of a urinary incontinence drug, because “a person of ordinary skill in the art would ... have perceived a reasonable likelihood of success”.²¹⁶ Similarly, in *Abbott Labs v Andrx Pharms, Inc*,²¹⁷ an injunction to prevent manufacture of a controlled-release antibiotic was denied by the Federal

²⁰⁵ W Tang “Revitalizing the Patent System to Incentivize Pharmaceutical Innovation: The Potential of Claims with Means-Plus-Function Clauses” (2013) 62 Duke Law Journal 1069 at 1094 citing SC Hemphill and BN Sampat “When Do Generics Challenge Drug Patents?” (2011) 8(4) Journal of Empirical Legal Studies 613 at 643.

²⁰⁶ Hemphill and Sampat above n 145, at 327

²⁰⁷ *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (Federal Trade Commission, 2002) at 13.

²⁰⁸ *Pfizer, Inc v Apotex, Inc* 480 F3d 1348 (Fed Cir 2007).

²⁰⁹ U.S. Patent No 4,879,303.

²¹⁰ U.S. Patent No 4,572,909.

²¹¹ Modifying an existing drug to create different pharmaceutical ‘salts’ is a common strategy in patent ‘evergreening’. See generally, R Chalmers “Evergreen or Deciduous? Australian Trends in Relation to ‘Evergreening’ of Patents” (2006) 30(1) Melbourne University Law Review 29.

²¹² *Pfizer, Inc v Apotex*, at 1363,

²¹³ At 1368.

²¹⁴ At 1396.

²¹⁵ *Alza Corp v Mylan Labs, Inc* 464 F3d 1286 (Fed Cir 2006).

²¹⁶ At 1295.

²¹⁷ *Abbott Labs v Andrx Pharms, Inc* 452 F 3d 1331 (Fed Cir 2006).

Circuit on the basis of obviousness because “the reduction of systemic side effects [of the drug] would not be surprising and would not be unexpected.”²¹⁸

With regard to new drug combinations, in *Merck & Co v Biocraft Labs, Inc.*,²¹⁹ the Federal Circuit held that the properties of a combination of two diuretics “was to be expected from the known natriuretic properties of the two diuretics.”²²⁰

Secondly, due to the inherent unpredictability of drug development, it is possible that the reformulated drug will be less effective than the ‘public domain’ version, which means society does not get the benefit of the best drug. This is more likely where an innovative drug is discovered through ‘phenotypic screening’ using animal models, which means that the mechanism of action is usually not known.²²¹

The third fundamental reason why ‘evergreening’ can be ineffective relates to the concept of free riding on the R&D costs of the innovator once they have validated the ‘proof of concept’. As an illustration, assume the original design for the Wright brothers’ airplane was in the public domain and could not be patented.²²² A patent attorney may point out that it is possible to obtain a patent over a minor improvement by modifying the aerofoils in a certain way, which is analogous to an ‘evergreening’ modification. As the aviation regulator will only allow the exact design plane to be built, once it has been proven as safe and effective, it will not be possible for competitors to ‘design around’ the patent that claims the original design and the improved aerofoils. However, the problem is that the Wright brothers have undertaken the significant risk of showing that aeroplanes having the original design are viable.²²³ Other companies will be able to make their own minor modifications and get to market at a much reduced risk, knowing that the basic design of the plane is functional. In an analogous way, an innovator which validates a drug target using a novel active ingredient may find that they cannot guarantee market exclusivity against free-riders developing ‘me-too’ drugs after they have spent considerable financial resources on validating the proof of concept.²²⁴

²¹⁸ At 1345–1347.

²¹⁹ *Merck & Co v Biocraft Labs, Inc* 874 F.2d 804 (Fed Cir 1989).

²²⁰ At 809.

²²¹ ‘Phenotypic screening’ occurs where the activity of a drug is assessed by ‘trial and error’ against living cell lines or animal models. See Chapter Two, n 157.

²²² In this illustration, the basic design of the airplane is analogous to a novel active ingredient of a drug.

²²³ By analogy to the drug development process, by researching a novel active ingredient, the first innovator has taken on a higher risk of failure of Phase I-III trials.

²²⁴ Notably, it has been argued that most drugs approved by the FDA are ‘me-too’ drugs that work in a similar way to existing drugs, and are not truly novel. The problem of innovators developing ‘me-too’ drugs to get a proportion of monopoly rents of a lucrative drug will be discussed further in this chapter below.

3 *When can patent evergreening be effective?*

Notwithstanding the above, ‘evergreening’ strategies can be very effective when combined with aggressive marketing campaigns. Esomeprazole (Nexium), a popular antacid, is a textbook example. Esomeprazole is a more recently-patented derivative of an older drug, omeprazole (Prilosec).²²⁵ As the patent over omeprazole was expiring, AstraZeneca began one of the largest marketing campaigns in the history of the United States, spending over USD 500 million per annum on direct-to-consumer advertising regarding ‘the purple pill’, which resulted in 40 per cent of patients switching over from generic omeprazole to Nexium.²²⁶ This was despite the fact that Nexium was ten times the price of generic omeprazole, and had similar efficacy.²²⁷

However, it is arguable that such evergreening strategies are only useful for commodified ‘high volume’ or ‘over-the-counter’ drugs which can be marketed directly to the public.²²⁸ For the same reason, Ultracet’s successful launch, considered above by Outterson,²²⁹ may have only been possible because it is an ‘over-the-counter’ painkiller drug. Patents may not even be necessary for such drugs. For example, Bayer’s Aspirin has been off-patent for 80 years, and still generates hundreds of millions of dollars in annual revenues because of strong branding.²³⁰

The recent emergence of a drug ‘repurposing’ industry - also referred to as drug ‘repositioning’ – is further evidence that evergreening techniques can indeed rescue patentability in some circumstances. In particular, drug repurposing companies may be willing to take either a failed or generic drug to market on the strength of a method of use or reformulation patent alone.²³¹ Repurposing failed or generic drugs is

²²⁵ Omeprazole is a racemic mixture comprising L and R isomers of the active ingredient. Esomeprazole is an L-isomer. These isomers are referred to as enantiomers or ‘mirror-images’ of a drug molecule. Typically, a drug contains both L and R isomers, which is referred to as a ‘racemic’ drug. Frequently one drug isomer has improved pharmacological properties over the other, therefore, patenting enantiomers is a common ‘evergreening’ technique.

²²⁶ Dwivedi, Hallihosur and Rangan, above n 189, at 328.

²²⁷ See B Goldacre *Bad Pharma: how drug companies mislead doctors and harm patients* (Fourth Estate, London, 2012) at 148.

²²⁸ Similarly, see discussion below regarding the profitable reformulation of a dietary supplement for fish oil, ‘Lovaza’.

²²⁹ Outterson, above n 63, at 48.

²³⁰ See N Kresge “Bayer Aspirin is Feeling Plenty Healthy” Bloomberg Businessweek (online ed, New York, 23 June 2011).

²³¹ AM Thayer “Repurposing Drugs” (2012) 90(40) Chemical and Engineering News 15 at 15; M Wadman “New Cures Sought from Old Drugs” (2012) 490 Nature 15 at 15; TT Ashburn and KB Thor “Drug repositioning: identifying and developing new uses for existing drugs” (2004) 3(8) Nature reviews Drug Discovery 673 at 673. Some publicly funded research agencies and charities are also involved in drug repurposing: see TI Oprea and others “Drug Repurposing from an Academic Perspective” (2011) 8(3-4) Drug Discov Tod Ther Strat 61 at 61; M Allison “NCATS launches drug repurposing program” (2012) 30(7) Nature Biotechnology 571 at 571.

approximately half the cost of typical drug development, because expensive pre-clinical and safety testing has already been completed.²³²

Large pharmaceutical companies also undertake drug repurposing,²³³ although typically only if the initial indication over a drug has failed.²³⁴ Notably, however, failed drug candidates have only 2.5 per cent chance of success for a second indication if the first indication fails versus 59.4 per cent chance of success for a second indication if the first indication achieves regulatory approval.²³⁵

Despite the higher risk of repurposing failed drugs, various drugs achieved financial success on the basis of a new method of use patent. One of the most famous examples is sildenafil, known as Viagra. This compound was originally developed by Pfizer as a hypertension medication and was subsequently repurposed to treat erectile dysfunction (ED). A method of use patent filed in 1994 was upheld by the District Court for the Eastern District of Virginia in *Pfizer, Inc v Teva Pharmaceuticals USA, Inc*,²³⁶ on the basis that, having regard to the prior art, it was not expected that oral administration of sildenafil would be useful to treat ED.²³⁷

Another famous repurposed drug is azidothymidine (AZT), a failed cancer drug synthesised in the mid-1960s, which was subsequently developed as a groundbreaking treatment for HIV.²³⁸ In *Burroughs Wellcome Co v Barr Laboratories*,²³⁹ five patents filed between 1985 and 1987 over the method of treating HIV with AZT were challenged by generic drug companies on the basis that government scientists conceived of the invention and were fraudulently omitted as inventors.²⁴⁰ Although a challenge on the basis of inventorship was not considered in the previous discussion of unpatentability factors, this is another example of ‘unpatentability under law’. The Federal Circuit upheld the patents on the basis that

²³² Roin, above n 43, at 47.

²³³ For example, the New Indications Discovery Unit at Novartis, the Common Mechanism Research at Bayer, and the Indications Discovery Unit at Pfizer.

²³⁴ Thayer, above n 228, at 16-17. This is because clinical trials for repurposing may uncover adverse effects which impact on the sales of the drug for the primary indication, as happened with Merck’s painkiller Vioxx when it was tested for use in colon cancer. Merck initiated the recall of Vioxx after the increase in adverse cardiovascular events was uncovered.

²³⁵ JA DiMasi and others “Clinical Approval Success Rates for Investigational Cancer Drugs” (2013) 94(3) *Clinical Pharmacology & Therapeutics* 329 at 329.

²³⁶ *Pfizer, Inc v Teva Pharmaceuticals USA, Inc* No 10-CV-00128 (ED Va Aug 12, 2011).

²³⁷ At 78.

²³⁸ S Broder “The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic” (2010) 85(1) *Antiviral Research* 1 at 4.

²³⁹ *Burroughs Wellcome Co v Barr Laboratories* 40 F 3d 1223 (Fed Cir 1994).

²⁴⁰ 35 USC § 102(f).

the scientists only “confirmed the operability of the inventions”²⁴¹ The method of use patents eventually expired in 2005 and were not invalidated.

Therefore, notwithstanding the weakness of ‘secondary patents’, it is possible to use evergreening techniques to ‘rescue’ failed drugs, particularly where the drug has not already achieved regulatory approval. However, in absence of empirical data, it is almost impossible to predict how many therapies for unmet medical needs have not been funded because secondary patents are considered too weak to withstand challenge.

Summary

Although empirical data is largely absent, the proportion of promising drug candidates that are screened or abandoned due to insufficient patent protection may be very high. To the extent these otherwise medically viable but unpatentable therapies cannot be ‘rescued’ using flexibilities within the patent system, they represent a significant problem. It may not be possible to obtain an enforceable patent over a repurposed drug if its properties are not sufficiently novel and unexpected in light of the prior art. While evergreening techniques are better at preventing generic competition over drugs that initially failed to achieve regulatory approval, these are less likely to become useful drugs.

Further, when a drug has become available as a generic, evergreening techniques are unlikely to be effective. In particular, unless a method of use or reformulation patent can effectively block ‘off-label’ competition by the generic drug, it will not be possible to enforce a monopoly price. Accordingly, finding new uses for generic drugs falls within a broader category of ‘unmonopolisable therapies’, which will now be discussed.

E The Problem of ‘Unmonopolisable Therapies’

For certain types of medical therapies, it is not possible to enforce the market exclusivity necessary to recover innovators’ costs, because patients can access the therapy at a cheap or nonexistent cost from multiple sources. The author refers to these as ‘unmonopolisable therapies’. The inability to practically enforce property rights over a therapy creates a situation referred to by economists as “the tragedy of the commons”, which occurs when a resource cannot be effectively or efficiently

²⁴¹ *Burroughs Wellcome Co v Barr Laboratories*, above n 237, at [35].

exploited.²⁴² In the present case, the ‘commons’ would be medically valuable information regarding which unmonopolisable therapies are safe and effective treatments, and the ‘tragedy’ is the lack of private incentives to generate this medically valuable information because of the inability to exclude others from using it. Commentators have noted the pharmaceutical industry’s bias towards monopolisable therapies at the expense of unmonopolisable therapies creates an environment where the latter are systematically marginalised.²⁴³

However, similarly to unpatentable therapies, the concept of unmonopolisable therapies does not imply an absolute standard. Rather, such therapies exist along a continuum from ‘less unmonopolisable’ to ‘highly unmonopolisable’ therapies. Kapczynski and Syed recognised this “continuum of excludability” for certain informational goods with medical value.²⁴⁴ Accordingly, various types of unmonopolisable therapies’ starting from the least to the most ‘unmonopolisable’, will be discussed below in turn: second uses of generic drugs, dietary supplements, diets, uses of readily available chemicals, lifestyle interventions and negative information about drugs.²⁴⁵

1 Second uses of generic drugs

Various scholars have considered how finding new uses for generic drugs lack private incentives for clinical trials because doctors are free to prescribe generic drugs for new indications ‘off-label’.²⁴⁶ The next sections will analyse the reasons why patents over methods of use and new formulations or combinations cannot prevent such ‘off-label’ competition in many cases.

²⁴² See generally, G Hardin “The Tragedy of the Commons” (2009) 1 *Journal of Natural Resources Policy Research* 243. See also M Abramowicz “Perfecting Patent Prizes” (2001) 56 *Vanderbilt Law Review* 114 at 181-183 and BD Wright “The Economics of Invention Incentives: Patents, Prizes, and Research Contracts” (1983) 73 *Amer Econ Rev* 691 at 694, discussing the “common pool problem”. Compare MA Heller and RS Eisenberg “Can Patents Deter Innovation?: The Anticommons in Biomedical Research” (1998) 280 *Science* 698 at 698.

²⁴³ Kapczynski and Syed, above n 44, at 1947; see also M Brezis “Big pharma and health care: unsolvable conflict of interests between private enterprise and public health” (2008) 45(2) *Israel Journal of Psychiatry and Related Sciences* 83 at 83.

²⁴⁴ Kapczynski and Syed, above n 44, at 1915-1916. Kapczynski and Syed refer to ‘highly non-excludable’ therapies, which is broadly synonymous with the term ‘unmonopolisable therapies’, coined by the author.

²⁴⁵ While surgical methods are also ‘unpatentable therapies’ subject to lack of patentability under law, they share many characteristics with unmonopolisable therapies, such as the impracticality of enforcing a monopoly price. As the author has already discussed examples of surgical methods which lack private incentives under the current system in the previous section, surgical methods will not be discussed in this section.

²⁴⁶ Eisenberg, above n 1, at 729; Syed, above n 133, at 3; H Grabowski and others “Does Generic Entry Always Increase Consumer Welfare” (2012) 67 *Food & Drug LJ* 373 at 382.

- (a) The problem with using method of use patents to enforce a monopoly

As noted in Chapter Two, generic drug companies can use ‘skinny labelling’ to ‘carve out’ a patented use from their labels. This means that method of use patents cannot stop the generic companies from supplying the drug to the market, provided that the patent over the original indication has expired.²⁴⁷

In New Zealand, the Pharmaceutical Management Agency (PHARMAC) helps indirectly enforce second medical use patents by not permitting the reimbursement of generic drugs which are prescribed for an indication covered by an innovator’s method of use patent. Pharmaceutical reimbursement will be discussed further in Chapter Four. However, the legal position in the United States does not encourage finding second uses for generic drugs. In particular, many state laws require mandatory substitution with a cheaper generic drug where it is available.²⁴⁸ Moreover, generic drug companies have successfully challenged attempts by innovator companies to leverage ‘method of use’ patents to prevent competition.²⁴⁹

Roin suggests solving this problem by imposing restrictions on ‘off-label’ prescribing by doctors and allowing limited access to electronic medical records in order for pharmaceutical companies to monitor infringement.²⁵⁰ However, this is likely to raise privacy issues, and as noted in Chapter Two, pharmaceutical companies are generally reluctant to sue doctors and patients,²⁵¹ as opposed to suing generic drug manufacturers.

Accordingly, as discussed above, carve-out labeling has become a common way for generics to enter the United States market, with 11 such drugs approved by the FDA in 2010.²⁵² Innovator companies struggle to enforce method of use patents against generic drug companies, even when it is known they can be used in an infringing manner. In *Warner-Lambert Co v Apotex*,²⁵³ the Federal Circuit held that mere knowledge by a generic drug company that its drugs are being used for a

²⁴⁷ See discussion of ‘skinny labeling’ in Chapter Two; see also A Rai “Use Patents, Carve-Outs, and Incentives - A New Battle in the Drug-Patent Wars” (2012) 367(6) *New England Journal of Medicine* 491; *Bristol-Myers Squibb v Shalala* 91 F 3d 1493 (DC Cir 1996).

²⁴⁸ HG Grabowski and JM Vernon “Substitution Laws and Innovation in the Pharmaceutical Industry” (1979) *Law and Contemporary Problems* 43 at 49, 56.

²⁴⁹ *Caraco Pharmaceutical Laboratories, Ltd. v Novo Nordisk A/S* 566 US __ (2012).

²⁵⁰ Roin, above n 41, at 59-65.

²⁵¹ Similar problems with enforceability occur for preventing widespread copyright infringement of music and film on the Internet. For this reason, while Roin’s proposal is worthy of merit, it will not be considered further in this thesis.

²⁵² Rai, above 244, at 491.

²⁵³ *Warner-Lambert Co v Apotex* 315 F 3d 1348 (Fed Cir 2003).

patented use is not sufficient to show ‘inducement’ to infringe, unless there is evidence the drug was being specifically promoted for the carved out use.²⁵⁴ It is unclear whether the Court would reach a similar position in New Zealand in light of broader grounds for contributory infringement under s 141 of the Patents Act,²⁵⁵ but in any case, it is likely that the generic drug company could take precautions to reduce the chance of contributory infringement.

(b) The problem with using reformulation and combination patents to enforce a monopoly

As noted in the previous section, patents over reformulations or combinations of generic drugs can prevent generic competition in some circumstances. However, according to Smith:²⁵⁶

The success of such composition of matter patents in protecting the repositioned drug product will depend in large part on the availability of generic products that can be substituted through off-label use to achieve the same therapeutic result as the repositioned product.

It is notable that where drug companies have attempted to create business models based on treating new diseases using combinations of generic drugs, these have generally not been successful.²⁵⁷ However, it is difficult to know whether a significant contributor to this failure was a lack of adequate support from investors due to the potential for ‘off-label’ generic competition, rather than lack of medical viability. It is likely that both factors would be relevant.

Further, any attempt to establish a business model using drug combinations or formulations is frustrated by the large number of pharmacies that provide ‘compounding’ services. This is a process whereby pharmacies can mix drug compounds in particular ratios or prepare specific formulations for their customers.

²⁵⁴ At 1363.

²⁵⁵ Patents Act 2013, s 141. In Australia, ‘contributory infringement’ of method of use claims by generic drug companies was successfully made out under the similarly-worded s 117 of the Patents Act 1990 (Cth): see *Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd v (No 2)* [2012] FCAFC 102.

²⁵⁶ RB Smith “Repositioned drugs: integrating intellectual property and regulatory strategies” (2011) 8 Drug Discovery Today: Therapeutic Strategies 131 at 133.

²⁵⁷ For example, NitroMed developed a new drug based on a combination of two generic drugs, which was found to be more effective in one racial group, African-Americans, but failed to achieve profitability: see D Armstrong “NitroMed Halts Marketing of Drug” *Wall Street Journal* (online ed, New York, 16 January 2008). Another company, CombinatoRx, based its business model on combining generic drugs to find new indications, but ultimately failed to produce any viable drugs: see A Pollack “CombinatoRx matches old generic drugs for powerful new medications” *New York Times* (online ed, New York, 1 July 2007); M Wadman “The Right Combination” (2006) 439 *Nature* 390; L Timmerman “CombinatoRx Reckoning Arrives: Stock Crashes on Failed Arthritis Trial” Xconomy <www.xconomy.com>.

This issue has been subject to controversy. In *Thompson v Western States Medical Center*²⁵⁸ the Supreme Court declared that an attempt by the FDA to restrict advertising for compounding services was unconstitutional. Currently the FDA permits the compounding of drugs provided that there are no public safety concerns and they are not “manufacturing” the drug in large quantities.²⁵⁹ Arguably, reluctance by the FDA to regulate compounding services will interfere with the ability of innovators to invest in this space.²⁶⁰

Therefore, the only way drug reformulations can defend the risk of ‘off-label’ competition from generic drugs is to demonstrate significantly increased safety, efficacy or convenience in the new patented formulation. As noted by Smith above, repositioning will not be successful if cheap generics can be substituted with the same clinical result.²⁶¹ The risk that the generic can be prescribed or compounded in a manner which achieves the same clinical result means that most drug companies have a significant private disincentive to repurpose ‘off-patent’ generic drugs.²⁶²

(c) Examples of second uses of generic drugs which lack private funding incentives

As noted above, doctors are legally allowed to prescribe medicines for ‘off-label’ uses.²⁶³ Accordingly, doctors play a major role in the discovery of new off-label uses for drugs.²⁶⁴ Roin notes the large potential social benefits from developing second uses for generic drugs.²⁶⁵ Medicines have many ‘off-target’ effects on the body, which

²⁵⁸ *Thompson v Western States Medical Center* 535 US 357 (2002).

²⁵⁹ See *Compliance Policy Guidance for FDA Staff and Industry Sec 460.200 Pharmacy Compounding* (United States Food and Drug Administration, May 2002) at 3.

²⁶⁰ An example is the case of Makena (hydroxyprogesterone caproate). K-V Pharmaceutical had achieved FDA approval over Makena in 2011 as a treatment for reducing risk of preterm births. The FDA initially indicated that pharmacies were not able to compound the drug, which had previously been available for approximately USD 300. As a result, K-V Pharmaceutical Company increased prices for the medicine to USD 30,000, resulting in a public backlash and retraction by the FDA: see generally J Armstrong “Unintended consequences — the cost of preventing preterm births after FDA approval of a branded version of 17OHP” (2011) 364(18) *N Engl J Med* 1689. As a result of the FDA’s change in policy, the future of K-V Pharmaceutical is in doubt: see E Silverman “FDA Statement about Makena Compounding Clouds KV Pharma’s Future” *Forbes* (online ed, New York, 18 June 2012).

²⁶¹ Smith, above n 256, at 136.

²⁶² See T Agres “New Life for Old Drugs” *Drug Discovery & Development* (online ed, 29 July 2011): ‘Some large drug companies are not completely convinced of the value of drug repurposing. This is particularly true when drugs have gone off-patent and generics are available. While the FDA will give marketing exclusivity for a new indication, there is little to prevent physicians from prescribing a generic version in its place. ‘Highlighting new uses for off-patent drugs may be exciting, but it is a challenge for companies to get enough value out of it to fund clinical trials’.

²⁶³ *Federal Trade Commission v Simeon Mgmt Corp* 391 F Supp 697 (N.D. Cal. 1975) at 706-707; Section 25 Medicines Act 1981.

²⁶⁴ See HJ Demonaco and others “The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies” (2006) 26 *Pharmacotherapy* 323 at 323.

²⁶⁵ Roin, above n 43, at 42-46.

means they are typically useful to treat more than one disease.²⁶⁶ A 2009 study suggested that the average drug has over 18 off-label indications which are prescribed by doctors in practice.²⁶⁷ However, the lack of private incentives for clinical trials of ‘off-label’ uses means that such therapies will often lack clinical trial data supporting safety and efficacy.²⁶⁸ The harm to the public caused by this lack of data could be considerable.

As noted in Chapter Two, approximately 80 per cent of current drug prescriptions are generic.²⁶⁹ The number of generic drugs on the market expands every time a drug loses patent protection, which increases the number of drugs that lack private incentives for finding new uses. For example, Roin notes how recent computational screening technology has identified many off-patent drugs that can be used as potential treatments for various diseases including cancer, Alzheimer’s disease, diabetes, stroke, tuberculosis, and malaria.²⁷⁰ The author has also identified a large number of unmonopolisable therapies involving off-patent generic drugs.²⁷¹ However, it is beyond the scope of this thesis to analyse each of these therapies in depth, although a couple will be mentioned.

Firstly, dichloroacetic acid, received considerable media attention as a potential cancer treatment, but no interest from the pharmaceutical industry, allegedly because the drug compound is off-patent.²⁷² Notably, this is despite the fact that a method of use patent was granted to the researchers.²⁷³

Secondly, the 1950s nonsteroidal anti-inflammatory drug oxyphenbutazone has demonstrated effectiveness against *Mycobacterium tuberculosis*, which typically requires many years of multi-drug therapy.²⁷⁴ The principal investigator stated: “[n]o drug firm will pay for clinical trials if they don’t expect to make a profit on the agent.

²⁶⁶ I Nobeli, AD Favia and JM Thornton “Protein promiscuity and its implications for biotechnology” (2009) 27(2) *Nature biotechnology* 157 at 157.

²⁶⁷ SM Walton and others *Developing Evidence- Based Research Priorities for Off-Label Drug Use* (Effective Health Care Research Report No. 12, May 2009) at 5.

²⁶⁸ M Oates “Facilitating Informed Medical Treatment through Production and Disclosure of Research into Off-Label Uses of Pharmaceuticals” (2005) 80 *NYU L Rev* 1272 at 1283.

²⁶⁹ *The Use of Medicines in the United States: Review of 2010* (IMS Institute for Healthcare Informatics, April 2011) at 3; Roin, above n 43, at 45.

²⁷⁰ At 44-45. See, for example, MJ Keiser and others “Predicting new molecular targets for known drugs” (2009) 462(7270) *Nature* 175.

²⁷¹ Examples of such therapies, along with other unmonopolisable therapies identified by the author are available at <www.crowdfundcures.org/about>.

²⁷² A Coghlan “Cheap, safe drug kills most cancers” (2007) 2857 *New Scientist* 13.

²⁷³ US Patent No 8,609,724.

²⁷⁴ B Gold and others “Nonsteroidal anti-inflammatory drug sensitizes *Mycobacterium tuberculosis* to endogenous and exogenous antimicrobials” (2012) 109(40) *Proceedings of the National Academy of Sciences* 16004 at 16004.

And that would be the case for an off-patent drug that people can buy over the counter for pain in most of the world.”²⁷⁵

2 Dietary supplements

Dietary supplements are also good candidates for unmonopolisable therapies, as they can legally be sold to any member of the public without conducting clinical trials, provided that they are not advertised as medicines. This is a regulatory ‘grey area’ with limited oversight, which can frustrate attempts to enforce a monopoly price.

(a) Regulation of dietary supplements

New Zealand defines dietary supplements as anything comprising an amino acid, edible substance, herb, mineral, synthetic nutrient, or vitamin.²⁷⁶ Under the Dietary Supplements Regulations 1985 of the Food Act 1981, dietary supplements can be placed on the market without clinical trials provided that therapeutic claims are not made.²⁷⁷

The United States has a similar definition for dietary supplements²⁷⁸ and allows them to be marketed without having to obtain regulatory approval, provided that such marketing is not false and misleading. The FDA has a list of pre-approved, carefully worded statements that can be made in respect to supplements or food, but do not allow health claims relating to the prevention or treatment of any disease.²⁷⁹

Despite this, there is a large amount of information, regarding the use of supplements in the treatment and prevention of disease.²⁸⁰ However, the unique regulatory environment means there is a lack of private incentives to conduct large clinical trials. In particular, because dietary supplements can be put on the market

²⁷⁵ “1950s NSAID Kills Resistant Tuberculosis” *Genetic Engineering and Biotechnology News* (online ed, New York, 11 September 2012).

²⁷⁶ Dietary Supplement Regulations 1985, reg 2A.

²⁷⁷ Reg 11. See also Medicines Act 1981, s 4, s 58(1).

²⁷⁸ Dietary Supplement Health and Education Act of 1994 21 USC § 321.

²⁷⁹ “Health Claims Meeting Significant Scientific Agreement (SSA)” (19 July 2013) Food and Drug Administration <www.fda.gov>. For example, dietary supplements are permitted to make claims that the product supports the structure of function of the body, for example, ‘calcium supplements help build strong bones’), which are called ‘structure/function’ claims. These can be contrasted with medical claims, for example, ‘calcium supplements can be used to treat osteoporosis’.

²⁸⁰ “Integrative Medicine. About Herbs, Botanicals, and other products” Memorial Sloan Kettering Cancer Centre <www.mskcc.org>. This website has a comprehensive list of dietary supplements and herbs with scientific evidence regarding their efficacy for treatment and prevention of disease.

without requiring regulatory approval,²⁸¹ method of use patents will not be able to enforce a monopoly price against competition. Paradoxically, these regulations can further disincentivise finding new medical uses for dietary supplements, because of the risk they would be considered licensed drugs. For example, any claim that a dietary supplement is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals”, will mean that it will be considered a drug that requires regulatory approval.²⁸² Therefore, the more clinical evidence available that dietary supplements may be useful as treatments for disease, the more likely they will attract adverse attention from regulatory authorities.

(b) Problems with monopolising dietary supplements

Notably, in some cases, regulatory oversight triggered by scientifically demonstrating medicinal use of dietary supplements can be leveraged by companies that wish to monopolise them. In particular, in some circumstances, the FDA has removed competing dietary supplements from the market that contain a naturally occurring active ingredient that has received regulatory approval for treatment of a disease on the basis that the supplements contain an ‘unlicensed drug’.

A notable example is red yeast rice (RYR), used traditionally in China for circulatory disorders, which was discovered to contain a naturally occurring form of the cholesterol lowering drug lovastatin. As a result, in 1998, the FDA controversially banned RYR dietary supplements containing lovastatin.²⁸³

In another example, dietary supplements containing pyridoxamine, a form of vitamin B6, were removed by the FDA pursuant to a ‘citizen petition’ by Biostratum, which had filed a patent application over pyridoxamine to treat diabetic neuropathy.²⁸⁴ The FDA petition was successful on the basis that it was considered a drug under investigation.²⁸⁵ The outcome of clinical trials is still uncertain and pyridoxamine has not received regulatory approval.²⁸⁶

²⁸¹ In fact, the FDA can only remove a dietary supplement from the market if it is adulterated with an ingredient that ‘presents a significant or unreasonable risk of illness or injury’: see 21 USC § 342(f).

²⁸² Federal Food, Drug, and Cosmetic Act, s 201(g)(1)(B).

²⁸³ See M McCarthy “FDA bans red yeast rice product” (1998) 351(9116) *The Lancet* 1637.

²⁸⁴ US Patent Application No 20130011379. This patent was filed on 13 April 2012, but was abandoned on 9 January 2013 due to failure to respond to an examination report.

²⁸⁵ Letter from MA Chappel (Acting Associate Commissioner for Regulatory Affairs, Food and Drug Administration) to KM Sanzo (External legal counsel, Biostratum) regarding FDA Response to Biostratum, Inc Citizen Petition (12 January 2009) at 6.

²⁸⁶ “NephroGenex acquires rights to the diabetic nephropathy drug” (10 May 2006) *Renal Business Today* <www.renalbusiness.com>.

Similarly, colchicine is a natural plant extract that was available as a cheap dietary supplement to treat gout, however, it had not been proven safe and effective. Controversially, URL Pharma paid for the clinical trials required to obtain regulatory approval for using colchicine to treatment of familial Mediterranean fever, obtaining 7 years market exclusivity as an orphan drug designation.²⁸⁷ Subsequently, the FDA removed all the unlicensed versions of colchicine, resulting in the price rising from \$0.09 to \$4.85 per tablet.²⁸⁸

Despite this, for many dietary supplements, it is impossible for the FDA to remove them from the market. In particular, under the ‘grandfathering’ provisions of the Dietary Supplement Health and Education Act of 1994, the FDA cannot remove a supplement which was available in the United States before 1994.²⁸⁹ Colchicine was an exception because it is a rare example of a supplement that was already deemed an ‘unlicensed drug.’ However, the grandfathering provisions would apply to many vitamins and common supplements that may be promising treatments for many diseases. Some examples include Vitamin C in treatment of cancer,²⁹⁰ HIV,²⁹¹ drug resistant tuberculosis²⁹² and Alzheimer’s disease,²⁹³ vitamin B to prevent dementia²⁹⁴ and colon cancer,²⁹⁵ vitamin D for treatment and prevention of breast cancer²⁹⁶ and Crohn’s disease,²⁹⁷ and Vitamin E for treating Alzheimer’s disease.²⁹⁸ These

²⁸⁷ Orphan drug exclusivity will be discussed in Chapter 6A.

²⁸⁸ See AS Kesselheim and DH Solomon “Incentives for drug development--the curious case of colchicine” (2010) 362 (22) *N Engl J Med* 2045 at 2046.

²⁸⁹ See 21 USC § 321(ff)(3)(B).

²⁹⁰ C Kuiper and others “Low Ascorbate Levels Are Associated with Increased Hypoxia-Inducible Factor-1 Activity and an Aggressive Tumor Phenotype in Endometrial Cancer” (2010) 70 *Cancer Res* 5749; LJ Hoffer and others “Phase I clinical trial of i.v. ascorbic acid in advanced malignancy” (2008) 19(11) *Annals of Oncology* 1969.

²⁹¹ S Harakeh, RJ Jariwalla and L Pauling “Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells” (1990) 87(18) *Proc Natl Acad Sci* 7245.

²⁹² C Vilchèze and others “Mycobacterium tuberculosis is extraordinarily sensitive to killing by a vitamin C-induced Fenton reaction” (2013) 1881 *Nature Communications* 4.

²⁹³ DJ Foley and LR White “Dietary intake of antioxidants and risk of Alzheimer disease: food for thought” (2002) 287(24) *JAMA* 3261.

²⁹⁴ G Douaud and others “Preventing Alzheimer’s disease-related gray matter atrophy by B-vitamin treatment” (2013) 110(23) *PNAS* 9523.

²⁹⁵ SC Larsson, N Orsini, A Wolk “Vitamin B6 and risk of colorectal cancer: a meta-analysis of prospective studies” (2010) 303(11) *JAMA* 1077; SC Larsson, E Giovannucci, and A Wolk “Vitamin B6 Intake, alcohol consumption, and colorectal cancer: A longitudinal population-based cohort of women” (2005) 128 *Gastroenterology* 1830; E Theodoratou and others “Dietary vitamin B6 intake and the risk of colorectal cancer” 17(1) *Cancer Epidemiol Biomarkers Prev* 171.

²⁹⁶ Saint Louis University Medical Center “Vitamin D holds promise in battling a deadly breast cancer” (22 January 2013) *ScienceDaily* <www.sciencedaily.com>; K Robien, GJ Cutler, and D Lazovich “Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women’s Health Study” (2007) 18(7) *Cancer Causes Control* 775; ML Neuhauser and others “Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors” (2008) 88(1) *Am J Clin Nutr* 133.

²⁹⁷ SP Jørgensen and others “Clinical trial: vitamin D3 treatment in Crohn’s disease - a randomised double-blind placebo-controlled study” (2010) 32(2) *Aliment Pharmacol Ther* 377.

²⁹⁸ MW Dysken and others “Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA Cooperative randomized trial” (2014) 311(1) *JAMA* 33.

supplements are ubiquitous, and an attempt to enforce patent protection over them would be futile. It would be like an attempt to ‘patent the sun’, even if this were possible.²⁹⁹

(c) Problems with patenting dietary supplements

Despite the above, the primary way to enforce a monopoly price over a supplement is to patent a new composition of matter which will not be susceptible to competition. Many drugs were developed by medicinal chemists by extracting and concentrating active chemicals from natural products and turning them into ‘drug-like’ compounds.³⁰⁰ However, in practice, it is difficult to obtain a patent over the active chemical of a natural product due to anticipation or obviousness, especially if their properties are already known in traditional medicine or have been prior published in academic research.

In *Ex parte Pfizer, Inc.*,³⁰¹ the BPAI cancelled a claim by Pfizer over the use of phosphodiesterase inhibitors to treat ED³⁰² in light of the traditional use of the herb Yin Yang Huo (Horny Goat Weed). The latter contained an ingredient (icariin) that was a weak selective phosphodiesterase inhibitor. As a result, Pfizer could not prevent competition from other ‘me-too’ phosphodiesterase inhibitor drugs developed by Eli Lilly (makers of Cialis) and Bayer (makers of Levitra).³⁰³

In *Creagri, Inc v Pinnacle Inc.*,³⁰⁴ the District Court of the Northern District of California invalidated Cre-Agri’s patents over a dietary supplement containing the phenolic compounds hydroxytyrosol and oleuropein, which are naturally present in olive oil.³⁰⁵ In particular, one of its patents was anticipated by a patent and academic

²⁹⁹ In fact, a major source of vitamin D for humans is from sunlight, in particular, exposing the skin to ultraviolet light. Accordingly, the use of vitamin D to treat disease could also be an unmonopolisable ‘lifestyle intervention’ discussed below.

³⁰⁰ For example, an ingredient from willow bark, salicylic acid, was modified and chemically synthesised as acetylsalicylic acid (Aspirin) in 1897 by Bayer into a less-irritating version: see RL Mueller RL and S Scheidt “History of drugs for thrombotic disease. Discovery, development, and directions for the future” (1994) 89 *Circulation* 432 at 436. Examples of more modern drugs developed from natural sources include digoxin (brand name Lanoxin), which is derived from the foxglove plant (*Digitalis lanata*), and is approved for treatment of various heart conditions and capsaicin (brand name Qutenza), which is a chemical isolated from chili peppers, and approved as a dermal patch for treatment of neuropathic pain.

³⁰¹ *Ex parte Pfizer, Inc* No 2009-004106 (BPAI February 12, 2010).

³⁰² US Patent 6,469,012 (filed Mar 4 1996, issued Oct 22 2002).

³⁰³ See *Pfizer Inc., et al v Lilly ICOS LLC et al* No 02-1561 (D Del Oct 22, 2002).

³⁰⁴ *Creagri, Inc v Pinnacle Inc* No 11-CV-6635-LHK (ND Cal January 1, 2013).

³⁰⁵ At 6.

publication³⁰⁶ and the other was held invalid due to lack of written description and utility.³⁰⁷

Accordingly, pharmaceutical companies that attempt to develop dietary supplements for mainstream medicinal uses struggle to become financially viable. Scotia Pharmaceuticals Limited failed to successfully promote development of gamma-linolenic acid - which is a fatty acid contained in evening primrose oil - as a pharmaceutical product.³⁰⁸ It has been recognised that the difficulty in obtaining patent protection for gamma-linolenic acid created a barrier to development.³⁰⁹ Ultimately, the failure may have been due to a lack of demonstrated efficacy,³¹⁰ although conceivably, lack of funding may have contributed to this.³¹¹

Despite this, some dietary supplements that have been patented as new formulations have generated ‘blockbuster’ revenues. An example is Lovaza, a new formulation of fish oil used for treatment of cardiovascular disease, with a ‘me-too’ competitor, Vascepa, on the horizon, despite the fact that these treatments may offer nominal benefits.³¹²

Another example of a ‘blockbuster’ dietary supplement is Niaspan, available on prescription for treatment of cardiovascular disease. Niaspan generated over USD 5.11 billion in sales between 1997 and 2012,³¹³ despite being a slow release formulation of a common dietary supplement, niacin, and recent comparative trials showing no benefit from taking this ‘drug’.³¹⁴

However, notably, these cases are similar to the ‘evergreening’ of Ultracet and Nexium above, where a broad, high volume market - heart disease - and strong marketing has helped achieve commercial success.³¹⁵ It is questionable whether the

³⁰⁶ At 7.

³⁰⁷ At 20. See also S Barazza “Slipping on (olive) oil: key patents on olive-derived phenolic supplements declared invalid” (17 January 2014) PatLit <www.patlit.blogspot.com>.

³⁰⁸ P Lapinskas “The development of gamma-linolenic acid (GLA) as a pharmaceutical product” (paper presented to Speciality Chemicals for the 21st Century (International Seminar), Valbonne, France, 16-17 September 1999) .

³⁰⁹ At [29].

³¹⁰ HC Williams “Editorial: Evening primrose oil for atopic dermatitis - Time to say goodnight” (2003) 327(7428) *BMJ* 1358 at 1358.

³¹¹ There is a ‘catch-22’ situation for therapies which lack a viable market; these often have limited evidence of safety and efficacy due to a lack of incentive to fund large clinical trials.

³¹² M Herper “Could A Fish Oil Backlash Wash Out Amarin Pharmaceuticals?” *Forbes* (online ed, New York, 19 November 2012).

³¹³ D Armstrong “Abbott Doubled Niaspan U.S. Sales Before Trials Cut Use” (11 June 2013) Bloomberg <www.bloomberg.com>.

³¹⁴ H Krumholz “Five Lessons From Niaspan's Disappointing Study” *Forbes* (online ed, New York, 31 May 2011).

³¹⁵ Herper, above n 312.

same approach would work for a dietary supplement used to treat a disease with high social costs, but low marketing potential.

However, with regard to reformulations of generic drugs, already discussed above, unless a reformulated supplement will perform significantly better than the supplement already available on the market and taken ‘off-label’, it is unlikely that a private company will fund clinical trials.

3 *Diets*

Diets are examples of ‘highly unmonopolisable therapies’. Obviously, it is not possible to enforce a monopoly price over whole foods if they are readily available. Various studies have shown the potential efficacy of foods for the prevention and treatment of disease including osteoarthritis,³¹⁶ cancer,³¹⁷ and cardiovascular disease.³¹⁸ However, large, well-controlled clinical trials regarding diets are typically rare or non-existent.

Research suggests that many of the medicinal benefits of fruits and vegetables are due to the complex additive and synergistic combination phytochemicals present in whole foods.³¹⁹ Even if extracting and patenting these phytochemicals as a drug were possible, it may not be as safe or effective as whole foods.

According to the World Health Organization, cardiovascular disease and cancer are the leading causes of death worldwide, 17 million and 7.6 million

³¹⁶ FMK Williams and others “Dietary garlic and hip osteoarthritis: evidence of a protective effect and putative mechanism of action” (2010) 11(1) BMC Musculoskeletal Disorders 280; M Roberts “Broccoli slows arthritis, researchers think” (27 August 2013) BBC News <www.bbc.com>.

³¹⁷ NP Seeram “Berry fruits for cancer prevention: current status and future prospects” (2008) 56(3) Journal of Agricultural and Food Chemistry 630; RW Owen and others “The antioxidant/anticancer potential of phenolic compounds isolated from olive oil” (2000) 36(10) European Journal of Cancer 1235; T Kim and others “Ethyl alcohol extracts of *Hizikia fusiforme* sensitize AGS human gastric adenocarcinoma cells to tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis” (2009) 12(4) Journal of Medicinal Food 782; V Benetou and others “Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort” (2008) 99(1) British Journal of Cancer 191.

³¹⁸ V Kapil and others “Inorganic Nitrate Supplementation Lowers Blood Pressure in Humans: Role for Nitrite-Derived NO” (2010) 56 Hypertension 274; K Ried and others “Effect of garlic on blood pressure: a systematic review and meta-analysis” (2008) 8 BMC Cardiovasc Disord 13; K Ried and others “Does chocolate reduce blood pressure? A meta-analysis” (2010) 8 BMC Med 39; SA Mortensen and others “The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure. Results from the Q-SYMBIO study” (2013) Heart Failure Congress 2013 Final Programme Number 440; S Tokunaga and others “Green tea consumption and serum lipids and lipoproteins in a population of healthy workers in Japan” (2002) 12(3) Ann Epidemiol 157.

³¹⁹ RH Lui “Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals” (2003) 78(3) Am J Clin Nutr 517S.

respectively, in 2008.³²⁰ In New Zealand, cardiovascular disease and cancer caused 35 per cent of all health losses.³²¹ The large number of potentially cost-effective treatments for cardiovascular disease and cancer based on diets and dietary supplements highlight the significant impact on society's disease burden, and increased pressure on its healthcare budget, due to a lack of private incentives to fund larger clinical trials.

4 *Uses of readily available chemicals*

There are highly unmonopolisable therapies involving readily available chemicals that can have significant health impact. For example, the discovery of oral rehydration therapy (ORT), which involves the administration of a salt, sugar and water solution for the treatment of cholera, has been stated as “potentially the most important medical advance [of the 20th] century”.³²² Between 1980 and 2006, ORT has reduced deaths from cholera from 5 million to 2 million per annum, the majority of which are children under the age of five.³²³ Ruxin notes the failure to adopt this cheaper and superior treatment in the United States is a result of the perverse incentives for hospitals to use an expensive therapy³²⁴ in order to “maximise insurance reimbursement”.³²⁵ Another example of using readily available chemicals is the injection of methylene blue for the effective treatment of lower back pain.³²⁶

5 *Lifestyle interventions*

Lifestyle interventions are also highly unmonopolisable therapies that may have significant medical benefits, but lack private incentives for clinical trials. For example, studies have shown that exercise can be as effective as anti-depressants,³²⁷

³²⁰ A Alwan (ed) “Global status report on noncommunicable diseases” (World Health Organization, 2011) at 9.

³²¹ *Health Loss in New Zealand: A report from the New Zealand Burden of Diseases, Injuries and Risk Factors Study, 2006–2016* (Ministry of Health, Wellington, 2013).

³²² (ed) “Water with Sugar and Salt” (1978) 312 (8084) *The Lancet* 300 at 300. In particular, the treatment protocol requires 30mls of sugar with 2.5mls of salt in 1 litre of water, administered to the patient in the same quantities as fluid is lost.

³²³ At 300.

³²⁴ The alternative to ORT is the intravenous administration of fluid, which requires a longer recovery time.

³²⁵ JN Ruxin “Magic bullet: the history of oral rehydration therapy” (1994) 38(4) *Medical History* 363 at 397. See Chapter Four discussing pharmaceutical reimbursement in the United States.

³²⁶ B Peng and others “Intradiscal methylene blue injection for the treatment of chronic discogenic low back pain” (2007) 16(1) *European Spine Journal* 33; B Peng and others “A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain” (2010) 149(1) *Pain* 124. Notably, this treatment was shown to have a success rate of over 91 per cent.

³²⁷ ME Donaghy “Exercise can seriously improve your mental health: Fact or fiction?” (2007) 9(2) *Advances in Physiotherapy* 76 at 76.

and lowers future risk of depression.³²⁸ Other studies have shown the significantly adverse health effects of prolonged sitting.³²⁹ Commentators have noted the adverse health consequences of the pharmaceutical industry's bias away from cheap, health promoting therapies such as cardiac rehabilitation which lack adequate support.³³⁰

6 *Negative information*

Negative information, such as information about the harmful effect or inferiority of certain drugs³³¹ and the extent that environmental chemicals or certain foods may have a causative link to disease,³³² is highly unmonopolisable.³³³ Similarly, pharmaceutical companies are unlikely to fund research which shows that less medication is required to achieve the same or better effect as this will adversely affect sales.³³⁴

This problem is not unique to pharmaceuticals, and various studies have shown that supplements may also cause harm. For example, a recent study showed that high intake of omega-3 fatty acids either from supplements or fish results in over twice the risk of developing aggressive prostate cancer.³³⁵ A large scale study of over 35,000 men in 2011 found that vitamin E supplementation also significantly increased

³²⁸ G Mammen and G Faulkner "Physical Activity and the Prevention of Depression: A Systematic Review of Prospective Studies" (2013) 45(5) *American Journal of Preventive Medicine* 649 at 649.

³²⁹ R Seguin and others "Sedentary Behavior and Mortality in Older Women: The Women's Health Initiative" (2014) 46(2) *American Journal of Preventive Medicine* 122 at 122; MT Hamilton and others "Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease" (2007) 56(11) *Diabetes* 2655.

³³⁰ Brezis, above n 243, at 88.

³³¹ BR Davis and others "Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT)" (2002) 288(23) *JAMA* 2981. This well-known clinical trial demonstrated that more expensive patented 'ACE-inhibitor' hypertensive medicines were actually inferior to cheaper generic diuretic pills. Even excluding the cost of potential harm to patients from ACE-inhibitors, the ALLHAT researchers [at 2994] estimated that USD 3.1 billion could have been saved between 1982 and 1992 if doctors had not switched to the newer patented medicines.

³³² For example, exposure to environmental pollutants and chemicals, nutritional deficits, and smoking have been found to play a role in development of heart disease: see TE O'Toole "Environmental risk factors for heart disease" (2008) 23(3) *Reviews on Environmental Health* 167 at 167. Further, according to the World Health Organization over 30 per cent of cancer deaths can be prevented by avoiding certain environmental risk factors: see "Cancer: Fact sheet No 297" (February 2014) World Health Organisation <www.who.int>.

³³³ Kapczynski and Syed. above n 46, at 1923-1925.

³³⁴ For example, in New Zealand, PHARMAC recently funded a clinical trial to compare efficacy of a 9-week regimen of Herceptin versus 12 months: see S Metcalfe and J Evans "PHARMAC responds on Herceptin assumptions and decisions" (2007) 120(1260) *NZMJ* 1.

³³⁵ TM Brasky and others "Serum Phospholipid Fatty Acids and Prostate Cancer Risk: Results From the Prostate Cancer Prevention Trial" (2011) 173(12) *Am J Epidemiol* 1429.

the risk of prostate cancer.³³⁶ Finally, a 2012 study by the well-respected Cochrane Collaboration found “[b]eta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A”.³³⁷

Summary

The sections above have highlighted the social need for incentivising large clinical trials to validate the health impact of unmonopolisable therapies. Although patents have been used over reformulated generic drugs and dietary supplements that treat high-volume therapies such as cardiovascular disease, this is likely due to the power of direct marketing. This can be contrasted with therapies that are not easily commodified. It is impossible to enforce patents over highly unmonopolisable therapies such as diets, readily available chemicals, lifestyle interventions and negative information about drugs. Crucially, the inability to enforce property rights over unmonopolisable therapies has no correlation to the medical value of the information generated. This represents a significant gap in the current patent system as a mechanism to incentivise the development of socially valuable therapies.

F The Problem of ‘Unprofitable Therapies’

There are certain therapies that are inherently ‘unprofitable’, irrespective of whether exclusivity can be enforced, as there will be insufficient return on investment to justify development. While ‘unprofitable therapies’ is a catch-all category in the sense that unpatentable and unmonopolisable therapies are also unprofitable, the author uses this term to refer to distinct types of therapies.

Under the current system, the social value of a therapy does not always reflect its private value. However, the latter is the most important consideration when a pharmaceutical executive is making a ‘Go/No-Go’ funding decision. For example, when deciding which projects will be funded, the pharmaceutical executive calculates the ‘net present value’ (NPV) of the project, which takes into account risk of failure and likely future profits.³³⁸

³³⁶ EA Klein and others “Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT)” (2011) 306(14) JAMA 1549 at 1549.

³³⁷ G Bjelakovic and others “Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases” (2012) 2 Cochrane Database Syst Rev 1 at 1-2.

³³⁸ JJ Stewart, PN Allison and RS Johnson “Putting a price on biotechnology” (2001) 19(9) Nat Biotechnol 813 at 813.

Projan illustrates how the NPV of medicines can vary by therapeutic class, as shown in Table 1 below.³³⁹

Table 1: Table showing risk adjusted NPV (in millions of USD) of a new drug by therapeutic class³⁴⁰

Project therapeutic class	Risk adjusted NPV x\$1,000,000
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable Antibiotic (Gm+)	100
MS- Psoriasis	60
Liver Transplant	20
Oral Contraceptive	10

With reference to Table 1, it can be seen that musculoskeletal diseases which require ongoing maintenance medication for many years, such as arthritis, have the highest NPV. Neurological diseases such as depression, schizophrenia, Alzheimer’s disease and dementia also have a high NPV, because of the need to take ongoing medication.

By contrast, ‘one off’ treatments, such as vaccines, are much less commercially attractive to pharmaceutical companies, despite their potential to have a large health impact.³⁴¹ Similarly, there are limited private incentives to develop antibiotics due to the fact that they are more effective, the less they are used.³⁴² A course of antibiotics is also short, because a patient typically recovers quickly, and when resistance develops, the drug becomes obsolete.³⁴³ Therefore, antibiotics are ‘unprofitable’ to the extent that regulatory exclusivity or patent protection may not be enough to incentivise development.³⁴⁴

³³⁹ SJ Projan “Why is big Pharma getting out of antibacterial drug discovery?” (2003) 6 Current Opinion in Microbiology 427.

³⁴⁰ At 428.

³⁴¹ PA Offit “Why are pharmaceutical companies gradually abandoning vaccines?” (2005) 24(3) Health Affairs 622 at 622.

³⁴² In fact, the current system incentivises the innovator to encourage the overprescribing of antibiotics because they have a limited time under patent.

³⁴³ See Projan, above n 337, at 428; see also Brezis, above n 241, at 85.

³⁴⁴ ML Katz and others “Where have all the antibiotic patents gone?” (2006) 24 Nature Biotechnology 1529 at 1531.

According to a 2004 report by the Infectious Diseases Society of America, of more than 506 drugs in development, only five were for new antibiotics.³⁴⁵ The same report indicated that over 70 per cent of pathogenic bacteria were resistant to at least one antibiotic.³⁴⁶ The lack of new antibiotics is recognised as a major global health issue, especially in light of the emergence of antibiotic-resistant superbugs such as Methicillin-resistant *Staphylococcus aureus*.³⁴⁷

Moreover, there is little private incentive to develop medicines specifically for third world or so-called ‘neglected diseases’, which would have the greatest impact on global health. For example, it is estimated that only 10 per cent of global R&D spending is spent on treatments that relate to 90 per cent of the global disease burden.³⁴⁸ Drugs for neurological disorders or cancers are 13 times more likely to achieve market approval than drugs for neglected diseases.³⁴⁹ The overall numbers of approved drugs for neglected diseases bear witness to this market failure for unprofitable therapies. For example, of the 1393 new chemical entities achieving regulatory approval between 1975 and 1999, only 16, or 1.1 per cent were for neglected diseases.³⁵⁰ Similarly, between 2000 and 2011, of 850 approved therapeutic products, only 37, or 4 per cent, were for neglected diseases.³⁵¹

In respect of stimulating R&D for neglected diseases, the Commission on Intellectual Property Rights established by the British government, noted that intellectual property protection “hardly plays any role at all, except for those diseases where there is a large market in the developed world (for example, diabetes or heart disease)”.³⁵² Because drug companies are unlikely to recoup their investment from developing countries, under the current patent system, there is a significant lack of incentive to create medicines for neglected disease.

³⁴⁵ *Bad bugs, no drugs: as antibiotic R&D stagnates... a public health crisis brews* (Infectious Diseases Society of America, 2004) at 14.

³⁴⁶ At 9.

³⁴⁷ *The evolving threat of antimicrobial resistance: Options for Action* (World Health Organization 2012) at 4.

³⁴⁸ A Kapczynski and others “Addressing global health inequities: An open licensing approach for university innovations” (2005) 20 *Berkley Technology Law Journal* 1031 at 1037; R Hecht, P Wilson and A Palriwala “Improving Health R&D Financing for Developing Countries: A Menu of Innovative Policy Options” (2009) 28 *Health Affairs* 974 at 975; P Stevens *Diseases of poverty and the 10/90 Gap* (International Policy Network, November 2004).

³⁴⁹ P Trouiller and others “Drug development for neglected diseases: a deficient market and a public-health policy failure” (2002) 359(9324) *Lancet* 2188 at 2188.

³⁵⁰ At 2188.

³⁵¹ B Pedrique and others “The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment” (2013) 1 *The Lancet Global Health* 371 at 374.

³⁵² JH Barton and others *Integrating intellectual property rights and development policy: report of the commission on intellectual property rights* (Commission on Intellectual Property Rights (UK), 2002) at 33.

The 2012 Global Funding for Innovation in Neglected Diseases (G-FINDER) report confirmed the R&D funding disparity under the current system.³⁵³ For example, in 2011, two-thirds of funding for research of neglected diseases came from high-income countries (USD 1.9 billion), and the rest from charities (USD 570.6 million) and pharmaceutical companies (USD 525.1 million).³⁵⁴

Another category of ‘unprofitable therapies’ are ‘orphan drugs’, which are therapies for very rare diseases. Because of the small commercial market, companies were unwilling to invest in these therapies.³⁵⁵ However, since orphan drug reforms were implemented in the United States in 1983, which provided seven years of market exclusivity and 50 per cent tax breaks, they have become very profitable. Chapter 6A will consider these orphan drug reforms in more detail.

Summary

To the extent the above-mentioned ‘unprofitable therapies’ lack incentives for private funding under the current system, it is unlikely that anything but publicly funded clinical trials will be available to validate them. The absence of additional private incentives for development of such therapies causes a significant impact on disease burden, particularly in the developing world.

G Other Problems with the Patent System

In the remaining sections of this chapter, problems with the patent system other than the aforementioned gaps in private funding incentives for unpatentable, unmonopolisable and unprofitable therapies will be discussed.

1 The use of litigation and settlement agreements to prevent competition by generic drug companies

As discussed in Chapter Two, the Hatch-Waxman Act of 1984 was implemented in the United States to facilitate generic competition while balancing the needs of innovators by providing a minimum period of exclusivity. In particular, after a data

³⁵³ M Moran and others *G-FINDER 2012 Neglected disease R&D: A five-year review* (Policy Cures, 2012) at 10.

³⁵⁴ At 11. Funding from private pharmaceutical companies here is likely to be on the basis of corporate social responsibility.

³⁵⁵ L Rin-Laures and D Janofsky “Recent developments concerning the Orphan Drug Act” (1991) 4 *Harv J Law & Tec* 4 269 at 269.

exclusivity period of five years, a generic drug company can file a ‘Paragraph IV’ challenge to the validity of the innovator’s patent. The first generic drug company that successfully invalidates an innovator’s patent is provided 180-days of exclusivity. This has led to a significant increase in litigation, with the chance of a patent challenge to an innovator’s drug increasing from 17 per cent in 1995 to 81 per cent in 2012.³⁵⁶

Since then, commentators have noted that innovator companies and generic companies are entering into lucrative ‘pay-for-delay’ agreements to keep generic drugs off the market, which results in higher monopoly prices.³⁵⁷ In *Federal Trade Commission v Actavis*,³⁵⁸ the Supreme Court of the United States held that while such ‘pay-for-delay settlements’ are not presumptively illegal, they can be challenged by the Federal Trade Commission (FTC) for being anti-competitive.

There has also been an increase in the launch of ‘authorised generics’ by innovator companies. Authorised generics are when the innovator enters the market with cheap versions of its own medicine, which undermines the profits of a generic company during their 180-day exclusivity period, and their incentives to challenge patents.³⁵⁹ Such developments are controversial, and the FTC has noted that innovator companies may use the threat of launching authorised generics as a bargaining chip when entering ‘pay-for-delay settlements’ with generic drug companies.³⁶⁰

As noted in Chapter Two, according to the Generic Pharmaceutical Association, increases in generic competition pursuant to patent challenges under the Hatch Waxman Act has resulted in USD 1.1 trillion in savings over the past 10 years.³⁶¹ However, according to the FTC, pay-for-delay settlements are estimated to add USD 3.5 billion in costs every year.³⁶² Therefore, it is arguable that the patent system incentivises both wasteful litigation and ‘gaming’ by way of ‘pay-for-delay’ settlements, which increases costs to society overall.

³⁵⁶ Grabowski, Long and Mortimer, above n 151, at 211.

³⁵⁷ AS Kesselheim “Using Market Exclusivity Incentives to Promote Pharmaceutical Innovation” (2010) 363(19) *New England Journal of Medicine* 1855 at 1858.

³⁵⁸ *Federal Trade Commission v Actavis* 570 US 756 (2013).

³⁵⁹ An analysis by the United States Federal Trade Commission determined that competition by innovators launching AGs within reduced generic revenues by 53 to 62 per cent within 30 months of the 180-day exclusivity: see *Authorized Generic Drugs: Short-Term Effects and Long-Term Impact* (Federal Trade Commission, August 2011) at iii.

³⁶⁰ At iv.

³⁶¹ Generic Pharmaceutical Association “New Study finds Generic Prescription Drugs Saved Consumers and the US Health Care System \$1 Trillion over Past Decade” (press release, 21 September 2011).

³⁶² *Pay-For-Delay: How Drug Company Pay-offs Cost Consumers Billions* (Federal Trade Commission, 2010) at 2.

2 *Whether the increased cost of drugs due to patent monopolies justifies the benefit to society and whether pharmaceutical companies are incentivised to conduct excessive marketing*

An important question is whether the patent system ensures that fair prices are charged for medicines. The mechanism of determining pricing under the current system will be discussed further in Chapter Four. However, as noted in Chapter One, patents over medicines cause a significant financial burden on society, increasing global drug costs by approximately USD 500 billion per annum due to monopoly prices.³⁶³ As will be discussed in Chapter Four, monopolies can result in deadweight losses, which is the situation where patients lose access to a medicine, because the price is not affordable.³⁶⁴ Chapter Four will also discuss how governments and health insurers can use their purchasing power to negotiate lower prices for medicines.

The large monopoly markup for patented drugs also has the counterproductive effect of encouraging the manufacture of counterfeit drugs. This is the situation where a drug is fraudulently manufactured to pass off as a branded drug, but does not have the same active ingredient.³⁶⁵

Further, due to the large monopoly profits available, pharmaceutical companies are incentivised to develop medicines for diseases that require ongoing treatment, as noted above with regard to unprofitable therapies. For example, the biologic drugs adalimumab (Humira) and infliximab (Remicade), both maintenance treatments for incurable chronic illnesses such as arthritis and Crohn's disease, were the top selling drugs in the world in 2012, earning USD 9.2 billion per annum and USD 8.2 billion per annum respectively.³⁶⁶ This can be compared to treatments for 'one-off' treatments such as vaccines³⁶⁷ or treatments that cure the underlying condition rather than merely treating the symptoms.³⁶⁸

³⁶³ See Chapter One, n 14 citing J Love and T Hubbard "The Big Idea: Prizes to Stimulate R&D for New Medicines" (2007) 82 Chi-Kent L Rev 1519 at 1522 and *The Global Use of Medicines: outlook through 2016* (IMS Institute for Healthcare Informatics, July 2012) at 8.

³⁶⁴ See, for example, C Parahi "Pharmac won't fund prostate cancer drug" (1 May 2014) One News <www.tvnz.co.nz>; N Trigg "NHS says no to new breast cancer drug Kadcyla" (7 August 2014) BBC News <www.bbc.com>.

³⁶⁵ D Bagozzi "Fact Sheet No 275: Substandard and Counterfeit Medicines" (November 2003) World Health Organization <www.who.int>.

³⁶⁶ "Top 20 Best Selling Drugs of 2012" (5 March 2013) Genetic Engineering and Biotechnology News <www.genengnews.com>.

³⁶⁷ Offit, above n 341, at 622.

³⁶⁸ For example, see CA Black "The Cure for Deadly Patent Practices: Preventing Technology Suppression and Patent Shelving in the Life Sciences" (2003) 14 Alb LJ Sci & Tech 397 at 421 regarding the finding in 1982, by two Australian researchers, that the bacterium *Helicobacter pylori*,

Black argues, controversially, that under the current system, pharmaceutical companies are incentivised to engage in “patent shelving” by purchasing the rights to a potential cure and abandoning the project, or “suppression” of a potential cure through aggressive marketing, in order to safeguard monopoly profits from maintenance medications.³⁶⁹ Although Black provides limited evidence of such practices, it is noted that, as with regard to evidence of patentability screening discussed above, the public would never find out if research is ‘shelved’ or ‘suppressed’ at an early stage, as the majority of promising drug candidates do not achieve regulatory approval.³⁷⁰

Another issue is that pharmaceutical companies may actually attempt to block attempts by government healthcare agencies to use cheaper treatments that threaten monopoly profits. For example, it was discovered that an anti-cancer drug, bevacizumab (Avastin) could be used ‘off label’ to treat age-related macular degeneration (AMD).³⁷¹ Various hospitals in the United Kingdom decided to fund Avastin at a cost of GBP 60 per monthly injection compared to GBP 740 per monthly injection for the licensed drug, ranibizumab (Lucentis).³⁷² Novartis, the license holder for Avastin in the United Kingdom, filed for judicial review of this decision on the basis that it was inconsistent with government policy and possibly compromises patient safety.³⁷³ However, studies have shown that the cheaper Avastin is equivalent to Lucentis for treating AMD.³⁷⁴ This issue has generated significant controversy in the United States, where Genentech - the manufacturer of Avastin and Lucentis - provided confidential payments to eye specialists who prescribed Lucentis.³⁷⁵ This issue can be seen as part of the broader problem of lack of incentives to find second uses for cheap drugs, discussed above.

caused peptic ulcer disease, and that it could be cured with an antibiotic regimen. Despite this, it took 14 years from the discovery to obtain regulatory approval for antibiotic treatment, compared with the industry-endorsed regimen which involved regular use of the patented blockbuster antacid medication omeprazole (Prilosec), which had to be taken daily and arguably only addressed the symptoms of ulcers, not the cause.

³⁶⁹ At 418-422.

³⁷⁰ See Figure 1, above n 26, showing that of an average of 24 drug candidates in pre-clinical trials only 8 enter clinical trials in humans, and only one achieves regulatory approval.

³⁷¹ The CATT Research Group “Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration” (2011) 364 N Engl J Med 1897 at 1897.

³⁷² B Jeffreys “NHS faces judicial review from Novartis over Avastin” (12 April 2012) BBC News <www.bbc.com> at 1.

³⁷³ At 1.

³⁷⁴ The CATT Research Group, above n 368, at 1897; A Tufail and others “Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study” (2010) 340 BMJ 1 at 1.

³⁷⁵ A Pollack “Genentech Offers Secret Rebates for Eye Drug” *The New York Times* (online ed, New York, 3 November 2010). It was found that in 2008, despite fewer injections of Lucentis to treat macular degeneration, it cost United States government health insurance (Medicare) over USD 537 million compared to only USD 20 million for Avastin injections.

The current patent system also encourages excessive marketing costs in order to maximise profits for the duration of exclusivity. For example, spending on ‘continued medical education’ seminars targeting doctors, usually conducted at exotic locations, has increased from USD 301 million per annum in 1998 to USD 1.2 billion per annum in 2007.³⁷⁶ As discussed above with reference to ‘evergreening’, drug companies conduct massive advertising campaigns in order to get patients and doctors to switch to a new patented formulation of a drug once a generic version is available.³⁷⁷ Sales representatives are specifically trained in how to influence doctors³⁷⁸ and the benefits of meeting with such representatives have been questioned.³⁷⁹

Arguably, under the current system it is highly profitable for a company to spend money on the advertising and marketing of its branded drugs, which may actually mislead doctors and harm patients by distorting evidence from clinical trials.³⁸⁰ For example, it is estimated that approximately twice as much is spent on marketing branded drugs than medical R&D.³⁸¹

Pharmaceutical companies are also incentivised to ‘game’ the system by obtaining regulatory approval for treating one disease or ‘indication’, and then illegally marketing their branded drugs ‘off label’.³⁸² This is evidenced by record-breaking fines issued in recent years to major pharmaceutical companies. For example, *inter alios*, Pfizer was fined USD 2.3 billion in 2009 for illegally marketing an anti-psychotic drug and painkiller drug and GlaxoSmithKline was recently fined USD 3 billion in 2012 for improper off-label marketing and failing to report safety data regarding Paxil, Wellbutrin, Avandia and the other drugs.³⁸³ A USD 3 billion fine

³⁷⁶ MA Steinman, CS Landefeld and RB Baron “Industry support of CME - are we at the tipping point?” (2012) 366 N Engl J Med 1069 at 1069.

³⁷⁷ See Dwivedi, Hallihosur and Rangan, above n 187, at 328, and discussion of Nexium advertising campaign.

³⁷⁸ A Fugh-Berman and S Ahari “Following the Script: How Drug Reps Make Friends and Influence Doctors” (2007) 4(4) PLoS Med 621 at 621.

³⁷⁹ MA Fischer “Prescribers and Pharmaceutical Representatives: Why Are We Still Meeting?” (2009) 24(7) J Gen Intern Med 795 at 795.

³⁸⁰ Goldacre, above n 227, at 246.

³⁸¹ M Gagnon and J Lexchin “The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States” (2008) 5(1) PLoS Med 29 at 29; Goldacre, above n 227, at 245.

³⁸² S Grossman “Off-Label Promotion: Best Resolved by Congress, Not Courts” (12 December 2012) FDA Matters <www.fdamatters.com>.

³⁸³ See K Thomas and MS Schmidt “Glaxo Agrees to Pay \$3 Billion in Fraud Settlement” New York Times (online ed, New York, 2 July 2012) at 1. Abbott Laboratories also settled for USD 1.6 billion regarding the marketing of an anti-seizure drug Depakote, and Johnson & Johnson could be fined USD 2 billion for off-label marketing of its anti-psychotic Risperdal; see also G Harris “Pfizer Pays \$2.3 Billion to Settle Marketing Case” The New York Times (online ed, New York, 2 September 2009) which stated that in 2009, Eli Lilly agreed to pay USD 1.4 billion over the marketing of its antipsychotic Zyprexa; see also United States Department of Justice “Bristol-Myers Squibb to Pay

may seem like a significant deterrent; however, GlaxoSmithKline earned USD 27.9 billion from the sale of the same drugs during the relevant period covered by the fine.³⁸⁴

3 *Whether patent exclusivity causes an ‘anti-commons’ effect due to ‘patent thickets’*

If there are multiple individual patent holders over a particular invention, this creates cross-licensing inefficiencies referred to as a “patent thicket”.³⁸⁵ Heller and Eisenberg have argued that this is a potential barrier to biotechnology and medical research, which was coined the “tragedy of the anti-commons”.³⁸⁶ As noted above with regard to unmonopolisable therapies, the ‘tragedy of the commons’ is caused by the inability to enforce property rights. Here is the opposite problem; if multiple parties hold property rights, namely, patents with overlapping claims over a certain medicine, nobody has the freedom to operate without inefficient cross-licensing negotiations with each party, which impedes innovation.³⁸⁷ For example, Heller claims that a pharmaceutical executive told him that patents held by multiple parties has prevented a cure for Alzheimer’s disease - so-called “Compound X” - from getting to market.³⁸⁸

Other academics have doubted that increased patenting activity has led to an ‘anti-commons’ for biomedical research, at least in the area of gene patenting and research tools.³⁸⁹ Broad patent claims over research tools, genes, and drug targets, are referred to as “upstream patents”, which may be infringed in the process of developing medicines “downstream”.³⁹⁰ However, it has been argued that historically, ‘upstream patents’ over inventions have slowed scientific progress, particularly

More Than \$515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing” (press release, 28 September 2007) stating that in 2007, Bristol-Myers Squibb paid USD 515 million to resolve allegations of illegal drug marketing and pricing.

³⁸⁴ Thomas and Schmidt, at 1.

³⁸⁵ C Shapiro “Navigating the Patent Thicket: Cross Licences, Patent Pools and Standard Setting” In AB Jaffe, J Lerner and S Stern *Innovation Policy and the Economy, Volume 1* (MIT Press, Cambridge (Mass), 2001) 119 at 119.

³⁸⁶ Heller and Eisenberg, above 242, at 698.

³⁸⁷ A Kingsbury “Patent Collaboration: Licensing, Patent Pools, Patent Commons, Open Source and Communities of Innovation” (2013) 7 NZIPJ 3 at 4; G Van Overwalle *Gene Patents and Collaborative Licensing Models: Patent Pools, Clearinghouses, Open Source Models, and Liability Regimes* (Cambridge University Press, Cambridge, 2009) at 383.

³⁸⁸ M Heller *The gridlock economy: How too much ownership wrecks markets, stops innovation, and costs lives* (Basic Books, New York, 2008) at 4-6. It is unfortunate that this is only hearsay, although it is understandable in light of the author’s problems with obtaining evidence for his survey.

³⁸⁹ See T Caulfield and others “Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies” (2006) 24 *Nature Biotechnology* 1091 at 1092; RA Epstein and BN Kuhlik “Is There a Biomedical Anticommons?” (2004) 27 *Regulation* 54 at 56.

³⁹⁰ Heller and Eisenberg, above n 242, at 698.

incremental innovation, and that an ‘open source’ approach is preferable.³⁹¹ These problems highlight the need for reforms which may incentivise development of new therapies but prevent the inefficiencies due to patent thickets. For example, ‘open source’ approaches as incentives for medical research will be discussed in Chapter 6C.

4 *Whether the patent system incentivises development of ‘me-too’ drugs rather than breakthrough medicines*

As discussed above, the business model for pharmaceutical companies involves the pursuit of lucrative blockbuster drugs.³⁹² The high monopoly profits earned by such blockbusters encourages other pharmaceutical companies to develop ‘me-too’ drugs³⁹³ which can share in the lucrative market.

It has been argued that the majority of drugs are actually ‘me-too’ drugs with little therapeutic advantages over existing drugs.³⁹⁴ Typically, me-too drugs either have the same or similar active ingredient, or act on the same or similar drug target to the original drug.³⁹⁵ Light cited various independent reviews as evidence that 85-90 per cent of new drugs offer little or no clinical benefit to patients.³⁹⁶ Another study showed that of the 1035 new drugs approved by the FDA between 1989 and 2000, 76 per cent offered no significant clinical improvement over currently marketed products.³⁹⁷

The problem is exacerbated as there is no specific regulatory incentive to develop better drugs than what already exist. As regulatory approval requirements for ‘efficacy’ only require ‘substantial evidence’, this can be established by comparison

³⁹¹ M Boldrin, D Levine and A Nuvolari “Do patents encourage or hinder innovation? The case of the steam engine” (2008) 58 *The Freeman* 12 at 12. The article described the technological progress of improved steam engines in Cornwall, England, between 1772 and 1852, which were pivotal to the industrial revolution. The authors argue that patents suppressed incremental innovation, and that an ‘open source’ approach was more useful as it encouraged periods of rapid innovation.

³⁹² As discussed above, these are drugs which achieve more than USD 1 billion in sales per annum.

³⁹³ A ‘me-too’ drug is defined as a drug with enough differences to be patentable and to avoid an innovator’s patents, but having limited benefits over existing drugs. ‘Me-too’ drugs generally work by modulating the same drug target as existing drugs.

³⁹⁴ See M Angell *The Truth About the Drug Companies: How They Deceive Us and What to Do About It* (Random House, 2004) at 74; DW Light and JR Lexchin “Pharmaceutical research and development: what do we get for all that money?” (2012) 345(1) *BMJ* 1 at 1.

³⁹⁵ For example, the blockbuster drug sildenafil (Viagra) is an inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5). Me-too variations of PDE5 inhibitors were subsequently developed by competitors such as tadalafil (Cialis) and vardenafil (Levitra). Other examples of me-too drugs are the eight cholesterol-lowering statin drugs on the market: see JJ Gagne and NK Choudhry “How many ‘me-too’ drugs is too many?” (2011) 305(7) *JAMA* 711 at 711.

³⁹⁶ Light and Lexchin, above n 394 at 1-2.

³⁹⁷ *Changing patterns of pharmaceutical innovation* (National Institute for Health Care Management, 2002) at 8.

to placebo.³⁹⁸ Some commentators have argued that this standard is too low and that new drugs should be tested against the latest ‘first-in-class’ treatments.³⁹⁹

However, commentators have noted that me-too drugs are helpful as they offer more treatment options for doctors when a patient has failed to tolerate or respond to a previous drug,⁴⁰⁰ and also help reduce costs of drugs through price competition.⁴⁰¹ To the extent me-too drugs offer incremental improvements, they are also beneficial.⁴⁰²

Arguably, however, the current system lacks incentives to develop drugs for unmet medical needs and over-incentivises me-too drugs that have an established market.

H Conclusion

Unfortunately, the reliance on patents by pharmaceutical companies means that expenditure on medical research is biased towards ‘monopolisable therapies’ at the expense of socially valuable unpatentable, unmonopolisable and unprofitable therapies, which is likely to have an adverse effect on disease burden as well as contribute to the current productivity crisis facing the industry. The current patent system also encourages pharmaceutical companies to engage in excessive litigation and excessive marketing to maximise monopoly profits, even when this could harm patients. Furthermore, there is a potential anti-commons effect due to the possibility of competitors holding overlapping patents. Finally, there is an incentive to develop me-too drugs in order to obtain a share of lucrative monopoly rents in a proven market.

The next chapter will discuss the ways that governments and health insurers currently try to exercise control of monopoly prices over pharmaceuticals in order to ensure value for money.

³⁹⁸ Federal Food, Drug, and Cosmetic Act, s 505(d)

³⁹⁹ AB O’Connor “Building Comparative Efficacy and Tolerability Into the FDA Approval Process” (2010) 303(10) JAMA 979 at 979.

⁴⁰⁰ A Wertheimer, R Levy and T O’Connor “Too Many Drugs? The Clinical and Economic Value of Incremental Innovations” in I Farquhar, K Summers and A Sorkin (eds) *Investing in Health: The Social and Economic Benefits of Health Care Innovation* (Volume 14, JAI Press, United Kingdom, 2001) 77 at 78-79.

⁴⁰¹ Government Accountability Office, above n 21, at 29.

⁴⁰² J Cohen, L Cabanilla and J Sosnov “Role of follow-on drugs and indications on the WHO Essential Drug List” (2006) 31(6) Journal of Clinical Pharmacy and Therapeutics 585.

IV Pricing and Reimbursement of Medicines

A Introduction

Chapter Four will provide an overview of how the pricing and reimbursement of new medicines is determined under the current incentive system, which, as discussed in the previous chapter, relies on patent exclusivity to incentivise innovators to develop new medical therapies. The chapter will first discuss pharmacoeconomic analysis, which is a process used by governments and health insurers to assess cost-efficacy of medicines. As part of that discussion, the use of health metrics as pharmacoeconomic tools will be considered. Subsequently, the process of using these tools to determine pharmaceutical reimbursement in New Zealand and the United States will be compared.

B Pharmaceutical Pricing and Reimbursement by Payers

Global sales for patented medicines exceeded USD 596 billion in 2011.¹ Under the current system, the majority of the cost of patented medicines is reimbursed by government agencies and private health insurers, which are referred to in this thesis as ‘payers’. Price discovery in the pharmaceutical market is atypical because payers have a major role of determining price and overall rewards, as opposed to typical markets where the consumer decides what to pay.

As will be discussed in Chapter Five, payers reduce deadweight losses that would otherwise occur if the medicine was only available to consumers at the high monopoly price. For this reason, a negative or unfavourable reimbursement decision by a payer will effectively mean that the drug will not be available to the majority of patients. In a sense, because the reimbursement price allows the medicine to be available to consumers at a marginal cost, the decision to reimburse a medicine shares a lot in common with a government prize, discussed further in Chapter 6B, although the latter does not allow a ‘market-based’ negotiation of price after the medicine has been developed.² Accordingly, it is important to understand what factors are taken into account when payers negotiate reimbursement pricing, as this will affect

¹ *The Global Use of Medicines: outlook through 2016* (IMS Institute for Healthcare Informatics, July 2012).at 8. Total global spending on both branded on-patent and generic pharmaceuticals in 2011 was USD 956 billion.

² In particular, as will be discussed in Chapter Five, a market-based mechanism involves a negotiation of price between a willing buyer and seller regarding a product. By contrast, for prizes, criteria for calculating the price are ‘pre-determined’.

incentives for development of medical therapies, and is useful for considering how rewards may be calculated under alternative reimbursement mechanisms.

In general, the payer's task is to maximise the health benefits gained within a limited pharmaceutical budget. Payers accomplish this by evaluating the cost-effectiveness of drugs and leveraging their bulk buying power to negotiate lower prices. However, the responsibility of payers to obtain the most cost-effective price must be balanced against the need to ensure pharmaceutical companies are adequately incentivised to undertake research into new medicines. The mechanism used by payers to determine pricing and reimbursement decisions is called pharmacoeconomic analysis.

1 Pharmacoeconomic analysis

Pharmacoeconomics is a sub-discipline of health economics, which is used by payers to determine the optimal price for a medicine.³ The use of so-called health metrics is one of the major tools used in pharmacoeconomic analysis, as they are a means to measure the health impact provided by a particular medical intervention.

(a) Health metrics

Health metrics are used to estimate the health impact of medical therapies. There are various types of health metrics,⁴ however, the Quality-Adjusted Life Year is the preferred metric used by most payers in developed countries with public-healthcare systems to determine drug pricing and reimbursement decisions.

(i) Quality-Adjusted Life Years

Quality-Adjusted Life Years (QALYs) are a measure of health-related quality of life. They are calculated by adding the life expectancy gained as a result of a medical intervention, and multiplying a health 'utility' value that accounts for severity of disease, where zero is equivalent to death and 1 is perfect health.⁵ In order to account for the inherent uncertainty of future events, a discount rate,⁶ is applied to any future

³ *A Prescription for Pharmacoeconomic Analysis* (Pharmaceutical Management Agency, 2012) at 9.

⁴ S Whitehead and S Ali "Health outcomes in economic evaluation: the QALY and utilities" (2010) 96 *British Medical Bulletin* 5 at 18-19. Alternative health metrics to Quality-Adjusted Life Years [QALYs] include the Disability-adjusted-life year (DALY), the Healthy-years equivalent (HYE) and Willingness-to-pay (WTP). A discussion of the advantages and disadvantages of these alternative health metrics is outside the scope of this thesis.

⁵ L Prieto and JA Sacristán "Problems and solutions in calculating quality-adjusted life years (QALYs)" (2003) 1(80) *Health Qual Life Outcomes* 1 at 2.

⁶ For example, between three to five per cent per annum.

estimate of QALYs.⁷ For example, if a medical intervention is estimated to add three years of life at a health utility value of 0.2, then, the total health impact provided by that intervention will be 0.6 QALYs, minus the discount rate applied to the second and third year.

While it is easy to measure the length of time a patient survives, an estimate of health utility is difficult because it requires a subjective assessment of disease severity or quality of life.⁸ A benefit of using QALYs is that collecting data is not cognitively challenging, only requiring a few minutes to complete a questionnaire.⁹ However QALYs can be criticised, primarily because the assumption they can be added together is an oversimplification, and that they may discriminate against older and sicker patients that may benefit less from an intervention.¹⁰ Despite this, QALYs are a useful ‘universal’ health metric that allow a meaningful comparison between therapeutic interventions in different disease classes.

Theoretically, it is possible for payers to use QALYs to enforce a threshold above which they will be unlikely to subsidise a medicine.¹¹ For example, this could be \$50,000 per QALY gained. This ensures that expenditure on a less cost-effective intervention does not displace expenditure on a more cost-effective intervention.

⁷ E Nord, N Daniels and M Kamlet “QALYs: some challenges” (2009) 12 Value Health S10 at S13.

⁸ The basic QALY standard, EQ-5D-5L, asks a patient to rate the severity of their disease state within five health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by selecting one of five levels of severity ((1) no problem, (2) slight problems (3) moderate problems, (4) severe problems (5) extreme problems or unable). This generates a combination of 3127 possible health states ($5^5 = 3125$ plus unconscious and dead) which is used to provide an estimate of health utility from zero to 1. Another measurement used to estimate health utility is referred to as the Visual Analogue Scale (VAS). The patient is asked to rank their health from zero to 100 with zero representing worst imaginable health and 100 representing the best imaginable health. QALYs are used globally by researchers and many of the largest pharmaceutical companies to monitor outcomes in clinical trials, with the most popular measurement standard, EQ-5D, having been translated into most languages. See R Rabin and F de Charro “EQ-5D: a measure of health status from the EuroQol Group” (2001) 33 Ann Med 337.

⁹ A standard EQ-5D-5L questionnaire is available from <www.euroqol.org>.

¹⁰ A detailed analysis of the criticisms of QALYs is beyond the scope of this thesis. However, some brief comments can be made. First, the presumption of ‘additivity’ for QALYs is an oversimplification, in that certain health states may be perceived as having more severity, the longer they are experienced: see HJ Sutherland and others “Attitudes toward quality of survival—the concept of ‘maximal endurable time’” (1982) 2 Med Decis Making 299 at 299; BJ O’Brien and others “Is there a kink in consumers’ threshold value for cost-effectiveness in health care?” (2002) 11 Health Econ 175. Second, QALYs may be perceived as discriminating against interventions for older and sicker people who would benefit less from interventions compared with younger and healthier persons: see PJ Neumann and MC Weinstein “Legislating against use of cost-effectiveness information” (2010) 363 N Engl J Med 1495 at 1496. Nevertheless, it is possible to use different ‘weightings’ to QALYs in order to make adjustments that reflect society’s values and can balance the interests of various stakeholders. For example, if society rates health changes in certain groups as more important than others, such as if a person starts life in poorer health or is a member of a vulnerable group, this can be reflected by an increased weighting to changes in those health states: see Nord, above n 7, at S13.

¹¹ See C McCabe, K Claxton and AJ Culyer “The NICE cost-effectiveness threshold: what it is and what that means” (2008) 26 Pharmacoeconomics 733.

Wealthier societies may apply an increased QALY threshold, which reflects a willingness to pay a higher price to add one year of healthy life. In practice, however, the application of QALY thresholds by payers is controversial and not officially endorsed by payers.¹²

(ii) Condition-specific metrics

The general applicability and relative simplicity of measuring QALYs means they can lack the specificity required to delineate incremental improvements in health, particularly for certain conditions.¹³ In that event, it may be more appropriate to use the condition-specific health metrics typically used to measure clinical trial outcomes which are submitted to the FDA or Medsafe in order to obtain regulatory approval.¹⁴ For example, these can include progression-free-survival or overall survival, which are used in clinical trials of cancer therapeutics,¹⁵ the Crohn's Disease Activity Index used in clinical trials for Crohn's disease,¹⁶ and biomarkers such as cholesterol levels used in clinical trials of cardiovascular disease.¹⁷ The use of condition-specific health metrics to determine rewards under a proposed optimal prize-based incentive mechanism will be discussed in Chapter Seven.

Summary

Health metrics are an important tool to compare efficacy of new medical therapies and determine the appropriate level of rewards for innovators. QALYs attempt to quantify abstract concepts like 'health status' and 'quality of life'. The main benefits

¹² KL Rascati "The \$64,000 question - What is a quality-adjusted life-year worth?" (2006) 28 *Clinical therapeutics* 1042 at 1042. Some commentators in the United States have argued that QALY thresholds could result in inefficiencies. In particular, if the threshold is below the economic value of the health benefit to society, this can result in underinvestment in R&D, whereas if the threshold is too high, this may result in inefficient wastage of R&D spending: see JA Vernon, R Goldberg and J Golec "Economic evaluation and cost-effectiveness thresholds: signals to firms and implications for R & D investment and innovation" (2009) 27 *Pharmacoeconomics* 797 at 797, 804.

¹³ Whitehead, above n 4, at 10.

¹⁴ *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (Food and Drug Administration, May 2007) at 5. It should be noted that QALYs are also used globally by researchers and many of the largest pharmaceutical companies to monitor outcomes in clinical trials: Rabin and de Charro, above n 8, at 341.

¹⁵ Progression-free survival (PFS) is the length of time after treatment which a cancer tumor does not increase in size. This is correlated with the length of overall survival (OS). OS is more important but takes longer to measure than PFS: see *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* at 5, 8.

¹⁶ Crohn's disease Activity Index is a composite of various clinical and non-clinical measurements which assign a score to rate the severity of a flare of Crohn's disease, an autoimmune disorder. A score above 250 points is indicative of active disease while a score below 150 is indicative of remission.

¹⁷ Biomarkers are measured characteristics which are linked to the presence of disease. High cholesterol levels are useful biomarkers for predicting the risk of cardiovascular disease, therefore, a drug which lowers cholesterol would conceivably lower disease risk.

of QALYs are that they are administratively simple to measure and can be used as a ‘universal health metric’ to assess the efficacy of different therapies across various disease states. However, QALYs are a blunt tool for measuring incremental improvements, therefore other condition-specific health metrics may be used to measure incremental health impact, although these are less useful for comparing efficacy of a therapeutic intervention between different diseases.

(b) Pharmacoeconomic analysis

QALYs are a fundamental part of pharmacoeconomic analysis. For example, ‘Cost-Utility-Analysis’ (CUA) uses QALYs to determine the cost-effectiveness of medical interventions. In particular, CUA compares medical interventions by using an incremental cost-effectiveness ratio (ICER).¹⁸ ICER is calculated as the difference between the cost of two treatments divided by the difference between their effectiveness. This can compare an old and new medicine to determine whether the incremental health improvements provided by a new medicine falls within a particular cost per QALY threshold.¹⁹

Because regulatory approval in most countries is only based on demonstrating superiority to placebo, pricing and reimbursement decisions by payers based on ICER are an important market-based mechanism to incentivise drug companies to develop new drugs which are superior or cost-effective compared to existing medicines. As will be discussed below, this particularly reduces incentives to develop ‘me-too’ drugs, especially where the equivalent pioneer drug is close to becoming available as a generic.

2 *Pharmaceutical Payers*

Countries with single payer public-healthcare systems rely more on QALYs in pharmacoeconomic analysis to determine prices of new medicines. These countries include New Zealand, Australia,²⁰ the United Kingdom,²¹ some European Union

¹⁸ $ICER = (C1 - C2) / (E1 - E2)$ where C1 is the cost of the first intervention and C2 is the cost of the second intervention, and E1 and E2 are the effectiveness of the first and second medicine respectively. The cost can be expressed in dollars and the effectiveness in QALYs gained.

¹⁹ For example, if a payer adopts a QALY threshold of \$50,000, a therapy X, which costs \$5,000 and adds 1 year of life at a utility of 0.4 ($1 \times 0.4 = 0.4$ QALYs) can be compared to therapy Y which costs \$35,000 and adds 1.5 years of life at a utility of 0.6 ($1.5 \times 0.6 = 0.9$ QALYs). The difference in cost between X and Y (\$30,000) divided by the difference in QALY benefits ($0.9 - 0.4 = 0.5$ QALYs) equates to an ICER of \$60,000 per QALY, which is above the adopted \$50,000 threshold. In that situation, a payer is unlikely to reimburse a medicine unless its price can be reduced so that the cost per QALY is below \$50,000.

²⁰ J Raftery “Paying for cost pharmaceuticals: Regulation of new drugs in Australia, England and New Zealand” (2008) 188 *Med J Aust* 26 at 26.

countries,²² and Canada.²³ This analysis is typically referred to as “health technology assessment”.²⁴ Notably, Australia, New Zealand and the United Kingdom were among the first countries to use QALYs to determine cost-effectiveness, although the specific appraisal criteria can differ.²⁵

By contrast, pharmaceutical reimbursement decisions in the United States are not made by a publicly-funded single payer, and tend to avoid the use of QALYs in pharmacoeconomic analysis.²⁶ The following sections will discuss and compare the approach to pharmaceutical reimbursement by payers in New Zealand and the United States.

(a) Pharmaceutical reimbursement in New Zealand

PHARMAC is a Crown entity with the role of determining pricing and reimbursement of new medicines in New Zealand. PHARMAC is funded from the Combined Pharmaceutical Budget (CPB), which is set by the Minister of Health, after consultation with the District Health Boards and the Ministry of Health.²⁷ Under section 47 of the New Zealand Public Health and Disability Act 2000, PHARMAC’s primary objective is “to secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achieved from pharmaceutical treatment and from within the amount of funding provided.”

PHARMAC uses its ‘monopsony’ power to negotiate a lower price for reimbursement. The official reimbursement list is referred to as the ‘Pharmaceutical Schedule’, which complies with the requirement under s 6 of the Act for a:²⁸

... list of pharmaceuticals for the time being in force that states, in respect of each pharmaceutical, the subsidy that the Crown intends to provide for the supply of that pharmaceutical to a person who is eligible for the subsidy.

²¹ At 26.

²² See L Garattini, D Cornago and PD Compadri “Pricing and reimbursement of in-patent drugs in seven European countries: A comparative analysis” (2007) 82 Health policy 330 at 330. The seven countries referred to are Belgium, France, Germany, Italy, the Netherlands, Spain, and the United Kingdom.

²³ Patents Act RSC 1985 c P-4, s 83(1).

²⁴ See D Menon and D Marshall “The internationalization of health technology assessment” (1996) 12 IJTAHC 45 at 45. Health technology assessment includes diagnostics and surgical interventions in addition to pharmaceuticals.

²⁵ Raftery, above n 20 at 26.

²⁶ Rascati, above n 12, at 1043.

²⁷ *Infosheet 08: Setting and managing the combined pharmaceutical budget (CPB)* (Pharmaceutical Management Agency, 2013) at 1. One of PHARMAC’s roles is to ensure the combined pharmaceutical expenditure does not exceed the combined pharmaceutical budget.

²⁸ New Zealand Public Health and Disability Act 2000, s 6.

PHARMAC, acting in accordance with its advisory committee,²⁹ makes use of CUA³⁰ and QALYs to determine funding choices for pharmaceuticals.³¹ Notably, however, cost-effectiveness is only one of nine criteria used by PHARMAC to make funding decisions.³² In addition, PHARMAC uses a range of strategies to reduce costs. For example, reference pricing fixes the price of a new drug at the lowest cost pharmaceutical in the same therapeutic class.³³ Another strategy is to use rebates, whereby pharmaceutical companies offer to reimburse the cost of a pharmaceutical if a spending cap is exceeded or a particular clinical outcome is not met.³⁴ PHARMAC also uses a competitive tender process with generic drug suppliers which can reduce the cost of generic drugs by over 90 per cent.³⁵

PHARMAC monitors existing patent rights and will not fund a generic drug for an indication which is covered by a patent.³⁶ This is an illustration of how PHARMAC provides an effective indirect ‘enforcement’ of ‘weaker’ second medical use patents, as doctors would usually only prescribe drugs to patients that are

²⁹ New Zealand Public Health and Disability Act 2000, s 50(1)(a). In particular, this section provides for the appointment of the Pharmacology and Therapeutics Advisory Committee (PTAC), ‘to provide objective advice to Pharmac on pharmaceuticals and their benefits’. In accordance with the PTAC Appointment Protocol 2010, ‘PTAC comprises senior health practitioners from multiple specialities selected for their expertise in critical appraisal as well as broad experience and knowledge of pharmaceuticals and their therapeutic indications’: see *Protocol for the Appointment of Pharmacology and Therapeutics Advisory Committee (PTAC) Members by the Director-General of Health* (Pharmaceutical Management Agency, 2010) at 3.

³⁰ See discussion above regarding ‘Cost-Utility-Analysis’.

³¹ *A Prescription for Pharmacoeconomic Analysis*, above n 3 at 10.

³² At 10. In particular, PHARMAC’s nine decision criteria are:

- (1) the health needs of all eligible people within New Zealand;
- (2) the particular needs of Maori and Pacific peoples;
- (3) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things;
- (4) the clinical benefits and risks of pharmaceuticals;
- (5) the cost-effectiveness of meeting health needs by funding pharmaceuticals; rather than by using other publicly funded health and disability support services;
- (6) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;
- (7) the direct cost to health service users;
- (8) the Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere; and
- (9) any other criteria that PHARMAC thinks are relevant.

PHARMAC will carry out the necessary consultation whenever it intends to take any ‘other criteria’ into account.

³³ See *Purchasing Medicines Information Sheet* (Pharmaceutical Management Agency, 16 September 2011) at 2. Notably, reference pricing decisions by PHARMAC are subject to judicial review: see *Pharmaceutical Management Agency Ltd v Roussel Uclaf Australia Pty Ltd* [1998] NZAR 58 (CA).

³⁴ *Purchasing Medicines Information Sheet*, above at 2.

³⁵ At 1.

³⁶ For example, see *Request for Proposals – Supply of Imatinib* (Pharmaceutical Management Agency, 23 August 2012). Although PHARMAC has approved funding for a generic version of Glivec (Imatinib), it will not fund the generic for use in gastrointestinal tumors, because of a patent held by Novartis.

reimbursed by the government. However, this would not be effective for over-the-counter medication, which is not subsidised.

Even though PHARMAC has denied using a specific QALY threshold in practice,³⁷ and uses multiple alternative strategies, QALY calculations provide important scientific evidence for PHARMAC to use in negotiations with innovators and ensure that funded medicines maximise health impact.³⁸

(b) Pharmaceutical reimbursement in the United States

The United States does not use single payer pharmaceutical reimbursement. Reimbursement occurs via multiple payers which include government-funded Medicare³⁹ and private health insurers. The latter reimburse the majority of medical costs in the United States, and are funded by significant premiums paid by employers on behalf of employees.⁴⁰ Medicare is funded by tax levies payable to the Federal Government,⁴¹ however, it is restricted to American citizens over 65 and certain vulnerable groups of patients,⁴² therefore, in 2012, 48 million people lacked health insurance coverage.⁴³

Rather than using a single pharmaceutical schedule, pharmaceutical reimbursement in the United States involves a complex system of tiered ‘formulary’ lists, with patients being liable for increasing co-payments for drugs that are deemed less cost-effective. Pharmacy Benefit Managers (PBMs) act as intermediaries between insurers and drug companies to generate the formulary lists and negotiate with drug companies to lower their prices. The most cost-effective drugs (usually generics) are on the lowest tier, which encourages their use, with less cost effective drugs being

³⁷ S Metcalfe and others “PHARMAC has no cost effectiveness threshold” (2012) 135 NZ Med J 99 at 99; *A Prescription for Pharmacoeconomic Analysis*, above n 3, at 14.

³⁸ For example, according to the PHARMAC 2012/2013 annual report, funded medicines cost an average of NZD 37,000 per QALY [expressed as 27 QALYs per NZD 1 million], compared to NZD 52,600 per QALY [expressed as 19 QALYs per NZD 1 m] for all proposals assessed. See *Pharmaceutical Management Agency Annual Report For the year ended 30 June 2013: Presented to the House of Representatives pursuant to Section 150(3) of the Crown Entities Act 2004* (Pharmaceutical Management Agency, 2013) at 23.

³⁹ Medicare is a national health insurance program established under the Social Security Amendments of 1965 Pub L No 89-97.

⁴⁰ Approximately 57 per cent of employers in the United States offer health insurance benefits to employees: see *Employer Health Benefits 2013 Annual Survey* (Kaiser/HRET, 2013) at 5. Private health insurance premiums are expensive, with average annual premiums of USD 5,884 for single coverage and USD 16,351 for family coverage in 2013 [at 22].

⁴¹ See *Medicare and you* (Centers for Medicare & Medicaid Services, 2014) at 27.

⁴² At 15.

⁴³ D DeNavas-Walt, BD Proctor and JC Smith *Income, Poverty, and Health Insurance Coverage in the United States: 2012* (US Census Bureau, 2013) at 22.

placed on higher tiers requiring a greater co-payment percentage.⁴⁴ PBMs use cost-effectiveness analysis, including a form of reference pricing to determine whether to list a drug in a specific formulary and tier,⁴⁵ although they do not tend to use QALYs.⁴⁶ Medicare has also been reluctant to use QALYs in making reimbursement decisions.⁴⁷ The Social Security Act specifically prohibits using QALYs “as a threshold” for analysing the cost-effectiveness of health care interventions.⁴⁸ The United States has also resisted price controls in light of arguments that it would result in a significant reduction in private R&D expenditure.⁴⁹ Despite this, the use of QALYs to measure public health outcomes is recommended by the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine.⁵⁰ Therefore, concern about rising healthcare costs and unsustainability may encourage more widespread adoption of QALYs in the United States.⁵¹

Higher prices over pharmaceuticals in the United States have also created a lucrative ‘grey market’ for pharmaceuticals imported from countries such as Canada.⁵² This opportunity for arbitrage reduces profits available to innovators, and impacts on their willingness to supply medicines to low income countries at a reduced price.⁵³ However, it may be impossible to prevent exports due to the Internet facilitating sale of medicines by online pharmacies. There is also considerable political pressure in the United States to allow importation of patented drugs from Canada because of large number of Americans without any health insurance.⁵⁴

⁴⁴ D Blumenthal “Employer Sponsored Insurance – Riding the Health Care Tiger” (2006) 355 *New Eng J Med* 195 at 199.

⁴⁵ H Grabowski and CD Mullins “Pharmacy benefit management, cost-effectiveness analysis and drug formulary decisions”(1997) 45 *Social Science & Medicine* 535 at 538.

⁴⁶ M Drummond and others “Toward a consensus on the QALY” (2009) 12 *Value in Health* S31 at S34.

⁴⁷ A Brower “Is It Time To Take a Harder Look at the QALY?” (2008) 5(3) *Biotech Healthc* 47 at 48.

⁴⁸ Social Security Act 42 USC §1182(e): ‘The Patient-Centered Outcomes Research Institute ... shall not develop or employ a dollars per quality adjusted life year (or similar measure that discounts the value of a life because of an individual's disability) as a threshold to establish what type of health care is cost effective or recommended. The Secretary shall not utilize such an adjusted life year (or such a similar measure) as a threshold to determine coverage, reimbursement, or incentive programs under title XVIII.’ See also Neumann and Weinstein, above n 10, at 1495.

⁴⁹ See JA Vernon “Drug research and price controls” (2002) 25 *Regulation* 22 at 22.

⁵⁰ See generally, MR Gold and others “Identifying and valuing outcomes” in Gold MR and others *Cost-Effectiveness in Health and Medicine* (Oxford University Press, New York, 1996) at 82.

⁵¹ Drummond, above n 46 at S34.

⁵² K Outterson “Pharmaceutical arbitrage: balancing access and innovation in international prescription drug markets” (2005) 5 *Yale J Health Pol’y L & Ethics* 193 at 275.

⁵³ P Kanavos and others “The economic impact of pharmaceutical parallel trade in European Union member states: A stakeholder analysis” (Special Research Paper, London School of Economics and Political Science, 2004) at 25, 27.

⁵⁴ PW Grubb and PR Thomsen “Patents for Chemicals, Pharmaceuticals and Biotechnology: Fundamentals of Global Law, Practice and Strategy” (5th ed, Oxford University Press, New York, 2010) at 431.

Outterson argues that the existence of pharmaceutical arbitrage under the grey market may still allow innovators to obtain optimal patent rents between high income countries such as the United States and Canada.⁵⁵ However, there would likely be a significant reduction of patent rents if drugs could be imported from developing countries at low prices without restriction.⁵⁶ On the other hand, if payers can subsidise medicines so they can be purchased at the marginal cost, this will reduce incentives for arbitrage.

C Conclusion

While QALYs have been criticised as an oversimplification, and their use as part of enforcing a strict threshold is avoided, in practice, they are a useful tool to link innovator rewards to health impact. Payers in New Zealand and other jurisdictions with publicly-funded healthcare systems have embraced the use of QALYs and the United States may be likely to follow suit if healthcare costs increase to an unsustainable level.

Having considered the methods used by payers to determine rewards payable for medicines, the next chapter will discuss the goals and criteria of an ideal system that would incentivise innovators to develop therapies that maximise human health.

⁵⁵ Outterson, above 52, at 197.

⁵⁶ Grubb, above n 54, at 430.

V Goals and Criteria of the Ideal Incentive System

A Introduction

Chapter Five will first discuss the international obligations and goals to implement the highest standards of health, which should arguably be the purpose of the ideal incentive system. Subsequently, the chapter will propose eight criteria which the ideal system would satisfy. Finally, the current incentive system,¹ which relies on patents, will be assessed against these ideal criteria.

B International Obligations and Goals to Implement the Highest Standards of Health

It is arguable that various international agreements compel New Zealand to adopt incentive mechanisms to implement the highest standards of health. The most relevant is the International Covenant on Economic, Social and Cultural Rights (ICESCR) which entered into force in 1976.² Article 12 of the ICESCR refers to the “right of everyone to the enjoyment of the highest attainable standard of physical and mental health.”³ ICESCR signatories have agreed to take the steps required to “achieve the full realization of this right”, including those necessary for “[t]he prevention, treatment and control of epidemic, endemic, occupational and other diseases.”⁴

The ICESCR has been ratified by 160 countries (including New Zealand),⁵ although it has only been signed, but not ratified by the United States.⁶ Each signatory must report to the UN Committee on Economic, Social and Cultural Rights, which monitors compliance.⁷ However, New Zealand has not yet ratified the Optional

¹ As noted in Chapter One, the current system refers to the patent system, regulatory environment, and reimbursement mechanisms that incentivise development of new medicines in New Zealand and the United States.

² International Covenant on Economic, Social and Cultural Rights 993 UNTS 3 (Opened for signature 16 December 1966, entered into force 3 January 1976) [ICESCR].

³ art 12.

⁴ art 23.

⁵ “International Covenant on Economic, Social and Cultural Rights” (accessed 7 August 2014) Ministry of Justice <www.justice.govt.nz>.

⁶ A Piccard “The United States’ Failure to Ratify the International Covenant on Economic, Social and Cultural Rights: Must the Poor Be Always with Us?” (2010) 13(2) *St Mary's L Rev Min Iss* 231 at 231.

⁷ ICESCR, above n 2, art 16.

Protocol to the ICESCR,⁸ an enforcement mechanism that would allow filing of individual and inter-state complaints.⁹

According to a Statement by the Committee on Economic Social and Cultural Rights, article 15(2) of the ICESCR requires that States “undertake steps necessary for the conservation, development and diffusion of science and culture” and that “intellectual property regimes should be conducive to realizing these goals.”¹⁰ Further, under Article 15(4), signatories “recognize the benefits to be derived from the encouragement and development of international contacts and cooperation in the scientific and cultural fields.”¹¹ The General Assembly also recognised:¹²

the need for further international cooperation and research to promote the development of new drugs, vaccines and diagnostics tools for diseases causing a heavy burden in developing countries ...taking into account that the failure of market forces to address such diseases.

Therefore, it is arguable that states have an obligation to cooperate internationally to implement incentive mechanisms that achieve the full realisation of the right to health, including addressing neglected diseases.¹³

Various academic commentators have also recognised the obligations of governments to implement incentive systems that do not obstruct the human right to health,¹⁴ and that the patent system should not impede affordable access to medicines.¹⁵ For example, compulsory licenses and international arbitration by parallel importing can reduce the cost of medicines by up to 90 per cent.¹⁶

⁸ *Optional Protocol to the International Covenant on Economic, Social and Cultural Rights* GA Res 63/117 (2008).

⁹ Above n 5.

¹⁰ *Substantive Issues Arising in the Implementation of the International Covenant on Economic, Social and Cultural Rights. Statement on Human Rights and Intellectual Property*, E/C.12/2001/15 (2001).

¹¹ art 15(4).

¹² *Resolution adopted by the General Assembly on 22 December 2003* GA Res 58/173, A/58/508 (2004).

¹³ At [11]: ‘General Legal Obligations: ... parties are urged to ensure that intellectual property regimes contribute, in a practical and substantive way, to the full realization of all the [ICESCR] rights.’ See also P Hunt “Neglected diseases: A human rights analysis” (Social, Economic and Behavioural (SEB) Research Special Topics No 6, World Health Organization, 2007) at 38.

¹⁴ WW Fisher and T Syed “Global justice in healthcare: developing drugs for the developing world” (2006) 40 *UC Davis L Rev* 581 at 645 citing T Pogge *World Poverty and Human Rights* (Polity Press, Cambridge (UK), 2002) at 50-51.

¹⁵ P Cullet “Patents and medicines: the relationship between TRIPS and the human right to health” (2003) 79 *International Affairs* 139 at 151-152.

¹⁶ L Ferreira “Access to Affordable HIV/AIDS Drugs: The Human Rights Obligations of Multinational Pharmaceutical Corporations” (2002) 71 *Fordham L Rev* 1133 at 1135.

Accordingly, in November 2001, the Doha Declaration on the TRIPS Agreement and Public Health (Doha Declaration) was adopted by the WTO Ministerial Conference.¹⁷ Paragraph 4 of the Doha Declaration provides that TRIPS “can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all.”¹⁸ Specifically, paragraph 5 allows governments to disregard patent rights and issue compulsory licences in order to achieve this purpose, and paragraph 6 allows member countries to export to countries with insufficient or no pharmaceutical production capabilities.¹⁹ For example, section 171 of the Patents Act allows compulsory licenses to export pharmaceuticals required to address a serious public health problem to WTO members and other eligible countries (for example, an epidemic of HIV/AIDS, tuberculosis or malaria).²⁰ However, notably, pharmaceuticals subject to a compulsory license under this provision must have distinguishing features such as special packaging, colouring or shaping “if including those features is feasible and does not impact on price”,²¹ which presumably is to address the risk of arbitrated re-sale in developed countries.

It is important to note, however, that permitting compulsory licensing will not solve the problem of inadequate incentives for development of unprofitable therapies for neglected diseases in the first place. In particular, allowing compulsory licences will reduce *ex ante* incentives for innovators to develop these medicines. Therefore, it is apparent that new incentives are needed in order to maximise the right to health.

Summary

Pursuant to ICESCR, it is arguable that UN Member States are obligated to implement mechanisms to support the full realisation of the right to health both amongst its citizens and citizens of developing countries. Intellectual property regimes are recognised as having an important role in securing the human right to health. For example, the Doha Declaration allows compulsory licenses to be issued for patents when necessary to protect public health. However, permitting compulsory licenses may actually result in reduced private investment for addressing unmet medical needs. Therefore, it is arguable that in order to fulfill international

¹⁷ *Declaration on the TRIPS Agreement and Public Health, Fourth Ministerial Conference of the WTO*, WT/MIN(01)/DEC/2, 20 November 2001 [Doha Declaration].

¹⁸ At [4].

¹⁹ At [6]. However, formal adoption requires an amendment to TRIPS. The proposed amendment has not been ratified by two thirds of WTO members. See *Amendment of the TRIPS Agreement – Fourth Extension of the Period for the Acceptance by Members of the Protocol Amending the TRIPS Agreement* WT/L/899 (27 December 2013).

²⁰ Patents Act 2013, s 171(1)(b), s 172.

²¹ s 173(2)(b).

obligations, UN member states must go beyond the patent system and support the implementation of alternative incentive mechanisms that can maximise the human right to health, both locally and internationally.

C Criteria for the ideal incentive system

This thesis will propose eight criteria for an ideal incentive system against which the current and various alternative incentive mechanisms can be assessed. Each criterion will be rated from one (lowest) to five (highest). Baker²² used a similar type of analysis to rate four alternatives to the patent system²³ using a five-point scale against seven criteria.²⁴ However, Baker's analysis was lacking in several respects. Firstly, Baker did not consider the problem of unpatentable, unmonopolisable, and unprofitable therapies under the patent system. Secondly, Baker provided no explanation of what each point on the scale meant with reference to each criterion. By contrast, the criteria below will specify the reason for awarding a particular score. Where there is some overlap or uncertainty regarding the appropriate score that should be provided, the author will award a half point increment, for example 3.5 or 2.5. Thirdly, Baker only considered four alternatives to the patent system using seven criteria,²⁵ whereas this thesis will analyse six alternatives against eight criteria. Thus, it is anticipated that this thesis will permit a more in-depth and robust analysis of alternative incentive systems.

1 Incentivising unpatentable therapies

The ideal incentive system should ensure that socially valuable unpatentable therapies are developed, despite the presence of 'unpatentability factors'.²⁶ A rating of five means that no unpatentable therapies will be subject to 'patentability screening'²⁷;

²² See D Baker "Financing drug research: What are the issues?" (Center for Economic and Policy Research, 2008).

²³ At 3.

²⁴ At 4. The seven criteria are: (1) Marginal Cost Pricing (2) Excessive Marketing (3) Adequate Financing for Biomedical Research (4) Incentives for Copycat Research (5) Political Interference with Research Priorities (6) Secrecy of Research Findings and (7) International Co-ordination.

²⁵ In particular, Baker considered (1) a proposal by Tim Hubbard and James Love for funding medical research using an employer-based research fee distributed via intermediaries, (2) a proposal by Aidan Hollis, for the Health Impact Fund, discussed in Chapter 6B (3) a proposal for patent auction by Michael Kremer, and (4) a proposal by Congressman Dennis Kucinich for public funding of drug development via competing research centers.

²⁶ It is important to note that, unpatentable does not imply an absolute standard, rather, patentability exists along a continuum from strong to relatively weak patentability, having regard to the presence of one or more 'unpatentability factors' from Chapter Three.

²⁷ As discussed in Chapter Three under Deadly Gaps in the Patent System, pharmaceutical companies will assess drug candidates for patentability during pre-clinical and clinical development. Any drug candidates which are determined to have insufficient patentability (for example, due to the presence of

four means that most (75 per cent or less) will not be screened; three means that a majority (between 50 and 75 per cent) will not be screened; two means a significant amount (between five and 50 per cent) will not be screened; and one means only an insignificant amount (less than five per cent) will not be screened. Unfortunately, as noted in Chapter Three, due to the high levels of secrecy in the pharmaceutical industry, there is limited empirical data available on the levels of patentability screening.²⁸ Therefore, a ranking under this criterion will necessarily require the author's subjective assessment, based on what can be logically inferred from available information and a comparison with the rankings provided to similar incentive mechanisms.

2 *Incentivising unmonopolisable therapies*

The ideal incentive system will also address the lack of private funding incentives for unmonopolisable therapies.²⁹ Rating scores will be assigned as per the first criterion, but with reference to screening of unmonopolisable therapies, *mutatis mutandis*. As noted above, scoring is necessarily a subjective assessment due to the lack of empirical data.

3 *Incentivising unprofitable therapies*

The ideal incentive system will help incentivise development of unprofitable therapies. Rating scores will be assigned as per the first and second criteria above, but with reference to screening of unprofitable therapies.

4 *Balancing dynamic and static efficiency.*

The fourth criterion requires the ideal system to balance long term benefits from the development of new and more effective medical therapies with short term incentives to lower prices and minimise deadweight loss by allowing competition. In economic

an unpatentability factor such as lack of novelty or inventive step) will be screened out of the development pipeline.

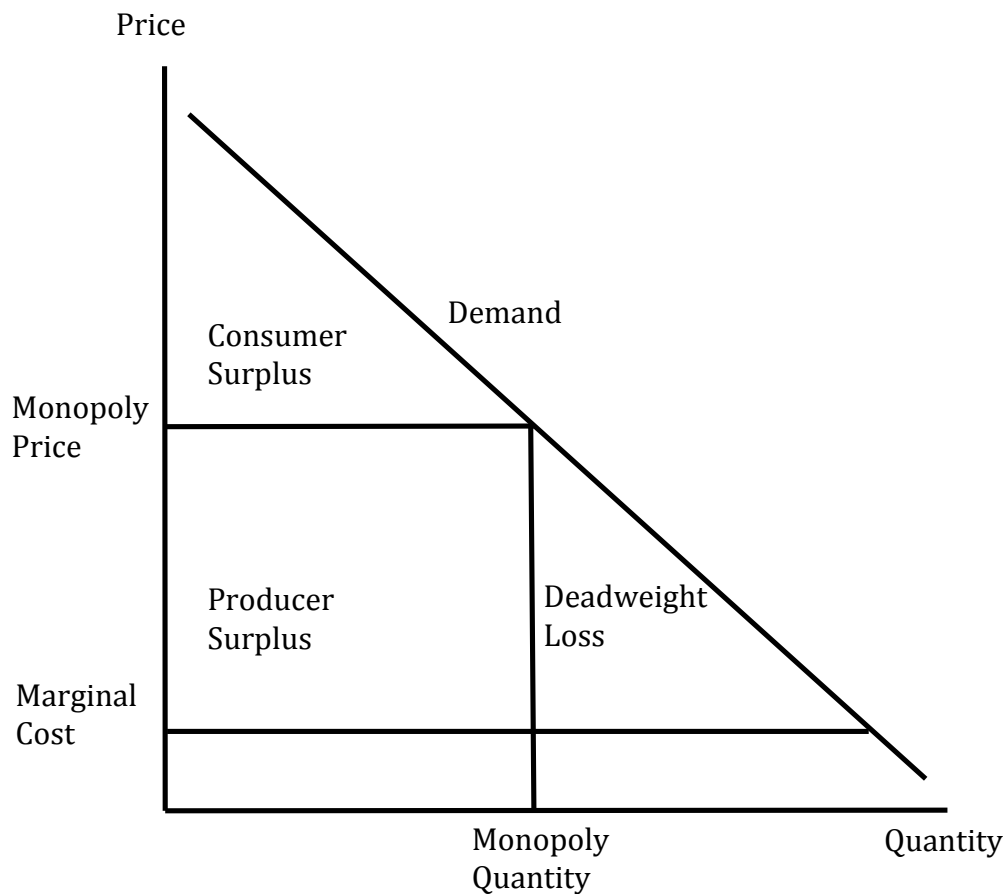
²⁸ As noted in Chapter Three, the author did not receive sufficient level of response to a survey of members of the pharmaceutical industry in order to an empirical assessment. This survey is attached in Appendix One.

²⁹ As discussed in Chapter Three under The Problem of Unmonopolisable Therapies, the name should not imply an absolute threshold, as they exist along a 'continuum of excludability'.

theory, this can be described as the process of balancing dynamic and static efficiency.³⁰

For example, the current patent system achieves dynamic efficiency by allowing an innovator to charge a monopoly price for a limited time. In particular, as illustrated by Figure 2 below, charging a monopoly price allows an innovator recover an amount significantly greater than the marginal cost of producing the medicine. This area is referred to as the ‘producer surplus’.

Figure 2: Producer surplus, deadweight loss and consumer surplus at the monopoly price.



Unfortunately, a temporary monopoly creates two suboptimal effects. First, it reduces the amount of ‘consumer surplus’, which represents consumers who would have been willing to pay a greater amount than the current price. Second, it increases the amount of ‘deadweight loss’, which represents consumers that would have been willing to pay for the drug at below the current monopoly cost, but above the marginal cost of production. Notably, it is theoretically possible to eliminate deadweight loss by using differential pricing, which means charging each customer what they can

³⁰ TB Cueni “International Price Referencing Is there a “right“ way to perform?” (seminar presented to ISPOR, 15th Annual European Congress, Second Plenary Session, Berlin, 6 November 2012) at 2; JE Stiglitz and CE Walsh *Economics* (4th Ed, WW Norton, London, 2006) at A-3.

afford, provided that arbitrage does not occur.³¹ However, this will also eliminate consumer surplus.³² Payers can also reimburse the innovator at the monopoly price by subsidising the medicine, which can eliminate deadweight loss and maximise consumer surplus.³³ However, this assumes that payers can afford the monopoly price, which may be unlikely in developing countries,³⁴ and even developed countries.³⁵

In addition, differential pricing and payer reimbursement do not permit static efficiency, which is brought about through generic competition. As discussed in Chapter Two, generic entry causes the monopoly profits of an innovator to rapidly drop a process referred to as the ‘patent cliff’.³⁶ Static efficiency increases as more generic competitors enter the market until it reaches the marginal cost with eight or more generic competitors.³⁷

It should be noted that long-term dynamic efficiency, to incentivise development of new and improved medicines, and short-term static efficiency, allowing price competition to minimise deadweight loss, are not necessarily mutually exclusive. For example, it is possible to incentivise development of new medical therapies without preventing competition with exclusivity, such as using prize-based ‘pull’ incentives³⁸ or ‘push’ incentives such as grant funding.³⁹ These incentive mechanisms will be analysed in Chapters 6.2 and 6.3.

For rating purposes, this criterion will take the following four elements into account:

- (1) private incentives for new and improved R&D (dynamic efficiency);
- (2) competition (static efficiency);
- (3) minimising deadweight loss; and
- (4) maximising consumer surplus.

³¹ P Yadav “Differential Pricing for Pharmaceuticals: Review of current knowledge, new findings and ideas for action” (Department for International Development, 2010) at 39.

³² M Abramowicz “Perfecting patent prizes” (2003) 56 Vand L Rev 115 at 159.

³³ W Fisher “Intellectual Property and Innovation: Theoretical, Empirical and Historical Perspectives” (seminar on Intellectual Property and Innovation in the Knowledge-Based Economy, The Hague, 2001) at 12; D Lakdawalla and N Sood “Health Insurance as a Two-Part Pricing Contract” (NBER Working Paper No 12681, 2006) at 2.

³⁴ Fisher, at 12.

³⁵ See, for example, C Parahi “Pharmac won't fund prostate cancer drug” (1 May 2014) One News <www.tvnz.co.nz>; N Trigg “NHS says no to new breast cancer drug Kadcyla” (7 August 2014) BBC News <www.bbc.com>.

³⁶ B Hirschler “Drugmakers face \$140 bln patent ‘cliff’ – report” (1 May 2007) Reuters <www.reuters.com>.

³⁷ D Reiffen and MR Ward “Generic drug industry dynamics” (2005) 87(1) Rev of Econ & Stat 37 at 37.

³⁸ See discussion of prize-based ‘pull incentives’ in Chapter 6B.

³⁹ See discussion of ‘push’ funding in Chapter 6C.

A rating of five means that the system provides all (1)-(4) without delay. A rating of four means providing at least three of (1)-(4) without delay, and a rating of three means providing at least two of (1)-(4) without delay. A rating of two means providing only one of (1)-(4) without delay, and a rating of one means providing (1)-(4) with delay.

5 *Linking rewards to improved health outcomes*

The ideal system will link rewards to improved health outcomes in a manner that maximises health impact, irrespective of the treatment modality or class of disease, for example, whether it is monopolisable, unpatentable, unmonopolisable, or unprofitable. A score of five means that the system can maximise health impact gained for the rewards paid, irrespective of the therapy type or class of disease; four means that the system can maximise health impact for rewards in respect of more than one type of therapy or classes of disease; three means the system can maximise health impact, but only in respect of one type of therapy or class of disease, or alternatively, links rewards to health impact for more than one type of therapy, but does not maximise the same; two means the system is capable of linking rewards to health impact but is unlikely to maximise the same; and one means the system links rewards paid to health impact poorly or not at all.

6 *Minimising administration costs to determine rewards*

The ideal incentive system would minimise the administration costs required to determine the appropriate level of rewards by using a market-based mechanism through voluntary negotiations between a willing buyer (payer) and seller (innovator).⁴⁰ It would ideally ‘piggyback’ on an existing reimbursement mechanism, because it would be more expensive to establish a new framework and guidelines. This can be contrasted with the use of a non-market or *sui-generis* mechanism used to determine rewards. Hemmel and Ouellette note that a non-market mechanism such as a government-set award is less efficient because it requires the government to foresee the value of a potential invention in advance, which may result in significant over or underpayment.⁴¹ It is important that costs do not exceed the social surplus gained from implementing the incentive system.

⁴⁰ Although the innovator has a monopoly right and the payer generally has monopsony power, this is deemed a market mechanism for the purpose of this thesis because both parties are free to negotiate pricing. This may also be referred to as a ‘quasi-market’ mechanism.

⁴¹ DJ Hemel and LL Ouellette “Beyond the Patents--Prizes Debate” (2013) 92 Texas Law Review 303 at 327.

A score of five means that determination of the appropriate level of rewards has minimal costs⁴² by using a market-mechanism or existing mechanism; four means using a market mechanism or non-market mechanism which has minimal costs but requires a sui generis mechanism; three means using a market or non-market mechanism which has significant costs to administer;⁴³ two means using a market or non-market mechanism which has high costs to administer;⁴⁴ and one means using a mechanism with extremely high costs to administer.⁴⁵

7 *Minimising waste/inefficiency*

The ideal system will have an absence of the following waste/inefficiency factors namely: (1) incentives for excessive marketing, (2) risk of costly litigation, for example, between generics and innovators or between innovators over conflicting patent rights,⁴⁶ (3) opportunities for gaming, (4) arbitrage due to grey markets, (5) incentives to counterfeit drugs, (6) incentives for low transparency and duplication of R&D efforts due to races to be first to file a patent, (7) incentives to develop me-too drugs, (8) anti-commons effect, (9) rent-seeking, and (10) free-riding. The first eight factors have already been discussed in the previous chapters with reference to problems with the current patent system. Rent-seeking means the use of political manipulation to increase private rewards such as the ‘regulatory capture’ of a government agency to serve certain private interests.⁴⁷ Free riding means benefiting from new therapies without contributing, either directly or indirectly to their development by innovators through the payment of rewards.

A score of five means the absence of all waste/inefficiency factors; four means the absence of all but one or two factors, three means absence of all but three or four

⁴² Minimal costs are defined as costs which are not likely to exceed 10 per cent of the potential social surplus gained as a result of administering the incentive system. Social surplus is calculated as the sum of producer and consumer surplus, which represents the total welfare gain as a result of administering the incentive system.

⁴³ Significant costs means costs which are likely to exceed 10 per cent of the potential social surplus gained.

⁴⁴ High costs means higher than significant costs, but that are not likely to exceed 100 per cent of potential social surplus gained.

⁴⁵ Extremely high costs means costs that are likely to exceed 100 per cent of the potential social surplus gained.

⁴⁶ See PW Grubb and PR Thomsen *Patents for Chemicals, Pharmaceuticals, and Biotechnology: Fundamentals of Global Law* (5th ed, Oxford University Press, New York, 2010) at 434. This is particularly an issue for biotechnology companies, where litigation regarding conflicting patents can often exceed 15 years, by which time there may be limited patent length remaining.

⁴⁷ See A Krueger “The Political Economy of the Rent-Seeking Society” (1974) 64 *American Economic Review* 291; ME Levine and JL Forrence “Regulatory Capture, Public Interest, and the Public Agenda: Toward a Synthesis” (1990) 6 *J of L Econ and Org* 167.

factors, two means the absence of all but five to seven factors, and a score of one means the absence of all but eight or more factors.

8 *Incentivising incremental innovation and breakthroughs*

Lastly, while the ideal system should not encourage ‘me-too’ drugs, it would still reward incremental innovations,⁴⁸ as most technological advances occur in this manner.⁴⁹ For example, slight improvements in ‘me-too’ drugs can sometimes provide large social benefits.⁵⁰ However, there should be a correspondingly greater reward for fundamental breakthroughs, such as a drug with a new mechanism of action, particularly where other innovators have benefited from such breakthroughs. Despite this encouragement, the ideal system should not compromise patient safety.

A score of five means that the system incentivises incremental innovation and breakthroughs optimally⁵¹; four means incentivising either incremental innovation or breakthroughs optimally and either incremental innovation or breakthroughs significantly;⁵² three means incentivising both incremental innovation and breakthroughs significantly or incentivising incremental innovation or breakthroughs optimally; two means incentivising either incremental innovation or breakthroughs significantly; and one means incentivising neither incremental innovation nor breakthroughs significantly. Compromising safety, such as increasing the likelihood of harm or adverse events occurring to patients, will reduce the score by one point.

Evaluating the criteria scores

The eight criteria can be used to provide an overall score to each incentive system by averaging the scores received for each criterion. This provides a benchmark to facilitate a comparison of the strengths and weaknesses of the different incentive systems.

⁴⁸ See O Tur-Sinai “Cumulative Innovation in Patent Law: Making Sense of Incentives” (2010) 50 IDEA 723 at 736-740.

⁴⁹ AI Wertheimer and TM Santella “Pharmacoevolution: the advantages of incremental innovation” (IPN Working Papers on Intellectual Property, Innovation and Health, 2004) at 6.

⁵⁰ See discussion of ‘me-too’ drugs in Chapter Three, citing A Wertheimer, R Levy and T O’Connor “Too Many Drugs? The Clinical and Economic Value of Incremental Innovations” in I Farquhar, K Summers and A Sorkin (eds) *Investing in Health: The Social and Economic Benefits of Health Care Innovation* (Volume 14, JAI Press, United Kingdom, 2001) 77 at 78-79.

⁵¹ Optimally means that over 75 per cent will not be screened for ‘commercial reasons’. Because of the lack of empirical data on this issue, as with the first three criteria, this will be a subjective assessment based on what the author can infer from available information.

⁵² ‘Significantly’ means over 25 per cent of therapies will not be screened for ‘commercial reasons’. As above, this will be the author’s subjective assessment, based on what can be inferred from available information.

Excluding criteria

It is arguable that if the purpose of a particular incentive mechanism is not to incentivise either unpatentable, unmonopolisable or unprofitable therapies, it would be unfair to include them in the calculation of the overall score. In that case, the overall score will be obtained by averaging the scores of the number of criteria analysed. For example, the purpose of an incentive mechanism may only be to incentivise unprofitable therapies such as neglected diseases. Where the purpose of an incentive mechanism is not disclosed, it can be inferred from relevant legislative records or academic commentary.

D Comparison of the Current Incentive System with the Ideal Criteria

This thesis defines the current incentive system as comprising of several aspects, with the primary incentive being the patent system, but also including the regulatory environment and limited data exclusivity, and the pharmaceutical reimbursement system, as it applies to New Zealand and the United States. It is apparent that the current system provides significant private incentives to develop patentable therapies, as demonstrated by the USD 135 billion spent annually on R&D.⁵³ However, as will now be discussed, it performs sub-optimally for many of the ideal criteria.

Should any criteria be excluded?

As noted above, the current incentive system includes the patent and pharmaceutical reimbursement mechanisms. Section 3 of the Patents Act 2013 states that one of its purposes is to provide an “efficient and effective patent system” that “promotes innovation and economic growth while providing an appropriate balance between the interests of inventors and patent owners and the interests of society as a whole”.⁵⁴ During parliamentary debates of the Patents Bill, the central role of the patent system for incentivising development of medicines was emphasised.⁵⁵ Section 3 of the New Zealand Public Health and Disability Act 2000, which establishes the pharmaceutical reimbursement system, states of its purposes is to “achieve for New Zealanders... the improvement, promotion, and protection of their health”. Therefore, it is arguable that the current incentive system should not exclude incentivising development of socially valuable unpatentable, unmonopolisable and unprofitable therapies, as this would not incentivise therapies that would improve overall health of New Zealanders.

⁵³ *The Pharmaceutical Industry and Global Health Facts and Figures 2012* (International Federation of Pharmaceutical Manufacturers and Associations, 2012) at 10, Chart 2.

⁵⁴ Patents Act 2013, s 3(a)(i).

⁵⁵ (27 August 2013) 693 NZPD 12948.

1 *Incentivising unpatentable therapies*

As discussed in Chapter Three, drug candidates are subject to multiple patentability checks during pre-clinical and clinical development. Therapies which are deemed to be unpatentable are screened out, regardless of social value. ‘Evergreening’ techniques, such as filing new formulations or method of use patents may be used to ‘rescue’ patentability, particularly where a medicine has not yet received regulatory approval.⁵⁶ However, evergreening is only effective in limited circumstances where off-label competition is not possible. Despite the lack of empirical data due to the level of secrecy in the industry, an arguably conservative estimate is that only between five and 50 per cent of socially valuable unpatentable therapies will not be screened. Therefore, the patent system receives a score of two under this criterion.

2 *Incentivising unmonopolisable therapies*

Chapter Three discussed the lack of incentives to fund unmonopolisable therapies including second uses of generic drugs, supplements, and therapies based on diet, readily available chemicals, lifestyle interventions, and negative information about drugs. The latter categories are highly unmonopolisable because infringement is practically impossible to detect. It is also difficult or impossible to prevent new uses of generic drugs, even with a patent over the new use.⁵⁷ However, on rare occasions, generic drugs and supplements may be successfully monopolised if off-label substitution can be restricted⁵⁸ or where it is possible to rely on marketing. Therefore, recognising these significant obstacles, it is likely that less than 5 per cent of socially valuable unmonopolisable therapies will be developed, and the patent system receives a score of one under this criterion.

3 *Incentivising unprofitable therapies*

As discussed in Chapter Three, there is a large bias in R&D spending against neglected diseases⁵⁹ and antibiotic research.⁶⁰ Incentives under the current system are based on the ability to extract high monopoly profits from sales. As this is not

⁵⁶ See discussion of ‘evergreening’ in Chapter Three.

⁵⁷ See discussion of ‘skinny labelling’ and unmonopolisable second uses for generic drugs in Chapter Two and 3; *Bristol-Myers Squibb v Shalala* 91 F 3d 1493 (DC Cir 1996).

⁵⁸ See discussion of ‘evergreening’ and the feasibility of preventing ‘off-label’ competition from generic drugs in Chapter Three.

⁵⁹ See discussion of unprofitable therapies in Chapter Three.

⁶⁰ SJ Projan “Why is big Pharma getting out of antibacterial drug discovery?” (2003) 6 *Current Opinion in Microbiology* 427.

possible for unprofitable therapies under the patent system, alternative incentives are required. Therefore, it is likely that far less than 5 per cent of socially valuable unprofitable therapies will be developed, and the current patent system receives a score of one in respect of this criterion.

4 *Balancing dynamic and static efficiency*

The patent system is often considered “a trade-off between static and dynamic efficiency”.⁶¹ Publicly-funded healthcare systems such as New Zealand can avoid deadweight losses of monopoly prices by subsidising medicines, but only to the extent the payer can bear the monopoly price of new pharmaceuticals.⁶² For example, New Zealand ranks 14th globally in the uptake of new medicines, which are the most expensive, compared to the United States which ranks first.⁶³ However, in a non-publicly funded healthcare system such as the United States, while more medicines are available, deadweight losses are greater because higher costs are borne by patients. These deadweight losses were estimated as between USD 3 to 30 billion in 1995,⁶⁴ and between USD 60 to 105 billion in 2013.⁶⁵ Notably, the latter exceeds the USD 48.5 billion that pharmaceutical companies in the United States spend annually on researching new medicines.⁶⁶

Once exclusivity expires, the static efficiency goal of price competition is achieved when generic competitors enter the market. As noted above, pharmaceutical prices drop rapidly upon generic entry, eventually reaching the marginal cost of production with eight or more competitors⁶⁷ which eliminates deadweight loss. However, as discussed in Chapter Three, generic competition can be frustrated by ‘pay-for-delay’ settlements.

It is also possible for pharmaceutical companies to use differential pricing to minimise deadweight loss by charging payers a lower price according to per capita income level. However, this does not tend to occur in the international markets, likely

⁶¹ JA Ordovery “A Patent System for Both Diffusion and Exclusion” (1991) 5(1) *J of Econ Persp* 43 at 43.

⁶² AM Jones (ed) *The Elgar Companion to Health Economics* (2nd ed, Edward Elgar Publishing, Cheltenham (UK), 2012) at 117; above n 39.

⁶³ *Did You Know?* (Medicines New Zealand, 2013) at 8.

⁶⁴ RC Guehl and M Fischbaum “Toward Allocative Efficiency in the Prescription Drug Industry” (1995) 73 *Milbank Q* 213 at 226.

⁶⁵ Baker, n 22, above at 14-15.

⁶⁶ *Biopharmaceutical Research Industry Profile* (Pharmaceutical Research and Manufacturers of America, July 2013) at 31, Figure 10.

⁶⁷ Reiffen and Ward, above n 41, at 37.

due to the risk of arbitrage.⁶⁸ It is preferable to use payer reimbursement to minimise deadweight loss and maximise consumer surplus, assuming it is affordable to the payer.

Therefore, the current patent system provides (1) private incentives and allows (2) competition. However, both of these occur with some delay as monopoly rents can only be obtained from sales after regulatory approval over the length of the exclusivity period, and competition is only possible when the patent expires. It is possible to (3) minimise deadweight loss and (4) maximise consumer surplus with payer reimbursement without delay. Differential pricing can minimise deadweight loss but this will eliminate consumer surplus. Therefore, because the current system can provide (3) and (4) without delay, the current system is provided a rating of three under this criterion.

5 *Linking rewards to improved health outcomes*

The use of pharmacoeconomic principles and QALYs by payers has the potential to maximise health impact in accordance with rewards paid to innovators. However, as discussed in Chapter Three, the current system is biased towards monopolisable therapies at the expense of other safe and effective therapies. As noted by Cook, patents are poorly suited to protect socially valuable clinical trial data.⁶⁹ Patents are the primary incentive to produce clinical trial data under the current system, and do not incentivise research into unpatentable, unmonopolisable and unpatentable therapies. Therefore, because the current system has the potential to maximise health impact of rewards only for one type of therapy, namely ‘monopolisable therapies’, it achieves a rating of three under this criterion.

6 *Minimising administration costs to determine rewards*

The current patent system has long-established legal precedents to allow the grant and enforcement of patents. Payers negotiate with pharmaceutical companies under an established market-mechanism allowing payers to use pharmacoeconomic principles. Litigation between innovators and generic companies, while expensive, is borne by the private industry and not part of the direct administration costs of determining rewards. Therefore the current incentive system achieves a rating of five under this

⁶⁸ For example, Chile and Mexico apparently pay similar pharmaceutical prices to European countries, despite lower income per capita. See PM Danzon and MF Furukawa “Prices and Availability of Pharmaceuticals: Evidence from Nine Countries” (2003) *Health Affairs* W3-521 at 527.

⁶⁹ T Cook “How IPRs, like Nature, Abhor a Vacuum, and What Can Happen When They Fill it - Lacunae and Overlaps in Intellectual Property” (2012) 17 *JIPR* 296 at 299.

criterion, because it has minimal administration costs and uses an existing and established mechanism to determine rewards.

7 *Minimising waste/inefficiency*

Regarding criterion seven, as already discussed in Chapters 3 and 4, the following waste/inefficiency factors are arguably not absent in the current system: (1) incentives for excessive marketing, (2) risk of excessive litigation (such as patent challenges between generics and innovators), (3) opportunity for gaming⁷⁰ (4) arbitrage due to grey markets, (5) incentives to counterfeit drugs, (7) incentives to develop me-too drugs, and (8) anti-commons effect.

However, the patent system has various aspects which reduce waste/inefficiency. The sufficiency requirement under the patent system encourages transparency via full public disclosure in the patent specification, which is published 18 months after filing. Awarding exclusivity rights from the date the patent is filed can also prevent ‘races’ to commercialisation.⁷¹ These effects negate (6) incentives for low transparency and duplication of R&D efforts due to races. Regarding (9) rent-seeking, there is limited evidence of political influence on the process of granting patents, or that regulatory approval and payer reimbursement is subject to significant political influence. Finally, (10) free-riding is minimised under the current patent system, except to the extent that countries may be able to issue compulsory licenses pursuant to the Doha Declaration without adequately compensating the innovator. However, compulsory licensing has rarely occurred in practice.⁷²

Accordingly, because of the absence of all but seven waste/inefficiency factors, the current patent system is awarded a score of two under this criterion.

8 *Incentivising incremental innovation and breakthroughs*

With regard to criterion eight, the current patent system has the flexibility to allow broad ‘genus’ claims which reward breakthroughs,⁷³ and narrow ‘species’ claims

⁷⁰ Examples of gaming include ‘patent evergreening’ and ‘off-label’ promotion, as discussed throughout Chapter Three.

⁷¹ M Abramowicz “The inducement standard of patentability” (2011) 120 Yale LJ 1590 at 1647-1648. discussing Kitch’s prospect theory. See also discussion in Chapter Two.

⁷² According to a 2012 paper by Kuhn and Beall, government officials have only threatened compulsory licensing 24 times since 1995, with a significant drop since 2008. See R Beall and R Kuhn “Trends in Compulsory Licensing of Pharmaceuticals Since the Doha Declaration: A Database Analysis” 9 PLoS Med 1 at 3.

⁷³ For example, a broad claim over a class of drugs which modulate a newly discovered protein target that has been implicated in a disease process.

which promote incremental innovation.⁷⁴ However, to the extent a broad claim over a pioneering drug cannot prevent competition from me-too drugs, the latter may cannibalise rents and arguably reduce incentives to develop breakthrough medicines, which may have novel mechanisms of action.⁷⁵ Pharmacoeconomic principles such as reference pricing may help alleviate this effect by reducing profits for me-too drugs when the pioneering drug becomes available as a generic. Arguably, therefore, the current system is flexible enough to significantly incentivise breakthroughs and optimally incentivise incremental innovation. Further, the current system does not encourage breakthroughs that compromise public safety because of the requirement to obtain regulatory approval to obtain rewards, and the fact that the patent holder will be liable if the marketed drug is unsafe. The current system is therefore granted a rating of four in respect to fulfilment of this criterion.

Summary

Assuming it is appropriate to include the first three criteria, the rating achieved by the current patent incentive system is 2.63 out of five.⁷⁶ It is apparent that the current system is not optimal, particularly in respect of the first three criteria and the seventh criterion. As discussed above, and as will be discussed in the next two chapters, this means that the ideal incentive system is likely to involve alternative incentive mechanisms that can address the lack of incentives for unpatentable, unmonopolisable, and unprofitable therapies, while also achieving the highest possible scores under the other criteria.

E Conclusion

This chapter has argued that international legal obligations compel the implementation of alternative incentives that will address inadequacies in the current incentive system to maximise the right to health. The criteria and ratings devised in this chapter will now be used to assess various alternative incentive mechanisms proposed in Chapter Six, some of which have already been implemented in the United States and in other countries. As a consequence of this analysis, an optimal incentive system will be proposed in Chapter Seven.

⁷⁴ For example, a claim over a specific formulation of a previous drug which has an improved safety or efficacy profile.

⁷⁵ Refer to discussion of 'me-too' drugs in Chapter Three.

⁷⁶ 21 total points divided by the 8 criteria.

VI Alternative Incentives for Medical Therapies

A Introduction

Chapter Six will introduce alternative incentive mechanisms for medical therapies and compare these to the ideal criteria from Chapter Five. These incentive mechanisms are divided into three broad categories. Chapter 6A will address exclusivity-based ‘pull’ incentives¹ that provide exclusivity rights as the primary incentive to reward innovators: patent extensions, extended regulatory exclusivity, and Orphan Drug reforms.² Chapter 6B addresses various prize-based ‘pull’ incentives that reward innovators with payment of money for developing a therapy: fixed prizes, flexible prizes, and advance market commitments. Chapter 6C will address ‘push’ incentives, that support innovators during development of a therapy, such as public funding for clinical trials and open source approaches.

Some of the following incentive mechanisms have already been implemented, whereas others have only been proposed. Nevertheless, their existence supports the notion that the current patent system is not performing adequately, and that alternative mechanisms are required, particularly for incentivising unpatentable, unmonopolisable, and unprofitable therapies.³

VIA Exclusivity-based ‘Pull’ Incentives

In a similar manner to the patent system, exclusivity-based ‘pull’ incentives incentivise development of new medicines, by extending the period of exclusivity against competition for an innovator that obtains a particular goal, such as regulatory approval of a new medicine.

¹ A ‘pull’ incentive rewards the achievement of a particular goal after it has been fulfilled. These can be contrasted with ‘push’ incentives, which assist in the achievement of the goal during development: see F Mueller-Langer “Neglected infectious diseases: are push and pull incentive mechanisms suitable for promoting drug development research?” (2013) 8(2) H Econ Pol L 185 at 187, Fig 1.

² Notably, orphan drug reforms include tax breaks and other grants, and is therefore a ‘hybrid’ mechanism containing ‘push’ incentives. However, as will be discussed below, the primary incentive is exclusivity.

³ It will be observed – and expanded upon in Chapter Seven - that in general, exclusivity-based ‘pull’ incentives in Chapter 6A more suited to incentivise unpatentable therapies, whereas the prize-based ‘pull’ mechanisms in Chapter 6B and government-funded ‘push’ mechanisms in Chapter 6C are more suited for incentivising unmonopolisable and unprofitable therapies.

Patent extension regimes allow pharmaceutical patents to be extended beyond their 20-year length guaranteed by TRIPS. The ostensible rationale for patent extension is to compensate innovators for the reduction in patent length due to long development times and delays in obtaining regulatory approval. As discussed in Chapter Three, a medicine can take an average of 9 to 12 years to develop and achieve regulatory approval, which means that innovators may have less than 10 years of patent exclusivity left to recover their costs.⁴ Accordingly, there is a significant private funding cooling effect for medical therapies with insufficient patent length. An intuitively attractive solution is to provide patent extensions to compensate.

As discussed in Chapter Two, the United States passed the Hatch-Waxman Act in 1984, which established the generic approval pathway to incentivise generic drug companies to challenge patents and rapidly enter the market upon patent expiry. As a counterbalance to these pro-generic reforms, 35 USC § 156(c) provided pharmaceutical patent extensions of up to five years for time lost during clinical trials and regulatory approval, to a maximum of 14 years after FDA approval.⁵ Whilst generally, only one patent extension is available per new active ingredient,⁶ the Federal Circuit has more recently interpreted the Act to allow patent extensions over derivative “drug products” such as salts, enantiomers, and drug combinations.⁷ Arguably, this interpretation would reward “evergreening” attempts by drug companies.⁸

Other jurisdictions have also adopted five-year patent extensions for pharmaceuticals including Europe,⁹ Australia¹⁰ and Japan.¹¹ However, neither Canada

⁴ JA DiMasi, HG Grabowski “The Cost of Biopharmaceutical R&D: Is Biotech Different?” (2007) 28 *Manage Decis Econ* 469 at 475; See also M Dickson and JP Gagnon “The cost of new drug discovery and development” (2009) 4(22) *Discovery Medicine* 172 at 172.

⁵ 35 USC § 156(c), (g)(1)(B), (g)(6). The patent term extension is calculated by adding half of the time spent by a drug in clinical development to the time taken up by regulatory submissions to the FDA: 35 USC § 156(c) (2). See also *Astra v Lehman*, 71 F 3d 1578 (Fed Cir 1995).

⁶ *Fisons v Quigg*, 876 F 2d 99 (Fed Cir 1989).

⁷ *Ortho-McNeil Pharm., Inc v Lupin Pharms, Inc*, 603 F 3d 1377 (Fed Cir 2010) and *Photocure v Kappos* 603 F 3d 1372 (Fed Cir 2010).

⁸ Compare the position in Australia, which allows patent extensions on composition of matter claims but not method of use or process claims: *Boehringer Ingelheim International v Commissioner of Patents* [2000] FCA 1918 at [16].

⁹ Regulation 1768/92 concerning the creation of a supplementary protection certificate for medicinal products [1992] OJ L1821. By contrast with the approach of the United States Federal Circuit to “evergreening”, patent extensions are only available where a drug “product” falls within the claims of the earliest “basic patent”, which would generally exclude derivative drugs: see Case C-431/04 *Massachusetts Institute of Technology* [2006] ECR I-4089; but see *Neurim Pharmaceuticals (1991) Limited v Comptroller-General of Patents* [2010] EWHC 976 (Pat).

¹⁰ Patents Act 1990 (Cth), ss 70, 77(1)-(2).

¹¹ Patent Act No 121 of 1959 (JP), art 76(2).

nor New Zealand has reciprocated with their own patent extension regimes to date.¹² Significantly, Canada filed a complaint to the WTO alleging that the European patent extension provisions were a breach of Article 27.1 of TRIPS because they discriminate the scope of protection by reference to a particular industry (albeit in a positive manner).¹³

In New Zealand, the Ministry of Economic Development released a paper in 2003 recommending patent extensions for pharmaceutical patents.¹⁴ However, this was not implemented by the Labour cabinet, likely due to increased burden on healthcare costs.¹⁵ The reluctance to implement patent extensions in New Zealand is understandable, given that it would increase healthcare costs for a country that is a net importer of new medicines. Arguably, for countries that primarily import new medicines, the main reason to adopt patent extension reforms is to prevent allegations of ‘free riding’¹⁶ or as part of concessions under a free trade agreement.¹⁷ These trade agreements, such as the Trans-Pacific Partnership Agreement currently being negotiated in secret with New Zealand and 11 other countries, are colloquially referred to as ‘TRIPS-Plus’ because they attempt to expand patent protection over the minimum standards guaranteed by TRIPS, often as a result of intensive lobbying by industry representatives in the United States.¹⁸ The proliferation of such ‘TRIPS-Plus’ agreements is often subjected to criticism by foreign aid organisations on the basis of restricting access to generic medicines.¹⁹

Various academics have proposed flexible patent extension mechanisms. For example, Civan proposes extending patent lengths to compensate for unmet medical

¹² T Harris, D Nicol and N Gruen *Pharmaceutical Patents Review Report* (Pharmaceutical Patents Review Committee, Canberra, 2013) at ix.

¹³ *European Communities - Patent Protection for Pharmaceutical and Agricultural Products, complaint by Canada* WT/DS153/1, 2 December 1998.

¹⁴ *Review of the Patents Act 1953: The Pharmaceutical Patent Term in New Zealand: A Discussion Paper* (Ministry of Economic Development, June 2003).

¹⁵ S Frankel "Intellectual Property in New Zealand and the TPPA" in J Kelsey (ed) *No Ordinary Deal. Unmasking The Trans-Pacific Partnership Free Trade Agreement* (Bridget Williams Books, Wellington, 2010) 163 at 172. The Australian government also recently convened the Pharmaceutical Patents Review Committee, which recommended reducing the maximum length of patent extension after regulatory approval to 10 or 12 years: see T Harris, D Nicol and N Gruen at xv, Recommendation 4.1.

¹⁶ Ministry of Economic Development, above n 14, at 10.

¹⁷ For example, New Zealand may yet introduce patent extensions as part of the controversial Trans-Pacific Partnership Agreement (TPP) being negotiated in secret between various Asia-Pacific countries, currently including the United States, Japan, Canada, Australia, Singapore, Brunei, Chile, Malaysia, Mexico, Peru, Vietnam, and New Zealand: see R Wyber and W Perry *The Trans-Pacific Partnership: An analysis of the impact on health in New Zealand* (Nyes Institute, 2013) at 4, 10.

¹⁸ TA Faunce and R Townsend "The Trans-Pacific Partnership Agreement: challenges for Australian health and medicine policies" (2011) 194(2) *Med J Aust* 83 at 84, Box 1.

¹⁹ K Bhardwaj and C Oh "The Trans-Pacific Partnership Agreement: Implications for Access to Medicines and Public Health (UNITAID, World Health Organization, March 2014) at 32; See also "TRIPS, TRIPS Plus and Doha" (July 2011) Médecins Sans Frontières <www.msfaccess.org>.

need involving drugs for neglected diseases.²⁰ Abramowicz proposes the implementation of patent extension auctions,²¹ which would counteract the incentives under the patent system to file for patent protection as early as possible.²² Patent extension proposals will now be analysed against the ideal criteria.

1 Comparison of the patent extension regimes with the ideal criteria.

Should any criteria be excluded?

The purpose of patent extensions is linked to the purpose of the patent system, which, as discussed in Chapter Five, is arguably to incentivise innovation that benefits society as a whole. Therefore, incentivising unpatentable, unmonopolisable, and unprofitable therapies should not be excluded from the following analysis.

(a) Criterion one: incentivising unpatentable therapies

The main benefit of patent extension regimes is their ability to compensate for the unpatentability factor caused by lack of patent length. Although patent extensions would not address the other four unpatentability factors,²³ they would help facilitate ‘evergreening’ if they are available for ‘secondary’ patents.²⁴

As discussed in Chapter Three, there is limited empirical evidence regarding how many therapies are screened due to insufficient patent length. However, a five year patent extension would increase patent length by 25 per cent. Arguably, this would lower the rate of screening compared to the current patent system, and between 50 to 75 per cent of unpatentable therapies will not be screened out.²⁵ For that reason, patent extensions receive a score of three out of five in respect of this criterion.

²⁰ A Civan “An Alternative Patent Mechanism for Pharmaceutical Drugs for Tropical Diseases” (2009) 2(1) EJEPS 21 at 27.

²¹ See M Abramowicz “The Danger of Underdeveloped Patent Prospects” (2007) 92 Cornell L Rev 1065 at 1112-1116. The innovator would propose an auction for a patent extension length and allow third parties to make bids on purchasing the patent extension. The innovator would then be required to purchase the patent extension at a certain markup over the highest bid (for example 25 per cent), or will be liable to pay a fine.

²² At 1065.

²³ Namely, lack of novelty, lack of inventive step, insufficiency/inutility, and unpatentability under law.

²⁴ See above, n 8.

²⁵ Compare the score of two provided for criterion one under the current patent system discussed in Chapter Five.

(b) Criterion two: incentivising unmonopolisable therapies

To the extent that the current patent regime fails to incentivise unmonopolisable therapies, patent extensions would also fail. As discussed when comparing the ideal criteria to the current patent system, patents can only enforce a monopoly price if it is possible to prevent ‘off-label’ substitution of the therapy with a cheap ingredient. This problem would not be solved by a patent extension regime *per se*, therefore, it receives a score of one under this criterion.

(c) Criterion three: incentivising unprofitable therapies

As discussed in Chapter Three and Chapter Five, patent exclusivity does not provide adequate incentives for unprofitable therapies. Studies have already shown that the availability of patent protection has not increased the level of investment in neglected diseases.²⁶ This is not surprising, given that developing countries cannot afford to pay the monopoly price required for an innovator to recoup their investment.²⁷ For example, the above proposal by Civian to extend patents regarding treatment of neglected diseases would have relatively little value as the market for neglected diseases is non-lucrative. For that reason, patent extensions also receive a score of one out of five with respect to this criterion.

(d) Criterion four: balancing dynamic and static efficiency

Patent extensions share the advantages and disadvantages of the current patent regime under the fourth criterion. Increasing the length of exclusivity will provide greater private incentives for development, but will also delay competition and potentially increase the amount of deadweight losses and reduce consumer surplus, to the extent that payers cannot afford to subsidise the monopoly price.

Notably, exclusivity-based incentives may be self-correcting as innovators may charge a lower monopoly price due to a longer period of exclusivity, assuming only such a price will be reimbursed by payers. However, in practice, pharmaceutical companies will charge the highest price the market can bear, and may refuse to supply the drug to a country which cannot afford the monopoly price. This is no different to the position under the current patent system.

²⁶ MK Kyle and AM McGahan “Investments in Pharmaceuticals Before and After TRIPS” (2012) 94(4) Review of Economics and Statistics 1157 at 1157; see also J Lanjouw and I Cockburn “New Pills for Poor People? Empirical Evidence After GATT” (2001) 29 (2) World Development 265 at 265.

²⁷ As discussed below, while increasing the length of exclusivity may allow a lower price to be charged, the net amount payable is unchanged, because an extension would merely push monopoly costs into the future.

Flexible patent extensions could allow length of market exclusivity to exactly match the incentive required to motivate R&D expenditure required for commercialisation. However, this would be administratively difficult to accomplish. Further, as noted above with regard to Canada's complaint to the WTO, attempts to vary patent length could be objected to under the anti-discrimination provisions in article 27.3 of TRIPS.²⁸

Ultimately, patent extensions provide (1) private incentives because of a longer period of exclusivity rights, although there is delay as rewards are only obtained from sales over the period of exclusivity. There is also a longer delay before (2) competition. However, payer reimbursement can (3) minimise deadweight loss and (4) maximise consumer surplus, assuming the medicine is affordable. Accordingly, patent extension regimes are equivalent to current patent system, and are awarded a score of three.

(e) Criterion five: linking rewards to improved health outcomes

As noted in Chapter Five, pharmacoeconomic principles used by payers to negotiate prices have the potential to maximise health impact, at least with respect to monopolisable therapies. For example, innovators are less likely to secure a premium for a me-too drug unless its incremental health benefit is justified, especially where cheaper generics are available. However, as with the current patent system, patent extensions do not reward unmonopolisable and unpatentable therapies. Therefore, because patent extensions, like the patent system, have the potential to maximise health impact for only one type of therapy, namely, monopolisable therapies, they also receive a score of three with respect to this criterion.

(f) Criterion six: minimising administration costs to determine rewards

Administration costs for patent extensions are relatively low compared with prize-based 'pull' incentives and 'push' incentives discussed below. While some controversy exists regarding patent extensions for patents covering previously approved drugs, the determination of which patents qualify for extensions and calculation of patent length is straightforward. The enforcement of monopolies under the patent system also has significant legal precedent. While disputes between innovators and generic drug companies are expensive, these are not costs borne by administrators of the extension mechanism to determine rewards per se.

²⁸ TRIPS, art 27.3.

Similarly to the current patent regime, patent extensions also operate within the current quasi-market model for determining pharmaceutical prices, which resemble a negotiation between a willing buyer and seller, although each seller has exclusivity over their product and there is a limited number of buyers. On the other hand, flexible patent mechanisms, such as those proposed by Civian and Abramowicz, would require a sui generis mechanism of determining patent length. Assuming that flexible patent regimes require a sui generis mechanism, a rating of four is provided. Otherwise, patent extension mechanisms achieve a score of five, as the current patent system is subject to minimal administration costs. Averaging these gives a score of 4.5.

(g) Criterion seven: minimising waste/inefficiency

Patent extensions have many of the same waste/inefficiency factors as the patent system, namely, (1) incentives for excessive marketing, (2) litigation between generics and innovators, (4) arbitrage due to grey markets, (5) incentives to counterfeit, (7) incentives to develop me-too drugs, and (8) an anti-commons effect.

In addition, there is a potential for fixed patent extensions to encourage (9) rent seeking because, as discussed above, their implementation is typically imposed as a result of political pressure under “TRIPS-plus” agreements.²⁹ Flexible patent extension mechanisms would have an even greater risk of ‘rent-seeking’ behavior if the amount of extension is at the discretion of a government agency.

As with the patent system, there is an (3) opportunity for gaming due to ‘evergreening’. Further, (10) free-riding may be an issue, especially where other jurisdictions have chosen to implement patent extension legislation. The only waste/inefficiency factor absent is (6) incentives for low transparency and races to regulatory approval, because exclusivity is provided from the date of filing the patent.

Therefore, as patent extensions have nine waste/inefficiency factors that are not absent, a score of one is provided under this criterion. By contrast, there are seven waste/inefficiency factors under the current patent system.

(h) Criterion eight: Incentivising incremental innovation and breakthroughs

As discussed in Chapter Five with regard to the existing patent system, patent extensions mechanisms allow broad ‘genus’ claims to reward pioneer innovators, and

²⁹ Faunce, above n 18.

‘species’ claims to reward incremental innovation. However, there is a potential for me-too drugs to cannibalise profits from pioneering drugs to the extent it is possible to design around a broad claim.³⁰ Therefore, a patent extension mechanism can significantly incentivise breakthroughs and optimally incentivise incremental innovation; a rating of four can be granted.

Summary

Patent extension regimes receive an average score of 2.56 out of five, slightly worse than the current patent system. Most of the major benefits and drawbacks provided by patent extensions are shared with the existing patent regime. While the patent extension regime improves private incentives to develop medicines due to insufficient patent length, there are more opportunities for waste and inefficiency due to increased rent-seeking (particularly for flexible patent extension proposals) and free-riding.

B Extended Regulatory Exclusivity

Chapter Two discussed how regulatory agencies grant limited periods of data exclusivity from the date of regulatory approval of a new medicine. The United States and New Zealand provide different lengths of data exclusivity for small molecule drugs and biologics.³¹ These rights fall outside the known categories of intellectual property rights.³²

Chapter Two described how data exclusivity prevents competitors from using clinical trial data results to obtain regulatory approval for their generic drug upon demonstration of “bioequivalence” with a branded drug irrespective of patent protection.³³ However, data exclusivity does not prevent a competitor from conducting their own trials, although this rarely occurs in practice.³⁴ The importance of securing data exclusivity is recognised in Article 39.3 of TRIPS, which requires signatories to protect data required to be submitted for regulatory approval against “unfair commercial use”.³⁵

³⁰ For example, a claim to any medicine that modulates a drug target could not be designed around. However a claim to a medicine with an active ingredient that acts on a drug target could potentially be designed around to the extent the drug target can be modulated with another active ingredient.

³¹ Refer to discussion of regulatory environment in Chapter Two. Medsafe New Zealand provides five years of data exclusivity for all new medicines, whereas the FDA provides five years for small molecule drugs and 12 years for biologics.

³² Namely, patents, trademarks, copyrights, and trade secrets.

³³ *New Zealand Regulatory Guidelines for Medicines - Part D* (ed 6.15, Medsafe, November 2011) at 11; see also 21 CFR § 320.1(e).

³⁴ This would defeat the competitive advantage of generic drug companies relying on the innovators’ clinical trial data.

³⁵ TRIPS, art 39.3.

Market exclusivity differs from data exclusivity in that it prevents competitors from obtaining regulatory approval over a drug for the exclusivity period regardless of whether the competitors undertake their own clinical trials.

In general, regulatory exclusivity has distinct advantages over patent exclusivity. It runs from the date of regulatory approval regardless of clinical development times, whereas patents run from the date of filing. Unlike patents, exclusivity periods are also not susceptible to invalidity challenges. As noted in Chapter Two, generic drug companies are incentivised to challenge an innovator's patents, particularly for failure to satisfy any of the patentability criteria.

Certain academic commentators³⁶ have highlighted the discrepancy between the requirements for a valid patent and the more onerous requirements for regulatory approval. The advantages of regulatory exclusivity over patents in this regard have led to various proposals for reform. For example, Eisenberg,³⁷ Morgan³⁸ and Roin³⁹ propose that fixed length exclusivity regimes could be used as a replacement for patent monopolies. Basheer⁴⁰ proposes a variable length exclusivity regime which depends, *inter alia*, on the health value of a drug.

However, the flexibility of regulatory extension regimes is also the source of its main disadvantage: exclusivity may be adjusted according to the political whims of the current government. By contrast, the minimum standards of patent protection under TRIPS cannot be amended without risk of WTO sanctions. Despite this, notwithstanding TRIPS, governments are also permitted to issue compulsory licenses to protect public health in accordance with the Doha Declaration, as discussed in Chapter Five.

³⁶ T Cook "Regulatory Data Protection in Pharmaceuticals and Other Sectors" in A Krattiger and others (eds) *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (MIHR, Oxford, United Kingdom, 2007) at 438-439; S Benjamin and A Rai "Who's Afraid of the APA? What the Patent System Can Learn from Administrative Law" (2007) 95 Geo L R 269 at 278; M Lemley and D Burk "Patent Policy Levers" (2003) 89 Va L Rev 1575 at 1678.

³⁷ R Eisenberg "The Shifting Functional Balance of Patent and Drug Regulation" (2001) 20(5) Health Aff 119 at 123-124; see also R Eisenberg "The Problem of New Uses, 5 Yale J. Health Pol'y. L. & Ethics 717 (2005) and R Eisenberg "The Role of the FDA in Innovation Policy" (2007) 13 Mich Telecomm & Tech L Rev 345 at 364.

³⁸ MR Morgan "Regulation of Innovation Under Follow-On Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanism" (2010) 11 Columbia Science and Technology Law Review 93 at 98.

³⁹ BN Roin "Unpatentable Drugs and the Standards of Patentability" (2009) 87Texas Law Review 503 at 564.

⁴⁰ S Basheer "The Invention of an Investment Incentive for Pharmaceutical Innovation" (2012) 15(5-6) The Journal of World Intellectual Property 305.

Accordingly, extended regulatory reforms can address many problems with the patent system, particularly for incentivising unpatentable therapies. The MODDERN Cures Act of 2013 (MODDERN Cures Bill),⁴¹ is a bill that has recently been re-introduced into the 113th United States Congress.⁴² The MODDERN Cures Bill provides a 15-year “protection period” of extended regulatory exclusivity upon regulatory approval of a “dormant therapy”.⁴³ A dormant therapy and unpatentable therapies are synonymous, and the purpose of the regime is to address the lack of incentives under the patent system for such therapies. MODDERN Cures Bill defines dormant therapies as a drug or biological product for an unmet medical need.⁴⁴ An unmet medical need is defined as a life threatening disease for which no therapy exists, or which can be combined with other therapies to offer better outcomes on diseases not known to be affected by alternative therapies.⁴⁵

The MODDERN Cures Bill also grants patent extensions over a medicine comprising the ‘dormant therapy’ for a minimum protection period of 15 years after regulatory approval.⁴⁶ Further, the innovator has ‘clinical exclusivity’⁴⁷ from the date they apply for dormant therapy status, unless a follow-on innovator’s medicine would have “clinical superiority”,⁴⁸ meaning greater effectiveness, safety or otherwise demonstrating a “major contribution to patient care”.⁴⁹ However, in order to retain clinical exclusivity, the innovator must supply regular “development certifications”.⁵⁰ In light of soaring healthcare costs, it is uncertain whether a reform calling for additional guaranteed exclusivity for new drugs will enter into law, despite the unmet medical need.

⁴¹ MODDERN Cures Act of 2013, HR 3091 [MODDERN Cures Bill]. Relevant extracts from the Bill are attached as Appendix Two.

⁴² Leonard Lance “Lance Legislation Designed to Help Patients with Chronic Diseases and Disabilities” (press release, 12 September 2013). This Bill was originally introduced into the 112th Congress as the MODDERN Cures Act of 2011, HR 3497.

⁴³ MODDERN Cures Bill, s 201(i)(4).

⁴⁴ s 201(i)(3).

⁴⁵ s 201(i)(1).

⁴⁶ s 201(e)(2).

⁴⁷ Clinical exclusivity means that another innovator may not seek ‘dormant therapy’ designation for the same medicine in advance of regulatory approval. As discussed below, this helps prevent wasteful ‘races’ to regulatory approval.

⁴⁸ s 201(e)(1)(C)(ii).

⁴⁹ s 201(e)(1)(C)(ii)(I)-(III).

⁵⁰ Section 201(g). No details are provided as to the information that must be provided in such ‘development certifications’.

2 *The GAIN Act*

Exclusivity-based reforms have been proposed to provide incentives for specific types of unprofitable therapies. For example, as discussed above in Chapter Three, antibiotics are good examples of unprofitable therapies that lack private incentives for development but with large potential health impact and unmet medical needs.⁵¹ In an attempt to address this problem, the United States passed the Generating Antibiotic Incentives Now Act (GAIN Act), which was signed into law in July 2012 as part of title VIII of the Food and Drug Administration Safety and Innovation Act.⁵² The GAIN Act grants five years of data exclusivity (in addition to the current five years) for a new drug classified as a "qualified infectious disease product", being a drug that treats listed antibiotic or antifungal resistant pathogens, in addition to fast track status and priority review.⁵³

3 *Pediatric exclusivity*

Pediatric exclusivity is another regulatory exclusivity mechanism that attempts to incentivise an unprofitable therapy, namely, testing safety and efficacy of new medicines in children, which is a small and unprofitable market. For example, in the United States, pursuant to a written request from the FDA, an additional 6 months of regulatory exclusivity can be granted over a drug, if the drug company conducts requested clinical trials testing safety and efficacy of the drug in children.⁵⁴ The exclusivity only applies to the active ingredient of the drug, and the clinical trials do not need to show any increase in safety or effectiveness (which recognizes the inherent value of negative data).⁵⁵ The European Union⁵⁶ and Canada⁵⁷ have implemented similar pediatric exclusivity regimes.

⁵¹ See Shaoyu Chang and Anthony So "Fostering Innovation to Combat Antimicrobial Resistance" In World Health Organisation *The evolving threat of antimicrobial resistance: options for action* (WHO Press, Geneva, 2012) 77 at 82.

⁵² The Food and Drug Administration Safety and Innovation Act Pub L No 112-144.

⁵³ See KF Morron, G Yu "The Gain Act: Providing Additional Market Exclusivity for Antibiotics to Treat Drug-Resistant Infections" (11 October 2012) Schiff Hardin LLP <www.schiffhardin.com>.

⁵⁴ Best Pharmaceuticals for Children Act of 2007 Pub L No 110-85, codified under 21 USC § 355(a).

⁵⁵ WH Schacht and JR Thomas *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984* (Congressional Research Service, 10 January 2005) at CRS-29.

⁵⁶ Regulation 1901/2006 on medicinal products for pediatric use [2006] OJ L378/1; Regulation No 1902/2006 amending Regulation 1901/2006 on medicinal products for paediatric use [2006] OJ L 378/20. The European Union Pediatric Regulations provide for a 6-month extension in addition to the current five-year patent extension. The Pediatric Regulations also provide 10 years of Pediatric Usage Marketing Authorisation exclusivity for drugs that have already received previous market authorization but do not have patent or SPC coverage, and are developed exclusively for use for pediatric patients: see Regulation No 1901/2006, art 30.

⁵⁷ Food and Drug Regulations CRC c 870, C08.004.1(4). Canada provides a 6-month pediatric extension to a drug which would qualify for an 8 year period of data protection, provided that the

4 *Comparison of extended regulatory exclusivity regimes with the ideal criteria*

Should any criteria be excluded?

The purpose of extended regulatory exclusivity under the MODDERN Cures Bill is to compensate for unpatentable therapies that have insufficient patent protection.⁵⁸ Therefore, the first criterion will not be excluded. By contrast, unmonopolisable therapies are, by definition, non-excludable. Hence, exclusivity proposals are arguably not suited to address such therapies and this criterion should be excluded. However, exclusivity mechanisms have been proposed to incentivise specific unprofitable therapies, such as antibiotic and pediatric exclusivity. Accordingly, incentivising unprofitable therapies will be included the following analysis.

(a) Criterion one: incentivising unpatentable therapies

Patentability is not a requirement for regulatory approval, which means that regulatory exclusivity can incentivise development of unpatentable therapies irrespective of the presence of ‘unpatentability factors’ identified in Chapter Three. As noted by Hemphill and Sampat, the average length of patent exclusivity post-regulatory approval is 12.2 years.⁵⁹ Arguably, if the length of regulatory exclusivity is equivalent to the average length of effective patent protection, this will ensure that otherwise viable medicines will not be subject to patentability screening.⁶⁰ The MODDERN Cures Bill anticipates a “protection period” of 15 years from regulatory approval,⁶¹ which would exceed the average level of protection under the patent regime. Accordingly, there would be no reason to screen unpatentable therapies, and a score of five is achieved for this criterion.

innovator files the results of clinical trials which increase knowledge about the use of the drug in pediatric populations.

⁵⁸ MODDERN Cures Bill, s 3(7): ‘In addition, there is reason to believe that potential treatments with tremendous value to patients are never developed or are discontinued during research and development due to insufficiencies in the intellectual property system.’ See Appendix Two.

⁵⁹ SC Hemphill and BN Sampat “Evergreening, patent challenges, and effective market life in pharmaceuticals” (2012) 31(2) *Journal of Health Economics* 327 at 330. See discussion in Chapter Three.

⁶⁰ Antibiotic exclusivity and pediatric exclusivity reforms provide less than 12 years of exclusivity, and therefore are unlikely to provide incentives under this criterion.

⁶¹ MODDERN Cures Bill, s 201(i)(4)(B).

(b) Criterion three: incentivising unprofitable therapies

Exclusivity-based incentives are less than ideal for unprofitable therapies because the size of the market is small. Notably, however, pediatric exclusivity reforms have been broadly successful, with over 300 studies funded in the United States.⁶² This is likely because of the potential for ‘gaming’, by seeking pediatric exclusivity for drugs which have a large and profitable adult market.⁶³ It is too early to determine the success of the GAIN Act due to the long development cycle for new medicines.

As it may be possible for exclusivity to incentivise unprofitable therapies in some circumstances, it is arguable that between five and 50 per cent of unprofitable therapies will not be screened out. For that reason, exclusivity reforms receive a score of two out of five in respect of this criterion.

(c) Criterion four: balancing dynamic and static efficiency

Both data and market exclusivity are capable of providing dynamic efficiencies, as they prevent generic competition for the protection period. It has been noted that data and market exclusivity is superior to patent protection for biologics, because of the difficulty of proving “literal” infringement, because of naturally high variation between biologic drugs.⁶⁴ Another important advantage is that regulatory exclusivity runs from the date of regulatory approval, which means that increased clinical development time does not reduce incentives.⁶⁵

However, because regulatory exclusivity runs from the date of regulatory approval, this may also increase delays until competition can be achieved, similarly to patents and patent extensions. Moreover, regulatory exclusivity shares the inefficiencies of patents caused by deadweight losses, due to monopoly prices charged above marginal costs. Price competition or static efficiency can only occur once exclusivity expires and generics can gain regulatory approval.

⁶²JS Li and others “Economic return of clinical trials performed under the pediatric exclusivity program” (2007) 297 JAMA 480 at 480.

⁶³ See discussion of waste/inefficiency factors below.

⁶⁴ J Freilich “Patent Infringement in the Context of Follow-On Biologics” (2012) 16 Stan Tech L Rev 9 at 12; see also PW Grubb and PR Thomsen *Patents for Chemicals, Pharmaceuticals, and Biotechnology: Fundamentals of Global Law* (5th ed, Oxford University Press, New York, 2010) at 286, 298. In particular, biologic drugs can have similar composition, but different therapeutic effects because of differences in the manufacturing processes. This creates problems for drafting claims over the chemical formula of a biologic as a means to define the scope of a monopoly, which can arguably disincentivise private investment.

⁶⁵ Compare E Budish, BN Roin and H Williams “Do fixed patent terms distort innovation? Evidence from cancer clinical trials” (NBER Working Paper No 19430, September 2013).

Arguably, the greater flexibility of regulatory exclusivity means that it could strike an effective balance between the interests of innovator and generic drug companies. However, this increased flexibility creates a risk of ‘rent-seeking’ by governments who may reduce the length of exclusivity as political climates change.

Apart from the increased flexibility, extended regulatory exclusivity regimes are similar to patents, in the sense that innovators can price discriminate according to the consumer’s ability to pay, which theoretically, can minimise or even prevent deadweight loss. On the payer side, reimbursement agencies subsidising medicines can minimise deadweight loss and maximise consumer surplus. Therefore, like the patent system, regulatory exclusivity still provides (1) private incentives for R&D and (2) competition with delay, but also has the potential to (3) minimise deadweight loss and (4) maximise consumer surplus without delay. Accordingly, it also receives a score of three out of five with respect of this criterion.

(d) Criterion five: Linking rewards to improved health outcomes

As with patent regimes, extended regulatory exclusivity will only incentivise development of monopolisable therapies, although it has the potential of maximising health impact for rewards through the process of negotiation with payers. Therefore, regulatory exclusivity receives a score of three under this criterion.

(e) Criterion six: minimising administration costs to determine rewards

The administrative costs of providing regulatory exclusivity rewards are low, like patents and patent extensions, because there is no requirement for a sui generis regime to determine rewards, and there is also a well-established quasi-market model for determining price of new therapies through negotiation between the innovator and payers, as discussed in Chapter Four. Due to low administration costs, a fixed length of regulatory exclusivity receives a score of five with respect to this criterion, however, a flexible exclusivity period,⁶⁶ would require a sui generis mechanism to determine exclusivity length, and would receive a rating of four. Therefore an overall rating of 4.5 is granted.

(f) Criterion seven: minimising waste/inefficiency

A major benefit of a guaranteed period of regulatory exclusivity is that it reduces waste due to (2) costly litigation between generics and innovators, as it is less

⁶⁶ See for example, Basheer, above n 40.

susceptible to legal challenges compared to patents. Under the proposed MODDERN Cures Bill, extended exclusivity can also negate (7) incentives to develop ‘me-too’ drugs, to the extent that exclusivity is only granted to therapies for unmet medical needs and therapies that are clinically superior. Further, there is unlikely to be (8) an anti-commons effect as market exclusivity will only be provided for a single drug which achieves regulatory approval and will not be granted over ‘upstream’ research.⁶⁷

However, there are various factors causing waste/inefficiency. Because rewards are only obtained through sales at monopoly prices, there are still (1) incentives for excessive marketing. Regulatory exclusivity can also provide (3) an opportunity for gaming, whereby innovators can wait until just before exclusivity expires on a previous product before seeking regulatory approval for an improved product.⁶⁸ The potential for gaming has also been noted with regard to pediatric exclusivity, whereby pharmaceutical companies only perform pediatric clinical trials on drugs which have a large adult market.⁶⁹ The high monopoly prices available due to monopoly rents will also encourage (4) arbitrage due to grey markets and (5) incentives to counterfeit drugs.⁷⁰

In respect of the MODDERN Cures Bill, the possibility of obtaining regulatory exclusivity over an unpatentable ‘public domain’ drug may (6) incentivise low transparency, particularly if it is possible to use a competitor’s publicly available data to obtain exclusivity over their drug. Data exclusivity may also encourage wasteful ‘duplication’ if a market is lucrative enough, because competitors may conduct their own clinical trials to gain market entry (at no risk of failure).⁷¹ In addition, market exclusivity may encourage wasteful ‘races’ to regulatory approval, unless ‘clinical exclusivity’ can be secured in advance, as provided for under the MODDERN Cures Bill.⁷² It is arguable, therefore, that this waste/inefficiency factor is only half absent.

There is a possibility for (9) rent seeking, if the length of regulatory exclusivity is susceptible to political interference. This may create an unacceptable risk for

⁶⁷ See discussion of ‘patent thickets’ in Chapter Three.

⁶⁸ However, it is difficult to assess the impact of this issue without analysing the regulations that would prescribe how ‘clinical exclusivity’ will be provided to innovators in advance of regulatory approval.

⁶⁹ AS Kesselheim “Using market-exclusivity incentives to promote pharmaceutical innovation” (2010) 363(19) *New England Journal of Medicine* 1855 at 1857.

⁷⁰ D Bagozzi “Fact Sheet No 275: Substandard and Counterfeit Medicines” (November 2003) World Health Organization <www.who.int>.

⁷¹ See discussion of data exclusivity in Chapter Two.

⁷² MODDERN Cures Bill, s 201(e)(1)(C)(ii). “Clinical exclusivity” is an important requirement for securing funding at the early stages of a drug development project because trade secrecy is difficult to maintain once clinical trials commence. By comparison, there is no provision for “clinical exclusivity” under the Orphan Drug Act, discussed below, and there have been occasions where multiple sponsors entered wasteful “races” to regulatory approval.

investors, because lead times for drug development can be 10-15 years or more.⁷³ Free riding (10) is a potential issue, unless it is possible to obtain international co-operation at least from jurisdictions with large pharmaceutical markets.

Therefore, as over seven waste/inefficiency factors are not absent for extended regulatory exclusivity, the criterion receives a score of two out of five.

(g) Criterion eight: incentivise incremental innovation and breakthroughs

Regulatory exclusivity under proposals such the MODDERN Cures Bill is less flexible than patent protection, as it would only cover a specific molecule for treating a particular disease upon regulatory approval, and is only available for therapies for ‘unmet medical needs’.⁷⁴ However, this can provide optimal incentives for breakthrough innovations by preventing a follow-on drug from obtaining exclusivity rights unless it was “clinically superior”, as provided for in the current draft of the MODDERN Cures Bill.⁷⁵

While the lower flexibility is not optimal for incremental innovation, this can be significantly incentivised by allowing exclusivity over a modified drug (provided that it is ‘clinically superior’).⁷⁶ By contrast, antibiotic and pediatric exclusivity are awarded for fulfillment of specific criteria, which means they would not optimally incentivise incremental innovation.

Taking these various regimes into account, extended regulatory exclusivity receives a score of four under this criterion.

Summary

The main benefit of regulatory exclusivity over the patent system is its capacity to incentivise unpatentable therapies. It also has the ability to significantly incentivise incremental innovations and optimally incentivise breakthroughs. However, the benefits of exclusivity (such as antibiotic and pediatric exclusivity) for incentivising unprofitable therapies are equivocal.

⁷³ As noted above, the possibility of a WTO member bringing an action under Article 27.1 of TRIPS would discourage political interference with the 20-year guaranteed length of patent exclusivity.

⁷⁴ MODDERN Cures Bill, s 201(i)(1).

⁷⁵ MODDERN Cures Bill, s 201(i)(3).

⁷⁶ MODDERN Cures Bill, s 201(e)(1)(C). There are equivalent ‘clinical superiority’ provisions in the Orphan Drug Act, discussed in the next section: see 21 USC § 360bb(a)(2); 21 CFR § 316.3(b)(2) and (13)(i)-(ii).

Overall, regulatory exclusivity scores an average of 3.36, assuming incentivising unmonopolisable therapies is excluded as a criterion. Therefore, it is arguable that extended regulatory exclusivity is a significant improvement on both the current patent system and patent extension regimes.

The next section will discuss a hybrid incentive system, which has been successful in using extended regulatory exclusivity (in conjunction with other ‘push’ incentives) to address a market failure for treating rare diseases.

C Orphan Drug Reforms

Orphan Drug reforms provide private incentives for development of so-called ‘orphan drugs’, which treat rare diseases that would otherwise be unprofitable due to the small market. The principal R&D incentive under orphan drug reforms is a minimum period of market exclusivity upon regulatory approval, with tax incentives and government assistance providing additional ‘push’ incentives.⁷⁷ Orphan drug reforms can therefore be considered a hybrid ‘pull’ and ‘push’ mechanism, although exclusivity is the primary incentive, as discussed below.⁷⁸

In the United States, a treatment will be eligible for ‘Orphan Drug designation’ under the Orphan Drug Act of 1983 (Orphan Drug Act)⁷⁹ if it is for a “rare disease or condition” which: (a) affects less than 200,000 Americans; or (b) affects greater than 200,000 Americans, but for which there is no reasonable expectation of recovering the cost of making it available in the United States from domestic sales.⁸⁰

The Orphan Drug Act provides seven years of market exclusivity over the active ingredient of a drug⁸¹ used to treat a particular rare disease, unless a subsequent drug containing the same active ingredient is “clinically superior”.⁸² Clinical superiority means that the drug has greater safety, greater effectiveness, or otherwise makes a major contribution to patient care.⁸³ There are similar provisions in the MODERN Cures Bill, which help prevent ‘evergreening’ and ‘me-too’ competition. Notably, however, a competitor can obtain market exclusivity over the same drug for treating another rare disease, or another drug for treating the same disease.⁸⁴

⁷⁷ ‘Push’ incentives for medical research will be discussed further in Chapter 6C.

⁷⁸ Kesselheim, above n 69, at 1857.

⁷⁹ Orphan Drug Act of 1983 Pub L No 97-414.

⁸⁰ 21 USC § 360bb(a)(2).

⁸¹ This is referred to as the “active moiety” of a drug: see 21 CFR § 316(b)(2).

⁸² 21 USC § 360bb(a)(2): see also 21 CFR § 316.3(b)(2) and (13)(i)-(ii).

⁸³ 21 CFR § 316.3(b)(3).

⁸⁴ *Genentech, Inc v Bowen* 676 F Supp 301 (DDC 1987); *Sigma-Tau Pharms. v Schwetz* 288 F3d 141 (4th Cir 2002).

Market exclusivity is the primary incentive of the Orphan Drug Act.⁸⁵ Other incentives include a 50 per cent R&D tax rebate, grants, clinical research design support and a fee waiver.⁸⁶ Another advantage is that orphan drugs have a better chance of obtaining regulatory approval, as smaller and shorter clinical trials are permitted due to the rarity of patients.⁸⁷

Europe also offers 10 years of market exclusivity for orphan drugs,⁸⁸ while Japan,⁸⁹ and Australia offer tax breaks and reduced fees to apply for regulatory approval, but not regulatory exclusivity.⁹⁰ New Zealand has not implemented an incentive regime for orphan drugs.

Pharmaceutical industry commentators have heralded orphan drug reforms as an unprecedented success.⁹¹ For example, only 10 orphan drugs were approved by the FDA in the decade prior to the enactment of the Orphan Drug Act, and over 350 orphan drugs for rare diseases have been approved since the adoption of the reforms.⁹² However, other commentators have noticed the potential for excessive profits and gaming caused by such reforms,⁹³ which raises the question as to what extent they fulfill the optimal criteria.

1 How does the Orphan Drug regime compare against ideal criteria?

Should any criteria be excluded?

It is arguable that market exclusivity provided by Orphan Drug reforms can incentivise unpatentable therapies that happen to be therapies for rare diseases. However, the core purpose of Orphan Drug reforms is to incentivise treatments for

⁸⁵ Kesselheim, above n 69, at 1857; R Rogoyski “The Orphan Drug Act and the Myth of the Exclusivity Incentive” (2006) 7 Colum Sci & Tech L Rev 1 at 4.

⁸⁶ Rogoyski, at 5.

⁸⁷ KN Meekings, CSM Williams and JE Arrowsmith “Orphan drug development: an economically viable strategy for biopharma R&D” (2012) 17(13) Drug Dis Today 660 at 663. The authors explain the economic advantages of orphan drug development due to smaller clinical trials, faster development time and increased chance of regulatory approval.

⁸⁸ Regulation 141/2000 on orphan medicinal products [2000] OJ L18/1.

⁸⁹ DL Scott and others “Orphan Drug Programs/Policies in Australia, Japan and Canada” (2001) 35 Drug Information Journal 1 at 6.

⁹⁰ At 4 and 10.

⁹¹ WArmstrong “Pharma's Orphans” *Pharmaceutical Executive* (online ed, United States, May 2010). See also E Rensi “The Orphan Drug Act Has Been a Huge Success” (23 June 2008) Wall Street Journal. <www.online.wsj.com>.

⁹² Rensi, above.

⁹³ Kesselheim, above n 69, at 1857.

rare diseases.⁹⁴ As discussed in Chapter Three, because of the small market, these fall within the category of unprofitable therapies. For that reason, incentivising unmonopolisable therapies will not be included in the following analysis.

(a) Criterion one: incentivising unpatentable therapies

Orphan Drug reforms provide a minimum period of exclusivity for a therapy, irrespective of the presence of unpatentability factors. The main disadvantage is that the orphan drug exclusivity period⁹⁵ is shorter than the average period of 12 years of patent protection after regulatory approval.⁹⁶ Another disadvantage is that the exclusivity only applies to rare diseases. However, as will be further discussed below, orphan drug reforms provide the ability to game the system by seeking regulatory approval over a sub-category of patients as a ‘rare disease’ while expecting a sales in the ‘off-label’ market.⁹⁷ This means that Orphan Drug exclusivity may incentivise a broad range of unpatentable therapies which could be framed as ‘rare diseases’.⁹⁸ Other incentives include tax breaks and faster regulatory approval.⁹⁹ As a result of these synergistic incentives, orphan drug reforms can incentivise between five and 50 per cent of unpatentable therapies, and therefore receive a score of two under this criterion.

(b) Criterion three: incentivising unprofitable therapies

As discussed above, the purpose of Orphan Drug reforms is to incentivise development of therapies for rare diseases. While it has been very successful in that area, it will not incentivise broader categories of unprofitable therapies such as neglected diseases and antibiotics that do not have a lucrative ‘off-label’ market. For that reason, it is unlikely to incentivise more than 5 per cent of overall unprofitable therapies, and therefore achieves a rating of one under this criterion.

⁹⁴ L Rin-Laures and D Janofsky “Recent developments concerning the orphan drug act” (1991) 4 Harv J Law & Tec 4 269 at 272.

⁹⁵ Seven years in the United States and 10 years in Europe.

⁹⁶ SC Hemphill and BN Sampat “Evergreening, patent challenges, and effective market life in pharmaceuticals” (2012) 31(2) Journal of Health Economics 327 at 330; H Grabowski, G Long and R Mortimer “Recent trends in brand-name and generic drug competition” (2013) 17(3) Journal of Medical Economics 207 at 207.

⁹⁷ Kesselheim, above n 69, at 1857. However, in an attempt to prevent such ‘gaming’, new FDA regulations issued in 2011 state that it is only possible to obtain orphan drug designation over a subset of patients with a particular disease if there is a ‘medically plausible’ reason to do so: see 21 CFR § 316.20(b)(6).

⁹⁸ An example is imatinib (Gleevec), which received orphan drug designation for treating a rare blood cancer, but is now a blockbuster drug for treating various types of cancer.

⁹⁹ Meekings, Williams and Arrowsmith, above n 87, at 663.

(c) Criterion four: balancing dynamic and static efficiency

The ability to enforce broad market exclusivity over a particular disease category¹⁰⁰ allows orphan drugs to be very profitable, which provides considerable private incentives for development.¹⁰¹ Orphan drugs are typically the most expensive drugs on the market, such as the case of Soliris,¹⁰² at over USD 400,000 per annum, and Myozyme,¹⁰³ at over USD 300,000 per annum.¹⁰⁴ Notably, PHARMAC has refused to fund either of these drugs, arguing the cost is not justifiable relative to the health benefits provided.¹⁰⁵ However, this position has subjected it to criticism from the media and patient groups.¹⁰⁶

There are also examples where orphan drug exclusivity in the United States has caused previously cheap prices for a drug to become exorbitant.¹⁰⁷ Similar examples from Europe resulted in the mandatory replacement of cheap unlicensed drugs with the expensive licensed orphan drug.¹⁰⁸

Despite this, it is apparent that the orphan drug regime provides significant (1) private incentives for R&D. However, it only allows (2) competition after the regulatory exclusivity period has expired. Notably, while exclusivity incentives are provided with delay, incentives such as tax breaks, grants, and clinical trial design assistance are provided without delay prior to regulatory approval. Monopoly prices caused by

¹⁰⁰ This is referred to as a 'therapeutic indication'.

¹⁰¹ Meekings, Williams and Arrowsmith, above n 81, at 660.

¹⁰² Soliris (generic name Eculizumab), is a biologic for treating a rare, progressive and sometimes life-threatening blood disorder, aroxyssmal nocturnal hemoglobinuria (PNH). Soliris is recommended to be continued for the patients lifetime.

¹⁰³ Alglucosidase alfa (Myozyme) is an enzyme replacement therapy for Pompe disease (Glycogen storage disease type II).

¹⁰⁴ See M Herper "The World's Most Expensive Drug" *Forbes Magazine* (online ed, New York, 22 February 2010) . See also G Miller "The world's most expensive drugs" (2 March 2010) *FiercePharma Manufacturing* <www.fiercepharmamanufacturing.com>.

¹⁰⁵ See P Moodie *Response regarding funding for Myozyme for adult-onset Pompe Disease* (Pharmaceutical Management Agency, 17 June 2011); *PHARMAC decision on eculizumab (Soliris) funding* (Pharmaceutical Management Agency, 12 December 2013).

¹⁰⁶ See C Harris "Funding system for costly drugs 'unfair'" *The Dominion Post* (online ed, Wellington, 21 January 2014); see also M Johnson "Plea: Give us Miracle Drug" *New Zealand Herald* (online ed, Auckland 24 Jan 2013). Controversially, drug companies hire public relations firms and lawyers to manage patient groups in order pressure government payers to fund expensive drugs. See Ben Goldacre *Bad Pharma: How drug companies mislead doctors and harm patients* (Fourth Estate, Great Britain, 2012) at 254.

¹⁰⁷ SM Murphy and others "Unintended effects of orphan product designation for rare neurological diseases" (2012) 72(4) *Journal Ann Neurol* 481 at 482. See also AS Kesselheim and DH Solomon DH "Incentives for drug development--the curious case of colchicine" (2010) 362(22) *N Engl J Med* 2045 at 2046. See discussion of FDA removal of colchine from the market in Chapter Three.

¹⁰⁸ F Godlee "Stop exploiting orphan drugs" (2010) 341 *BMJ* 1; see also A Goldberg "Drug firms accused of exploiting loophole for profit" (21 November 2010) *BBC News Health* <www.bbc.co.uk>. The latter article highlighted the case of 3,4 Diaminopyridine (DAP) which formerly had an annual cost between GBP 800 and GBP 2,000 whereby the licensed "brand" (Firdapse) costs GBP 40,000 per annum, despite being the identical molecule.

lack of competition can cause deadweight losses, unless this price is subsidised by payers,¹⁰⁹ which means it is possible to (3) minimise deadweight loss and (4) maximise consumer surplus without delay. Thus, because it is possible to provide at least some (1) private incentives without delay, and (3) and (4) without delay, this criterion achieves a score of 3.5.

(d) Criterion five: linking rewards to improved health outcomes

As mentioned above, the Orphan Drug Act has been highly successful which suggests the reforms have had a significant health impact. However, the reforms only incentivise a single class of therapies: rare diseases. Further, orphan drugs are typically the most expensive in the world, which means they are likely to exceed a payer's cost per QALY threshold. These very high costs are only possible because of market exclusivity and the shortage of therapeutic alternatives for patients with rare diseases. For these reasons, it is arguable that orphan drug reforms are unlikely to maximise health impact for rewards provided. Accordingly, orphan drug reforms achieve a score of two points under this criterion.

(e) Criterion six: minimise administration costs to determine rewards

As with extended regulatory exclusivity, administrative costs of orphan drug regimes are minor and do not rely on a sui generis mechanism. These regimes fit within the current quasi-market model that allows the appropriate price to be negotiated between the innovator and payer. Tax rebates are also relatively simple to administer, although the allocation of grants may cause a small increase in costs of administration. For that reason, a score of 4.5 is provided under this criterion.

(f) Criterion seven: minimising waste/inefficiency

Orphan drug reforms have some inherent advantages which reduce waste/inefficiency. Firstly, (1) incentives for excessive marketing costs are likely to be absent due to the small market for rare diseases. Secondly, (2) costly litigation between generics and innovators can be avoided because regulatory exclusivity cannot be challenged.¹¹⁰ Thirdly, despite high monopoly mark-ups for orphan drugs, (4) arbitrage due to grey markets and (5) incentives to counterfeit drugs is less likely, because it will be easier to prevent unauthorised imports and restrict access to the

¹⁰⁹ It is notable that PHARMAC is the last OECD country which is unwilling to fund Soliris. See "Pharmac refusing to fund blood disorder drug" (14 December 2013) One News <www.tvnz.co.nz>.

¹¹⁰ Further, generic drug companies do not compete with orphan drugs because the market is smaller.

licensed drug when the patient population is small. Fourthly, the requirement that only ‘clinically superior’ orphan drugs can be granted exclusivity reduces (7) incentives to develop me-too drugs. Finally, there will not be an (8) anti-commons effect because market exclusivity is only granted upon regulatory approval.

Nonetheless, there are several waste/inefficiency factors which are arguably not absent. As discussed above, there is (3) opportunity for gaming by seeking orphan drug status for drugs for an indication with a small patient population and relying on ‘off label’ sales to a much broader class of patients,¹¹¹ despite the fact that off-label marketing is illegal.¹¹² As there is no provision for ‘clinical exclusivity’ in advance of regulatory approval¹¹³ there are (9) incentives for low transparency and duplication of R&D efforts due to ‘races’.¹¹⁴ There is also the potential for (10) free-riding by countries that do not provide orphan drug exclusivity.

Therefore, mainly because of the specialised market, orphan drug reforms are relatively free of all but three waste/inefficiency factors, and receive a score of three under this criterion.

(g) Criterion eight: incentivising incremental innovation and breakthroughs

Orphan drug exclusivity provides optimal incentives to develop new breakthrough medicines as it covers a broad class of drugs having the same active ingredient.¹¹⁵ Subsequent registrations are blocked unless they are clinically superior, which prevents competition from me-too drugs that do not improve patient outcomes. To some extent, this may also provide significant incentives for incremental innovation because of the possibility of follow-on competition. However, it is also arguable that the ability to obtain regulatory approval with only small clinical trials and incentives for ‘off-label’ promotion may compromise patient safety. Accordingly, orphan drug reforms are granted a rating of 3 in respect of this criterion.

¹¹¹ Kesselheim, above n 69 at 1857. An example is Gleevec (imatinib), which is a blockbuster drug that was granted Orphan Drug designation.

¹¹² 21 USC § 333(a)(2).

¹¹³ That is, multiple sponsors may hold orphan drug designation over the same drug in advance of regulatory approval.

¹¹⁴ See C Rabe “Competition Between Orphan Drug Sponsors – Good for Patients, Strategic Complexities for Sponsors” (22 December 2011) The Weinberg Group <www.weinberggroup.com>.

¹¹⁵ 21 CFR § 316(b)(2).

Summary

Orphan drug exclusivity has been highly successful in its particular context of rare diseases, by allowing innovators to leverage market exclusivity and charge high prices due to the lack of viable alternative treatments. In the broader context, it achieves an average rating of 2.71 in respect of the seven criteria analysed, which is an improvement over the current patent system.

D Conclusion

It can be seen that, in general, pull-based exclusivity reforms are suited towards incentivising unpatentable therapies, rather than unmonopolisable and unprofitable therapies. For example, patent extensions can address the unpatentability factor caused by insufficient patent length. Extended regulatory exclusivity, such as that provided by the proposed MODDERN Cures Bill, could optimally incentivise unpatentable therapies by negating all of the unpatentability factors.

Reforms such as antibiotic exclusivity, pediatric exclusivity, and orphan drug exclusivity have been proposed to address specific unprofitable therapies, but are susceptible to gaming, and fail to incentivise unprofitable therapies generally. By contrast, prize-based proposals, which will be discussed in the next section, have the ability to reward innovators regardless of whether exclusivity can obtain monopoly rents.

VIB Prize-based 'Pull' Incentives

As discussed above, exclusivity-based 'pull' incentives have various disadvantages including deadweight losses,¹¹⁶ and are less effective for incentivising unmonopolisable and unprofitable therapies. By contrast, prize-based 'pull' incentives can overcome many of these problems. The replacement of the patent system with prizes has been debated since the 19th century,¹¹⁷ with a resurgence of interest in more recent scholarship.¹¹⁸ The main advantages of prizes are that they avoid

¹¹⁶ Unless payer reimbursement is available and the subsidised price is affordable to patients.

¹¹⁷ See A Tabarrok *The Entrepreneurial Economist: Bright Ideas from the Dismal Science* (Oxford University Press, 2002) at 246.

¹¹⁸ EAA de Laat "Patents or Prizes: Monopolistic R&D and Asymmetric Information" (1996) 15 Int'l J Inust Org 369 at 370; BJ Nalebuff and JE Stiglitz "Prizes and Incentives: Towards a General Theory of Compensation and Competition" (1983) 14 Bell J Econ 21; S Shavell and T van Ypersele "Rewards Versus Intellectual Property Rights" (2001) 44 J L & Econ 525; BD Wright "The Economics of Invention Incentives: Patents, Prizes, and Research Contracts" (1983) 73 Amer Econ Rev 691.

deadweight losses and do not rely on exclusivity to reward an innovator. Provided that the amount of the prize does not exceed amount of social surplus gained, a prize-based pull incentive regime is worthwhile.¹¹⁹

The next two sections will discuss two different prize mechanisms and compare them to the ideal criteria: *ex-ante* fixed and *ex-post* flexible prizes.

A *Ex-ante Fixed Prizes*

An *ex-ante* fixed prize is a unilateral agreement to pay a specific reward to an innovator that fulfils certain criteria for achieving a prize. The use of *ex-ante* fixed prizes to incentivise technological achievements has a long history. In 1714, the British government passed the Longitude Act, which authorised the Board of Longitude to award 20,000 pounds to the person that developed a practical method of accurately determining longitude at sea.¹²⁰ The prize was ultimately awarded in 1773 to a watchmaker, John Harrison, who developed a watch that accurately worked at sea. Significantly, the full prize was only awarded after a decades-long dispute with the Board of Longitude, which was anticipating a mathematical solution based on the use of astronomical charts, not a mechanical solution.¹²¹

In another example, Napoleon's Society for the Encouragement of Industry offered a prize of 12,000 francs in 1795 for a method of food preservation that could be used by the French military.¹²² Further, during the 18th and 19th Century, the Paris Academy of Sciences used prizes to fund medical research rather than the current grant-based system.¹²³

A more recent example is the USD 10 million Ansari X-Prize, awarded in 2004 for developing a reusable spacecraft that could reach 100 kilometer altitude, and repeat the trip within two weeks.¹²⁴ Interestingly, the Ansari X-Prize was estimated to have incentivised R&D spending of over USD 100 million,¹²⁵ despite the prize being one tenth of that amount, however, this may have been because the value of publicity would exceed the amount of the prize.

¹¹⁹ M Abramowicz "Perfecting patent prizes" (2003) 56 Vand L Rev 115 at 140.

¹²⁰ Lee N Davis "Should We Consider Alternative Incentives for Basic Research? Patents vs. Prizes" (Paper presented to the DRUID Summer Conference, Copenhagen/Elsinore, 2002) at 11.

¹²¹ See "John Harrison and the finding of Longitude" (2004) Royal Naval Museum Library <www.royalnavalmuseum.org>.

¹²² At 12. The winning invention was a method of heating food within sealed champagne bottles.

¹²³ R Hanson "Patterns of Patronage: Why Grants Won Over Prizes in Science" (University of California, Berkeley, 1998) at 10.

¹²⁴ "Innovation prizes: And the winner is..." *The Economist* (online ed, San Francisco, 5 August 2010).

¹²⁵ At 1.

Stiglitz¹²⁶, Horrobin¹²⁷ and others¹²⁸ have proposed using large prizes to stimulate medical R&D and drug development. Unfortunately, these proposals are lacking in specificity regarding how the prize would be calculated and administered. Various charitable organisations have also used *ex-ante* prizes to incentivise breakthroughs in pre-clinical research.¹²⁹

Ex-ante fixed prizes have the advantage of providing certainty to an innovator regarding the amount of a reward and the criteria to be fulfilled, and do not cost anything while the prize is unclaimed. The main disadvantage of prizes is that the prize administrator may have insufficient information to determine the optimal prize amount. It is also administratively difficult to design criteria for incentivising the most socially valuable outcomes, which are also flexible enough to reward unforeseen solutions.

1 *How do ex-ante fixed prizes compare against ideal criteria?*

Should any criteria be excluded?

As noted above, there have been various proposals to replace patents with prizes, which makes it arguable that one of the purposes of fixed prizes is to incentivise unpatentable therapies. Prizes can also incentivise unmonopolisable and unprofitable therapies, because the criteria for receiving rewards can be designed to be independent of the monopolisability or profitability of a therapy. Therefore, no criteria will be excluded from the following analysis of fixed prizes.

(a) Criterion one: incentivising unpatentable therapies

It is possible for an *ex-ante* fixed prize to incentivise unpatentable therapies generally, but only if the prize is greater than the likely R&D expenditure required to secure the prize. For example, a fixed prize could be awarded upon a new drug achieving regulatory approval. The problem is that a rational prize administrator would set the reward at just above the ‘average’ development cost of a new drug, say, between USD

¹²⁶ JE Stiglitz "Prizes, Not Patents" (2007) 42 PA Econ Rev 48 at 49.

¹²⁷ DF Horrobin "Glittering Prizes for Research Support" (1986) 324 Nature 221 at 221; see also J Stiglitz "Scrooge and Intellectual Property Rights: A medical prize fund could improve the financing of drug innovations" (2006) 333 BMJ 1279 at 1279.

¹²⁸ See BG Charlton "Mega-prizes in medicine: Big cash awards may stimulate useful and rapid therapeutic innovation" (2007) 68 Medical Hypotheses 1.

¹²⁹ See Prize4Life Foundation "Prize4Life Awards \$1M ALS Biomarker Prize!" (press release, 7 February 2011); Methuselah Foundation "Methuselah Foundation Launches NewOrgan Prize" (press release, 6 April 2010).

1 to 3 billion, to avoid the risk of overcompensating an innovator. A solution may be to amend the amount of *ex-ante* prize rewards according to the likely R&D expenditure by therapeutic and disease category, but this is likely to be administratively difficult. In addition, unless it is possible to obtain an amount equivalent to the monopoly profits available for the most lucrative blockbuster drugs, prizes are unlikely to incentivise development of all therapies.¹³⁰ Accordingly, a fixed prize is likely to only incentivise between 50 and 75 per cent of unpatentable therapies, as therapies with higher than average development costs may be screened. For that reason, fixed prizes receive a score of three under this criterion.

(b) Criterion two: incentivising unmonopolisable therapies

Setting the optimal amount of an *ex-ante* fixed prize to incentivise unmonopolisable therapies is also problematic. This creates a risk that the prize amount would not incentivise socially valuable unmonopolisable therapies with higher than average development costs. For the same reasoning noted above with regard to unpatentable therapies, fixed prizes receive a score of three.

(c) Criterion three: incentivising unprofitable therapies

The same valuation problems with *ex-ante* fixed prizes occur with regard to incentivising unprofitable therapies, namely, the risk that the prize would be insufficient to incentivise unprofitable therapies with greater than average development costs. Hence, a score of three is also provided under this criterion.

(d) Criterion four: balancing dynamic and static efficiency

Ex-ante fixed prizes can potentially provide immediate (1) private incentives upon satisfying the criteria for being awarded the prize. Nevertheless, there is potential for delay if there are protracted disputes over fulfillment of the prize criteria. However, the therapy would be released to the public domain upon fulfillment of the prize, which would allow (2) competition and static efficiency while also (3) minimising deadweight loss and (4) maximising consumer surplus without delay. A perfect score may be achievable, but due to the potential for delay in the allocation of prize rewards because of disputes, a score of 4.5 is provided under this criterion.

¹³⁰ For example, Pfizer's blockbuster drug Lipitor has earned over USD 125 billion in sales since 1997. See (ed) "Lessons from Lipitor and the broken blockbuster drug model" (2011) 378 *The Lancet* 1976.

(e) Criterion five: linking rewards to improved health outcomes

Although *ex-ante* fixed prizes are capable of linking rewards to improved health outcomes¹³¹ for multiple types of therapies, the inherent lack of flexibility of such prizes means that they are unlikely to maximise health outcomes with respect to rewards paid. Therefore, fixed prizes receive a score of two under this criterion.

(f) Criterion six: minimising administration costs to determine rewards

A major issue with *ex-ante* fixed prizes is the lack of a true market mechanism to determine the prize value. This is problematic, as often the value of a particular therapy is not apparent until many years after it is commercialised. In addition, generating well-designed prize criteria in advance is technically complex with high administration costs, especially if new criteria have to be developed for each new disease category or type of therapy. Further, where multiple parties may have fulfilled the criteria, it may be difficult for the prize administrator to determine who should receive the reward. Because fixed prizes require a non-market mechanism to determine rewards, and have significant costs of administration, they receive a score of three.

(g) Criterion seven: minimising waste/inefficiency

Advantageously, *ex-ante* fixed prizes lack many of the waste/inefficiency factors which are common to exclusivity-based incentives. The payment of an up-front prize means that there are no (1) incentives for excessive marketing. As monopoly pricing enforced by exclusivity is not necessary, there would also be no opportunities for (4) arbitrage due to grey markets, (5) incentives to counterfeit drugs, (7) incentives to create me-too drugs and an (8) anti-commons effect.

Despite this, fixed prizes have a number of disadvantages. As noted with reference to the Longitude prize, there is a (2) risk of costly litigation due to disputes over fulfillment of the prize criteria, which highlights the need for criteria to be unambiguous. Conceivably, fixed prizes also create (3) an opportunity for gaming, whereby innovators would perform the minimum R&D required to fulfill the criteria and receive the reward. The prize administrators may also force innovators to take a

¹³¹ For example, the criteria for winning the prize may be tied to the achievement of a specific outcome with a high QALY impact, such as a cure for a chronic illness or development of an effective one-off vaccine.

reduced reward after they have already incurred significant R&D costs.¹³² This is referred to by economists as the “time inconsistency problem”.¹³³

In addition, without a mechanism to provide ‘clinical exclusivity’ in advance to competitors, a fixed prize could (6) incentivise low transparency and produce wasteful races.¹³⁴ Moreover, because a fixed prize is likely to be large, and prize administrators are responsible for determining fulfillment of the criteria, there is a potential for (9) rent seeking. Also problematic is that the absence of an international treaty to make contributions towards a prize fund means that any prize regime could be subject to (10) free riding by other countries.¹³⁵

Therefore, because of the absence of all but five waste/inefficiency factors, a score of two is granted under this criterion.

(h) Criterion eight: incentivise incremental innovation and breakthroughs

An ‘all or nothing’ fixed prize would be optimally suited towards incentivising medical breakthroughs rather than incremental innovations, although the prize criteria may involve payment of a lesser sum for incremental innovations, which could significantly incentivise the latter. However, the potential to obtain a large reward may increase risk that fixed prizes would compromise patient safety. In particular, the innovator will not be responsible with how the therapy performs in the wider population after the prize is claimed. This can be contrasted with exclusivity rights, where a single party will market the drug and will be liable in the event of harm. For this reason, a score of three is provided under this criterion.

Summary

In theory, *ex-ante* fixed prizes could provide sufficient incentives to ensure the majority of unpatentable, unmonopolisable, and unprofitable therapies are not

¹³² See JA DiMasi and H Grabowski “Patents and R&D incentives: Comments on the Hubbard and Love trade framework for financing pharmaceutical R&D” (Submission to the Commission on Intellectual Property Rights, Innovation and Public Health, 2004) at 12. Administration agencies which game the system in this way can gain in the short term, but lose long-term benefits as innovators are discouraged from participating in a prize system in the future.

¹³³ JA DiMasi and HG Grabowski “Should the patent system for new medicines be abolished?” (2007) 82(5) *Clinical Pharmacology & Therapeutics* 488 at 489.

¹³⁴ SF Kieff “Property rights and property rules for commercializing inventions” (2000) 85 *Minn L Rev* 697 at 710-711. Kieff refers to ‘rent dissipation’ from races of multiple innovators towards a large prize causing a reduction in the overall value of the prize.

¹³⁵ T Hubbard and J Love “A New Trade Framework for Global Healthcare R&D” (2004) 2 *PLOS Biology* 147 at 150. It could be argued that such “free-riding” already occurs in countries with weaker patent protection or which implement compulsory licensing or price controls for new medicines.

screened the majority of the time. However, the lack of flexibility and a suitable market mechanism to determine rewards means there is a reliance on the design and administration of optimal criteria in advance of the therapy being incentivised, which may not be practical. The focus of prizes on achieving breakthroughs, rather than incremental innovation, may also compromise patient safety, particularly as innovators will not be responsible for putting the therapy on the market. Overall, fixed prizes achieve an average score of 2.94, which is an improvement over the current patent system.

B Ex-post Flexible Prizes

Ex-post flexible prize regimes calculate an innovator's reward based on the health impact of the therapy after it has been developed, rather than determining rewards *ex-ante*. The earliest manifestation of a flexible prize regime involved patent buy-outs, whereby the government would pay a reward to an inventor for their patent, which is subsequently placed into the public domain. For example, the United States Atomic Energy Act of 1954 authorised the Patent Compensation Board to provide rewards for patents over inventions relating to atomic energy, because it was illegal to sell such inventions.¹³⁶ The Soviet Union also implemented a flexible prize-based system to pay a reward to inventors rather than granting exclusivity rights, such as a percentage of costs savings as a result of their invention.¹³⁷ However, there were significant problems, including poor administration, misattribution of inventorship, and under compensation.¹³⁸

The major problem with patent buy-outs is that the amount of the reward may not reflect the social or market value. Kremer proposed a private auction mechanism,¹³⁹ whilst Abramowicz¹⁴⁰, Guell & Fischbaum¹⁴¹ and Shavell & van Ypersele¹⁴² also

¹³⁶ M Kremer "Patent buyouts: A mechanism for encouraging innovation" (1998) 113(4) *The Quarterly Journal of Economics* 1137 at 1145.

¹³⁷ HF Clesner "Payment for Discoveries and Innovations in the Soviet Union" (1961) 5 *Pat. Trademark & Copy J Res & Ed* 52 at 55.

¹³⁸ At 60.

¹³⁹ Kremer, above n 136. Kremer's mechanism is a hybrid of a private auction and government acquisition. In particular, multiple parties bid to purchase rights to the patent, and have a 10 per cent chance of receiving the patent. The other 90 per cent of the time, the government will purchase the patent at the highest auction bid, which is arguably the market value of the patent. In order to ensure the purchase price reflects the amount of social surplus, Kremer suggests that the government multiplies the highest bid by a particular value (for example, times 2.5), although he provides no justification regarding why this would be an appropriate multiplier.

¹⁴⁰ Abramowicz, above n 119. Abramowicz suggests a valuation performed by a government agency that would distribute rewards in delayed and retrospective fashion. The crucial advantage of delayed rewards is that the government will have better information about how to value the patent after the drug is already on the market for several years. The main problems with this proposal is that delayed rewards would reduce the value of this option to innovators, and a non-market mechanism to determine the amount of rewards is likely to be inefficient and/or at a risk of "agency capture".

proposed a patent buyout system as a replacement to the patent system, which used a government-set reward, an extrapolated value based on sales on a test market, and a mathematical formula, respectively. Finally, Outterson proposes a buy-out of patents for neglected diseases,¹⁴³ based on an estimate of sales.

Despite patent buy-outs technically being a flexible prize mechanism, the amount of rewards are tied to the market value of a patent, therefore, they would exclude therapies which are not incentivised under the current patent system. For that reason, patent buy outs will not be analysed with reference to the ideal criteria. Instead, two flexible prize proposals will be considered which allocate rewards based on the health impact of a therapy: the Medical Innovation Prize Act, and the Health Impact Fund.

1 The Medical Innovation Prize Act

The Medical Innovation Prize Fund (MIPF)¹⁴⁴ is a bill for a flexible prize mechanism that was proposed by Senator Bernie Sanders in response to concerns about escalating health care costs due to pharmaceutical monopolies. The MIPF is based on a similar proposal by Love and Hubbard to abolish patent monopolies for pharmaceuticals and replace them with a prize mechanism.¹⁴⁵ The MIPF would establish a Board of Trustees, comprised of government officials and stakeholders from the public and private sector, that allocates rewards based on certain criteria, including incremental health benefit and whether a newly approved drug meets certain pre-determined disease priorities.¹⁴⁶ Under the MIPF, the incremental health benefit is not determined

¹⁴¹ RC Guell and M Fischbaum “Toward allocative efficiency in the prescription drug industry” (1995) *The Milbank Quarterly* 213. The Guell and Fischbaum proposal involves determining the value of the patent by test marketing the new drug within a small geographical area then buying the patent based on an extrapolated calculation of profit in the wider market. There are several problems with this proposal. Firstly, while the test marketing occurs, presumably the drug would not be made available in a wider geographical area, which means there is a delay in the time that patients would benefit from the treatment. In addition, as the amount of the prize would be determined by judges, there is a risk of human error or bias. Finally, there is also the risk that the results from the test market cannot be extrapolated more broadly.

¹⁴² Shavell and van Ypersele, above n 118, propose a more scientific approach using a specific algorithm to estimate the demand curve and social value of a patented drug. The government would pay the expected social surplus based on the average of the range of values generated by the algorithm. The accuracy of the calculation depends on the quality of information held by the government about expected demand. However, Shavell and van Ypersele provide no details of how to make the initial calculation of the probability of demand.

¹⁴³ K Outterson “Patent Buy-Outs for Global Disease Innovations for Low and Middle-Income Countries” (2006) 32 *Amer J L & Med* 159 at 171.

¹⁴⁴ Medical Innovation Prize Fund Act, S 627; Medical Innovation Prize Act of 2007, S 2210. This thesis will refer to provisions from both bills.

¹⁴⁵ J Love and T Hubbard “The Big Idea: Prizes to Stimulate R&D for New Medicines” (2007) 82 *Chi Kent L Rev* 82 1519 at 1532.

¹⁴⁶ Medical Innovation Prize Act of 2007 S 2210, § 9(c)(1), (2) and (3). Disease priorities are currently stated as: (A) current and emerging global infectious diseases; (B) severe illnesses with small client populations (such as indications for which orphan designation has been granted under section 526 of

using QALYs, rather, it involves calculating the number of patients that benefit from a drug and its “incremental therapeutic benefit”.¹⁴⁷

The MIPF would require a USD 80 billion annual prize fund comprising 0.6 per cent of United States gross domestic product.¹⁴⁸ This would be distributed annually to ‘registered’ FDA-approved drugs for 10 years from registration, proportional to their respective health impact.¹⁴⁹ Total payments to any one drug ‘registered’ with the prize fund would be capped to 5 per cent of the total prize fund,¹⁵⁰ and a follow-on drug must allocate some of its rewards to a pioneer drug to the extent it was “based on or benefitted from” the pioneer drug.¹⁵¹ Patents would still be used to determine eligibility to receive prize rewards, but cannot prevent generic competition.¹⁵²

2 *The Health Impact Fund*

The Health Impact Fund (HIF) is another flexible prize incentive mechanism proposed by academics Thomas Pogge and Aidan Hollis, and promoted by Incentives for Global Health.¹⁵³ The mechanism is similar to the MIPF, whereby the HIF would pay annual rewards from a USD 6 billion annual prize fund over ten years following ‘registration’ of an innovator’s drug according to its incremental health impact.¹⁵⁴ In order to be eligible for ‘registration’ it is necessary to either obtain regulatory approval for the innovator’s drug or allow the HIF to do so (and subtract this cost from the rewards payable).¹⁵⁵ It is proposed that health impact can be determined by measuring incremental QALYs gained from an innovator’s registered drug against a ‘baseline’,¹⁵⁶ in any given year compared to other registered drugs.¹⁵⁷

the Federal Food, Drug, and Cosmetics Act (21 U.S.C. 360bb)), and (C) neglected diseases that primarily afflict the poor in developing countries.

¹⁴⁷ At § 9(c)(1),(2).

¹⁴⁸ At § 15(a)(2).

¹⁴⁹ At § 9, 11(c).

¹⁵⁰ At § 9(d)(4), 15(a)(2).

¹⁵¹ At § 9(d)(1). Specifically, payments would continue to be made to the pioneer drug to “the degree that the new . . . product, or manufacturing process was based on or benefitted from the development of the existing . . . product, or manufacturing process.”

¹⁵² Love and Hubbard, above n145 at 1532.

¹⁵³ See A Hollis and T Pogge *The Health Impact Fund: Making New Medicines Accessible for All: a Report of Incentives for Global Health* (Incentives for Global Health, 2008).

¹⁵⁴ At 44.

¹⁵⁵ At 9.

¹⁵⁶ At 15. The ‘baseline’ is set at the expected health of patients at the time or two years prior to when the ‘registered’ drug was introduced.

¹⁵⁷ At 9, 29. For example, the incremental QALY impact of a particular drug can be calculated according to the following crude formula: $Q_1 - Q_2 \times N/D$, where Q_1 is the average QALY impact for each patient treated by the registered drug in clinical trials, Q_2 is the average QALY impact for each patient undertaking a ‘baseline’ treatment, N is the number of registered drugs sold or distributed, and D is the average number of registered drugs taken by each patient. Assuming, on average, a registered drug adds 2 QALYs per patient, and the baseline treatment adds 0.5 QALYs per patient, and each

Importantly, this provides a self-correcting market mechanism for the determination of rewards. In particular, with an increasing number of registered drugs, a firm may choose not to participate as the rewards are too low.¹⁵⁸ In turn, as fewer firms register drugs, this will increase the proportion of rewards payable to the other registrants and eventually incentivise more innovators to participate. Ideally, this ensures the reward levels are optimal (assuming high turnover possible for registration and re-registration).

The innovator company would be required to offer the drug at specified low price during the ten-year reward period, and then subsequently provide a royalty-free open license for other generic manufacturers to produce the drug.¹⁵⁹

A smaller ‘pilot’ for the HIF based on one drug within a small geographical area has been proposed to determine its feasibility.¹⁶⁰ Another proposed use for the HIF is to incentivise the development of antibiotics, which is a known ‘unprofitable therapy’.¹⁶¹ Barbados, Bolivia, Suriname and Bangladesh also proposed a similar mechanism to the HIF, whereby rewards would be paid to developers who openly licensed drugs for certain neglected diseases including HIV, tuberculosis, and malaria, to generic drug companies in a manner that allows developing countries to have access.¹⁶² Thus flexible prize mechanisms have been proposed to incentivise a wide variety of therapies.

patient requires two doses on average, the sale of 10,000 drugs would provide an incremental health benefit of 7500 QALYs.

¹⁵⁸ At 23.

¹⁵⁹ At 3.

¹⁶⁰ T Pogge “Getting the Incentives Right: the Health Impact Fund, a Concrete Contribution to Global Justice and an Innovation in Global Health” (Friedrich Ebert Stiftung International Policy Analysis, July 2011) at 7.

¹⁶¹ K Outterson, A Hollis, and T Pogge “Combatting antibiotic resistance through the Health Impact Fund” in Glenn I Cohen (ed) *The Globalization of Health Care* (Oxford University Press, New York, 2013).

¹⁶² *A Prize Fund to Support Innovation and Access for Donor Supported Markets: Proposal by Barbados, Bolivia, Suriname and Bangladesh* (World Health Organization, 15 April 2009). In a similar manner to the HIF, ‘registered’ drugs would share an annual prize fund according to proportional DALY/QALY impact. The prize would be funded using 10 per cent of current development assistance by participating countries.

3 *How do flexible prize regimes compare against ideal criteria?*

Should any criteria be excluded?

One of the stated purposes of the MIPF is “de-linking research and development incentives from product prices” and “eliminating legal monopolies”.¹⁶³ By contrast, the HIF has been proposed as an optional supplement to the patent regime.¹⁶⁴ However, under both the MIPF¹⁶⁵ and the HIF,¹⁶⁶ patents are not a necessary condition to be eligible to receive rewards. Therefore, such prize mechanisms have been suggested as a means to incentivise socially valuable therapies based on health impact, irrespective of whether they are unpatentable,¹⁶⁷ unmonopolisable¹⁶⁸ or unprofitable.¹⁶⁹ Accordingly, no criteria will be excluded in the following analysis.

(a) Criterion one: incentivising unpatentable therapies

Ex-post flexible reward regimes such as the MIPF and HIF would provide rewards for ten years according to health impact of a therapy irrespective of the presence of unpatentability factors. As noted above, under a fixed prize fund, the amount of rewards available are reduced according to the number of ‘registered’ drugs. Annual rewards available could provide an adequate return on investment for registrants, provided that the size of the overall fund would incentivise registration of at least two or more therapies.¹⁷⁰ Innovators may also be less likely to screen unpatentable therapies with higher R&D costs but higher health impact, because of the chance of obtaining a greater proportion of the annual fund.

¹⁶³ Medical Innovation Prize Fund Act of 2013, §2(3).

¹⁶⁴ Hollis and Pogge, above n 153, at 2.

¹⁶⁵ Medical Innovation Prize Fund Act of 2013, §9(b)(1). Rewards may be paid to “the first person to receive market clearance with respect to the drug or biological product”.

¹⁶⁶ T Syed “Should a Prize System for Pharmaceuticals Require Patent Protection for Eligibility?” (IGH Discussion Paper No 2, Incentives for Global Health, June 10, 2009) at 4-6. Compare Hollis and Pogge, above n 153, at 9, where it is noted that to be eligible to receive rewards a company must hold a patent over a drug product.

¹⁶⁷ M Wei “Should Prizes Replace Patents? A Critique of the Medical Innovation Prize Act of 2005” (2007) 13 Bos Uni J Sci Tech L 25 at 28; Syed at 4-5.

¹⁶⁸ See Hollis and Pogge, above n 153 at 17, 25, noting that the HIF could incentivise funding new uses for generic drugs, which are ‘unmonopolisable therapies’.

¹⁶⁹ At 5, 55.

¹⁷⁰ If only one therapy was registered, then it is likely that the maximum annual size of rewards are not optimal. Also, the smaller the prize fund, the fewer potentially socially valuable therapies being incentivised. It may be possible to increase the size of the annual fund until an optimal amount of new therapies are ‘registered’ each year. The optimal amount could be benchmarked against the number of therapies achieving FDA-approval each year under the current patent system. For example, the FDA approved 39 new molecular entities in 2012. See *CDER Drug and Biologic Calendar Year Approvals for Calendar Year 2012* (Food and Drug Administration, 2012).

Despite the possibility of increased rewards, and a self-adjusting mechanism, it is unlikely that flexible prizes would be as attractive to innovators as monopoly rights, because the amount of rewards would be (arbitrarily) tied to the number of other therapies ‘registered’ with the prize fund at the time and their respective QALY impact.¹⁷¹ However, they would likely be more attractive to innovators than fixed prizes, and for that reason, capable of incentivising at least 75 per cent of unpatentable therapies. Accordingly, flexible prizes achieve a rating of four under this criterion.

(b) Criterion two: incentivising unmonopolisable therapies

Flexible prize mechanisms are capable of incentivising unmonopolisable therapies because rewards are not related to excludability.¹⁷² Notably, however, the MIPF is silent as to whether it would allocate rewards for second uses for generic drugs, or more highly unmonopolisable therapies such as diets, supplements, and lifestyle interventions.¹⁷³ By contrast, the HIF anticipates incentivising second uses for generic drugs,¹⁷⁴ because the reward mechanism “does not require exclusion” only “evidence that the existing drug was in fact used.”¹⁷⁵

Syed noted “possibility of fashioning the HIF’s criteria for added health benefits in such a way that it can reward the independent generation of further safety and efficacy information on already-approved products”.¹⁷⁶ Conceptually, it would be possible to reward generation of safety and efficacy information on highly unmonopolisable therapies such as supplements, diets and lifestyle interventions, although it is not clear how this would be implemented under the MIPF and the HIF. Ultimately, it is likely that flexible prize mechanisms are an improvement on fixed prizes, and could incentivise at least 75 per cent of unmonopolisable therapies to achieve a rating of four under this criterion.

¹⁷¹ For example, if a particular therapy ‘registered’ with the prize fund had a particularly large health impact in a certain year, this would reduce the proportional rewards available to the other registered therapies, irrespective of the total health impact provided overall.

¹⁷² However, there would have to be a practical and reliable way of measuring the number of patients treated by a particular therapy in order to determine health impact, such as using survey data.

¹⁷³ Wei, above 167 at 33.

¹⁷⁴ Hollis and Pogge, above n 153 at 14. Notably, the HIF only rewards new indications for five years, rather than 10 years.

¹⁷⁵ Hollis and Pogge, above n 153 at 17.

¹⁷⁶ Syed, above n 166 at 5.

(c) Criterion three: incentivising unprofitable therapies

One of the major advantages of flexible prize regimes such as the MIPF and the HIF is their ability to incentivise unprofitable therapies such as neglected diseases, with high potential health impact but low profitability. For example, the MIPF proposes to set aside 18 per cent of the fund for global neglected diseases (four per cent), orphan diseases (ten per cent), and infectious diseases with a global public health priority (four per cent).¹⁷⁷ For the reasons outlined above regarding unpatentable and unmonopolisable therapies it is arguable that flexible prize regimes could incentivise over 75 per cent of unprofitable therapies. Therefore, a rating of four is also provided under this criterion.

(d) Criterion four: balancing dynamic and static efficiency

Ex-post flexible prize regimes provide (1) long-term private incentives for R&D by rewarding innovators upon producing information about the safety and efficacy of new therapies. However, under the MIPF and HIF, these rewards are paid over ten years, which is similar to delays under exclusivity regimes. The MIPF would immediately abolish patent monopolies which would allow (2) competition without delay, which would provide static efficiency. By contrast, one of the criticisms of the HIF is that an innovator is not obliged to release the drug into the public domain.¹⁷⁸ However, this criticism can be rebutted by noting that sponsors would be incentivised to license ‘registered’ drugs to a generic company at a cost which maximised QALYs, which may even be at a price below marginal cost.¹⁷⁹

The use of prizes rather than exclusivity rights results in (3) minimising deadweight losses and (4) maximising consumer surplus without delay. However, due to delays in allocation of rewards, a score of four is provided under this criterion.

(e) Criterion five: linking rewards to improved health outcomes.

It is possible for flexible prize regimes such as the MIPF and HIF to link rewards to health impact irrespective of disease type. Notably, however, as currently drafted it is not clear how the MIPF and HIF would practically measure total health impact for

¹⁷⁷ Medical Innovation Prize Act of 2013, S 627, §10(b).

¹⁷⁸ See S Fukuda-Parr and A Proochista “Health Impact Fund – Raising Issues of Distribution, IP Rights And Alliances” (26 September 2011) *IP-Watch* <www.ip-watch.org>.

¹⁷⁹ T Pogge and J Hirsch-Allen “Inside Views: A Response From The Authors Of The Health Impact Fund” (3 October 2011) *IP-Watch* <www.ip-watch.org>.

highly unmonopolisable therapies which are not drugs, such as diets, surgical interventions, and lifestyle interventions.

In addition, by linking rewards to improved health outcomes, there are incentives to actually commercialise a therapy and ensure it gets to patients. This is referred to as overcoming the “last mile problem”.¹⁸⁰ Notably, however, developing therapies for rare diseases that have small patient populations with high unmet medical needs may not be as attractive under mechanisms such as the HIF because total QALY gains will be small. By contrast, the MIPF specifically includes orphan drugs in its criteria to be considered for determining the amount of prizes,¹⁸¹ although it is not clear how this will impact on the payment of rewards.

In light of the above, it is arguable that flexible prize regimes can be used to determine rewards that maximise health impact for more than one type of therapy or class of disease. Therefore, it is possible to grant a rating of four under this criterion.

(f) Criterion six: minimising administration costs to determine rewards

The main disadvantage of flexible prize regimes is that they do not use a market mechanism to determine rewards. As noted above, rewards under the MIPF would be determined by a Board of Trustees. Under the HIF, the Health Impact Assessment Branch would estimate the QALY impact of each ‘registered’ drug.¹⁸² Administration costs are likely to be high because of the necessity to measure incremental health benefit in a robust and fair manner to attract innovators.¹⁸³ For example, the HIF proposes to set aside 10 per cent of the fund as a budget for administering the calculation of QALYs. For USD 6 billion in annual rewards, the administration budget would be USD 600 million per annum, which would make the HIF the largest organisation in the world for measurement of health metrics.¹⁸⁴ Another major problem is how to determine whether increased health impact in a population was due to the innovator’s drug, particularly where patients outside a clinical trial setting may be taking different medications and have various co-morbidities.¹⁸⁵ As noted by commentators, prize administrators would not have access to the ‘perfect’ information required to calculate *ex-post* rewards.¹⁸⁶

¹⁸⁰ Hollis and Pogge, above n 153 at 71.

¹⁸¹ Medical Innovation Prize Fund Act of 2013, §9(c)(3)(B).

¹⁸² Hollis and Pogge, above n 153 at 40.

¹⁸³ Wei, above n 167 at 33.

¹⁸⁴ Hollis and Pogge, above n 153, at 31.

¹⁸⁵ Comorbidities are the presence of more than one disease in the same patient.

¹⁸⁶ J Penin “Patents versus ex post rewards: A new look” (2005) 34 Research Policy 641 at 645.

On the other hand, the MIPF and HIF allocate annual rewards from a fixed fund in a self-adjusting manner, such that if rewards are too low, then fewer innovators will register their drugs, and vice-versa. This could ensure the amount of registered drugs and corresponding rewards would reach a socially optimal equilibrium over time.¹⁸⁷

In summary, although flexible prize regimes have advantages over fixed prizes, such as a self-adjusting mechanism to determine rewards, the measurement of health metrics requires high administration costs. For that reason, flexible prize regimes receive a score of two under this criterion.

(g) Criterion seven: minimising waste/inefficiency

In a similar manner to fixed prize regimes, flexible prize regimes can avoid some of the waste/inefficiency factors present with exclusivity-based incentives. In particular, as rewards are paid independently of the price of the therapy, there are no incentives for (4) arbitrage due to grey markets, (5) incentives to counterfeit drugs and (7) incentives to create me-too drugs. The absence of exclusivity also means that an (8) anti-commons effect will not be present.

However, various waste/inefficiency factors are present with *ex-post* flexible prize regimes. For example, flexible prize regimes may encourage (1) excessive marketing costs if measurement of incremental health impact was based on the number of treatments provided to doctors or patients.¹⁸⁸

There is also a (2) risk of costly litigation with innovators over rewards where it is possible to dispute the methodology of calculating health metrics such as QALYs.¹⁸⁹ On the other hand, prize-based rewards will eliminate litigation between generic drug companies and innovators.¹⁹⁰ However, this is irrelevant if litigation costs regarding the allocation of rewards would possibly exceed the costs under the patent system.¹⁹¹

¹⁸⁷ J Love and T Hubbard “Prizes for innovation of new medicines and vaccines” (2009) 18 *Annals Health L* 155 at 167: “When designing for a single outcome, it is hard to chose the appropriate size of the “Prize.” Too small and the incentive will be insufficient to incentivise R&D. Too large and the mechanism is inefficient. A “Prize Fund” avoids this issue by allowing different R&D innovations to compete against each other. Over time the number of competitors and the scale of their investments in R&D innovations will equilibrate to match the overall size of the Prize Fund, ensuring efficient allocation.”

¹⁸⁸ DiMasi and Grabowski, above n 132, at 15. Notably, an open source approach may overcome the dissemination problem by encouraging sharing of information.

¹⁸⁹ See discussion of difficulties with measuring QALYs in Chapter Four, particularly determination of ‘health utility’, which is a measure of severity of disease from zero to one.

¹⁹⁰ Hollis and Pogge, above n 153 at 17.

¹⁹¹ Wei, above n 167 at 45.

Flexible prize mechanisms such as the MIPF and HIF may encourage (3) opportunities for gaming, depending on how health impact can be measured. For example, innovators may develop treatments for diseases where measurement of health impact may be highly subjective, such as mental illness. Innovators may also exaggerate the number of patients treated,¹⁹² or develop therapies with lower health impact and large patient population, at the expense of patients with unmet medical needs but smaller populations.¹⁹³ As with fixed prizes, there may also be a “time inconsistency problem”, whereby a prize administrator may reduce the rewards after an innovator has already committed R&D expenditure, and the innovator would have little choice but to accept, even if they were insufficient.¹⁹⁴

The MIPF and HIF could also (6) incentivise low transparency and wasteful races because innovators would compete to achieve registration first. However, by using patents to determine eligibility for registration,¹⁹⁵ it may be possible to secure ‘clinical exclusivity’ in advance to prevent races and increase transparency. For example, the latest MIFP Bill would provide an “open source dividend” of 5 per cent of the prize fund to encourage sharing of knowledge that contributed to the development of new drugs.¹⁹⁶

DiMasi and Grabowski point out that having a central authority responsible for allocation of rewards may be susceptible to (9) rent seeking and interference by third parties, which results in research priorities being directed according to political whims as opposed to scientific merit.¹⁹⁷ As with fixed prizes, there is also a potential for (10) free-riding by other countries who do not contribute to the prize fund. The HIF proposes a global contribution according to a 0.03 percent of gross national income,¹⁹⁸ however, securing and calculating the contributions of each country is likely to be politically difficult to implement. The MIFP would be funded by the United States Government, which also raises significant free-riding issues.

Having regard to the fact that six waste/inefficiency factors are arguably not absent, flexible prizes receive a score of two.

¹⁹² Hollis and Pogge, above n 153 at 30.

¹⁹³ As noted above, the MIPF would take rare disease populations into account for the purpose of allocating rewards, however, it is unclear how this would impact on allocation of rewards in practice: see Medical Innovation Prize Fund Act of 2013, §9(c)(3)(B).

¹⁹⁴ DiMasi and Grabowski, above n 133, at 489. Compare exclusivity rights, where an innovator can refuse to supply the drug if the remuneration is too low.

¹⁹⁵ The MIPF does not require patents for eligibility to receive rewards. The HIF requires that ‘registered’ drugs have patent protection in at least one specified jurisdiction. See Hollis and Pogge, above n 153, at 9.

¹⁹⁶ Medical Innovation Prize Fund Act of 2013, §15.

¹⁹⁷ DiMasi and Grabowski, above n 132; see also DiMasi and Grabowski, above n 133.

¹⁹⁸ Hollis and Pogge, above n 153 at 10.

(h) Criterion eight: incentivise incremental innovation and breakthroughs

An *ex-post* flexible prize mechanism can allocate rewards according to health impact, which would incentivise breakthroughs with large health impact and incremental breakthroughs to a lesser extent. For example, the MIFP provides for allocation of a proportionally greater reward to pioneer drugs compared to follow on drugs,¹⁹⁹ although it does not specify how such allocation will be determined in practice. The HIF also bases rewards on incremental health impact which means that smaller health benefits receive smaller rewards.²⁰⁰

Under the flexible prize mechanism, the innovator would be solely eligible to receive rewards for demonstrating health impact of their ‘registered’ drug. Therefore, the innovator would be involved in disseminating the drug to patients, which will reduce incentives to compromise patient safety.²⁰¹

As flexible prize mechanisms would incentivise breakthroughs optimally and incremental innovations significantly, without compromising patient safety, a rating of four is provided under this criterion.

Summary

In theory, the *ex-post* flexible reward regimes could incentivise unpatentable, unmonopolisable and unprofitable therapies by linking rewards to health impact. The main problem is the high administration costs required to calculate health impact, despite the fact that the allocation of rewards under a fixed annual prize fund would be self-adjusting. The presence of waste/inefficiency factors is problematic, including the potential for disputes over the calculation of health impact, susceptibility of a central prize administrator to rent-seeking and ‘agency capture’, and the fact non-contributing countries can ‘free-ride’ on the information generated by the flexible prize mechanism. Accordingly, the flexible prize regimes are unlikely to be politically feasible without strong international support and a practical means to overcome these problems. Nevertheless, flexible prizes achieve an average score of 3.5, which is an improvement over the current patent system, despite increased administration costs, due to the possibility of closer alignment between public health impact and private rewards.

¹⁹⁹ Medical Innovation Prize Fund Act of 2013, § 9(d)(1).

²⁰⁰ Hollis and Pogge, above n 153 at 124.

²⁰¹ Compare *ex-ante* fixed prizes where the reward has already been paid at the time the therapy is put on the market.

C Conclusion

In general, prize-based pull incentives have a significant advantage over exclusivity-based pull incentives for incentivising unmonopolisable and unprofitable therapies. While not optimal, *ex-post* flexible prize regimes achieve a rating of four in respect of those criteria. The main problem with prize-based pull incentives is the lack of a market mechanism to determine rewards and the potential for manipulation of rewards after R&D has been completed. Fixed-prize are inherently inflexible, because criteria have to be set in advance, and should not be subsequently adjusted due to the risk of gaming. Prize-based mechanisms also require international contributions to prevent free-riding, which is politically difficult to implement.

Flexible prize mechanisms may avoid the problems caused by the lack of a market mechanism by allocating rewards according to health impact from an annual prize fund such that the amount of rewards reaches ‘equilibrium’, provided that the method of calculating health impact is robust and fair. The use of prize-based ‘pull’ mechanisms as part of a potentially optimal incentive mechanism to incentivise unmonopolisable and unprofitable therapies will be explored further in Chapter Seven.

Despite these advantages, it may be argued that prize mechanisms would be expensive and displace funding for other mechanism such as direct grants for medical research, which may be a more socially beneficial means of incentivising development of new medicines.

VIC ‘Push’ Incentives

‘Push’ incentives involve mechanisms to directly support medical research during the process of drug development. These can be contrasted with exclusivity and prize-based ‘pull’ incentives, which do not reward innovators until a medicine has been developed. Typically, these ‘push’ incentives comprise research grants paid by governments or other publicly-funded organisations such as charities. The main difficulty is that ‘push’ incentives may reward medical research which does not ultimately lead to viable new treatments for patents.

There are other forms of miscellaneous ‘push’ incentives, such as increased tax breaks²⁰² and priority review of medicines,²⁰³ however, this thesis will focus on increased public funding for clinical trials and open source approaches.

A Increased Public Funding and Open Source Approaches

1 Increased public funding

While public funding accounts for approximately half of combined public and private spending on medical R&D,²⁰⁴ the primary focus is on basic research.²⁰⁵ The majority of public funding is administered through large government agencies.

In the United States, public funding for medical research is administered by the National Institutes of Health (NIH), which was allocated approximately USD 30 billion in 2014.²⁰⁶ The overall success rate for a typical grant application (R01) was 17.5 per cent in 2013.²⁰⁷ There is limited information on how much is spent on clinical trials specifically,²⁰⁸ however, grant applications for funding clinical trials have a much lower chance of success.²⁰⁹

²⁰² DJ Hemel and LL Ouellette “Beyond the Patents--Prizes Debate” (2013) 92 Texas Law Review 303 at 321-323; KM Lybecker and RA Freeman “Funding Pharmaceutical Innovation through Direct Tax Credits” (2007) 2 Journal of Health Economics Policy & Law 267 at 267; To amend the Internal Revenue Code of 1986 to provide a tax credit for medical research related to developing qualified infectious disease products Bill 2007 S 2351/HR 4200.

²⁰³ See “Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review: Expediting Availability of New Drugs for Patients with Serious Conditions” (accessed 4 June 2014) Food and Drug Administration <www.fda.gov>. The European Union also has implemented an “accelerated procedure” under Regulation 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [2004] OJ L136/1, art 14(9). This applies to an application for marketing authorization “in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation”, where such request is “duly substantiated”.

²⁰⁴ “Private and Public R&D Spending: Total biopharmaceutical company R&D, PhRMA member R&D, and NIH operating budget: 1995-2009” (accessed 5 June 2014) PhRMA <www.phrma.org>.

²⁰⁵ BN Sampat and FR Lichtenberg “What are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation?” (2011) 30(2) Health Affairs 332 at 332.

²⁰⁶ “NIH Budget: Research for the People” (11 March 2014) National Institutes of Health <www.nih.gov>. The NIH budget is allocated under the Consolidated Appropriations Act of 2014 Pub L No 113-76.

²⁰⁷ S Rockey “FY2013 By The Numbers: Research Applications, Funding, and Awards” (10 January 2014) Extramural Nexus <www.nexus.od.nih.gov>. The average size of an R01 grant was USD 405,874 in 2013, which is allocated over an average of 4.5 years: see S Rockey “How Long is an R01” (7 November 2013) Extramural Nexus <www.nexus.od.nih.gov>.

²⁰⁸ AL Buchman “The State of Clinical Research in America” (2010) Journal of Investigative Medicine 1 at 3.

²⁰⁹ TA Kotchen and others “NIH Peer Review of Grant Applications for Clinical Research” (2004) 291 JAMA 836 at 836, noting that grant requests for clinical research funding less likely be successful than requests for basic research funding; AN Schechter “The Crisis in Clinical Research: Endangering the Half-Century National Institutes of Health Consensus” (1998) 280 JAMA 1440 at 1441. See also

In New Zealand, public funding of medical research is administered by the Health Research Council (HRC), which was allocated government funding of NZD 84.64 million in 2013.²¹⁰ According to information received by the author from the HRC, approximately NZD 49 million was spent on publicly-funded clinical trials between 2009 and 2013.²¹¹ However, the overall success rate of grant applications was only 9 per cent between 2012 and 2013.²¹²

As mentioned in Chapter Three, it is estimated that 90 per cent of clinical trials are funded by private industry,²¹³ which creates a significant private funding cooling effect for unpatentable, unmonopolisable, and unprofitable therapies. Relying on private companies to fund the vast majority of clinical trials creates various socially undesirable outcomes. In particular, private companies may only publish clinical trials that show favorable results for their drug products,²¹⁴ and can manipulate the design of clinical trial methodologies to bias results in favor of their drugs.²¹⁵ It may even be possible that private companies will “shelve” or “suppress” medical research that would threaten profitable blockbuster revenues.²¹⁶

Independent studies have confirmed the “funding effect” bias due to financial conflicts of interest.²¹⁷ For example, studies have shown that clinical trials funded by for-profit organisations were significantly more likely to recommend an experimental drug (51 per cent) versus clinical trials funded by non-profit organisations (16 per

DG Nathan “Clinical Research: Perceptions, Reality, and Proposed Solutions” (1998) JAMA 1427 at 1427-1428.

²¹⁰ *Report of the Health Research Council of New Zealand for the year ended 30 June 2013, Presented to the House of Representatives Pursuant to Section 38 of the Health Research Council Act 1990* (Health Research Council of New Zealand, 2013) at 5.

²¹¹ Email from Stacey Pene (Health Research Council) to the author regarding HRC funding for clinical trials (20 June 2014).

²¹² At 33.

²¹³ O Vragovic “Developing Budgets for Research Projects with a Focus on Phase III Clinical Trials” (2010) Boston University Medical Campus <www.bumc.bu.edu>; Benjamin N Roin “Solving the Problem of New Uses” (1 October 2013) SSRN <www.ssrn.com> at 25.

²¹⁴ T Bodenheimer “Uneasy alliance: Clinical investigators and the pharmaceutical industry” (2000) 342 *New England Journal of Medicine* 1539 at 1539, 1541.

²¹⁵ See A Montedori and others “Modified versus standard intention-to-treat reporting: are there differences in methodological quality, sponsorship, and findings in randomized trials? A cross-sectional study” (2011) 28 *Trials* 58 at 58. See also Ben Goldacre *Bad Pharma: how drug companies mislead doctors and harm patients* (Fourth Estate, London, 2012) at 171-222.

²¹⁶ See discussion of CA Black “The Cure for Deadly Patent Practices: Preventing Technology Suppression and Patent Shelving in the Life Sciences” (2003) 14 *Alb LJ Sci & Tech* 397 in Chapter Three.

²¹⁷ S Krimsky “Combating the funding effect in science: What's beyond transparency?” (2010) 21 *Stanford Law & Policy Review* 101 at 109-110.

cent).²¹⁸ In some cases, this reporting bias may cause considerable harm to the public.²¹⁹

Accordingly, there have been calls to increase public funding of clinical trials for new medicines in New Zealand²²⁰ and the United States,²²¹ including a proposed global R&D treaty to replace the patent system.²²² However, several commentators have been critical of increased reliance on public funding for drug development. DiMasi and Grabowski note the significant risk of wasteful expenditure due to information asymmetries between grant-making bodies and grantees.²²³ In addition, to be efficient, grants require effective therapeutic candidates to be chosen in advance, and governments “do not have a good track record of picking winners”.²²⁴ By contrast, according to Demsetz, private intellectual property rights, such as patent exclusivity, are better at facilitating the efficient production of information regarding socially optimal research, and the amount of resources to commit towards it.²²⁵

One proposed solution is the establishment of public-private-partnerships (PPPs), where a publicly funded organisation partners with a company to help develop a medicine to address an unmet medical need.²²⁶ Government agencies have taken on

²¹⁸ Bodil Als-Nielsen and others “Association of Funding and Conclusions in Randomized Drug Trials: A Reflection of Treatment Effect or Adverse Events?” (2003) 290 JAMA 921 at 921.

²¹⁹ The 2004 recall of the Vioxx painkiller drug is a good example of the social costs of reporting bias. In 2007, Merck settled a USD 7 billion class action after an investigation discovered that they had suppressed clinical studies that Vioxx doubles the risk of heart attacks. See T Faunce, R Townsend and A McEwan “The Vioxx pharmaceutical scandal: Peterson v Merck Sharpe & Dohme (Aust) Pty Ltd (2010) 184 FCR 1” (2010) 18 Journal of Law and Medicine 38 at 38. Merck also paid US\$950 million in fines to the US justice department in 2011. See D Wilson “Merck to Pay \$950 Million Over Vioxx” *New York Times* (online ed, 22 November 2011).

²²⁰ *Inquiry into improving New Zealand’s environment to support innovation through clinical trials* (Report of the Health Committee, June 2011) at 37-39, 50-51.

²²¹ D Baker “The benefits and savings from publicly funded clinical trials of prescription drugs” (2008) 38 Int J Health Services 731 at 731. See also D Baker “The Benefits to State Governments from the Free Market Drug Act” (Center for Economic and Policy Research, Issues Paper, 2004). The latter paper comments on Free Market Drug Act introduced in the US Congress in 2004. The Act would allocate USD 25 billion to competing drug research centers to fund prescription drug R&D; See also A Jayadev and J Stiglitz “Two Ideas To Increase Innovation And Reduce Pharmaceutical Costs And Prices” (2009) 28 Health Affairs 165 at 166-167; TR Lewis, JH Reichman, and AD So “The case for public funding and public oversight of clinical trials” (2007) *The Economists' Voice* 1 at 1-2;

²²² T Hubbard and J Love “A New Trade Framework for Global Healthcare R&D” (2004) 2 PLOS Biology 147 at 148.

²²³ DiMasi and Grabowski, above n 132, at 7-11.

²²⁴ M Hart “The Chimera of Industrial Policy: Yesterday, Today and Tomorrow” (1993) 19 Can-US LJ 19 at 36.

²²⁵ H Demsetz “Information and Efficiency: Another Viewpoint” (1969) 12 JL & Econ 1 at 12. This landmark paper has been cited extensively to support the strengthening of intellectual property rights as an efficient means to allocate resources towards the production of socially useful information.

²²⁶ A recent example is the development of Kalydeco (Ivacaftor), a new drug treatment for cystic fibrosis which was developed jointly by Vertex Pharmaceuticals and the Cystic Fibrosis Foundation. See Cystic Fibrosis Foundation “Phase 3 Study of VX-770 Shows Marked Improvement in Lung Function Among People with Cystic Fibrosis with G551D Mutation” (press release, 23 February 2011).

the role of facilitating such PPPs to share the costs of clinical trials, such as the NCATS program at the NIH for accelerating drug development.²²⁷ However, the problem is that under the current system, PPPs will still ultimately need to rely on patent exclusivity rights for a new therapy to get to market. The NIH acknowledged that insufficient patent protection is a barrier to obtaining private investment, particularly for repurposing failed drugs.²²⁸

2 *Open source approaches*

Another proposed solution is an ‘open source’ approach²²⁹ through the formation of so-called “pre-competitive consortia” that encourage the sharing of information and resources at the pre-clinical stage, such as the validation of drug targets and generating new animal models for disease that allow testing.²³⁰ It may be appropriate to strengthen the experimental use exception to patent infringement in order to facilitate such “pre-competitive” research.²³¹ However, by definition, pre-competitive consortia anticipate the entry of a subsequent competitive phase where exclusivity rights are enforced. It is unclear when this competitive phase should ideally occur.

Patent pools are another concept related to the ‘open source’ movement. Patent pools involve a collective agreement to cross-license patents according to standard terms, in order to overcome the inefficiencies due to ‘patent thickets’, which, as discussed in Chapter Three, may result when multiple parties have overlapping patent rights to a medicine.²³² For example, under the Medicines Patent Pool, launched by the WHO-affiliated UNITAID in 2010, pharmaceutical companies license their patents over medicines to allow manufacture of HIV medication at generic prices.²³³ Other patent

²²⁷ JC Reed and others “The NIH’s role in accelerating translational sciences” (2012) 30(1) *Nature Biotechnology* 16 at 16.

²²⁸ *NIH-Industry Roundtable: Exploring New Uses for Abandoned and Approved Therapeutics* (National Institutes of Health, 21-22 April 2011) a 2: ‘Patent considerations. Off-patent drugs, or drugs whose patents are close to expiring, may not be attractive to industry because the financial return and market incentives for the product may be limited.’

²²⁹ ‘Open source’ refers to a development methodology which encourages the creation of new useful information through the free sharing of existing information without restrictive proprietary rights.

²³⁰ See J Hunter “Precompetitive Collaborations in Pharmaceutical Industry” (2011) *Col CompTech Bio Res* 55.

²³¹ See Patents Act 2013, s 143. It is not clear whether the New Zealand experimental use exception would include work involving pre-clinical research such as the use of patented animal models, assays or biomarkers. See also S Frankel “An Experimental use Exception for New Zealand” (2009) 17 *J World IP* 446. By contrast, the United States has limited the general experimental use exception to non-commercial use such as “amusement, to satisfy idle curiosity, or for strictly philosophical inquiry”: *Madey v Duke University*, 307 F.3d 1351 (Fed Cir 2002) at 1362. Article 30 of TRIPS also permits such exemptions provided they do not “unreasonably conflict with a normal exploitation of the patent”.

²³² M Heller *The gridlock economy: How too much ownership wrecks markets, stops innovation, and costs lives* (Basic Books, New York, 2008) at 4-6.

²³³ B Hirschler “GlaxoSmithKline unit joins patent pool for AIDS drugs” (27 February 2013) Reuters <www.reuters.com>.

pools have been suggested for neglected diseases, although these are not well-established.²³⁴

It will also be important to ensure that pre-competitive consortia and patent pools do not significantly restrict competition in a manner that may breach applicable law.²³⁵ Further, it is unclear how increased public funding can incentivise drug development in a manner which is not wasteful, and how to co-ordinate the granting of exclusivity rights to private industry using collaborative ‘open source’ approaches in a manner that will provide adequate private incentives to develop new therapies after the pre-competitive stage.

3 *How does increased public funding and open source approaches compare against ideal criteria?*

Should any criteria be excluded?

Various commentators have suggested replacing the current patent system with publicly funded clinical trials.²³⁶ Open source approaches can also be used to increase the efficiency of public funding, particularly in the pre-clinical stage. Additionally, the majority of current R&D spending on unmonopolisable and unprofitable therapies comes from publicly-funded sources because of the lack of private incentives to conduct clinical trials for such research.²³⁷ Therefore, it would not be appropriate to exclude any criteria from the following analysis.

(a) Criterion one: incentivising unpatentable therapies

As noted above, current levels of public funding are insufficient to develop new therapies without the involvement of private industry. Even with increased levels of public funding, pharmaceutical companies would be just as likely to screen unpatentable therapies, as under the current system. However, if drugs could be entirely funded from public sources (through grants available to private entities), it is arguable that such screening would not occur. Unfortunately, this assumes that government agencies can identify the most socially valuable research to fund and it is

²³⁴ H Masum and R Harris *Open Source for Neglected Diseases Magic Bullet or Mirage?* (Results for Development Institute, 2011) at 8.

²³⁵ Commerce Act 1986, s 27; Sherman Antitrust Act, 15 USC § 1-7; see A Kingsbury “Patent Collaboration: Licensing, Patent Pools, Patent Commons, Open Source and Communities of Innovation” (2013) 7 NZIPJ 3 at 7-8.

²³⁶ Baker, above n 221; Jayadev and Stiglitz above n 221; Lewis, Reichman and So, above n 221; Hubbard and Love, above n 222.

²³⁷ See discussion in Chapter Three with examples of publicly funded basic research; see also M Moran and others *G-FINDER 2012 Neglected disease R&D: A five-year review* (Policy Cures, 2012) at 11.

arguable that public agencies have an information asymmetry in this regard.²³⁸ Assuming that government agencies will have a limited healthcare budget,²³⁹ discretionary spending combined with information asymmetry means that otherwise viable socially valuable therapies may still be screened. Therefore, it is arguable that between 50 and 75 per cent of socially valuable but unpatentable therapies will not be screened. Accordingly, a score of three is provided under this criterion.

(b) Criterion two: incentivising unmonopolisable therapies

Increased public funding has the potential to optimally incentivise unmonopolisable therapies because a grant-making body can choose to fund research irrespective of whether it is highly ‘non-excludable’, such as dietary and lifestyle interventions.²⁴⁰ Unfortunately, however, the same problems discussed above with respect to unpatentable therapies militate against the likelihood that the government could choose the most socially valuable therapies to research with a limited budget. Therefore, it is likely that only 50 to 75 per cent of valuable unmonopolisable therapies will not be screened under this criterion, and a score of three is provided.

(c) Criterion three: incentivising unprofitable therapies

Unprofitable therapies could be incentivised with public funding. For example, the establishment of various PPPs for neglected diseases has had some degree of success.²⁴¹ However, in the absence of a viable market, it is likely that PPPs would have limited value to private industry, except from a public relations aspect. Further, the funding of unprofitable therapies by government agencies would involve significant financial risk.

Increased public funding for unprofitable therapies will require selectivity in order to choose lower risk projects to fund, compared to the private industry which may be more willing to bear risk. Therefore, it is likely that between 50 to 75 per cent of valuable unmonopolisable therapies will not be screened under this criterion, and a score of three is granted.

²³⁸ DiMasi and Grabowski, above n 132; Hart, above n 224; Demsetz, above n 225.

²³⁹ It would be politically feasible for clinical trials of all potentially viable therapies to be publicly funded, due to the high risks and costs of drug development. By contrast, the private capital markets have USD 600 trillion available to invest in profitable R&D. See *A world awash in money* (Bain & Company, November 2012).

²⁴⁰ See A Kapczynski and T Syed “The Continuum of Excludability and the Limits of Patents” (2013) 122(7) *Yale Law Journal* 1900.at 1915-1916, as discussed in Chapter Three under The Problem of Unmonopolisable Therapies.

²⁴¹ (ed) “Public-private partnerships for neglected diseases” 366 *The Lancet* 1752 at 1752.

(d) Criterion four: balancing dynamic and static efficiency

Public funding is awarded during development of a new medicine, therefore, it can provide (1) private incentives for R&D. However, it is arguable that there would be some delays during the process of determining where to allocate funding. The possibility of an open source approach allows (2) competition without delay and static efficiency once a publicly funded medicine is ready to be distributed.²⁴²

If government pays for all clinical trials then the drug can be made available at marginal cost, which (3) minimises deadweight losses and (4) maximises consumer surplus, both without delay. Therefore, because it is possible to provide (2), (3), and (4) without delay, and there is the possibility that (1) could have some delay, a rating of 4.5 is granted under this criterion.

(e) Criterion five: linking rewards to improved health outcomes

Public funding for pre-clinical and clinical research does not include a mechanism to link rewards to improved health outcomes. For example, publicly-funded research may cause significant breakthroughs without the original researcher obtaining any windfall benefit as a result. Further, providing such a benefit would be inconsistent with current scientific norms for medical researchers. Despite this, it is likely that a rational grant-making body would allocate increased funding towards therapies for unmet medical needs of the population as a whole. In that sense, increased public funding is capable of linking rewards to health impact. However, the requirement to allocate funds before therapeutic benefit has been established means that a grant mechanism is unlikely to maximise health impact for rewards paid. Therefore, a rating of two is provided under this criterion.

(f) Criterion six: minimising administration costs to determine rewards

Increased public funding creates a risk of high administrative costs due to a large taxpayer-funded bureaucracy and the lack of a market mechanism to determine the level of funding. Ouellete estimates administrative costs for grant funding comprise

²⁴² Notably, however, this would not be the case for a PPP where some form of exclusivity would need to be granted for the private partner to obtain a return on investment.

up to a third of the amount of the grant.²⁴³ In addition, government agencies will have to determine which projects to fund in advance and bear the high risks and costs of clinical trial failure.

Even having regard to the declining levels of R&D productivity in the private industry,²⁴⁴ it is likely that government agencies would be even more inefficient than the market. In particular, research grant recipients have no incentive to terminate a project, compared with the “quick win, fast fail” Darwinian selection approach of private drug development.²⁴⁵ By contrast, government agencies may continue to fund legacy projects with low chances of success, or fail to fund promising new therapies which do not fall within the current scientific paradigm. This is referred to as the “adverse selection” problem.²⁴⁶

For open source approaches, it would be administratively costly to determine the appropriate timing for entry into the competitive phase, and manage ownership of IP, unless the use of standard joint venture agreements is feasible.²⁴⁷

In light of the above, it is arguable that increased public funding would cause high administration costs. However, these would arguably not exceed potential social surplus gained because of the benefits from avoiding conflicts of interest and reporting biases.²⁴⁸ For this reason, a rating of two is provided under this criterion.

(g) Criterion seven: minimising waste/inefficiency

There are various advantages of increased public funding and an open source approach compared to the for-profit funding of clinical research. For example, publicly funded medicines will not encourage (1) excessive advertising. In addition, (2) costly litigation with generic drug companies can be avoided if medicines are released into the public domain immediately. On the other hand, for PPPs requiring exclusivity, there may still be a risk of litigation with generics. Further, with “pre-

²⁴³ Hemel and Ouellette, above n 202, at 362.

²⁴⁴ See JW Scannell and others “Diagnosing the decline in pharmaceutical R&D efficiency” (2012) 11(3) *Nature Reviews Drug Discovery* 191 at 191. Refer to discussion in Chapter Three.

²⁴⁵ SM Paul and others “How to improve R&D productivity: the pharmaceutical industry’s grand challenge” (2010) 9 *Nature Reviews Drug Discovery* 203 at 212, Figure 5.

²⁴⁶ DiMasi and Grabowski, above n 132, at 7-8.

²⁴⁷ For example, there are industry-standard contractual arrangements for joint-venture collaborations between academic centres and private industry such as “Lambert Agreements” define standard agreements which allow sharing of IP generated at a late stage as a result of joint efforts. See “Lambert Tool kit” (accessed 4 June 2014) UK Intellectual Property Office <www.ipo.gov.uk>.

²⁴⁸ For example, as discussed above, socially valuable privately funded research may be suppressed if there is a financial conflict of interest.

competitive consortia” prior to a competitive phase, there may be disputes between innovators if rights to intellectual property are uncertain or conflicting.

The lack of monopoly pricing means that there would be no need for (4) arbitrage due to grey markets, (5) incentives to counterfeit drugs, and incentives to develop (7) me-too drugs. Finally, an open source approach would discourage (6) low transparency and duplication of R&D efforts, and avoid an (8) anti-commons effect.²⁴⁹

Despite these advantages, there are various opportunities for waste/inefficiency with publicly-funded research. As noted above, DiMasi and Grabowski highlight the (3) opportunities for gaming, due to information asymmetry between the grantmaking body and the grantee, creating a “moral hazard” whereby the researcher is likely to change their behaviour once an agreement has been reached to fund the research. There is also a significant risk of (9) rent-seeking by political interference, especially where multiple parties compete for a larger pool of funding. It may also be difficult to manage such conflicts of interest, particularly where the pool of expertise limited.

Increased public funding can also cause a (10) free-riding issue if only one country provides the majority of funding. A proposed solution is the Medical Research and Development Treaty²⁵⁰ which would co-ordinate allocation of funds towards specific R&D priorities via tradable R&D credits (similar to carbon credits).²⁵¹ However, such proposals have been criticised due to complexity and not dealing with underlying intellectual property ownership issues.²⁵²

In light of the fact that all but three (or possibly four) waste/inefficiency factors are absent, a rating of three is provided under this criterion.

(h) Criterion eight: incentivise incremental innovation and breakthroughs

The high flexibility inherent for allocation of public funding has the potential to optimally incentivise incremental innovation and breakthroughs. Medical researchers often make major discoveries by chance, and many breakthrough medicines were discovered due to research undertaken by public sector research institutions.²⁵³ Open

²⁴⁹ M Heller *The gridlock economy: How too much ownership wrecks markets, stops innovation, and costs lives* (Basic Books, New York, 2008) at 4-6, 49-79.

²⁵⁰ A Farlow *A Global Medical Research and Development Treaty. An answer to global health needs* (International Policy Network, 2007).

²⁵¹ At 10.

²⁵² DiMasi and Grabowski, above n 133, at 489.

²⁵³ AJ Stevens and others “The role of public-sector research in the discovery of drugs and vaccines” (2011) 364(6) *New England Journal of Medicine* 535 at 535.

source approaches support the effectiveness of public funding by encouraging the exchange and validation of information.

A possible drawback of publicly-funded research is that, unlike when an innovator has exclusive rights, no one party will be responsible if the therapy causes harm. On the other hand, with publicly funded research, there is no incentive to suppress adverse clinical trial results, which will help protect patients from harm. Therefore, overall, it is arguable that public funding and open source approaches do not compromise patient safety.

Accordingly, increased public funding can optimally incentivise breakthroughs and incremental innovation without compromising patient safety, and that a score of five is awarded under this criterion.

B Conclusion

Public funding and open source approaches hold the most promise at the ‘pre-competitive’ stage of drug development prior to commencement of clinical trials. Public funding may also be beneficial for incentivising unpatentable, unmonopolisable, and unprofitable therapies. The main issue with public funding is the lack of an efficient mechanism to choose which projects to support, which means that rewards may not be linked to improved health outcomes. Further, the high costs and risks of failure for drug development during clinical trials means that publicly funding all drug development is likely to be inefficient. Despite this, the public funding of clinical trials can avoid many of the waste/inefficiencies factors present in the current incentive system, and can also optimally incentivise breakthroughs and incremental innovation.

Overall, increased public funding and open source approaches achieve a score of 3.19. Public funding could potentially be an optimal incentive system, if combined with an appropriate mechanism to help grant-makers select which therapies would have the greatest social value.

Overall Conclusion

Chapter Six has described and analysed various alternative mechanisms to overcome the current problems inherent in the patent system, with respect to the ideal criteria. Chapter Seven will propose two mechanisms as part of a hybrid system that combines the advantageous aspects of these alternative incentive mechanisms in a synergistic manner, and will specifically address the lack of incentives for development of unpatentable, unmonopolisable, and unprofitable therapies.

VII Proposed Optimal Incentive System

A Introduction

Chapter Three described how the high costs and risks of drug development created significant private funding cooling effects for unpatentable, unmonopolisable and unprofitable therapies. Chapter Five provided evidence of international obligations for countries to implement mechanisms that would maximise the right to health. Eight ideal criteria were suggested, against which the current incentive system was compared. This achieved a relatively low average rating of 2.63 out of five. Chapter Six described and analysed various alternative incentive mechanisms for medical therapies against these ideal criteria, which were separated into three categories: exclusivity-based ‘pull’ incentives, prize-based ‘pull’ incentives and ‘push’ incentives. Proposals for extended regulatory exclusivity and *ex-post* flexible prizes received the highest ratings of 3.36 and 3.5, respectively.

This Chapter 7 will propose that two incentive mechanisms should be implemented as part of an optimal model that would address the insufficient incentives under the patent system to develop unpatentable, unmonopolisable and unprofitable therapies, while satisfying the remaining ideal criteria to the maximum extent possible. In particular, the proposals involve providing extended market exclusivity for unpatentable therapies upon regulatory approval, and providing flexible prizes for early-stage clinical trials of unmonopolisable and unprofitable therapies in conjunction with increased public funding for late stage clinical trials. The policy justification for implementing these reforms is the same as all intellectual property regimes: to incentivise production of socially valuable information.¹

It should be noted that the following proposed regimes do not require amendments to the current patent system, for example, by raising the threshold tests for novelty, inventive step, and sufficiency, or abolishing the doctrine of inherent anticipation. This avoids an objection of “discrimination as to the ... field of technology” under Article 27.1 of TRIPS,² and also may also result in “abusive patenting strategies” by pharmaceutical companies.³ Although the patent system received a low ranking under the criteria, the abolition of the patent system would not be practical or even necessary, as pharmaceutical companies will gradually begin to

¹ P Menell and S Scotchmer “Intellectual Property Law” in AM Polinsky and S Shavell (eds) *Handbook of Law and Economics, Volume 2* (Elsevier, Netherlands, 2007) 1476 at 1476 -1482.

² TRIPS, art 27.1.

³ BN Roin “Unpatentable drugs and the standards of patentability” (2009) 87 Tex L Rev 503 at 557.

rely less on patent exclusivity if a robust alternative mechanism was implemented. Therefore, the chapter will propose alternative incentive mechanisms to operate alongside the current patent system. Benefits and limitations to these proposed mechanisms will also be discussed.

B Extended Market Exclusivity for Unpatentable Therapies

1 Why market exclusivity?

Chapter 6A discussed the advantages of regulatory exclusivity over patent exclusivity. There are two types of regulatory exclusivity: ‘data exclusivity’ protects clinical trial information submitted by an innovator to obtain regulatory approval, and ‘market exclusivity’ prevents a subsequent generic company from obtaining regulatory approval for the same drug, even if the latter conducts their own clinical trials. From an innovator’s perspective, market exclusivity is superior to data exclusivity, as the latter can be overcome by a competitor who undertakes the same clinical trials. Unlike patent rights, market exclusivity does not require any enforcement action by the innovator, because it is simply a result of the refusal by the regulatory authority to approve generic versions of a medicine until a minimum period of time has elapsed. Hence, market exclusivity is less susceptible to legal challenges, reducing the wasteful spending on litigation between innovators and generic drug companies. Although there may be a risk of compulsory licensing, as with the patent system, this has rarely occurred.⁴

In addition, market exclusivity is awarded to an innovator that undertakes the expensive and risky clinical trials required to establish safety and efficacy and achieve regulatory approval. This more accurately reflects ‘contract theory’, which justifies the ‘reward’ of exclusivity provided in exchange for the generation of socially useful information. This can be contrasted with the significantly lower ‘utility’ standard of patentability which only requires evidence of the usefulness of a therapeutic candidate shown in pre-clinical laboratory tests,⁵ which, as already discussed, has a very low chance of being shown as safe and effective in human clinical trials.⁶

⁴ R Beall and R Kuhn “Trends in Compulsory Licensing of Pharmaceuticals Since the Doha Declaration: A Database Analysis” 9 PLoS Med 1 at 3.

⁵ For the standard in the United States, see *Brenner v Manson* 148 USPQ 689 (S.Ct. 1966); *Lane Fox v Kensington & Knightsbridge Electric Lighting Co Ltd* (1892) 9 RPC 411.

⁶ For example, most compounds that have been found to have a potent anti-cancer effect in a petri dish or in mice have no therapeutic value in humans.

The other main advantage of market exclusivity is that it does not discriminate against therapies with long development times, for example, early interventions for diseases that have a gradual worsening of symptoms such as Alzheimer's disease and multiple sclerosis.⁷ Finally, for the purpose of determining rewards, market exclusivity has administratively low costs, using a market mechanism which allows the negotiation of price with the payer, according to the principles of pharmacoeconomic analysis.⁸ Bentham, a classical economist comparing prize-based rewards with exclusivity, noted that the latter is “more natural and less burdensome” and “produces an infinite effect and costs nothing”.⁹

Despite the aforementioned advantages of market exclusivity, some problems with exclusivity remain. For example, with patents, the 20-year term runs from the filing date, which may encourage a faster pace of clinical development than market exclusivity, which runs from the date of regulatory approval. Market exclusivity may also change the dynamic with the regulatory agency. In particular, regulatory agencies may be more willing to refuse requests for marketing approval. By contrast, if only patent protection was available, regulators may choose to allow market approval of a new drug rather than insist on more clinical trials, because of the risk that an innovator would abandon it due to insufficient patent length.¹⁰

Market exclusivity is also susceptible to gaming. For example, an innovator can wait until exclusivity has expired before seeking regulatory approval on a new version of a medicine. There may also be wasteful races to regulatory approval in absence of a suitable mechanism to provide ‘clinical exclusivity’ to the most appropriate innovator.

Awarding ‘clinical exclusivity’ creates issues, such as determining who should receive the right, and whether this right can be withdrawn or provided to a more appropriate candidate. Providing greater discretion to a government agency without clear guidelines increases the potential for ‘rent-seeking’ due to ‘agency capture’ and also increases the risk of wasteful disputes. For example, a regulatory agency may grant clinical exclusivity to one competitor over another as a result of a conflict of interest, which is then litigated under judicial review procedures.¹¹

⁷ See discussion of the ‘unpatentability factor’ of insufficient patent length in Chapter Three.

⁸ See discussion in Chapter Four.

⁹ F Machlup *An economic review of the patent system* (US Government Printing Office, 1958) at 19.

¹⁰ Although, this means that the regulatory agency is discharging its duties to deny unsafe or ineffective medicines from obtaining market approval.

¹¹ The availability of judicial review and appeal from decisions of the regulatory agency will be discussed below.

Chapter 6A also noted that the flexibility of market exclusivity makes it more susceptible to political manipulation. The advantage of the TRIPS agreement is that it guarantees a minimum period of patent exclusivity in all WTO member states, which minimises the potential for free-riding. By contrast, governments could be subject to political pressure to reduce the length of market exclusivity, especially with increasing healthcare costs, despite the detrimental effect this would have on long term dynamic efficiency. However, there is no reason why foreign governments cannot enter into reciprocal arrangements to guarantee a minimum period of market exclusivity.

On the other hand, avoiding TRIPS could be an advantage as it would permit the fine-tuning of the exclusivity period according to social need, rather than having a fixed 20-year period. For example, increased exclusivity could be provided for medicines with a greater health impact and shorter exclusivity for “me-too” drugs. However, flexible exclusivity would exacerbate the influence of political pressure and ‘rent-seeking’ in a highly-wasteful manner.

Thus, an opportunity exists to propose a legislative framework to grant a fixed period of market exclusivity for new medicines that obtain regulatory approval that can address the lack of private incentives to develop unpatentable therapies.

2 *Proposed legislative framework: The Unpatentable Therapies (Extended Market Exclusivity) Bill*

This thesis proposes the Unpatentable Therapies (Extended Market Exclusivity) Bill (EME Bill) to establish a legislative framework of extended market exclusivity for the purpose of ensuring that unpatentable therapies are not unnecessarily screened from development due to insufficient patent protection. In a sense, the EME Bill provides a form of ‘commercialisation’ patent which rewards companies that achieve regulatory approval for a safe and effective medicine as opposed to developing a medicine which fulfils the patentability standards of novelty, inventive step, and utility at the priority date. As noted in Chapter 6A, extended regulatory exclusivity achieved a perfect rating of five for incentivising unpatentable therapies and overall rating of 3.36. This supports the notion of a regulatory exclusivity regime as most appropriate choice for addressing this particular gap in the patent system.

The EME Bill will be similar, but not equivalent, to the proposed MODDERN Cures Bill, currently before United States Congress, as discussed in Chapter 6A. Relevant extracts from the MODDERN Cures Bill are attached as Appendix Two. Both proposals would incentivise unpatentable therapies, although the latter refers to

these as “dormant therapies”.¹² As discussed in Chapter 6A, the MODDERN Cures Bill would provide patent extensions and data exclusivity in a manner that would overcome insufficient patent protection. By contrast, the EME Bill will not include patent extensions, due to the risk that patents could be effectively extended for a period exceeding 40 years, as will be discussed below.

It will also be necessary to describe appropriate regulations behind the granting of ‘clinical exclusivity’ and ‘development certifications’ such that they are not susceptible to ‘gaming’ and ‘rent seeking’. Market exclusivity granted upon regulatory approval would be equivalent to a ‘method of use’ patent over the molecule in terms of the scope of protection granted, although it will not prevent approval of a competitor’s medicine which is ‘clinically superior’, as will be discussed below. Similarly to the patent regime, it should also be mandatory that innovators publish all clinical trial data regarding the medicine as a condition for receiving exclusivity.

The exact length of exclusivity to be provided under the EME Bill will be subject to disagreement.¹³ However, a period of at least 12 to 15 years would be required in order to correspond with the average period of exclusivity of new medicines under the patent system.¹⁴ As drafted, the current version of the MODDERN Cures Bill provides for 15 years of exclusivity from the date of regulatory approval of a medicine.¹⁵

The following sections will provide a draft purpose section of the EME Bill, and will subsequently discuss the composition and function of the body established to administer the regime, and the process of decision-making by the administrative body.

(a) Purpose of the EME Bill

A draft purpose section for the EME Bill is provided below:

¹² MODDERN Cures Bill, s 201.

¹³ For example, this issue has been recently debated in Australia as part of a government review of pharmaceutical patents: see T Harris, D Nicol and N Gruen *Pharmaceutical Patents Review Report* (Pharmaceutical Patent Review Committee, Canberra, 2013) at 84.

¹⁴ SC Hemphill and BN Sampat “Evergreening, patent challenges, and effective market life in pharmaceuticals” (2012) 31(2) *Journal of Health Economics* 327 at 330; H Grabowski, G Long and R Mortimer “Recent trends in brand-name and generic drug competition” (2013) 17(3) *Journal of Medical Economics* 207 at 207; S Shulman, JA DiMasi, KI Kaitin “Patent term restoration: the impact of the Waxman-Hatch Act on new drugs and biologics approved 1984–1995” (1999) 2 *Journal of Biolaw and Business* 63; HG Grabowski, J Vernon “Longer patents for increased generic competition in the US: the Waxman-Hatch Act after one decade” (1996) 10 *PharmacoEconomics* 110.

¹⁵ MODDERN Cures Bill, s201(i)(4).

“The purposes of the Act are to-

- (a) provide an efficient and effective incentive system for medicines that-
 - (i) prevents medicines with insufficient patent protection from being screened out or abandoned from development by providing a minimum period of market exclusivity upon regulatory approval; and
 - (ii) complies with New Zealand’s international obligations to maximise the human right to health; and
- (b) Ensures that exclusivity is granted-
 - (i) in return for undertaking the high risk and expense of obtaining regulatory approval for a new medicine; and
 - (ii) upon providing satisfactory evidence that a new medicine is clinically superior to existing medicines; and
- (c) Provides clinical exclusivity in advance of regulatory approval to potentially clinically superior medicines in a manner which promotes incremental innovation; and
- (d) Addresses concerns of Māori regarding medicines derived from indigenous plants and animals or from Māori traditional knowledge.”

This purpose section above is provided by way of example only, in order to illustrate the primary aims of the EME Bill.

(b) Unpatentable Therapies Advisory Committee

It is proposed that the EME Bill would amend the Medicines Act 1981 to provide for the establishment of the Unpatentable Therapies Advisory Committee (UTAC). The UTAC would be an independent advisory committee to the Minister of Health,¹⁶ who is currently responsible for determining regulatory approval of new medicines,¹⁷ and enforcement of data exclusivity.¹⁸ UTAC members would comprise persons with experience in the practice of medicine, pharmaceutical chemistry and clinical trial design. The UTAC will have the power to appoint subcommittees having members with expertise in the unpatentable therapy being evaluated, if necessary. There will be a conflicts register in place with members being required to declare any direct or indirect conflict of interest and abstain from any decision where a conflict exists. Funding for salaries and other expenses of the UTAC would be approved by the Minister of Health as an advisory board and paid out of money appropriated by Parliament.¹⁹

¹⁶ Notably, the function of the UTAC may be undertaken by the Medicines Assessment Advisory Committee, which currently advises the Minister on regulatory approval decisions.

¹⁷ Medicines Act 1981, s 21.

¹⁸ At s 23B.

¹⁹ At s 8, s 14.

The UTAC's function would be to evaluate applications by innovators for 'unpatentable therapy designation' (UPa Designation) according to specific criteria, discussed in the next section. UPa Designation would initially provide innovators with 'clinical exclusivity' over their proposed 'unpatentable therapy treatment protocol',²⁰ which is important to prevent inefficient 'races' to regulatory approval. The UTAC would also draft regulations to require the innovator to provide 'development certifications'²¹ at least every year that confirms clinical trials are ongoing, otherwise 'clinical exclusivity' will be rescinded. This is to ensure that innovators will actively commit sufficient resources towards clinical trials and are not merely using their 'clinical exclusivity' for strategic reasons, such as blocking competition to their own drug. Finally, the UTAC would determine the grant of 'market exclusivity' over a particular therapy and ensure that follow-on innovators would be unable to obtain exclusivity over the 'same drug' unless it was 'clinically superior'. Notably, even for pioneer drugs, it should only be possible for innovators to obtain UPa Designation if an unpatentable therapy is clinically superior compared to existing treatments.²² There should also be a discretion by the UTAC to deny UPa Designation in circumstances where it would conflict with policy issues, such as public order or morality exclusions to patentability discussed in Chapter Two. A definition of these terms and further commentary on the decision-making process of the UTAC will be provided in the next section.

(c) Decision-making process of the UTAC.

The UTAC would be responsible for determining UPa Designation, which would provide 'clinical exclusivity' to an innovator over their submitted clinical trial treatment protocol, and then will provide a minimum period of 'market exclusivity' upon regulatory approval. As noted above, an innovator must provide regular 'development certifications' to retain 'clinical exclusivity'. Preferably, the applicable regulations would provide that development certifications are delivered annually and include information regarding progress in recruitment and running of clinical trials. Relevant information would include a timetable and milestones for completion²³ as well as reasonable explanations for any deviations from the agreed timetable.

²⁰ A treatment protocol is a formal document which provides details of the design and methodology of a clinical trial. It would include details of the drug being tested and the appropriate dosing regimen, characteristics of patients who are eligible to participate in the clinical trial (and which patients must be excluded), and the process of randomising patients into treatment and placebo groups.

²¹ For comparison, see s 201(g) of MODDERN Cures Bill, attached in Appendix Two.

²² This will act as an 'anti-evergreening' provision and also ensure that the reward of exclusivity is granted in return for a commensurate health benefit to society.

²³ For example, entering the next phase of clinical trials within 30 months.

At the same, time, it must be necessary to balance incentives for incremental innovation and breakthroughs by allowing other innovators to develop improved clinical trial treatment protocols. For example, after the granting of UPa Designation, an innovator's clinical trial protocol, manufacturing information, and related clinical trial data would be published, thus establishing a quasi-'priority-date' to the innovator. This 'clinical exclusivity' will prevent subsequent innovators from conducting clinical trials over the 'same drug', which is defined as a drug which shares the same active ingredient for a small molecule drug or a 'similar' active ingredient²⁴ for a biologic drug.²⁵

However, it is important that the process of granting 'clinical exclusivity' and subsequent 'market exclusivity' does not block incentives for incremental innovation and breakthroughs. This can be accomplished by allowing a subsequent innovator to obtain UPa Designation over the 'same drug' despite the existence of 'clinical exclusivity', provided there is a scientifically plausible rationale that the follow-on drug would have a 'clinically superior effect'. The latter is defined as a drug which has improved safety, improved efficacy, or otherwise makes a major contribution to patient care (such as, greater convenience of administration).²⁶ The process of obtaining Orphan Drug designation is similar, whereby the innovator must provide a scientifically plausible rationale of why a drug may be clinically superior when obtaining orphan drug designation over the 'same drug'.²⁷ It will subsequently be possible for any follow-on innovator to obtain market exclusivity for a 'clinically superior drug', as long as this is ultimately demonstrated in clinical trials if regulatory approval is obtained. This promotes incremental innovation while also reducing incentives to file 'me-too' drugs. There is also a body of case law in the United States regarding the allocation of Orphan Drug designation and how to determine conflicts between innovators.²⁸

²⁴ Similarly, the Orphan Drug Act Regulations also define the 'same drug' as one having the same active ingredient for a small molecule drug or similar principal molecular structure for a biologic: see 21 CFR §316.3(b)(13); see also MODDERN Cures Bill, s 201(e)(1)(C).

²⁵ As noted in Chapter Two, as biologic drugs are based on proteins made in living organisms, the chemical structure of the 'same' drug may vary. Therefore, 'biosimilar' biologics are treated the same as 'bioequivalent' generic drugs under regulatory law.

²⁶ For a similar definition of clinical superiority in the Orphan Drug Regulations, see 21 CFR § 316.3(b)(3). An equivalent definition is also provided in the MODDERN Cures Bill, s 201(e)(1)(C)(ii).

²⁷ 21 CFR § 316.20(b)(5); 21 CFR § 316.25(a)(3).

²⁸ For example, Octapharma USA, Inc obtained orphan drug designation and regulatory approval for its drug, Wilate on the basis that it was clinically superior to an existing orphan drug, Humate-P, manufactured by CSL Behring. In a Citizen's Petition to the FDA, the latter argued that there was no evidence of 'significant therapeutic advantage' of Wilate over Humate-P, and the FDA agreed to withdraw orphan drug designation: see Letter from Leslie Kux (Assistant Commissioner for Policy, Food and Drug Administration) to Peter Turner (President, CSL Behring) regarding Citizen Petition to rescind Wilate Orphan Drug Designation (8 August 2012); see also *Genentech, Inc v Bowden* 676 F Supp 301 (DDC 1987) at 304.

With regard to the process of dispute resolution, decisions of the UTAC must be disputed within 90 days, with a right of appeal to the Medicines Review Committee under s 88 of the Medicines Act 1981, and further rights of appeal to the High Court and Court of Appeal under ss 89 and 93 of the Medicines Act 1981. In accordance with the decision of the Supreme Court of New Zealand in *Austin, Nichols Inc v Stichting Lodestar*, an appellate court can reconsider the decision of a lower court or tribunal on its merits without deferring to the lower court's decision, even if it requires an assessment of fact or degree.²⁹ In light of the high costs of drug development, the risk of 'agency capture'³⁰ of the UTAC would militate against including a privative clause or limiting the grounds of appeal, despite the fact this may increase the overall likelihood of prolonged litigation. By contrast, the United States traditionally has a deference to the decision-making process of the FDA as an 'expert agency',³¹ although Courts may be more willing to intervene as the perception of the FDA's independence from the pharmaceutical industry has lessened.³²

In conclusion, the proposed legislative framework allows the UTAC to award 'clinical exclusivity' to innovators in order to prevent wasteful races to regulatory approval, while also promoting incremental innovation. The proposed legislative framework of the EME Bill will now be analysed with reference to the ideal criteria.

3 *How does an extended market exclusivity regime for unpatentable therapies compare against ideal criteria?*

Should any criteria be excluded?

As outlined above, the purpose of the EME Bill is to incentivise unpatentable therapies. Accordingly, it would be inappropriate to include incentivising unmonopolisable and unprofitable therapies in the following analysis.

²⁹ *Austin, Nichols Inc v Stichting Lodestar* [2007] NZSC 41 at [16].

³⁰ As discussed in Chapter 6B, agency capture is the risk that a regulatory agency will be corrupted by private interests over which it exercises regulatory authority, in a manner which advances those private interests at the expense of public interests.

³¹ JT O'Reilly "Losing deference in the FDA's second century: judicial review, politics, and a diminished legacy of expertise" (2007) 93 Cornell L Rev 939 at 942.

³² At 959. For the standards of judicial review in the United States, see Administrative Procedure Act, 5 USC § 706(2).

(a) Criterion one: Incentivising Unpatentable Therapies

Provided that the length of market exclusivity under the EME Bill is greater than 12.2-years, which is the average period of exclusivity for drugs which have obtained regulatory approval,³³ and assuming equivalent levels of exclusivity are provided in the United States and other major jurisdictions, it is arguable that otherwise viable unpatentable therapies will not be screened during development. Hence, a score of five is achieved for this criterion.

(b) Criterion four: Balancing dynamic and static efficiency

An extended period of regulatory exclusivity over a molecule pursuant to the EME Bill would provide equivalent or potentially superior (1) private incentives for R&D, even compared to the exclusivity under the current patent system,³⁴ although the receipt of monopoly rents is only possible from sales over the protection period. Further, (2) competition and consequent static efficiency are delayed until exclusivity has expired.

As with all exclusivity-based alternative incentive mechanisms, the main drawback is that an innovator must charge a monopoly price above the marginal cost of production in order to recover their R&D costs. These monopoly profits have the potential to create deadweight losses. Arguably, both innovators and payers would negotiate a price which is acceptable for pharmaceutical reimbursement, as this will maximise sales and access to the greatest number of consumers.³⁵ Pharmaceutical reimbursement will (3) minimise deadweight loss and (4) maximise consumer surplus without delay. Accordingly, a score of three can be provided under this criterion.

(c) Criterion five: Linking rewards to improved health outcomes

The EME Bill would only incentivise one type of therapy, namely unpatentable therapies. However, as noted in Chapter 6A, under the current system, payers can use pharmacoeconomic analysis, health metrics such as QALYs, and reference pricing to maximise health outcomes for rewards. Hence, a score of three is provided under this criterion.

³³ Hemphill and Sampat, above n 14, at 330. See also discussion in Chapter Three.

³⁴ J Freilich “Patent Infringement in the Context of Follow-On Biologics” (2012) 16 Stan Tech L Rev 9 at 12.

³⁵ Unless the payers cannot afford the cost of the drug, however, it is likely that innovators would lower their price rather than risk not being reimbursed in a major jurisdiction.

(d) Criterion six: Minimisation of Administration Costs

As already discussed in Chapter 6A, extended regulatory exclusivity regimes such as the EME Bill can piggyback on the existing regime for regulatory approval. Market exclusivity allows the innovator and payers to negotiate a price in accordance with a quasi-market model.

One of the main administrative difficulties faced by the UTAC could be determining which innovator obtains the UPa Designation granting “clinical exclusivity”. However, providing such rights on a first-come-first-served basis is the simplest and cheapest to administer. While this could create a situation where clinical exclusivity is awarded to an innovator that did not pay for the underlying R&D, this would not result in an unfair expropriation of property rights because an unpatentable therapy is already effectively in the ‘public domain’. Allowing follow-on innovators to obtain UPa Designation and exclusivity if they demonstrate “clinical superiority” over a previously-approved drug with the same active ingredient also has minimal administrative costs, and there is significant precedent under the Orphan Drug Act in the United States. Assessing the genuineness of development certifications would also create a minimal administrative burden. In light of the above, it is possible to award a score of five under this criterion.

(e) Criterion seven: Minimisation of Waste/Inefficiency

Most of the advantages of extended regulatory exclusivity apply to the EME Bill with respect to minimisation of waste/inefficiency. As discussed in Chapter 6A, extended regulatory exclusivity cannot be challenged easily, therefore the EME Bill can avoid waste due to (2) costly litigation between generics and innovators. Furthermore, exclusivity under the EME Bill is only available to therapies which have been proven to be ‘clinically superior’, which can negate (7) incentives to develop ‘me-too’ drugs. However, the MODDERN Cures Bill would go further as it only allows dormant therapy designation for unmet medical needs.³⁶ Thus, there is a trade-off between restricting incentives for me-too drugs and incentivising incremental innovation. Another benefit under the EME Bill is the avoidance of (8) an anti-commons effect because both clinical and regulatory exclusivity are only available for new medicines with clinical superiority, as discussed above. In addition, an innovator applying for UPa Designation could rely on the ‘regulatory review’ defence to patent infringement

³⁶ This may negatively impact on incentives for incremental innovation, as will be noted when discussing criterion eight below.

under s 145 of the Patents Act, which excludes infringement “for uses reasonably related to the development and submission of information required under any law”.³⁷

The EME Bill can potentially prevent (6) low transparency and wasteful races to regulatory approval, due to the requirement to publish clinical trial protocols and data and the assignment of ‘clinical exclusivity’ in advance.³⁸ Despite this, competitors may be less willing to share information due to the risk that ‘clinical exclusivity’ over an unpatentable therapy can be obtained by competitors.³⁹ Therefore, it is unclear whether this waste/inefficiency factor is completely absent.

In addition, implementing the EME Bill has the potential for other waste/inefficiency factors to be present. For example, providing rewards through a temporary period of market exclusivity creates (1) incentives for excessive marketing, while also encouraging (4) arbitrage due to grey markets and (5) incentives to counterfeit drugs.⁴⁰ There may also be (3) opportunities for gaming, by ‘sitting’ on UPa Designation, in order to block a competitor, although the requirement for ‘development certifications’ should address this.

As noted in Chapter 6A, regulatory exclusivity can cause (9) rent seeking through political interference in the length of exclusivity. In absence of an international treaty, it will be difficult to address this issue as well as (10) free riding.

Therefore, as six or possibly seven waste/inefficiency factors are not absent for extended regulatory exclusivity under the EME Bill, a score of two is provided under this criterion.

(f) Criterion eight: Incentivise incremental innovation and breakthroughs

Regulatory exclusivity under the EME Bill would provide almost optimal incentives for incremental innovation, compared to the MODDERN Cures Bill, as it would

³⁷ Patents Act 2013, s 145. The United States provides a similar defence to infringement. See discussion of ‘*Bolar* exemptions’ in Chapter Two.

³⁸ As discussed in Chapter Two under the Overview of the Patent System, in accordance with Kitch’s prospect theory, this would encourage R&D expenditure necessary for commercialisation by protecting the innovator from competition for that time. See Edmund W Kitch “The Nature and Function of the Patent System” (1977) 20 *JL & Econ* 265.

³⁹ However, arguably the patent system can also cause appropriation of another company’s R&D by allowing the patenting of incremental improvements. Notably, it may be possible to counteract the increased tendency to keep trade secrets by increasing funding for open source approaches and pre-competitive consortia.

⁴⁰ D Bagozzi “Fact Sheet No 275: Substandard and Counterfeit Medicines” (November 2003) World Health Organization <www.who.int>.

allow exclusivity even if a therapy is not for an unmet medical need.⁴¹ However, in practice this will depend on the interpretation of “clinically superior” by the UTAC. Arguably, the threshold should not be too high in order to encourage incremental innovation. If market exclusivity only covers the molecule for use in a particular indication, this would also encourage finding new indications. However, if the threshold is too low, this may not encourage development of breakthroughs.

Despite this, arguably, providing extended market exclusivity over a molecule and preventing registration of a subsequent unpatentable therapy unless it is ‘clinically superior’ can optimally incentivise breakthroughs.⁴² Therefore, a score of 4.5 is awarded under this criterion.

Summary

The current patent system results in unpatentable therapies being screened or abandoned by innovator companies for reasons not related to therapeutic value. This is a fundamental problem with the patent system. The EME Bill, if enacted in the major jurisdictions, could negate this problem. It would work alongside the current patent system because patents would not be involved in the process of allocating exclusivity or determining priority rights. It would also encourage incremental innovation by awarding clinical exclusivity to clinically superior therapies, as well as ensuring that innovators actively progress through clinical trials by providing development certifications. Payers could negotiate with innovators to determine the appropriate price, according to well-established procedures under the current incentive system.

Overall, the incentive regime under the EME Bill scores an average of 3.75, which is significantly more optimal than the current patent system, at least for the purpose of incentivising unpatentable therapies. However, the main problem with the EME Bill is that it does not incentivise unmonopolisable and unprofitable therapies. This is of major concern, because such therapies are not incentivised under the current patent system either. The next section will propose an alternative mechanism to address this market failure.

⁴¹ However, as noted above, this would increase incentives to develop ‘me-too’ drugs, at least for the period that exclusivity has not expired, after which introduction of generic drugs would lower the monopoly rents which are available.

⁴² See, for comparison, MODDERN Cures Bill, s201(e)(1)(C)(ii).

C *Incentivising Unmonopolisable and Unprofitable Therapies with a Flexible Prize Fund and Increased Public Funding*

1 *Why use a flexible prize fund?*

As discussed in Chapter 6B, various commentators have noted that flexible prize-based mechanisms could incentivise development of unmonopolisable therapies, such as second uses for off-patent drugs,⁴³ and unprofitable therapies, such as neglected diseases.⁴⁴ In particular, prizes can incentivise unmonopolisable and unprofitable therapies, because, unlike exclusivity-based incentives, the amount of rewards is de-linked from the underlying sales of a medicine. The main problem with prize-based incentives is that the government may have insufficient information with which to determine the optimal prize amount.

According to Wright⁴⁵ and Gallini & Scotchmer⁴⁶ if the government is more informed about the social benefits of a particular therapeutic innovation, then prizes and contracts for research result in less societal loss than patents. The problem is that under the current system, the government may have insufficient information compared to the private sector regarding which therapeutic candidates should be funded.⁴⁷ As noted in Chapter Three, drug development has a high risk of failure, which means that governments are typically unwilling to fund large clinical trials. Therefore, it is proposed that a mechanism, to allow prizes to ‘de-risk’ viable therapies, is needed to address this information asymmetry, so that governments will be willing to fund larger clinical trials to validate their safety and efficacy.

The author proposes establishing a flexible prize fund mechanism to incentivise therapies at the so-called “valley of death” between basic research and clinical research.⁴⁸ In particular, this would involve establishing a number of small flexible prize funds for unmonopolisable and unprofitable therapies in specific disease

⁴³ T Syed “Should a Prize System for Pharmaceuticals Require Patent Protection for Eligibility?” (IGH Discussion Paper No 2, Incentives for Global Health, June 10, 2009) at 4.

⁴⁴ M Bakhom “TRIPS, Patent Rights and Right to Health: ‘Price’ or ‘Prize’ for Better Access to Medicine?” (Max Planck Institute for Intellectual Property, Competition & Tax Law Research Paper No 10-07, 2009) at 46.

⁴⁵ BD Wright “The Economics of Invention Incentives: Patents, Prizes, and Research Contracts” (1983) 73 *Amer Econ Rev* 691 at 703.

⁴⁶ N Gallini and S Scotchmer “Intellectual Property: when is it the best incentive system?” in AB Jaffe, J Lerner and S Stern (eds) *Innovation Policy and the Economy* (Volume 2, MIT Press, Cambridge (Mass), 2002) at 54.

⁴⁷ At 55.

⁴⁸ This is also referred to as the gap ‘from bench to bedside’: see BS Coller, RM Califf “Traversing the Valley of Death: A Guide to Assessing Prospects for Translational Success” (2009) 1 *Sci Transl Med* 10cm9; DJ Adams “The Valley of Death in anticancer drug development: a reassessment” (2012) 33 *Trends Pharmacol Sci* 173.

categories, similar to scaled-down versions of the HIF,⁴⁹ which can be used to “de-risk” successful clinical research at the Phase II (efficacy) stage of clinical trials.⁵⁰

Focusing on early-stage clinical research means that a prize fund can be relatively smaller than the MIPF and HIF proposals; the latter anticipate prize funds requiring billions of dollars annually,⁵¹ which makes them politically difficult to implement. Another problem with large prize funds is a significant risk of agency capture and gaming.⁵² For example, if a reward is increased based on number of patients treated or subjective measurements of health impact, innovators could find ways to exaggerate these amounts.⁵³ A small prize basing rewards on outcomes of standardised clinical trials would avoid this problem. Large flexible prizes would also be susceptible to the “time inconsistency problem”, whereby a prize administrator may force an innovator to take a lower reward once it has already sunk costs into R&D.⁵⁴ A smaller prize fund has lower stakes, and thus reduces these risks.

However, a prize fund must still be large enough to act as an incentive for investors. As noted by Hemel and Ouellete, the major problem with prizes is that researchers must secure investor funds in advance in order to compete for the prize.⁵⁵ This can be contrasted with public funding via grants where researchers receive funds in advance. Researchers may conclude that seeking investors to compete in a smaller prize fund may not be a cost-effective use of time. On the other hand, researchers already spend months applying for grants,⁵⁶ and only have approximately 20 per cent

⁴⁹ See discussion of Health Impact Fund in Chapter 6B.

⁵⁰ As discussed in Chapter Two under Regulatory Environment, Phase II clinical trials are used to provide initial proof of efficacy, after Phase I (safety). Phase II trials typically require at least 100 patients. Phase III clinical trials typically involve at least 1000 patients and are the last hurdle before regulatory approval.

⁵¹ As noted in Chapter 6B, the MIPF and HIF require annual funding of USD 80 billion and USD 6 billion, respectively.

⁵² See discussion of ‘agency capture’ in Chapter 6B.

⁵³ A Hollis and T Pogge *The Health Impact Fund: Making New Medicines Accessible for All: a Report of Incentives for Global Health* (Incentives for Global Health, 2008) at 30.

⁵⁴ JA DiMasi and HG Grabowski “Should the patent system for new medicines be abolished?” (2007) 82(5) *Clinical Pharmacology & Therapeutics* 488 at 489.

⁵⁵ DJ Hemel and LL Ouellette “Beyond the Patents--Prizes Debate” (2013) 92 *Texas Law Review* 303 at 336.

⁵⁶ See DL Herbert and others “On the time spent preparing grant proposals: an observational study of Australian researchers” (2013) 3(5) *BMJ Open* 1.

chance of being successfully funded.⁵⁷ Therefore, researchers are already likely to be amenable to seeking alternative funding sources,⁵⁸ including the private sector.

Under the second part of the optimal model, it is proposed that government agencies would increase public funding of clinical trials for “de-risked” unmonopolisable and unprofitable therapies, so they can enter into mainstream clinical practice. We now turn to this second part.

2 *Why use increased public funding?*

According to the Global Intellectual Property Center, a United States policy think tank, prizes are more suited to incentivising a proof of concept, rather than commercialising a new drug.⁵⁹ Chapter Three explained that under the current incentive system, patent exclusivity is relied on to bring new therapies to market, however, this is unable to incentivise new unmonopolisable and unprofitable therapies. Conversely, as noted in Chapter 6C, increased public funding can be used to incentivise unmonopolisable and unpatentable therapies, although such proposals have been criticised by various commentators on the basis that governments “do not have a good track record of picking winners”.⁶⁰ However, Gallini & Scotchmer note there are circumstances in which public funding can be a more optimal method of developing new innovations than intellectual property regimes:⁶¹

When both the costs and values of innovations are publicly observable to both firms and a public sponsor, [intellectual property] is not the best incentive scheme. A better scheme is for a public sponsor to choose the projects with the largest net social benefits, and pay for them on delivery, using funds from general revenue.

⁵⁷ See Chapter 6C, citing TA Kotchen and others “NIH Peer Review of Grant Applications for Clinical Research” (2004) 291 JAMA 836 at 836, noting that grant requests for clinical research funding less likely to be successful than requests for basic research funding; AN Schechter “The Crisis in Clinical Research: Endangering the Half-Century National Institutes of Health Consensus” (1998) 280 JAMA 1440 at 1441; DG Nathan “Clinical Research: Perceptions, Reality, and Proposed Solutions” (1998) JAMA 1427 at 1427-1428.

⁵⁸ Researchers are already looking for alternative funding sources for their scientific projects, including seeking donations from the public via Internet-based ‘crowdfunding’ campaigns. See “Crowdfunding science: could it work?” The Guardian (online ed, United Kingdom, 11 November 2013). Examples of website offering crowdfunding platforms for scientific projects include: <www.petriedish.org>, <www.experiment.com>.

⁵⁹ Global Intellectual Property Center *Prizes and Patent Pools Viable Alternatives to the Patent System?* (GIPC White Paper Series, 23 November 2009).

⁶⁰ M Hart “The Chimera of Industrial Policy: Yesterday, Today and Tomorrow” (1993) 19 Can-US LJ 19 at 36; see also JA DiMasi and H Grabowski “Patents and R&D incentives: Comments on the Hubbard and Love trade framework for financing pharmaceutical R&D” (Submission to the Commission on Intellectual Property Rights, Innovation and Public Health, 2004) at 7-11; H Demsetz “Information and Efficiency: Another Viewpoint” (1969) 12 JL & Econ 1 at 12.

⁶¹ Gallini and Scotchmer, above n 46 at 54.

Therefore, the critical issue is to ensure that governments have sufficient information to choose to fund therapies with the most potential therapeutic value. Hence, an opportunity exists for prize funds to provide governments with information regarding which clinical trials should receive increased public funding. Notably, it is not necessary to increase public funding to the extent required to achieve regulatory approval for a new treatment. For example, a high-quality Phase II trial of an unmonopolisable therapy listed in the relevant compendia of medically ‘proven’ therapies will allow reimbursement by payers.⁶² With reimbursement available for the costs of a therapy, doctors are more likely to prescribe it to patients. In addition, for unprofitable therapies involving neglected diseases, interested stakeholders such as government agencies, research hospitals, charities, or PPPs⁶³ can undertake further development.

3 *Proposed legislative framework: Medical (De-risking) Prize Fund Bill*

The Medical (De-risking) Prize Fund Bill (MPF Bill) is a legislative framework that would reward innovators that fulfill the requirements for ‘registration’ with a prize fund by showing that unmonopolisable and unprofitable therapies are effective in phase II clinical trials.⁶⁴ As noted above, the mechanism would be similar to the HIF, which achieved an overall rating of 3.63 as part of the *ex-post* flexible prize regime proposals analysed in Chapter 6B.

The first and most critical issue is the source of funding for prizes under the MPF Bill and the increased public funding for successful clinical trials. As discussed in Chapter 6C, in New Zealand, public funding of medical research is administered by the Health Research Council (HRC), which received funding of NZD 84.64 million in 2013.⁶⁵ The HRC currently is the main source of funding for clinical research of

⁶² For example, pursuant to s 1861(t)(2)(B)(ii) of the United States Social Security Act, reimbursement via Medicaid is permitted for ‘medically accepted indications’, which have not yet received regulatory approval, but have been referenced in the following compendia: the American Hospital Formulary Service-Drug Information, the US Pharmacopoeia-Drug Information, and the DRUGDEX Information. See American Society of Clinical Oncology “Reimbursement for cancer treatment: coverage of off-label drug indications” (2006) 24 J Clin Oncol 3206 at 3208.

⁶³ As discussed in Chapter 6C under Increased Public Funding and Open Source Approaches, PPPs are public-private-partnerships formed between governments or charities and private companies, in order to overcome a market failure for socially valuable research which has barriers to development.

⁶⁴ Phase II clinical trials are used to demonstrate efficacy of a therapy, and require at least 100 patients, as well as other minimum criteria. See further discussion below regarding the administration of the Medical (De-risking) Prize Fund Bill [MPF Bill].

⁶⁵ *Report of the Health Research Council of New Zealand for the year ended 30 June 2013, Presented to the House of Representatives Pursuant to Section 38 of the Health Research Council Act 1990* (Health Research Council of New Zealand, 2013) at 5.

unmonopolisable therapies in New Zealand.⁶⁶ The role of the HRC in administering the MPF Bill will be discussed in more detail below.

However, assuming additional funding is necessary, it is anticipated that PHARMAC will contribute funding for prizes and public funding for unmonopolisable therapies, which currently has an annual combined expenditure of NZD 783.6 million.⁶⁷ While it might be argued that these funds are required for spending on monopolisable therapies, a modest allocation from this budget would help redress the inefficient systemic bias against unmonopolisable and unprofitable therapies. It is notable that PHARMAC has a legislative mandate to conduct clinical trials to ensure the best outcomes are received from pharmaceutical treatment, which could include unmonopolisable therapies such as second uses for generic drugs.⁶⁸ In addition, a report of the New Zealand Health Committee has also recommended the implementation of an ‘innovation fund’ for co-sponsoring clinical trials which were specific to the New Zealand population,⁶⁹ which could be another source of funds.

With regard to unprofitable therapies that do not predominantly affect New Zealanders, such as neglected diseases, prizes⁷⁰ and increased public funding may conceivably be allocated from the current NZD 1.5 billion budget for overseas developmental assistance.⁷¹ Once the successful clinical trials for neglected diseases are published, the HRC, overseas governments, non-government organisations, PPPs and charities can fund additional clinical trials order to replicate the results and disseminate more valuable information regarding which therapies are clinically useful.

The next sections will provide a draft purpose section for the MPF Bill, and then will discuss the composition and function of the body established to administer the regime, and the process of decision-making by that administrative body.

⁶⁶ According to information the author received from the Health Research Council, approximately NZD 49 million was spent on publicly-funded clinical trials between 2009 and 2013. The author does not have information regarding the amount spent on clinical trials by charitable organisations in New Zealand, but it is likely to be a significantly lower due to limited donor fundraising. The vast majority of clinical trials related to unmonopolisable and unprofitable therapies.

⁶⁷ *Pharmaceutical Management Agency Annual Report For the year ended 30 June 2013, Presented to the House of Representatives pursuant to Section 150(3) of the Crown Entities Act 2004* (Pharmaceutical Management Agency, 2013) at 11.

⁶⁸ New Zealand Public Health and Disability Act 2000, s 47(a), s 48(c).

⁶⁹ P Hutchison *Inquiry into improving New Zealand’s environment to support innovation through clinical trials* (Report of the Health Committee, June 2011) at 39.

⁷⁰ It is anticipated that the HRC would also administer these prizes.

⁷¹ This is the amount made available to the Ministry between 2012-2015. See “Indicative programme allocations 2012/13 - 2014/15” (2012) Ministry of Foreign Affairs and Trade <www.aid.govt.nz>.

(a) Purpose of the MPF Bill

A draft purpose section for the MPF Bill is provided below:

“The purposes of the Act are to-

- (a) provide an efficient and effective incentive system for medical therapies that-
 - (i) provides incentives for clinical trials of unmonopolisable and unprofitable medicines by establishing flexible prize funds with an adequate level of rewards available to achieve the purpose of the Act; and
 - (ii) complies with New Zealand’s international obligations to maximise the right to health; and
- (b) Ensures that prize rewards granted-
 - (i) in return for undertaking the high risk and expense of validating the safety and efficacy of new medical therapies;
 - (ii) upon providing satisfactory evidence that a new medical therapy is a safe and effective treatment; and
- (c) Provides clinical exclusivity in advance of entitlement to prize rewards to potentially clinically superior medicines in a manner which promotes incremental innovation; and
- (c) Provides adequate public funding to validate the safety and efficacy of new medical therapies;
- (d) Addresses concerns of Māori regarding medical therapies derived from indigenous plants and animals or from Māori traditional knowledge.”

This purpose section above is provided by way of example only, in order to illustrate the primary aims of the MPF Bill.

(b) Prize Fund Advisory Committee

Under the MPF Bill, it is proposed that prize funds will be administered by the HRC. By way of background, the HRC was established as a Crown entity under s 5 of the Health Research Council Act. The main function of the HRC is, inter alia, to advise the Minister of Health on health research policy, to negotiate bulk funding applications from the government once every three years, and to support public health research.⁷²

⁷² Health Research Council Act, s 6

Support for public research occurs through the HRC's consideration of grant applications for medical research funding,⁷³ and has established the Biomedical Research Committee⁷⁴ and Public Health Research Committee⁷⁵ to assist the HRC in this respect. Pursuant to s 17 of the HRC Act, the functions of research committees are to generate a policy on priorities for health care research,⁷⁶ determine a policy for ranking grant applications for the purpose of health research,⁷⁷ advise the HRC on which applications for grants should be supported,⁷⁸ and monitor the performance of grantees.⁷⁹ Therefore, the HRC is arguably the most appropriate government body with expertise to administer the prize mechanism under the MPF Bill and allocate subsequent public funding to successful research.

The MPF Bill will establish another committee of the HRC, namely, the Prize Fund Advisory Committee (PFAC). The PFAC would administer prize funds for certain disease categories that can be subject to proposals from privately-funded innovators, as opposed to grant applications from established researchers under the current system.⁸⁰ Importantly, proposals from innovators will not be restricted to New Zealand, as the point of the prize mechanism is that it allows all of the private industry to participate in the discovery and funding of socially valuable unmonopolisable and unprofitable therapies.

Similar to the UTAC discussed above, PFAC members would comprise persons with relevant experience in the practice of medicine, pharmaceutical chemistry and clinical trial design, and will need to be subject to a conflict of interest policy which prevents them from acting where they have a direct or indirect financial or personal interest in any matter.⁸¹

The PFAC will have multiple functions. It will be responsible for providing 'unmonopolisable/unprofitable therapy designation' (Um/P Designation) for any new clinical trial proposal submitted under the particular prize fund disease category. This will allow the innovator to receive 'clinical exclusivity' over their protocol. The PFAC will also determine which clinical trials are eligible for 'registration' to the

⁷³ s 31.

⁷⁴ s 13.

⁷⁵ s 15.

⁷⁶ s 17(b).

⁷⁷ s 17(c).

⁷⁸ s 17(e).

⁷⁹ s 17(f).

⁸⁰ This proposal is not without some precedent. As noted in Chapter 6B, in the 18th century, medical research was generally funded using prizes rather than grants. See Robin Hanson "Patterns of Patronage: Why Grants Won Over Prizes in Science" (1998) University of California, Berkeley at 2.

⁸¹ See Health Research Council Act, s 20, which specifies criteria and personal attributes of members of HRC research committees.

prize fund by demonstrating clinical efficacy. In a similar manner to the process under the EME Bill, once a clinical trial is ‘registered’, it will not be possible for follow-on innovators to obtain exclusivity over the same clinical trial protocol unless it was ‘clinically superior’. The next section will provide further commentary on how these determinations by the PFAC will occur in practice.

(c) Decision-making process of the PFAC.

The first decision of the PFAC will be to establish the size of a prize fund in a particular disease category that is eligible to receive applications for Um/P Designation from innovators, as well as the criteria of a standardised clinical trial to allow ‘registration’. It is anticipated that the PFAC would initially establish pilot prizes in specific disease categories with the greatest social need, before subsequent expansion to other categories. The amounts allocated to the prize fund should initially be sufficient to incentivise ‘registration’ of at least two to three clinical trials for five years. For example, it would provide an innovator with a proportion of annual rewards over five years, by comparing the health impact of their ‘registered’ clinical trial with other ‘registered’ clinical trials. For clarity, the process of Um/P Designation and ‘registration’ of a clinical trial for an unmonopolisable therapy in the context of a pilot prize fund for heart disease will be described below.

The PFAC first announces an ongoing prize fund of NZD 3 million per annum for heart disease. PFAC would specify the criteria for clinical trial protocols eligible to receive Um/P Designation and ‘registration’ to the prize fund. For example, for a heart disease prize fund, this would include unmonopolisable therapies to treat heart disease, such as dietary supplements, diets, lifestyle interventions, or even avoiding the use of certain mainstream medicines. Standardised condition-specific metrics will be used in order to allocate rewards rather than using QALYs to determine health impact.⁸² For example, a standard condition specific metric for heart disease could be using the cholesterol levels in the blood as a biomarker.⁸³ The PFAC will also determine standardised inclusion and exclusion criteria of patients in order to prevent

⁸² This has the advantage of lower administration costs by avoiding the ‘weighting’ problems inherent in using QALYs, as already discussed in Chapter Four. In addition, use of standard measurements of clinical outcomes for a particular disease is a more objective and fair means to allocate rewards between innovators, which reduces the likelihood of costly litigation.

⁸³ As mentioned in the discussion of condition-specific health metrics in Chapter Four, a biomarker is a clinical measurement that is linked to the presence of disease. In this case, high cholesterol is linked to an increased risk of developing heart disease. Accordingly, the efficacy of many drugs (for example, statins) is based on their ability to lower cholesterol.

gaming,⁸⁴ and avoid any confounding factors such as co-morbidity. The treatment must also apply to the general population in order to maximise health impact. In the event a clinical trial protocol is designed to treat a subset of the population,⁸⁵ then the measurement of health impact will be reduced proportionally according to the ratio of that subpopulation to the general population.⁸⁶

In order to be eligible for Um/P Designation, clinical trial protocols must be new in that the intervention described by the clinical trial protocol must not have been shown to be effective in another published clinical trial at phase II equivalent or above. PFAC members will be expected to perform a search of published clinical trials to confirm this, which ensures that the prize fund will only incentivise development of new and useful information. Um/P Designation will also grant ‘clinical exclusivity’ over a clinical trial treatment protocol, although this will require publication of the clinical trial protocol, methodology, and any relevant pre-clinical trial data. It will also be necessary for an innovator to commence clinical trials within 1 year of the proposal in order to retain this exclusivity right. In order to minimise fraud, the clinical trials must be undertaken by an approved ‘contract research organisation’ which is independent of the innovator. All clinical trials conducted must be published, and as with the EME Bill, ‘development certifications’ must be filed annually to retain ‘clinical exclusivity’.

As mentioned above, rewards would be allocated to ‘registered’ clinical trials for five years annually according to their health impact.⁸⁷ In order to be registered, a clinical trial must be a randomised controlled trial,⁸⁸ which demonstrates statistical significance of therapeutic efficacy at a p-value of 0.05. This is the conventional

⁸⁴ For example, a typical method to manipulate clinical trial results is to select patients which are more likely to respond well to a therapy and exclude patients who do not respond or are less likely to respond. It is also important to measure all patient outcomes on an ‘intention to treat’ basis, which means that all patients are included in the final results even if they drop out of the clinical trial: see S Hollis and F Campbell “What is meant by intention to treat analysis? Survey of published randomised controlled trials” (1999) 319(7211) *BMJ* 670.

⁸⁵ For example, patients with certain genetic or physiological characteristics may respond better to a therapy. This is an example of ‘personalised medicine’.

⁸⁶ For example, if a particular unmonopolisable therapy was only effective in males, then the measurement of health impact would be reduced by approximately 50 per cent, having regard to the prevalence of males in the general population.

⁸⁷ According to Abramowicz, payment of prizes over a delayed period is optimal because it minimises fraud and ensures that sufficient information is available to determine the optimal level of rewards. See M Abramowicz “Perfecting patent prizes” (2003) 56 *Vand L Rev* 115 at 192.

⁸⁸ Randomised controlled trials [RCTs] are the “gold standard” for assessing whether a particular treatment is effective according to “evidence based medicine”. RCTs ensure that a treatment is compared against a placebo, which means that the health benefits can be attributed to the therapy, not the patient’s expectation. RCTs implement a ‘double blinding’ methodology with randomisation into treatment and placebo groups. This ensures that the patient and doctor are unaware of whether the treatment they receive is a placebo or genuine and reduces subconscious selection biases that may otherwise occur: see AW Chan and DG Altman “Epidemiology and reporting of randomised trials published in PubMed journals” (2005) 365 *The Lancet* 1159.

standard to ‘prove’ a therapy is effective in the medical profession, as it means there is only a 5 per cent chance that efficacy is due to random chance.⁸⁹ The clinical trial must compare the treatment plus ‘usual care’ with a placebo plus ‘usual care’.

Once a clinical trial is ‘registered’ the PFAC will calculate incremental health impact in order to determine the allocation of rewards. In particular, each clinical trial which establishes statistically significant efficacy of therapy will be eligible to receive a proportion of the annual rewards in accordance with its incremental health impact versus other registered clinical trials. Incremental health impact is calculated by comparing the treatment with ‘usual care’ according to the condition-specific metrics. For example, we can assume that three clinical trials are ‘registered’ to the fund one year: a treatment protocol involving green tea lowered cholesterol 10 per cent over usual care, a herbal extract X lowered cholesterol by 5 per cent over usual care and a high-intensity exercise regime lowered cholesterol by 15 per cent over usual care. In that situation, assuming ‘registration’ occurred at the same time, NZD 3 million would be allocated to each innovator annually in a ratio of 10/5/15 respectively.⁹⁰ Each innovator would be eligible to receive annual rewards for five years, assuming that another clinical trial is not subsequently ‘registered’, which will dilute the amount of available rewards proportionally.

As noted above, the ‘registration’ of clinical trials provides ‘clinical exclusivity’ with respect to the ‘same’ clinical trial protocol, which prevents ‘free-riding’ and ‘races’. The ‘sameness’ of a clinical trial protocol is determined with reference to its ‘active ingredient’ or the aspect of the intervention being tested which is known to cause the therapeutic effect. For example, if the cholesterol lowering effect of green tea is known to be caused by a particular phytochemical X, a supplement containing phytochemical X will be deemed the ‘same’ intervention, and will not be eligible for Um/P Designation and subsequent ‘registration’ unless a scientifically plausible rationale is provided that it would have ‘clinical superiority’ either by improved safety, efficacy or otherwise making a major contribution to patient care.⁹¹ The decision making process of the PFAC here will be equivalent to the decision to grant UPa Designation, as previously described with reference to the EME Bill. Therefore, as with the EME Bill proposed above, clinical exclusivity is provided on a first-come-first-served basis, although it will also allow incremental innovation, through the registration of a ‘clinically superior’ protocol to the prize fund.

⁸⁹ See HS Hochster “The power of “p”: on overpowered clinical trials and “positive” results” (2008) 2 *Gastro Can Res* 108 at 108.

⁹⁰ Therefore, annual rewards will be allocated as NZD 1 million/500,000/1.5 million.

⁹¹ See discussion of the determination of ‘clinical superiority’ in the context of the EME Bill above.

Another important function of the PFAC is to monitor developments in the medical literature which show that clinical result of a ‘registered’ clinical trial was not replicated in a subsequent clinical trial, performed under equivalent conditions. There is a known methodology which allows clinical trials to be combined, which is referred to as ‘systematic review’.⁹² In the event that a subsequent clinical trial puts the statistically significant efficacy of the registered clinical trial in doubt, it will be de-registered from the prize fund.

With regard to the dispute resolution process, as with the UTAC, the decisions of the PFAC must be made within 90 days. However, due to the increased administrative burden of the PFAC compared to the UTAC, there will be no general right of appeal, as this would interfere with administrative certainty and prolong litigation. Decisions made by public bodies can be challenged in an application for judicial review in the High Court under s 4 of the Judicature Amendment Act 1972 or under common law.⁹³ Grounds for judicial review are much narrower than the grounds for appeal,⁹⁴ and are typically limited to a consideration of how the decision was made, such as substantive unfairness and breach of natural justice,⁹⁵ failure to apply internal procedures consistently,⁹⁶ and unreasonableness,⁹⁷ rather than permitting a review of the decision on the merits. Moreover, as noted by Venning J in *New Zealand Climate Science Education Trust v National Institute of Water and Atmospheric Research Ltd*⁹⁸, a Court will be “cautious about interfering with decisions made and conclusions drawn by a specialist body... acting within its own sphere of expertise”,⁹⁹ unless there was some defect in the decision-making process or it could be shown that the decision was clearly wrong in principle or in law.¹⁰⁰ In particular, “the Court will be reluctant to adjudicate on matters of science and substitute its own inexpert view of the science if there is a tenable expert opinion”.¹⁰¹ Accordingly, deference to the decisions of the PFAC is more appropriate in order to minimise uncertainty and prevent excessive disputes.

⁹² An in-depth discussion of the process of ‘systematic review’ is beyond the scope of this thesis. The Cochrane Collaboration is an international network of medical professionals which conduct such systematic reviews of clinical trials to determine whether a treatment is effective according to available data: see <www.cochrane.org>.

⁹³ *Mercury Energy Ltd v ECNZ* [1994] 2 NZLR 385 (PC) at 388.

⁹⁴ *Compare Austin, Nichols Inc v Stichting Lodestar* [2007] NZSC 41.

⁹⁵ *Thames Valley Electric Power Board v NZFP Pulp & Paper Ltd* [1994] 2 NZLR 641 at 652 per Cooke P.

⁹⁶ *Pharmaceutical Management Agency Ltd v Roussel Uclaf Australia Pty Ltd* [1998] NZAR 58 (CA).

⁹⁷ *Wellington City Council v Woolworths New Zealand Ltd (No 2)* [1996] 2 NZLR 537.

⁹⁸ *New Zealand Climate Science Education Trust v National Institute of Water and Atmospheric Research Ltd* [2013] 1 NZLR 75 (HC).

⁹⁹ At [45].

¹⁰⁰ At [48].

¹⁰¹ At [47].

4 *How does a flexible prize fund and increased public funding for unmonopolisable and unprofitable therapies compare against ideal criteria?*

Should any criteria be excluded?

The purpose of the MPF Bill is to incentivise unmonopolisable and unprofitable therapies. Therefore, it will not be appropriate to include incentivising unpatentable therapies as a criterion in the following analysis.

(a) Criterion two: incentivising unmonopolisable therapies

The MPF Bill is capable of incentivising any type of unmonopolisable therapy, regardless of excludability because rewards are determined according to condition-specific metrics calculated during standardised clinical trials. Eligibility for rewards only requires a phase II equivalent trial, which means the MPF Bill has a relatively low cost compared to achieving ‘registration’ under the HIF or MIPF proposals. This also allows a relatively greater ‘impact’ for a smaller fund. Of course, if the MPF Bill is only implemented in New Zealand, funding levels may be too small to prevent screening of all unmonopolisable therapies. Therefore, as with the EME Bill, the assumption that there is some level of support from overseas jurisdictions, such as the United States. The availability of increased public funding to reproduce ‘de-risked’ clinical trials in larger studies will also be assumed.

However, as noted in Chapter 6B with reference to flexible prize funds, the amount of prize rewards depends arbitrarily on the health impact of other ‘registered’ clinical trials in a particular fund, which means that a flexible prize mechanism under the MPF Bill may be unlikely to provide equivalent incentives as guaranteed exclusivity. Despite this, it is likely that flexible prize mechanisms are an improvement on fixed prizes, and can incentivise at least 75 per cent of unmonopolisable therapies, especially when combined with increased public funding. Therefore a rating of four is provided under this criterion.

(b) Criterion three: incentivising unprofitable therapies

The existence of prizes under the MPF Bill could also incentivise unprofitable therapies because rewards are de-linked from the underlying sales of a therapy. It can also be assumed that de-risked unprofitable therapies with the greatest health impact can receive sufficient funding to receive clinical validation. However, as discussed above with reference to unmonopolisable therapies, the availability of rewards under a flexible prize regime is more uncertain than exclusivity, although it provides greater

incentives than fixed prizes. Hence, de-risking prize funds combined with public funding could arguably incentivise over 75 per cent of unprofitable therapies, and therefore receive a rating of four.

(c) Criterion four: balancing dynamic and static efficiency

Well-designed flexible prizes can provide (1) private incentives for innovators to undertake clinical trials, although under the proposed MPF Bill, prize rewards are allocated over five years. There are also likely to be some delays for determining the allocation of public funding to ‘registered’ therapies, although ‘de-risking’ of viable therapies will help reduce these delays. A prize also allows (2) competition without delay to provide static efficiency.

In addition, because unmonopolisable and unprofitable therapies will be made available at their marginal cost of production, flexible prizes and increased public funding can (3) minimise deadweight loss and (4) maximise consumer surplus. Because it is arguable that rewards and public funding will be delayed under the MPF Bill, a rating of 4 is provided under this criterion.

(d) Criterion five: linking rewards to improved health outcomes

The MPF Bill and increased public funding can incentivise more than one type of therapy. Further, prizes under the MPF Bill with well-designed and unambiguous criteria can specify condition-specific metrics that allows the government to fund the therapies that achieve the best relative clinical outcome compared to other ‘registered’ clinical trials. However, it is known that improved clinical outcomes do not typically extrapolate to improved outcomes for society generally, particularly in developing countries where co-morbidities may be present.¹⁰² Moreover, once a particular unmonopolisable or unprofitable therapy is used in clinical practice, unforeseen adverse events may arise, at which time, rewards have already been received. Hence, as the proposed MPF Bill and increased public funding can link rewards to health impact, but will not maximise the same, they achieve a score of three under this criterion.

¹⁰² Hollis and Pogge, above n 53 at 29.

(e) Criterion six: minimising administration costs to determine rewards

The main difficulty with administration of prizes is the lack of a market mechanism to determine rewards. However, as discussed above, a fixed annual prize fund has at least an indirect means for determining the rewards through a self-correcting mechanism according to the number of registered clinical trials. Further, the use of standard condition-specific metrics rather than QALYs can lower administration costs, at least compared to the HIF and MIPF proposals. On the other hand, the necessity of establishing separate prize funds and standard clinical endpoints would tend to increase administrative costs.

It is also recognised that administration costs are high for increased public funding, as discussed in Chapter 6C.¹⁰³ However, a de-risking mechanism under the MPF Bill will mean that the government has more information available about the appropriate therapy to fund. However, it would not tend to lower administration costs overall, especially if larger clinical trials must be managed.

Accordingly, the level of administration costs will be similar to proposed increased public funding mechanisms and flexible prize mechanisms. Therefore, a score of two is provided under this criterion.

(f) Criterion seven: minimising waste/inefficiency

There are various ways in which prize funds under the MPF Bill and increased public funding can create waste and inefficiency. First, there is a possibility for (2) costly litigation with the PFAC as to whether criteria for receiving rewards are satisfied, although as noted above, the scope of judicial review is limited. The design of unambiguous criteria and standard condition-specific metrics will help minimise disputes with innovators as to allocation of rewards. Second, there is also a potential for (3) gaming, whereby prize administrators exert pressure on participants to accept a smaller prize after the R&D expenditure has occurred, although this risk is lower with the smaller size of potential rewards under the MPF Bill compared to the HIF or MIPF. Again, the proper design of unambiguous criteria will help as well as the design of robust and transparent mechanisms for determining rewards.

Third, having an administrative body to determine levels of funding within prize fund categories and select therapies for public funding creates a significant risk

¹⁰³ DJ Hemel and LL Ouellette “Beyond the Patents--Prizes Debate” (2013) 92 Texas Law Review 303 at 362.

of (9) rent seeking due to political interference, even with conflict of interest policies in place. Fourth, there is also an opportunity for (10) free riding, especially if other major jurisdictions do not implement equivalent prize fund mechanisms and increase public funding to replicate de-risked clinical trials.

On the other hand, flexible prize mechanisms and public funding can avoid many waste/inefficiency factors associated with exclusivity-based incentives. For example, de-linking rewards from underlying sales of a therapy means no (1) incentives for excessive marketing. The lack of monopoly rents due to exclusivity means there is also no incentive to conduct (4) arbitrage due to grey markets and (5) incentives to counterfeit drugs.

In addition, by using a mechanism to provide ‘clinical exclusivity’ in exchange for publication of the innovators clinical trial protocol, it is possible to avoid (6) low transparency and duplication of R&D efforts. Moreover, including a mechanism to only allow ‘registration’ for ‘clinically superior’ therapies, it is possible to avoid (7) incentives for me-too drugs. The absence of monopoly rents from exclusivity rights will also assist here. Prizes can also avoid an (8) ‘anticommons’ effect because rewards are not based on patent rights, although, as noted above, innovators may not be able to rely on exemptions from infringement of patents held by others. By contrast, public funding will support an open sourced approach.

Therefore, four waste/inefficiency factors are arguably not absent, and accordingly, a score of three is provided under this criterion.

(g) Criterion eight: Incentivise incremental innovation and breakthroughs

Flexible prizes for early-stage clinical research have the potential to optimally incentivise incremental innovation and breakthroughs. With the MPF Bill, prizes will be provided for establishing clinical efficacy of a new type of unmonopolisable or unprofitable therapy. Breakthroughs will be incentivised by providing clinical exclusivity, and subsequent public funding, whereby incremental innovation will be facilitated by allowing ‘clinically superior’ therapies to achieve Um/P Designation and ‘registration’. In addition, public funding is flexible enough to incentivise both incremental innovation and breakthroughs.

As noted in Chapter 6C, with public funding there may be a risk that no party will be responsible for minimising harm to patients because multiple parties may be delivering a therapy. However, public funding and an open source approach will

ensure there are no incentives to suppress any adverse events which might harm patients. It is also notable that where unmonopolisable therapies are based on second uses of generic drugs, dietary supplements, diets, and lifestyle interventions, there is limited potential of harm to patients because they are inherently safer, at least compared to new ‘monopolisable’ drugs. Accordingly, it is possible to achieve a score of five under this criterion.

Summary

A prize-based flexible reward mechanism can incentivise unmonopolisable and unprofitable therapies in a manner which cannot be accomplished with exclusivity-based mechanisms. The MPF Bill would act synergistically with public research agencies to de-risk early stage clinical trials, and address the current information asymmetry between the private and public sectors. The most effective clinical trials will subsequently receive public funding. The public funding of research can also ensure that clinical trials are available to be used globally without restriction in a manner that can maximise human health. Overall, a flexible (de-risking) prize fund with increased public funding achieves an average score of 3.57, which is a significant improvement over the current patent system.

D Conclusion

The proposals for extended market exclusivity under the EME Bill and the proposal for a de-risking prize fund combined with increased public funding under the MPF Bill can optimally address the deficiencies in the current patent system with respect to the lack of incentives to develop unpatentable, unmonopolisable and unprofitable therapies. As shown on the comparison Table 2 below, these mechanisms achieve a significantly better outcome than the current patent system and alternative incentive mechanisms for incentivising development of socially valuable medicines.

Table 2: Comparison chart ranking current, alternative, and optimal incentive mechanisms¹⁰⁴

Criteria	Exclusivity ‘Pull’ Incentives				Prize ‘Pull’ Incentives		Push	Optimal	
	CPS	PE	RE	OD	FIP	FLP	PF	EME	MPF
1. UPa	2	3	5	2	3	4	3	5	-
2. UM	1	1	-	-	3	4	3	-	4
3. UPr	1	1	2	1	3	4	3	-	4
4. DSE	3	3	3	3.5	4.5	4	4.5	3	4
5. LR	3	3	3	2	2	4	2	3	3
6. AC	5	4.5	4.5	4.5	3	2	2	5	2
7. W/I	2	1	2	3	2	2	3	2	3
8.In/Br	4	4	4	3	3	4	5	4.5	5
Total	21	20.5	23.5	19	23.5	28	25.5	22.5	25
Avg	2.63	2.56	3.36	2.71	2.94	3.5	3.19	3.75	3.57

The EME Bill would arguably have a limited administrative burden to allocate ‘clinical exclusivity’, which would be similar to the process already undertaken by the successful Orphan Drug reforms. It would not result in an overall increase in healthcare costs, because it would incentivise development of unpatentable medicines that would otherwise not be available for purchase. However, as will be discussed in Chapter Eight, it will require support of the United States in order to have an effect on private incentives to develop unpatentable therapies.

With regards to the MPF Bill, there would be an administrative burden required to establish prizes for different disease categories and appropriate health metrics and criteria for each prize fund. However, this would arguably not be notionally different from the current administrative burden faced by government agencies that issue research grants, such as the HRC in New Zealand and the NIH in the United States.

¹⁰⁴ Legend: Criteria: One to Eight see Chapter Five; CPS=current patent system; PE=patent extension regimes; RE=extended regulatory exclusivity; OD=Orphan Drug reforms; FIP=fixed prizes; FLP=flexible prizes; PF=increased public funding; EME=extended market exclusivity bill; MPF=flexible prize fund bill.

VIII Conclusion

A Introduction

As noted in Chapter One, the aim of the thesis was to consider whether the current incentive system for medical therapies, comprising the patent system as well as its unique regulatory and reimbursement framework, adequately incentivises the development of socially valuable medical therapies, with reference to applicable law in New Zealand and the United States. It was determined that under the current incentive system there are certain broad categories of medical therapies that could have potentially high social value, but lack private incentives for development. The thesis proposes two reforms to optimally address these problems.

This chapter will summarise the main findings of Chapters Two to Seven by considering how they have addressed the four research objectives specified in Chapter One. It will then reiterate the need for international support and how the adoption of these reforms in New Zealand can facilitate an internationally co-ordinated implementation of an optimal incentive system. Finally, it will emphasise why the proposed reforms require urgent consideration by policymakers.

B Summary of Research Findings

As stated above, the aim of the research was to analyse whether the current system and alternative incentive mechanisms adequately incentivise development of socially valuable medical therapies and to propose an optimal system that addresses this issue. This aim was achieved through the satisfaction of four objectives.

The first objective was to provide background information regarding the legal requirements for patentability and regulatory approval for new medicines and describe how it is possible for innovators to lose exclusivity. In Chapter Two, it was shown that a medicine can lose patentability due to a prior disclosure, predictable benefits, or inadequate description, irrespective of the social value of that medicine. It was also shown how the loss of patentability may be unavoidable in many cases. Subsequently, it was shown that methods of medical treatment are excluded from patentability in New Zealand, although judicial inroads into those exclusions may allow patentability to be achieved certain cases. Finally, it was shown that competition from generic ‘off-patent’ drugs upon expiry or invalidity of patent protection can have a significantly adverse effect on profitability of a new medicine.

The second objective was to analyse why the pharmaceutical industry relies on patent protection to recover their development costs and the adverse consequences of such reliance. Chapter Three first discussed how the high costs and risks of drug development lead to screening of medicines on the basis of insufficient patentability irrespective of medical efficacy. It also discussed unpatentability factors that cause such screening, namely: lack of novelty, lack of inventive step, insufficiency/inutility, insufficient patent length, and unpatentability under law. It was argued that ‘patent evergreening’ techniques that can allegedly be used by the pharmaceutical industry to rescue such ‘unpatentable therapies’ are generally ineffective because they result in weaker ‘secondary patents’ and cannot always prevent ‘off-label’ competition from generic drugs. It also defined the category of ‘unmonopolisable therapies’ over which a monopoly price cannot practically be enforced, and the category of ‘unprofitable therapies’ that lack commercial viability generally. It explained that the funding bias towards ‘monopolisable therapies’, and away from these unpatentable, unprofitable and unmonopolisable therapies, is likely to significantly increase global disease burden and exacerbate the industry’s productivity crisis. Chapter Three also briefly considered other problems created by reliance on patents, such as excessive litigation, high monopoly prices creating deadweight losses¹ and incentivising excessive marketing for the duration of the patent,² a potential anti-commons effect,³ and encouraging the development of so-called ‘me-too’ drugs which are profitable but do not address unmet medical needs.⁴

The third objective was to consider the process of determining rewards under the current system, and to propose criteria for an ideal incentive system that would overcome the problems identified in Chapter Three. Chapter Four described the health metrics used in pharmacoeconomic analysis, which are a useful means to maximise health impact for a medicine within a given budget. Chapter Five emphasised that there were international obligations to implement mechanisms that maximise the human right to health. Criteria for an ideal incentive system were proposed, which included incentivising unpatentable, unmonopolisable and unprofitable therapies as well as maximising health and minimising administration costs and waste.

The fourth objective was to analyse the current system and alternative incentive mechanisms using the ideal criteria as a benchmark, in order to determine

¹ James Love and Tim Hubbard “The Big Idea: Prizes to Stimulate R&D for New Medicines” (2007) 82 Chi-Kent L Rev 1519 at 1522.

² Kalman Applbaum “Is Marketing the Enemy of Pharmaceutical Research?” (2009) 39(4) Hastings Center Report 13 at 13.

³ Michael A Heller and Rebecca S Eisenberg “Can Patents Deter Innovation?: The Anticommons in Biomedical Research” (1998) 280 Science 698 at 698.

⁴ DW Light and JR Lexchin “Pharmaceutical research and development: what do we get for all that money?” (2012) 345(1) BMJ 1 at 2.

which incentives were optimal. In Chapter Five, it was confirmed that the current patent system performs poorly with respect to incentivising unpatentable, unmonopolisable, and unprofitable therapies. Chapter 6A showed that, in general, exclusivity-based incentive mechanisms are more suited towards incentivising unpatentable therapies rather than unmonopolisable or unprofitable therapies, and that extended regulatory exclusivity achieves the highest ranking because, arguably, no screening of unpatentable therapies would occur.

In Chapter 6B, fixed *ex-ante* and flexible *ex-post* prize-based ‘pull incentives’ were analysed. It was shown that the main benefit of prize-based mechanisms is that they do not rely on enforcement of a monopoly price in order to provide incentives, and therefore, can incentivise unmonopolisable⁵ and unprofitable therapies.⁶ Flexible prize systems achieved the highest overall rating because, unlike fixed prizes, they could link increased rewards to improved health outcomes in a self-correcting manner. However, it was demonstrated that the main problem with prize-based proposals is the reliance on pre-determined criteria to calculate the appropriate level of rewards rather than a market-based mechanism.

In Chapter 6C, increased public funding and open source approaches as ‘push’ incentives were analysed, and it was concluded that publicly funding research, while avoiding many problems with the current system, has the potential for substantial waste and inefficiency because the government lacks information regarding which are the most socially valuable medicines that should be funded, and that open source approaches are incompatible with the notion of private ownership of medical research.

In Chapter Seven, the EME Bill was first proposed as part of an optimal incentive system. This would provide extended market exclusivity upon regulatory approval of unpatentable therapies, and would have significant advantages over the current patent system, as exclusivity could not be challenged under the patentability criteria. Practical issues were considered such as the establishment of an advisory committee to administer the allocation of ‘clinical exclusivity’ in advance of regulatory approval in order to prevent inefficient races, and reserving exclusivity for ‘clinically superior’ therapies in order to encourage incremental innovation. Equivalent provisions from the Orphan Drug Act and proposed MODDERN Cures Bill discussed Chapter 6A were used as examples of preferred wording. It was

⁵ For example, see T Syed “Should a Prize System for Pharmaceuticals Require Patent Protection for Eligibility?” (Incentives for Global Health Discussion Paper No 2 10 June 2009) at 4.

⁶ For example, see M Bakhom “TRIPS, Patent Rights and Right to Health: ‘Price’ or ‘Prize’ for Better Access to Medicine?” (Max Planck Institute for Intellectual Property, Competition & Tax Law Research Paper No 10-07, 2009) at 46.

concluded that the EME Bill would receive the highest overall rating for the purpose of incentivising unpatentable therapies.

With regard to incentivising unmonopolisable and unprofitable therapies, the MPF Bill was proposed, which would establish prize funds that leverage the private sector to de-risk a ‘proof-of-concept’ for the safety and efficacy of an unmonopolisable or unprofitable therapy in clinical trials. Public funding could then be used to validate the safety and efficacy of those therapies in larger clinical trials. It was argued that this is more efficient than the current system of grant funding, as ‘de-risking’ the potential benefits of the therapy means that the government does not have to ‘pick the winners’ in advance.⁷ An administrative body would establish prize funds in discrete disease categories to be paid out annually to innovators that fulfill the criteria for ‘registration’ with the prize fund. Standardised health metrics and criteria for each clinical trial could be used to compare health outcomes for each therapy as a basis for allocating an amount from the annual prize fund that is proportional to health impact of the therapy. It was argued this would be a fair and robust mechanism to determine rewards, with limited potential for inefficiencies or gaming. It was concluded that the proposed mechanism in the MPF Bill achieved the highest overall rating for the purpose of incentivising unmonopolisable and unprofitable therapies.

C The Need for Support from Major Jurisdictions

Unfortunately, the implementation of a regulatory exclusivity mechanism in New Zealand as proposed in the EME Bill would be unlikely to have any impact on private incentives to develop unpatentable therapies, unless equivalent reforms, such as the proposed MODDERN Cures Bill attached as Appendix Two, are passed in the United States. The latter is the largest market for pharmaceutical companies.⁸ Without a sufficient period of exclusivity in the United States, there is “no real point to even make the drug”.⁹ However, as with the Orphan Drug Act, if the United States takes the initiative, then Europe and other high-income countries are likely to follow.¹⁰

By contrast, the prize mechanism proposed in the MPF Bill could be established as a supplement to the typical grant funding process by the New Zealand

⁷ BD Wright “The Economics of Invention Incentives: Patents, Prizes, and Research Contracts” (1983) 73 *Amer Econ Rev* 691 at 703-704.

⁸ The United States accounting for 34 per cent of USD 950 billion global pharmaceutical sales in 2011: *The Global Use of Medicines: outlook through 2016* (IMS Institute for Healthcare Informatics, 2012) at 5.

⁹ T Bartfai and GV Lees *Drug Discovery from Bedside to Wall Street* (Elsevier, Burlington, 2006) at 138.

¹⁰ See DL Scott and others “Orphan Drug Programs/Policies in Australia, Japan and Canada” (2001) 35 *Drug Information Journal* 1 at 1.

Health Research Council to help researchers obtain private funding. Although using a flexible prize mechanism to determine rewards is novel, using prizes to fund medical research has historical precedent.¹¹ Successful results from the implementation of the MPF Bill mechanism in New Zealand are likely to inspire foreign jurisdictions to use prizes as private incentives for medical research.¹²

As discussed in Chapter Five, it is arguable that New Zealand and foreign jurisdictions have a legal (and ethical) obligation to implement these incentive mechanisms in order to maximise the human right to health.

D Closing the Deadly Gaps in the Patent System

The pharmaceutical industry spends over US 135 billion dollars on medical research and development every year.¹³ While this is significant, payers spend USD 500 billion every year in monopoly markups,¹⁴ and under the current system, innovators' revenues will be put back into developing new patentable medicines. This is how the current system works; patents are part of the 'social contract' that rewards innovator companies for conducting expensive and risky clinical research.¹⁵ However, the patent system is poorly equipped to incentivise development of medically valuable clinical research that does not fall within its framework.¹⁶ Therefore, it is time to "look beyond the patent system",¹⁷ and update the terms of the 'social contract' to account for a broader range of therapies.

¹¹ R Hanson "Patterns of Patronage: Why Grants Won Over Prizes in Science" (University of California, Berkeley, 1998) at 10.

¹² As discussed in Chapter Six under the discussion of the MPF Bill, proposals from innovators would not be restricted to New Zealand. The prize would be a unilateral offer to any participant who can fulfill the criteria for registration of a clinical trial.

¹³ *The Pharmaceutical Industry and Global Health: Facts and Figures 2012* (International Federation of Pharmaceutical Manufacturers & Associations, 2012) at 5.

¹⁴ In particular, patented or 'branded' drugs are approximately 12 times more expensive than off-patent or 'generic' drugs and global sales of branded drugs were USD 596 billion in 2011. See J Love and T Hubbard "The Big Idea: Prizes to Stimulate R&D for New Medicines" (2007) 82 Chi-Kent L Rev 1519 at 1522; *The Global Use of Medicines: outlook through 2016* (IMS Institute for Healthcare Informatics, July 2012) at 8.

¹⁵ V Denicolò and LA Franzoni "The Contract Theory of Patents" (2004) 23 International Review of Law and Economics 365 at 365.

¹⁶ T Cook "How IPRs, like Nature, Abhor a Vacuum, and What Can Happen When They Fill it - Lacunae and Overlaps in Intellectual Property" (2012) 17 JIPR 296 at 299; RS Eisenberg "Re-examining the Role of Patents in Appropriating the Value of DNA Sequences" (2000) 49(3) Emory Law Journal 783 at 799. Eisenberg was writing about genetic information, however, in the context of this thesis, the same argument applies to clinical trial data that cannot be protected under the current patent system.

¹⁷ Eisenberg, at 799.

With an ageing baby boomer population and 70 per cent of people over 65 having two or more chronic conditions,¹⁸ it is more important than ever to ensure that current incentive systems allocate funds towards developing therapies that can maximise health in a cost-effective manner. The most recognised therapies for treating age-related illness are based on diet and lifestyle interventions such as exercise,¹⁹ which lack private incentives under the current system.²⁰ Under an ideal incentive system, funding for medical therapies would be allocated on the basis of scientific merit and potential health impact, irrespective of patentability, monopolisability, market size, and other irrelevant considerations from the perspective of the patient. Patentability and commercial viability have no relevance to the safety and efficacy of a medical therapy. However, pharmaceutical companies are not blameworthy for attempting to maximise profits within a flawed incentive system.

This thesis defined three categories of medical therapies that are ignored under the current patent system, and showed that extended regulatory exclusivity is the most appropriate incentive for unpatentable therapies, while prizes and increased public funding are the most appropriate incentives for unmonopolisable and unprofitable therapies. It is recommended that further research is conducted to determine the extent of patentability screening in the industry, the consequences of a private funding bias away from socially valuable medical therapies, and that appropriate reforms are urgently implemented to address this.

¹⁸ L Fontana and others “Medical research: Treat ageing” (2014) 511 *Nature* 405 at 406.

¹⁹ At 406.

²⁰ See discussion of unmonopolisable therapies in Chapter Three.

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APPENDIX ONE

Human Ethics Committee Approval (p 269)

Information Sheet (pp 270-271)

Consent Form (p 272)

Survey (pp 273-278)

HUMAN ETHICS COMMITTEE

Secretary, Lynda Griffioen
Email: human-ethics@canterbury.ac.nz

Ref: HEC 2013/18/LR

22 April 2013

Savvas Kerdemelidis
School of Law
UNIVERSITY OF CANTERBURY

Dear Savvas

Thank you for forwarding your Human Ethics Committee Low Risk application for your research proposal “Does the patent system incentivise the funding of the best medical therapies? An analysis of alternative incentive models”.

I am pleased to advise that this application has been reviewed and I confirm support of the Department’s approval for this project.

Please note that this approval is subject to following:

- In the information sheet, please remove references to anonymity.

With best wishes for your project.

Yours sincerely

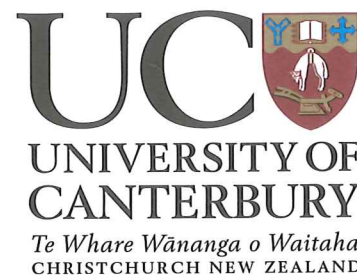


Lindsey MacDonald
Chair, Human Ethics Committee

School of Law

Tel: +64 3 364 2602, Fax: +64 3 364 2757
Email: law-enquiries@canterbury.ac.nz

8 July 2013



GAPS IN THE PATENT SYSTEM FOR INCENTIVISING DEVELOPMENT OF DORMANT AND UNMONOPOLISABLE THERAPIES

Information Sheet for Survey Participants

Dear Sir/Madam

My name is Savvas Kerdemelidis and I am currently a postgraduate student at the University of Canterbury studying towards a Master of Laws. My self-selected thesis involves collecting evidence of medical therapies that failed to attract private funding or were dropped from development primarily due to actual or perceived insufficient patent protection or lack of practical ability to use patents to enforce monopoly prices. The thesis focuses on suggesting legal or alternative reforms to address this private funding cooling effect and to adequately incentivise development of therapies for unmet medical needs.

I would personally like to invite you to participate in this study. Your participation in this study would involve completing an emailed survey, and possibly answering some additional follow up questions via email if you indicate that you are prepared to do so.

Your participation in this study is completely voluntary and you have the right to withdraw at any stage. If you choose to withdraw, I will do my best to remove any information relating to, or provided by, you, provided this is practically achievable. The stage at which information cannot be practically removed will be once the analysis of the information has occurred.

Please note that I will not refer to you by your actual name in the thesis. Nor will your personal or confidential information be given to anyone else without your permission. The survey and subsequent email correspondence will be retained in a filing cabinet, which will be accessible only by myself and my supervisor, Dr. Debra Wilson. This survey and email correspondence will be destroyed after five years.

There are minimal ethical risks involved in this interview due to the confidentiality plans discussed above.

The results from this survey will be used to provide evidence of a private funding cooling effect for otherwise potentially safe and effective therapies with actual or perceived insufficient patent protection or lack of practical ability to use patents to enforce monopoly prices. These results will also be made public on the publication of my thesis. As a participant, you can receive a report on the study if requested. This can be facilitated by contacting me on either of the contact details provided above. You are also more than welcome to contact me, or my supervisor Dr Debra Wilson, at any time if you have any questions. Dr Wilson can be contacted at debra.wilson@canterbury.ac.nz.

This project has been reviewed and has received ethical approval from the University of Canterbury Human Ethics Committee and any complaints should be addressed to the Chair,

Human Ethics Committee, University of Canterbury, Private bag 4800, Christchurch or human-ethics@canterbury.ac.nz.

Please complete the consent form attached if you understand and agree to take part in this study. This can be returned to me by sending a scanned copy to my email address at ske20@uclive.ac.nz or savva.kerdelmelidis@gmail.com or it can be mailed to my attention at the School of Law, University of Canterbury address.

If you have any concerns whatsoever about your potential involvement in this project, then I am more than happy to discuss these further with you.

I look forward to hearing from you.

Kind regards

A handwritten signature in black ink, appearing to be 'Savvas Kerdelmelidis', written over a horizontal line.

Savvas Kerdelmelidis

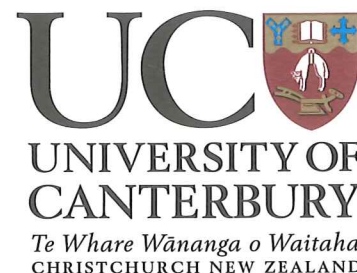
Telephone: + 64 22 080 5903

Email: ske20@uclive.ac.nz or savva.kerdelmelidis@gmail.com

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8 July 2013



GAPS IN THE PATENT SYSTEM FOR INCENTIVISING DEVELOPMENT OF DORMANT AND UNMONOPOLISABLE THERAPIES

Consent Form for Survey Participants

I understand that this survey will be used to collect evidence of medical therapies which failed to attract private funding or were dropped primarily due to actual or perceived insufficient patent protection or lack of practical ability to use patents to enforce monopoly prices. A full explanation of this project has been provided and I have been given an opportunity to ask questions.

I understand that a survey will be provided by email, and I may possibly answer some follow up questions via email if I indicate that I am prepared to do so.

I understand that my participation is voluntary and that I may withdraw at any stage without penalty.

I understand that any information or opinions that I provide will be kept confidential to the researcher. Any reported or published results will not identify my identity due to the use of an alias, or generic job description, unless permitted by me.

I understand that the survey and subsequent email correspondence will be kept in locked and secured facilities and will be destroyed after five years.

I understand the minimal risks associated with taking part in this project and that they will be managed by the researcher by ensuring confidentiality.

I understand that I am able to receive a report on the findings of the study if requested. This can be facilitated by contacting the researcher through either of the contact details provided above.

I understand that I can contact the researcher or his supervisor, Dr Debra Wilson, for further information. She can be contacted at debra.wilson@canterbury.ac.nz.

I understand that the University of Canterbury Human Ethics Committee has reviewed and approved this project.

Name:

Date:

Signature:

Email address to send a report of findings:

The interview participant can return a scanned copy of their signed consent form to savva.kerdelmidis@gmail.com or ske20@uclive.ac.nz. Otherwise, the interview participant can return the signed consent form by standard mail to the following address:

Attention: Savvas Kerdelmidis
School of Law
University of Canterbury
Private Bag 4800
Christchurch 8140
New Zealand.

Kind regards,

Savvas Kerdelmidis

Telephone: + 64 22 080 5903

Email: ske20@uclive.ac.nz or savva.kerdelmidis@gmail.com

GAPS IN THE PATENT SYSTEM FOR INCENTIVISING DEVELOPMENT OF DORMANT AND UNMONOPOLISABLE THERAPIES

1. Dormant Therapies

1.1 Are you aware of any drug candidates which failed to attract funding or were dropped from development where the primary reason was perceived or actual insufficient patent protection (e.g. due to prior publication or insufficient patent length) as opposed to (i) perceived or actual lack of safety or efficacy or (ii) other commercial reasons.

("Dormant Therapies")

- **Yes / No**

If so, can you specify the approximate number of Dormant Therapies you are aware of:

1.2 Are you aware of any such Dormant Therapies which are potential or actual treatments for unmet medical needs i.e. treatments for life-threatening or other serious diseases or conditions for which no therapy exists or are potentially or actually clinically superior to existing first-in-class therapies?

- **Yes / No**

If so, can you identify as many Dormant Therapies for unmet medical needs as possible for you to recall:

2. Rescuing Patent Protection for Dormant Therapies

2.1 Are you aware of any potentially Dormant Therapies that were dropped for insufficient patent protection but subsequently obtained funding by relying on patenting derivatives, metabolites, selection inventions, new formulations or combinations with the same active ingredient, new uses, methods of administration or methods of manufacture (i.e. patent “evergreening” techniques) and/or ‘regulatory’ exclusivity (i.e. Orphan Drug/data exclusivity)?

(“Rescued Dormant Therapies”).

- **Yes/No**

If yes, can you (a) specify the approximate number of Rescued Dormant Therapies you are aware of; and (b) identify as many Rescued Dormant Therapies as possible for you to recall:

2.2 In your view, having regard to the entire set of potentially Dormant Therapies, what would be the typical percentage that could be “rescued” with “evergreening” techniques and/or ‘regulatory’ exclusivity and obtain private funding (i.e. what proportion of potentially Dormant Therapies could become Rescued Dormant Therapies):

- **None of them / An insignificant amount (less than 5%) / A significant amount (between 5%-50%) / A majority (between 50-75%) / Most of them (greater than 75%) / Nearly all of them (greater than 90%) / All of them**

3. Perceived Impact on Society because of Dormant Therapies

In your view, having regard to the entire set of potentially safe and effective drug candidates for unmet medical needs, what would be the typical proportion that are Dormant Therapies.

- **None of them / An insignificant amount (less than 5%) / A significant amount (between 5%-50%) / A majority (between 50-75%) / Most of them (greater than 75%) / Nearly all of them (greater than 90%).**

In your view, what do you think is the impact on society's disease burden due to the lack of private incentives to develop Dormant Therapies for unmet medical needs?

- ***No impact / Low impact / Moderate impact / High impact / Severe impact***

Could you explain your reasoning?

4. THE MODDERN Cures Act

The MODDERN (Modernizing Our Drug and Diagnostics Evaluation and Regulatory Network) Cures Act was introduced in the U.S. House of Representatives on November 18, 2011. The Bill would incentivise development of Dormant Therapies by granting a sponsor 15 years of exclusivity to market the Dormant Therapy upon regulatory approval. Subject to the sponsor providing the FDA with regular development certifications that they are actively pursuing clinical trials, the Bill would allow the FDA to grant “clinical exclusivity” to the sponsor of the Dormant Therapy in advance of regulatory approval.

In your view, would a 15 year period of exclusivity granted by the FDA upon regulatory approval as proposed by the MODDERN Cures Act adequately incentivise development of Dormant Therapies with insufficient patent protection?

- **Yes / No**

Could you explain why?

5. Unmonopolisable Therapies

5.1 Are you aware of any therapies which failed to attract funding or were dropped from development where the primary reason was perceived or actual lack of ability to enforce monopoly pricing over the therapy as opposed to (i) perceived or actual lack of safety or efficacy or (ii) insufficient patent protection per se.

("Unmonopolisable Therapies")

[Examples of such therapies include, second indications for cheap generic drugs for which patents cannot be used to prevent "off-label" use by doctors or patients. For the same reason, patents cannot practically enforce monopoly prices for diets, dietary supplements, lifestyle interventions, surgical methods, "natural" remedies, and many complementary and alternative medicines. Therapies for neglected/third world diseases and other "unprofitable therapies" could also be considered a subset of this category, as an innovator company could not recover enough money from the market to justify significant R&D investment, even if they had patent protection].

- **Yes / No**

If so, can you specify the approximate number of Unmonopolisable Therapies you are aware of:

5.2 Are you aware of any Unmonopolisable Therapies which are potential or actual treatments for unmet medical needs (i.e treatments for life-threatening or other serious diseases or conditions for which no therapy exists or are potentially or actually clinically superior to existing first-in-class therapies?)

- **Yes / No**

If so, can you identify as many Unmonopolisable therapies for unmet medical needs as possible for you to recall:

6. Perceived Impact on Society because of Unmonopolisable Therapies

In your view, having regard to the entire set of potentially safe and effective medical therapies for unmet medical needs, what would be the typical proportion that are Unmonopolisable Therapies.

- **None of them / An insignificant amount (less than 5%) / A significant amount (between 5%-50%) / A majority (between 50-75%) / Most of them (greater than 75%) / Nearly all of them (greater than 90%).**

In your view, what do you think is the impact on society's disease burden due to the lack of private incentives to develop Unmonopolisable Therapies for unmet medical needs?

- **No impact / Low impact / Moderate impact / High impact / Severe impact**

Could you explain why?

7. Prize-based Incentives for Unmonopolisable Therapies

In your view, would a monetary (or equivalent) prize/royalty for demonstrating safety and efficacy of an Unmonopolisable Therapy (via randomised controlled trials) adequately incentivise development of Unmonopolisable Therapies?

- **Yes / No**

If no, could you explain why?

8. Follow up questions

Would you be prepared to answer some follow up questions on this survey by email?

- **Yes / No**

APPENDIX 2

MODDERN CURES Bill - Extract

SECTION 1. SHORT TITLE.

This Act may be cited as the "Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network Cures Act of 2013" or the "MODDERN Cures Act of 2013".

SEC. 2. TABLE OF CONTENTS.

The table of contents for this Act is as follows:

- Sec. 1. Short title.
- Sec. 2. Table of contents.
- Sec. 3. Findings.
- Sec. 4. Definitions.

TITLE I--ADVANCING DIAGNOSTICS FOR PATIENTS

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- Sec. 201. Dormant therapies.
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SEC. 3. FINDINGS.

The Congress makes the following findings:

(1) More than 133 million Americans, or 45 percent of the population, have at least one chronic condition. A quarter of Americans have multiple chronic conditions.

(2) Chronic diseases have become the leading cause of death and disability in the United States. Seven out of every 10 deaths are attributable to chronic disease. Chronic diseases also compromise the quality of life of millions of Americans.

(3) Despite \$80 billion spent annually on research and development, many diseases and conditions lack effective treatments.

(4) Many commonly used drugs are effective in only 50 to 75 percent of the patient population, which can lead to devastating long-term side effects, resulting in the potential risks outweighing the benefits for some patients.

(5) Advanced and innovative diagnostic tests have the potential to dramatically increase the efficacy and safety of drugs by better predicting how patients will respond to a given therapy.

(6) Despite their promise, many drugs and diagnostics may go undeveloped due to uncertain regulatory and reimbursement processes, among other reasons.

(7) In addition, there is reason to believe that potential treatments with tremendous value to patients are never developed or are discontinued during research and development due to insufficiencies in the intellectual property system.

(8) It is in the public interest to address the hurdles that may be precluding new treatments from reaching patients and to remove the disincentives for the development of therapies for these unmet needs.

SEC. 4. DEFINITIONS.

In this Act:

(1) The term "biological product" has the meaning given to that term in section 351 of the Public Health Service Act (42 U.S.C. 262).

(2) The term "drug" has the meaning given to that term in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).

(3) The term "medicine" means a biological product or a drug.

(4) The term "Secretary" means the Secretary of Health and Human Services.

[TITLE I--ADVANCING DIAGNOSTICS FOR PATIENTS – OMITTED]

TITLE II--CAPTURING LOST OPPORTUNITIES FOR PATIENTS

SEC. 201. DORMANT THERAPIES.

(a) Designation as Dormant Therapy.--The Secretary shall designate a medicine as a dormant therapy if—

(1) the sponsor of the medicine submits a request for such designation meeting the requirements under subsection (b), and the request has not been withdrawn under subsection (d)(1); and

(2) the Secretary determines that—

(A) the medicine is being investigated or is intended to be investigated for an indication to address one or more unmet medical needs;

(B) a suitable clinical plan for such investigations of the medicine has been developed by the sponsor;

(C) the sponsor intends to file an application pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) or section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) for approval or licensing of the medicine for an indication described in subparagraph (A); and

(D) the request for designation was made on or before the date of submission of any application under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262) for the approval or licensure of commercial marketing or use of a medicine that in the case of a drug shares an active moiety that is the same as, and in the case of a biologic contains an active moiety that is highly similar to, an active moiety in the medicine for which designation is being requested.

(b) Requirements for Request for Designation as Dormant Therapy.--A request under subsection (a)(1) with respect to a medicine may only be made by the sponsor of the medicine and shall contain each of the following:

(1) A listing of all patents and applications for patents under which the sponsor has rights and that may be reasonably construed to provide protection for the medicine.

(2) A waiver of patent rights to the extent required under subsection (c) to take effect, if at all, as provided under subsection (c)(3).

(3) Such additional information as the Secretary may require by regulation in order to determine eligibility for designation under subsection (a).

(c) Waiver of Patent Rights Expiring After the Protection Period

(1) Patent waiver.--

(A) In general.--Subject to subparagraph (B), the request under this subsection shall include a waiver of the right to enforce or otherwise assert any patent described in subsection (b)(1) (or any patent issued on the basis of an application described in subsection (b)(1)), which may expire after the end of the protection period for the dormant therapy, against any applicable product described in paragraph (2). The waiver shall be made by the owner of the patent or application for patent, as the case may be.

(B) Limitations on patent waiver.--Any patent waiver provided pursuant to this section, should it become effective—

(i) shall have no effect during the protection period for the medicine to which the waiver relates; and

(ii) shall have no effect with respect to the subject matter of a claimed invention in a patent that does not provide any protection for such medicine with respect to an applicable product described in paragraph (2).

(2) Applicable products described.--An applicable product is described in this paragraph only if—

(A) it is approved or licensed pursuant to an application that—

(i) is filed under section 505(b)(2) or 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(2), (j)) or section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)); and

(ii) references or otherwise relies upon the approval or licensure of the dormant therapy to which the waiver relates; and

(B) the approval of the product occurs after the expiration of the protection period applicable to the medicine to which the request under subsection (a)(1) relates.

(3) Effective date of waiver.--A waiver under subsection

(b)(2) with respect to a patent shall take effect, if at all, on the date the Director publishes the notice required under subsection (e)(2)(F) relating to the patent.

(d) Withdrawal of Request for Designation, Revocation by the Secretary.—

(1) In general.--The sponsor of a medicine may withdraw a request for designation under subsection (a)(1) with respect to a medicine unless the medicine has been approved or licensed under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262). The Secretary shall deny a designation request or revoke any designation granted if at any time the Secretary finds that the sponsor is not in compliance with subsections (c)(1) and (g)(1).

(2) Effects of withdrawal of request or revocation of designation.--If the sponsor of a medicine withdraws a request under subsection (b) or the Secretary denies a designation request or revokes a designation with respect to the medicine—

(A) any patent waiver submitted under this section with respect to the medicine, but not yet effective, is canceled and deemed a nullity;

(B) any patent waiver that has taken effect under this section with respect to the medicine shall remain in effect;

(C) any patent term extension granted by the Director under subsection (e)(2) with respect to the medicine shall be canceled, except that the Director shall maintain the patent term extension for one patent, to be selected by the sponsor of the medicine, for the period of extension that would have been applicable under section 156 of title 35, United States Code; and

(D) the designation, if made, otherwise shall be treated as never having been requested or made or having effect.

(3) Basis for revocation.--The Secretary may revoke a designation made under subsection (a), but only based upon a finding by the Secretary under paragraph (1).

(e) Guaranteed Protections for Dormant Therapies.—

(1) Applications filed during the protection period.--

During the protection period for a dormant therapy, notwithstanding any other provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) or the Public Health Service Act (42 U.S.C. 201 et seq.)—

(A) absent a right of reference from the holder of such approved application for the dormant therapy, the Secretary shall not approve an application filed pursuant to section 505(b)(2) or section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(2), (j)) or section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)) referencing or otherwise relying on the approval or licensure of the dormant therapy;

(B) the Secretary shall not approve—

(i) an application filed pursuant to such section 505(b)(2) or 505(j) that references or otherwise relies on the approval or licensure of a medicine that is not the dormant therapy, was approved subsequent to the approval of the dormant therapy, and contains the same active moiety as the active moiety in the dormant therapy (or if the dormant therapy contains more than one active moiety, all of the active moieties are the same); or

(ii) an application filed pursuant to such section 351(k) that references or otherwise relies on the approval or licensure of a medicine that is not the dormant therapy, was approved subsequent to the approval or licensure of the dormant therapy, and contains an active moiety that is highly similar to the active moiety in the dormant therapy (or if the dormant therapy contains more than one active moiety, all of the active moieties are highly similar); and

(C) the Secretary shall not approve an application filed pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)) for a drug that contains the same active moiety as the active moiety in the dormant therapy (or if the dormant therapy contains more than one active moiety, all of the active moieties are the same), or an application filed pursuant to section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) for a biological product that contains an active moiety that is highly similar

to the active moiety in the dormant therapy (or if the dormant therapy contains more than one active moiety, all of the active moieties are highly similar), unless—

(i) the information provided to support approval of such application is comparable in scope and extent, including with respect to design and extent of preclinical and clinical testing, to the information provided to support approval of the application for the dormant therapy under section 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(b)) or section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)); and

(ii) if such clinical testing had not commenced before the approval of the application for the dormant therapy, the clinical testing establishes clinical superiority in the form of a significant therapeutic advantage over and above that provided by the dormant therapy in one or more of the following ways:

(I) Greater effectiveness on a clinically meaningful endpoint.

(II) Greater safety in a substantial portion of the target populations.

(III) Where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

(2) Patent term alignment with data package protection period.—

(A) In general.--Notwithstanding any provision of title 35, United States Code, a sponsor of a medicine designated as a dormant therapy under subsection (a)(1), upon the approval or licensure thereof under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (42 U.S.C. 262), and in lieu of filing a patent term extension application under section 156(d) of such title 35, shall be entitled to patent term

extensions in accordance with this paragraph.

(B) Submission of final listing of patents and applications for patents following approval.—

(i) Submission.--The sponsor of the dormant therapy, within a period to be set by the Director of not less than 2 months beginning on the date the Secretary approves or licenses the dormant therapy, shall submit to the Director—

(I) the listing of patents and applications for patents provided to the Secretary under subsection (b)(1);

(II) any revisions to such listing as may be required for compliance with subsection (b)(1); and

(III) any documentation the Director may require from the patentee or patent applicant (as the case may be) of the waiver of patent rights required under subsection (b)(2).

(ii) Failure to provide sufficient documentation of waiver.--If the Director determines that the sponsor has not complied with the waiver requirements under subsection (c), after providing the sponsor the opportunity to remedy any insufficiency, the Director shall so notify the Secretary that the patent waiver requirements for designation have not been satisfied.

(C) Extension of patents.—

(i) In general.--Unless the Director has notified the Secretary of a determination under subparagraph (B)(ii), for each patent identified in a submission pursuant to subparagraph (B)(i), and for each patent issuing based upon an application for patent so identified, the Director shall, within the 3-month period beginning on the date of the submission, extend the patent to expire at the end of the protection period for the dormant therapy, if the patent would otherwise expire before the end of the protection period. If the Director has so notified the Secretary under

subparagraph (B)(ii), the Director shall extend one such patent, selected by the sponsor, for the period that would have been applicable had an application for extension been filed under section 156 of title 35, United States Code, with respect to such patent.

(ii) Application of certain provisions.-- During the period of an extension under clause (i)—

(I) the rights under the patent shall be limited in the manner provided under section 156(b) of title 35, United States Code; and

(II) the terms "product" and "approved product" in such section 156(b) shall be deemed to include forms of the active moiety of the dormant therapy and highly similar active moieties that might be approved by the Secretary based upon an application filed under section 505(b)(2) or 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(2), (j)) or under section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)) that references or otherwise relies upon the dormant therapy.

(D) Interim patent extensions.--Notwithstanding any provision of title 35, United States Code, with respect to any patent listed (or patent issuing on an application listed) under subsection (b)(1) that would otherwise expire before the sponsor could make a submission under subparagraph (B), the Director, upon application of the patentee, shall grant to the patentee an interim extension of such patent, subject to the limitations in section 156(d)(5)(F) of such title 35, for such period as may be necessary to permit the sponsor to submit the listing under subparagraph (B) and, if the patent is therein listed, to extend the patent as provided under subparagraph (C). The Director may require, for any patent extended under this subparagraph, that the sponsor of the dormant therapy to which the patent relates provide periodic certifications that development of the dormant therapy is continuing. The Director may terminate any interim extension for which a required certification has not

been made.

(E) Notice of extension.--For each patent that is extended under this paragraph, the Director shall publish a notice of such extension and issue a certificate of extension described in section 156(e)(1) of title 35, United States Code.

(F) Notice of waiver.--For each patent identified in a submission under subparagraph (B)(i), and each patent issuing based upon an application for patent so identified, that expires after the end of the protection period for the dormant therapy, the Director shall publish a notice that the patent is subject to the limited waiver of the right to enforce described in subsection (c)(1).

(f) Certain FDA Protections Inapplicable.--If a medicine has been designated as a dormant therapy under subsection (a), the protections otherwise applicable with respect to such medicine under sections 505A, 505E, and 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a, 355f, 360cc) shall not apply. The preceding sentence shall not be construed to affect any protections applicable with respect to a drug, including a drug designated under section 526 of such Act (21 U.S.C. 360bb) for a rare disease or condition, under provisions other than such sections 505A, 505E, and 527.

(g) Development Certifications.—

(1) In general.--The Secretary shall require that the sponsor of a dormant therapy provide periodic certifications that development of the dormant therapy to address one or more unmet medical needs is continuing.

(2) Determination of noncompliance.--If the Secretary concludes that the sponsor has not complied with paragraph (1), after providing the sponsor the opportunity to remedy any insufficiency, the Secretary shall, for purposes of subsection (d)(1), determine that the sponsor is not in compliance with the certification requirement under paragraph (1).

(h) Collaboration.--Nothing in this section shall be construed as preventing a sponsor from collaborating with other entities in developing a dormant therapy or applying for a dormant therapy designation.

(i) Definitions.--For purposes of this section:

(1) The term ``address one or more unmet medical needs'' refers to--

(A) addressing a need for medicines for the treatment of one or more life-threatening or other serious diseases or conditions for which no therapy exists; or

(B) if one or more therapies are available for the treatment of such a disease or condition, demonstrating through clinical investigations--

(i) one or more improved effects on serious outcomes of the disease or condition that are affected by alternative therapies, such as superiority of the medicine used alone or in combination with other therapies in an active controlled trial assessing an endpoint reflecting serious morbidity;

(ii) one or more effects on serious outcomes of the disease or condition not known to be affected by alternative therapies, such as progressive disability in multiple sclerosis when alternative therapies have shown an effect on exacerbations but have not shown an effect on progressive disability;

(iii) an ability--

(I) to provide one or more benefits in patients who are unable to tolerate or are unresponsive to alternative therapies, such as an antipsychotic agent that is effective in people failing standard therapy; or

(II) to be used effectively in combination with other critical agents that cannot be combined with alternative therapies;

(iv) an ability to provide one or more benefits similar to those of alternative therapies while—

(I) avoiding serious toxicity that is present in alternative therapies; or

(II) avoiding less serious toxicity that is common in alternative therapies and causes discontinuation of treatment

of a life-threatening or serious disease; or

(v) an ability to provide one or more benefits similar to those of alternative therapies but with improvement in some factor, such as compliance or convenience, that is shown to lead to improved effects on serious outcomes.

(2) The term "Director" means the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office.

(3) The term "dormant therapy" means a medicine designated as a dormant therapy under subsection (a).

(4) The term "protection period" for a dormant therapy means the period that--

(A) begins on the date on which the Secretary first approves an application under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) or section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) for the dormant therapy for any indication; and

(B) ends on the date that is 15 years after the date of such approval.

(5) The term "sponsor" for a dormant therapy is the person who takes responsibility for the designation and development of the dormant therapy. The sponsor may be a single entity or an entity collaborating with one or more other entities.

SEC. 202. STUDY REGARDING NEW INDICATIONS FOR EXISTING THERAPIES.

Not later than one year after the date of the enactment of this Act, the Secretary shall enter into an arrangement with the Institute of Medicine (or, if the Institute declines, another appropriate entity)--

(1) to conduct a study on intellectual property laws and their impact on therapy and diagnostic development in order to formulate recommendations on how to facilitate the clinical evaluation and development of therapies currently available on the market for new potential indications; and

(2) not later than 18 months after such date of the enactment, to submit a report to the Secretary and the Congress containing the results of such study.