

Trust, constraints and the counterfactual: Reframing the political economy of new drugs

Brita Anna Kollontai Pekarsky
Discipline of Public Health,
School of Population Health and Clinical Practice

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Abbreviations

AUSFTA	Australia–U.S. Free Trade Agreement
aICER	Average Incremental Cost Effectiveness Ratio
CABG	Coronary Artery Bypass Graft
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CEA_i	Cost Effectiveness Analysis applied in conjunction with a threshold of i
COAG	Council of Australian Governments
CSIRO	Commonwealth Scientific and Industrial Research Organization
DTM	Decision Theoretic Model
EBM	Evidence Based Medicine
EVCI	Economic Value of Clinical Innovation
FCUSS	Finance Committee of the US Senate
FDA	Food and Drug Administration
<i>FPP</i>	Firm's preferred price (per effect of a new drug)
GDP	Gross Domestic Product
GTM	Game Theoretic Model
HTA/CEA	Health Technology Assessment/Cost Effectiveness Analysis
ICER	Incremental Cost Effectiveness Ratio
<i>IMER</i>	Incremental Manufacturing Cost Effectiveness Ratio
IMS Health	Not an abbreviation but the name of a pharmaceutical data company
<i>IPER</i>	Incremental Price Effectiveness Ratio
ITA	International Trade Administration (US Government)
maxWTP	maximum Willingness To Pay
MRI	Magnetic Resonance Imaging
NB	Net Benefit
NICE	National Institute for Health and Clinical Excellence
NME	New Molecular Entity
NPV	Net Present Value
npvPH	Net present value of the population's health
OECD	Organisation for Economic Cooperation and Development
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PEA	Price Effectiveness Analysis
PEND	Political Economy of New Drugs
Pharma	The pharmaceutical industry
PhRMA	Pharmaceutical Researcher and Manufacturers of America
<i>PPP</i>	Purchaser's Preferred Price
QALY	Quality Adjusted Life Year
R&D	Research and Development
RCT	Randomised Controlled Trial
TGA	Therapeutic Goods Administration
WHO	World Health Organisation

Glossaries

Table 1 Glossary of Characters

Character	Definition	Reference
Firm	The capitalised “Firm” refers to a player in a Game. It is introduced in Game 1, Chapter 8 and it features in Games 2 and 3 in Chapters 9 and 10 respectively. It is capitalised, as is the convention in Game theory models. It has specific production functions and markets.	First use of “Firm” is Section 3.2 Examples of published pharma-economic games p. 116
firm	A firm with a small “f” is a pharmaceutical firm with no specific cost function who participates in the reimbursement process, invests in R&D and lobbies for higher prices. Its objective function is profit maximisation.	
Institution	The capitalised “Institution” refers to a specific institution that is a player in a Game. In these Games the Institution needs to consider how to respond to a threat from Pharma or a specific Firm. It has specific rules it must play by.	First use of “Institution” is in Game 1, Chapter 8, p. 112
institution	And institution with a small “i” is the collective term for the regulators involved in decisions about new drugs. The institutions of interest in this thesis are those that work in countries that use cost effectiveness analysis to make decisions about the reimbursement of new drugs, have universal health care schemes and constrained budgets.	The country such an institution works in is described in Section 2.1 p. 21
Reimburser	The Reimburser is the key character in this thesis. She is not an economist and not a clinician. She is bureaucrat who works with a clear objective function: to maximise the health gains possible from this and future budgets.	First use of Reimburser and Health Economic Adviser is in Chapter 3 p. 45
Health Economic Adviser	The Health Economic Adviser is the second character in this thesis. His task is to take the problems presented to him by the Reimburser and apply economic theory to solve them.	
Pharma	Pharma is the name given to the pharmaceutical industry, particularly those firms that invests in R&D.	
Displacer	The Displacer’s job description is to “find savings” in order to allow for the additional costs of programs such as the drug budget to be financed. He may or may not be able to find the least cost effective of existing programs and if he does he cannot always displace them. In most cases, he cannot displace patented health technologies.	The Displacer’s first appearance is in Chapter 6, p. 98.
Social Decision Maker	Drummond et al (2005) refer to three types of Analysts: A, B and C. Analyst C takes the position that the role of the economic analyst is to provide information on a “wide range of costs and consequences and present them in a way that helps health care decision makers form a better judgement”. (p. 18) The Social Decision Maker referred to in this thesis is the person in receipt of this information. He is not an economist. He is probably a clinician. He may have a preference for method of production, specifically, he may prefer to use a new drug rather than an existing drug, even if it is no more effective, because he values “newness”.	The Social Decision Maker is introduced in the Conclusion Section 3.3 p. 190

Table 2 Glossary of Phrases

Phrases	Definition
Universal health care	The term universal health care is used to distinguish between the health care schemes in countries such as the US and other developed countries such as Canada, Australia, New Zealand, England, Scotland, Denmark, Sweden, Finland, Norway and the Netherlands. The latter countries have not achieved equitable access to a minimum level of care for all patients and significant disparities in utilisation and health outcomes remain. In Australia, the gap in access to health care for Indigenous Australian compared to non-Indigenous Australians contributes to the significant 20 year gap in life expectancy at birth for males.
New drug price	New drug price refers to the phenomena of new drug price as the focus of heated debate. It refers to all new drugs, not a specific new drug.
Political economy of new drugs	The political economy of new drugs (PEND) is the economic expression of the heated debate about how the surplus associated with a new drug’s innovation should be allocated across consumers, institutional purchasers and firms via the price mechanisms.
Policy narrative	The policy narrative is the story that surrounds the development and implementation of a policy, such as how to regulate the price of new drugs. It could be a simple cause and effect narrative and may or may not make reference to evidence.
Evidence based policy narrative	The evidence based narrative is a term I use to describe a policy narrative that is populated by multiple references to empirical evidence but not evidence that justifies the actual policy choice. For example, reference to the burden of disease associated with a condition to justify a policy to screen for a condition, with no reference to the evidence of the effectiveness of that program in reducing that burden of disease.
New drug New NME	The new drug or new NME has recently been approved for prescribing by the FDA or TGA and now prices are being negotiated. Evidence of incremental cost and effect are available.
Future drug Future NME	The future drug is one that has not yet completed phase 3 trials or the molecule has not even been discovered. Evidence of incremental cost and effect is not available.
Future population’s health	One of the objectives of the conventional political economy of new drugs is to identify the health of a future population with or without additional future drugs. Of course it is by and large today’s population, just older, and with different medical technologies.
Present value of population’s future health	The present value of the population’s future health is the PV of expected life time health of a population in the future – not just the health in one year.
Net present value population’s health	This is the previous concept less the loss in health effects today as a consequence of higher prices today and hence less health today.

Table 3 Glossary of prices and costs in price effectiveness analysis

<i>FPP</i>	The firm’s preferred price is the price that the firm offers a new drug at and also a price that the firm justifies as the price that should be used.
<i>PPP</i>	The purchaser’s preferred price is the price that a purchaser believes maximises the objectives, whatever these are. The purchaser might be making a “mistake”
<i>IPER, f</i>	The incremental price effectiveness ratio is arithmetically identical to the ICER but price is recognised as endogenous and a function of the choice of the decision threshold rather than as exogenous.

$IMER, c$	The incremental cost to the firm of producing the incremental health effect compared to the previous drug.
$I\pi ER$	The incremental economic rent to the firm on the incremental health effect.

Table 4 Notation and parameters

Parameter	Description
β_c	The health shadow price: the aICER of the most cost effective strategy to increase the population's health where this strategy will typically include a combination of financing and expenditure. It is a function of the economic context, c , which includes the amount of resources that need to be displaced in order to finance a new drug, the prevailing prices of inputs and the existing degree of inefficiency in the health budget.
n	The aICER of the most cost effective program or technology in expansion or adoption.
m	The aICER of the most cost effective program or technology in contraction or disinvestment.
d	The aICER of the program or technology that is displaced to finance the additional costs of the new drug.
r	The conventionally measured rate of return on new drugs.
c	The $IMER$ in algebraic form. Can vary across drugs.
ΔL^P	The additional life years experienced by patients from a new drug or new drugs.
\mathcal{R}	The investment in R&D by the firm.
e	One alternative expression of return on R&D, incorporating the budget constraint.
f	The algebraic expression of the IPER at which the firm offers a new drug.
ω	The share of additional economic rent from higher prices that is allocated to new drug R&D.
H	The investment by public sector research groups I pharmaceutical R&D.
λ	The conventional shadow price of the budget constraint defined by relaxing the budget constraint by one unit.
ΔC^P	The incremental cost to the health budget of the new drug at the given price.
ΔE	The net increase in the health of the population due to any cause or combination of causes
The following are all net changes in health to a specific group of patients as a consequence of a specific action or strategy (two actions)	
ΔE^A	(A) reallocation from least to most cost effective of existing programs.
ΔE^D	(D) displacing the program that
ΔE^M	(M) expanding or contracting the least cost effective program.
ΔE^N	(N) expanding or contracting the most cost effective program

Parameter	Description
ΔE^P	(P) from the adoption of a new drug
ΔE^R	(R) from the strategy of reimbursement (the net effect of the new drug and the services displaced to finance it.
ΔE^T	(T) the most cost effective alternative strategy to reimbursement.
$NEBh^R$	Net economic benefit of the decision to reimburse, expressed in health units.
$EVCI$	The economic value of clinical innovation
β_c^a	The health shadow price corresponding to the alternative strategy set which comprises all possible opportunities to reallocate.
β_c^v	As above but corresponding to all investment strategies.
μ	The parameter that defines the increased productivity of a program if there is an investment in improving its technical efficiency.
λ_e^B	The shadow price of the budget constrain (B) defined in expansion (e)
$\lambda_{e c}^B$	The shadow price of the budget constraint (B) defined in expansion (e), given previous contraction (c).
$CEAi$	Cost effective analysis applied to inform reimbursement decision, using a threshold of i to correspond to either a NB or an ICER metric
$ICERi$	The conventional ICER compared to a threshold of i
NBi	The conventional net benefit calculated using i
A	The best alternative strategy to reimbursement that is a reallocation (contraction of least cost effective to financing of most cost effective)
R	The strategy of Reimbursement, which comprises adoption and financing. (Not to be confused with \mathcal{R} , which is the amount invested into R&D)
T	The best alternative strategy to Reimbursement

Abstract

This thesis uses an applied game theoretic framework to address the following question: *What is the population health maximising decision threshold price for a new drug?* This threshold accommodates: strategic behaviour; inefficiencies in the health care system; budget constraints; suboptimality of displacement to finance the additional cost of new drugs; failure of markets to develop evidence of unpatented services; and the relationship between drug price and future innovation and health.

A framework (price effectiveness analysis, PEA) for the analysis of the reimbursement process as a strategic interaction is proposed and tested. PEA uses the results of cost effectiveness analyses as inputs in a model that derives the population health outcomes of reimbursement: the net health effect of i) adoption of the new drug; and ii) displacement to finance its additional costs.

The first result is that the health shadow price, β_c , is the population health maximising decision threshold, under the conditions of a fixed and allocatively inefficient budget:

$$\beta_c = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

where n is the most cost effective of existing programs in expansion or adoption; m is the least cost effective in contraction, and d is the average ICER of services displaced to finance the additional costs of the new drug at the offer price. Allocative inefficiency is characterised by $m-n$ and suboptimality of displacement by $m-d$.

The second result is that there are restrictive conditions under which there is an incentive for a rational institution to pay a price above β_c to take into account the relationship between price and future innovation. However, if these conditions are met, the firm will prefer to raise funds through the capital market rather than contract with an institution.

Currently, reimbursing institutions provide an incentive to develop evidence of the cost and effect of patented health technologies. Adopting β_c as the new drug decision threshold places a value on evidence of the least and most cost effective services, regardless of whether they are being proposed for reimbursement. Hence, the market's failure to provide evidence of unpatentable and unpatented health services is addressed and the health gains possible from a budget increased.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Brita Anna Kollontai Pekarsky and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Brita Anna Kollontai Pekarsky

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Dedications

Professor Gavin Mooney

1943 - 2012

tietäjä

Dr. John A Vernon

1968 - 2012

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In 1980 I realised after one month at University of Adelaide that engineering was not where my heart lay, despite my passion for maths, computers and optimisation problems. **Bob Wallace** was a good friend and one of Australia's first academic health economists. He suggested I might like economics and he was right; economics was a perfect fit for me. For the next ten years Bob discussed economics with me on afternoons too numerous to count. When he retired, he gave me his copies of Penguin Readings in Health Economics and Cost Benefit Analysis (old school and very cool). I referred to these texts many times during this PhD.

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Platona, Prof. Michael Coory, Prof. Lloyd Sansom, Prof. Jonathan Craig, Prof. Jenny Doust and Mr Andrew Bruce.

Prof. Fabrice Collard listened to me patiently one morning in 2009 when I told him that after many months of trying I still could not solve this problem of finding an optimum price per health effect for a new drug. I explained to him that I had tried every model I could think of and tried every constraint I could place in these models. He listened while I described the economic problem to him. He asked me three questions and then he said: this is a game theoretic problem, not a non-strategic model. The pieces started falling into place that morning and although it took another two years before the models were completed, that conversation was critical to the direction of my research and the substance of this PhD. Well diagnosed Prof. Collard.

Dr Virginie Henderson was my PhD Microeconomics teacher for two semesters in 2007 and then a co-supervisor on my PhD from 2009. She told me to read Debreu (1959) - she was right, it is a profound and beautiful book. She made me laugh when I wanted to cry. She taught me about maths as a tool for telling economic stories. She made me look with fresh eyes at the fundamentals of microeconomics ("prices are beautiful - they capture so much information"). And look for the first time at the fundamentals of game theory. The title of "co-supervisor" understates her commitment to the supervision of my PhD and her guidance in the development of the three games that are integral to my thesis.

Prof. Jon Karnon very kindly agreed to be my principal supervisor in August 2009. Jon really knows pharmaco-economic simulations. He also has a great understanding of the economics of health care. Jon is respectful, rigorous in his thinking, well-read, curious, funny, reliable, firm, direct, honest, and knowledgeable; the perfect principal supervisor and mentor. It is certain that this thesis would not have been completed without his ongoing supervision.

Thanks also to my friends and colleagues who provided support, clarity, intellectual stimulation, laughter and encouragement: Ruth Talbot-Stokes, Annie Murray, Janet Spouse, Xin Deng, Kathy Mott, John Pilla, Peter Tyler, Michelle Carse, Eleni Labadas, Clair Mathews, Scott Clarke, Justine Burke, Paul Yerrell, Julie Way, Yvette Roe, Rebecca O'Shea, Larelle Veldhoen, Chilandu Mukuka and Jan Southgate. Special thanks to Shane Carr. Thanks also to Dr. Michael Sorich, who is an endless source of interesting ideas, debate and pertinent questions.

And many thanks to my dear family: Lucy, Don, Swetlana, Sunjay, Paul, Margaret and Ivan.

butter the edges of the bread first and the middle will look after itself

"No love lost"

Warsaw (Joy Division), Salford, 1977

(Trust)

"You want it all ... but you can't have it."

Faith No More, Sausalito, 1989

(Constraints)

"America's health care system is second only to Japan, Canada, Sweden, Great Britain, well ... all of Europe. But you can thank your lucky stars we don't live in Paraguay!"

Homer Simpson, Springfield, 1992

(The Counterfactual)

Benjamin Franklin once remarked, "In this world nothing can be said to be certain, except death and taxes." Spokespersons for the pharmaceutical industry might be inclined to argue that the benefit-generating capability of prescription drugs also belongs in this exclusive category. They could make a compelling case: *recent studies suggest* that pharmaceutical products increase longevity, improve quality of life, and often result in medical cost savings.

C. Giaccotto, R. Santerre and J.A. Vernon, 2005

(The political economy of new drugs)

Chapter 1: Introduction

1 Research question

At a time when evidence based medicine increasingly dominates decision making and health budgets are tightened, how should institutions respond to the following ostensibly evidence based claim?

Lowering the price of a new drug below the firm's preferred price will lead to suboptimal investments in R&D and lower health for the population than otherwise possible.

For institutions that use economic evaluation and decision thresholds to guide decisions about new drugs, this problem comes down to the following question:

What should the new drug decision threshold be, given the dynamic efficiency implications of the relationship between new drug price and the health benefits of future drugs?

Unsurprisingly, the debate surrounding this question is highly charged. “New drug price”¹ impacts both health and profits. Hence, this thesis starts with the economic expression of the debate; the political economy of new drugs. The active participants of this political economy include academics, industry, regulators, consumers and global organisations such as the World Health Organisation (WHO) and the Organisation for Economic Cooperation and Development (OECD).

Comanor observed in 1986 that the political economy of the pharmaceutical industry has shaped economists' research agenda since the Kefauver Committee of 1959.² He also noted that changes in the research agenda were driven by changes in the political debate. Comanor found that the one research question common to the disparate literature was the ratio of investment in R&D to the social return on this investment. However, he also found there was no methodologically sound estimate of this ratio at the time of his publication (1986). Comanor observed that the antagonistic nature of the political debate is reflected in two distinct positions held by economists: i) unregulated monopoly power by firms is essential to ensure there is sufficient innovation for the population; and ii) regulate to ensure that social welfare gains from pharmaceuticals are maximised. And finally he noted that the then (1986) current political economy and hence research agenda excluded one possible outcome of more competition (lower prices) today, namely, improved social welfare tomorrow. Hence, the trade-off that characterises the political economy might not exist under all regulatory structures; it could be possible to have more competition **and** more innovation and health tomorrow.

This thesis's research question is inspired by these observations by Comanor. I start by reframing the political economy in a way that will allow the economic research to find a solution to the choice of a decision threshold that is population health maximising, and takes into account the relationship between price and innovation. This alternative to the conventional political economy is framed from the perspective of an institution that is required to select and then enforce a decision threshold price

¹ Throughout this thesis I use the term “new drug price” in the context of new drug prices generally. If a specific price is referred to I use the term “the price of the new drug” or “the new drug's price”. See Glossary of Phrases Table 2 p. 11.

² Kefauver was a US Congressman then Senator from 1939 to his death in 1963. He chaired a number of significant US Senate Committees, including a 1950 committee on organised crime. The Kefauver Committee of 1959 was motivated by the “excess profits” of the US pharmaceutical industry. It was seen as an antitrust (market power) Committee rather than a drug safety and quality regulation Committee. His work on this Committee resulted in the Kefauver-Harris Drug Act of 1962. This committee explored the nature and consequences of market power and rent seeking in the pharmaceutical industry. Amongst other things, it challenged the pharmaceutical industry's payments to the American Medical Association in terms of the implications this would have for objective scientific reporting of new drugs. For further information, a good place for an economist to start is Comanor (1966).

that maximises the net present value of the population's health (npvPH). It starts with the following characterisation of the debate:

*Higher prices today mean increased economic rent for Pharma otherwise firms would not lobby for them. It is in Pharma's interest to protect and seek these economic rents. Whether higher prices and more R&D today increase future health remains an empirical question. If higher prices also mean a higher **net** present value of the population's health, then it is in the institution's interest to increase prices. Given the institution's objectives, the most effective strategy Pharma can use to protect these rents is "**the Threat**": **lowering prices is against the interest of health funders because it will reduce a population's future health.***

The research question is:

How should rational institutions respond to the Threat?

(Where a rational response is one that is consistent with a given institution's stated objective function, whatever this is.)

This introduction places this research question in the context of current evidence and research, by addressing the following:

- 1) Is it plausible that the Threat exists and that it influences the price of new drugs?
- 2) Is there rigorous empirical evidence that suggests that lower drug prices will result in less future health?
- 3) Is there agreement on a decision threshold for new drugs that accommodates characteristics of the health budget such as allocative and technical inefficiency?

Then, the method this thesis uses to explore the research question is summarised and the plan of the thesis is outlined.

2 Is it plausible that the Threat exists and influences the price of new drugs?

2.1 What is a Threat?

The claim by the pharmaceutical industry that lower prices today will make the population worse off is appropriately characterised as a Threat. In game theory, a threat is simply a claim by one player about his or her future behaviour, conditional on the decisions made by another player, today.³ This claim could be credible or, quite simply, a lie. The important point is that a threat is telling one player, who is making a decision, to take into account the likely response by another player. In the case of the price of new drugs, the industry uses a range of threats to provide an incentive for an institution not to lower prices in order to make savings today. For example, a firm could say: if your country lowers prices, we will not invest in innovation and there will be no more new drugs in the future. In game theory the issue is, how should the institution respond to this threat, given what is known about the firm and its motives.

The Threat is likely to be operating throughout the OECD, including the US. Of particular interest in this study is the influence that the Threat has in countries that: i) have universal health care; ii) have budget constraints; iii) have a fund holder with the broad objective of maximising a population's

³ See for example, Gibbons (1992), p. 56

health and welfare;⁴ iv) inform drug reimbursement decisions with HTA/CEA;⁵ and v) use an explicit or implicit decision threshold price in a new drug adoption decision where this threshold is expressed as an average incremental cost per unit incremental effect (ICER).

It is possible that the Threat is present (either explicitly or implicitly) each time an institution decides whether to reimburse a drug that has a high ICER compared to the institution's decision threshold. If this does occur in the private domain, it cannot be used as evidence in an academic study. The Threat does dominate international debate about drug price regulation, and this debate is largely in the public domain. The case of the Australia–U.S. Free Trade Agreement (AUSFTA) negotiations is an example.

2.2 A public domain expression of this threat: the Australian US FTA

In 2004, the negotiations between Australia and the US that resulted in the AUSFTA were almost derailed when the Australian practice of regulating the price of pharmaceuticals was challenged by the US government, which argued that the practice was against the principles of free trade.⁶ The US government argued that the Australian practice of using cost effectiveness analysis (CEA) to inform reimbursement decisions resulted in lower prices in Australia than in the US. Australia was therefore a free-rider on the significant investments made by US consumers into pharmaceutical R&D via higher drug prices. As a consequence of OECD-wide policies, including Australia's policies, US consumers had to pay higher prices for the same drugs in order that firms can finance pharmaceutical R&D; R&D that Australians can benefit from. The records of the Congress and US Senate Committees are rich with references to this debate, in particular, the 204 page document that is the record of a joint hearing of two subcommittees of the Finance Committee of the US Senate (FCUSS). Consider the opening remarks of this Joint Hearing, made by the Chair of the Health Care Subcommittee:

I have long thought that the prescription drug price controls employed by foreign countries amount to an unfair trade practice because they block the access of U.S. product to foreign markets, but worse is that the price controls impose unacceptable burdens on the United States as our consumers end up paying the bulk of the cost for research and development, probably up to 60 percent more for most prescription drugs compared to the citizens and countries that use price controls. Hon. Jon Kyl, U.S. Senator From Arizona, Chairman, Subcommittee On Health Care (Finance Committee US Senate 2004)

⁴ Of course this is a simplistic definition of the objective of a health care system. The main point is that this system does not explicitly value the following as part of the drug reimbursement process: the technology that is used to deliver the health gains. That is, whatever it is that the health system values, it is irrelevant to the Reimburser's decision whether the outcome is obtained using the newest drug or conventional old tech therapies. Specifically, this excludes the possibility that a clinical or institutional decision maker will be prepared to pay for "novelty". The possibility that this is the case is raised in the conclusion.

⁵ Relative to the early adopters (Australia and Canada) some European countries are late adopters of routine use of economic evaluation to inform drug decisions (post 2000), and the US is still to adopt this practice. How early did Australia and Canada start using economic evaluation of pharmaceuticals? From the 1994 first edition of the Canadian Economic Evaluation Guidelines: *"Australia was the first country to develop and implement guidelines for the economic evaluation of pharmaceuticals. Draft guidelines were released in 1990, revised in 1992, and are currently going through the process of second revision. In Canada, the process for developing these guidelines began when the Province of Ontario issued draft guidelines for comment in the Fall of 1991. During 1992 it was determined that it would be useful to develop a set of Canadian guidelines, that each Province could adopt, with or without modifications, as they saw fit."* (Canadian Coordinating Office for Health Technology Assessment 1994)

⁶ A summary of the issues is contained in Harvey et al. (2004)

And the opening remarks by the Chairman of the International Trade subcommittee reveal a concern for "the folks in Australia" should they reduce their control on pharmaceutical prices, but that this was a requirement of an AUSFTA that the US was not prepared to compromise on:

So I think that price setting is sort of, in a way, similar to a tariff that is put on the goods. It has a great impact on what happens here. To deal with these, Congress passed the Trade Act of 2002, which established a primary objective of tightening the regulatory practices that create market distortions and effectively deny U.S. companies global access. As we know, the issue of regulatory practices relating to pharmaceuticals was one of the last items resolved in the recently completed Australian Free Trade Agreement negotiations. It is a sensitive issue for the folks in Australia, and I respect their concerns. But it is an issue that deserved to be on the table, and one that needs to be raised in future negotiations. Hon. Craig Thomas, a U.S. Senator from Wyoming, Chairman, Subcommittee On International Trade (Finance Committee US Senate 2004)

Not only was pharmaceutical price regulation characterised as anti-competitive and analogous to tariffs on imports, it was also argued to reduce incentives for innovation and hence reduce the number of new drugs. The US government argued that as a consequence of widespread price controls, the health of the OECD's population was less than what would otherwise be possible. At around the same time as the AUSFTA was being negotiated, a US government agency, the International Trade Administration (ITA), published a report on the implications for US consumers of the OECD countries' practice of price control of new drugs (ITA 2004). This study found that if all OECD countries (apart from the US) stopped regulating drug prices **and** stopped using monopsonist purchasing power there would be an additional three to four NMEs each year; a consequence that would have significant positive value to all OECD consumers.

The ITA study also revealed a view amongst US pharma-economists that the process of using a threshold price above which the drug could no longer be considered value for money was price control under another name and hence the policy can be classified as a trade restriction.

Cost-effectiveness reviews, called the "fourth hurdle requirements" by industry, are defined as government consideration of "factors other than safety, efficacy, and quality in approving new drugs for marketing or reimbursement." Although the schemes differ from country to country, the determination that a new medicine is not cost-effective or "medically necessary" can work much like price controls because the analysis can be performed in a way that makes clear that a price reduction will make the drug acceptable. (International Trade Administration 2004 p. 6)

2.3 The Threat exists and it is plausible that it influences decisions

The Threat was applied during AUSFTA trade negotiations. The Finance Committee of the US Senate, US Pharma and US government economists appeared to be almost unanimous in their public position that the Australian Pharmaceutical Benefits Scheme (PBS) and similar institutions are restricting free trade and that this is at a cost to the future health of, not only US, but all of the world's citizens. A notable exception amongst the US pharma-economic literature is Reinhardt's criticism of the Free Trade argument and the associated estimates of the benefits to the US and other countries of removing price controls.⁷ (Reinhardt 2007) It is plausible that this Threat influenced the result of these

⁷ A second important exception was the statement by Prof. Gerard Anderson, of John Hopkins. His oral statement and the resultant discussion with the Joint Committee Hearing are both reproduced as Attachment 2. These excerpts capture the drama and intensity of the political economy of new drugs perfectly. And finally, Prof. Alan Sager from Boston School of Public Health gave a presentation in 2003 (around the same time) which summarises the issues regarding access from the position of the US. His set of slides "Three futures for the US pharmaceutical industry" are available at: www.sph.bu.edu Accessed 12-12-2011

negotiations, for example, by requiring that the AUSFTA include an additional annex that recognised the requirement for its pricing processes to recognise and reward pharmaceutical innovation.⁸

3 What is the evidence upon which this Threat is founded?

If there were unambiguous evidence that lowering a price below the firm's preferred price (*FPP*) would make a population worse off in terms of the npvPH, then an institution with the objective of maximising population health would prefer to price at the *FPP*. However, the question of whether such evidence exists, and its applicability to countries outside the US, is a contentious issue.

US pharma-economists have built a significant body of theoretical and empirical evidence that supports but rarely challenges the case for the *FPP* as the social welfare (and population health) maximising price.⁹ However this body of evidence is not straightforward to assess. For example, there are a number of ways in which this *FPP* is defined, including: i) the price that would occur in an unregulated unilateral monopoly market (International Trade Administration 2004); and ii) the maximum willingness to pay (maxWTP) for a health effect (Vernon, Goldberg et al. 2009). Furthermore, the theoretical and empirical analyses supporting the case for the *FPP* tend to assume that budgets are unconstrained, hence, the applicability of any results to countries that have fixed health budgets and alternatives other than pharmaceutical R&D to invest in improved future health is limited (See Chapter 3, Section 3, p. 48). Finally, the empirical studies that support the unregulated price often draw on private domain data bases that are costly to access, and hence the opportunity to analyse these data with models that specify health budgets as constrained (rather than uncapped) is limited.¹⁰ In summary, the empirical and theoretical evidence is not necessarily strong enough to support the case made by US pharma-economists, the US government and their agencies and Pharma.

4 What are the current options for the decision threshold?

4.1 Existing options for the decision threshold

If institutions wish to formally assess the *FPP*, then they would need to be compared against an alternative. Currently, there is no agreed purchaser preferred price (*PPP*) or decision threshold that could be compared to any given *FPP* in terms of its social welfare and health implications. Health economists have been debating the question of the choice of decision threshold price since 1992: for program adoption generally (Birch and Gafni 1992; Birch and Gafni 1993; Johannesson and Weinstein 1993); and for drugs specifically (Drummond 1992). Some institutions have claimed that there are no explicit thresholds, but reviews of their decisions seem to suggest otherwise (Devlin and Parkin 2004; George, Harris et al. 2001.). Around 2007, there was a shift away from support for the maxWTP, which was the preferred threshold of many health economists since 1993.^{11,12} (Culyer, McCabe et al. 2007; McCabe, Claxton et al. 2008)

⁸ See discussion of this issue in Chapter 4.

⁹ Not all US pharma-economists claim that existing evidence provides unambiguous support for the *FPP*. For example, Reinhardt (2007) and Comanor (1986) have critiqued the methods used in some pharma-economic studies.

¹⁰ See for example (Giacotto, Santerre et al. 2005) which accessed a data set from PhRMA that is not in the public domain.

¹¹ This preference for using the maxWTP as a threshold price (or "value for money" as a criterion) for adoption and reimbursement probably continues in many institutions. Since 1992 Birch and Gafni have pointed out that this strategy will not maximise a population's health from a given budget, unless the budget is sufficiently large to accommodate all programs that are value for money or that the budget continues to increase to accommodate these programs and technologies.

¹² The NICE Briefing paper for the Methods Working Party on the Cost Effectiveness Threshold provides a summary of the issues in 2007. Accessed 12-12-2011

One proposed alternative is a threshold of the average ICER of services displaced to finance the new drug, d (Sendi, Gafni et al. 2002). This threshold is likely to be sensitive to budgetary impact¹³ and minimises the risk that the reimbursement of new drugs results in a net reduction in the population's health. However, what if the threshold is revealed by institutions to be d and firms are strategic and price at this threshold? Then the net effect of ongoing displacement and new drug adoption on the population's health is zero; the new drug's innovation improves the health of a group of patients but there is no net gain in the population's health.

Such a result, pharmaceutical innovation being taken up, but having no net impact on a population's health, could be acceptable in a country that places a value on new technology adoption *per se*, independent of its impact on a population's health. Such a country could make claims such as: "Our country is the first to have all the latest medical technologies available for use by patients". However, if a country's primary rationale for new technology adoption is to improve the population's health, then research that found that new technologies are available rapidly, but that the population's health has not increased could lead that country to question their decision making.

4.2 The health shadow price as decision threshold

The research presented in this thesis proposes a new *PPP*: the health shadow price, β_c . To derive β_c , this research draws on a conventional CBA method of deriving a shadow price for an input (in this case a new drug) in the presence of market failure, by referencing the shadow price of the output (for which there is a market) (McKean 1972; Mishan and Quah 2007). This method can be summarised as defining the price of the input (without the market price) such that the decision maker is indifferent between adopting the strategy that includes that input and adopting the best alternative strategy, where all inputs have a market price. This conventional method is developed further in this thesis to accommodate a number of characteristics that economists would expect to find in a health sector, including:

- 1) suboptimal displacement (the services displaced to finance the additional costs of a new drug are not necessarily the least cost effective of current services); and
- 2) allocative and technical inefficiency in the health budget.

The result, β_c , is the ICER of a new drug, above which the population would be better off (the populations' health would be greater) if the institution chose the best alternative strategy, rather than the strategy of reimbursement. Improving the allocative or technical efficiency of the health budget is an alternative strategy considered in this thesis.

5 The framework for this research

5.1 Price effectiveness analysis

This thesis develops then applies a framework, Price Effectiveness Analysis (PEA) to address the research question. This framework accommodates strategic behaviour by both firms and institutions,

www.nice.org.uk/media/4A6/41/CostEffectivenessThresholdFinalPaperTabledAtWPMeeting5Sep3907KT.pdf

¹³ The budgetary impact is the net additional cost of adopting the new drug. The proposed threshold of d will be a function of budgetary impact if the cost per effect of displaced services changes as the amount of services displaced increases. This is in contrast to the most prominent option for the threshold k , the maximum willingness to pay for a health effect, which is exogenous to the state of the health budget.

in addition to the characteristics of the economic context as captured by β_c . The economic method used in this part of the research is applied game theory, which was selected for two reasons.

First, unlike decision theoretic models, game theoretic models can capture the consequence of more than one decision maker in the reimbursement process, for example both the firm and the institution, where these players (decision makers) act strategically. Acting strategically means that players consider the response of the other player when they make a decision such as choosing an offer price of a new drug. For example, a firm (which as a monopolist is a price maker) will consider whether or not an institution will reject a new drug at an offer price when it selects its offer price.

Second, a theoretical game, like most theoretical economics, is driven largely by making small changes to existing models, which might have very little relevance to the real world of health and economics. For example, consider a theoretically derived model that makes the following assumptions about the health sector: i) no budget constraints; ii) perfect and complete (public) information; iii) no strategic behaviour; iv) no failure in the market for evidence of the cost and effect of unpatented and unpatentable services; and v) economic efficiency. Conventionally, a piece of theoretical research would involve extending such a model by making small changes; for example, assuming that there is a budget constraint. However, the resultant adapted model would struggle to accommodate the characteristics of the health system that generate the very situations that are the subject of health economic research, in particular situations that arise because of the complexity of information in the health sector. In contrast, applied game theory draws its inspiration from the real world, not existing models, and the challenge is to generate models that capture vital real world characteristics. Therefore, game rather than decision theoretic models were used, and an applied rather than theoretic approach was used to develop these games.

5.2 The role of the narrative in the models and the research

The use of the narrative to capture the vital characteristics of an economic problem is a distinguishing characteristic of game theory. For example, the narrative of the Prisoner's Dilemma¹⁴ is reasonably well known, even if the application of economic theory to solve this game is not. This thesis also uses a narrative structure to develop models and concepts that capture an increasing number of the characteristics that influence the political economy of new drugs. This narrative takes the form of a series of problems that a Reimbursing in a hypothetical country has when she tries to select and then enforce a *PPP*. Each of the Chapters 3 to 11 start with the Reimbursing being presented with a specific dilemma, which is referred to as: The Reimbursing's Problem. The narrative uses three main characters (a Reimbursing, a Firm and a Health Economic Adviser) to set up, then explore, that Chapter's problem.

There are secondary cast members:

- 1) “**pharma**-economists”, who research and analyse the economics of the industry, pharmaceutical R&D and drug price; and
- 2) “**pharmaco**-economists”, who research and analyse the economics of the molecule, patients and the decision threshold.

There are also two key sectors:

- 1) “Pharma”, the pharmaceutical industry; and
- 2) “the Institution”, which is the broad group of government pharmaceutical decision makers, fund holders and regulators.

¹⁴ For a description of both the narrative and the associated economic model of the Prisoner's dilemma, see Gibbons (1992).

The Firm is a member of the former sector and the Reimburser of the latter. The narrative approach allows some of the debates and conversations that are common to drug reimbursement processes around the world - and often in the private domain - to be part of the games' narratives and the Reimburser's problems, without attributing specific actions or claims to any particular firm or regulator. The use of capitals to start terms such as "Firm" and "Institution" is necessary in the context of the three Games (Chapters 8 to 10). The use of capitals signifies it is a firm or institution with carefully specified characteristics, such as objective and cost functions and decision rules. The use of firm with a small "f" refers to any firm in the pharmaceutical industry. The use of capitals to refer to the Reimburser and the Health Economic Adviser is a literary (rather than methodological) device.

6 Summary of thesis

6.1 Six key concepts

The thesis develops and/or builds on six key concepts:

- 1) The political economy, as expressed via the policy narrative, is reshaped to identify additional research questions. This research agenda and the associated models are specified so as not to exclude any of the following outcomes of higher drug prices: an improvement, a reduction or no change in the present value of the population's future health.
- 2) The opportunity cost of a strategy in an institutional setting does not necessarily imply that the decision maker is physically choosing between these two strategies and their corresponding end state alternatives. Instead, it means that the decision maker is valuing all states of the world that could emerge under different allocations of resources. This definition is consistent with that used by Buchanan (2008).
- 3) Price effectiveness analysis is a method of assessing the decision to reimburse a new drug by testing the relationship between the price of the new drug and the population's health.
- 4) The strategy of reimbursement comprises the actions of adoption (substituting an existing with alternative therapy) and financing (displacing services or expanding the budget to fund the additional cost of the new drug).
- 5) The health shadow price, β_c , is:
 - a. the incremental cost per incremental health effects gained by the target patients
 - b. as a consequence of the strategy of reimbursing (adopting and financing) the new drug with clinical innovation ΔE and additional financial cost ΔC
 - c. such that the funder is indifferent between the strategy of reimbursement and the best alternative strategy (optimal adoption and displacement) available to the funder also using the resources ΔC
 - d. in a given economic context (c) which includes existing prices, inefficiency and budget expenditure required.
- 6) The economic value of clinical innovation, $EVCI = \beta_c \Delta E$ is the gross clinical benefit of the new drug compared to placebo, constrained twice: by the clinical opportunity cost (the best alternative therapy to the new drug) to obtain ΔE and the economic opportunity cost (the best alternative use of resources ΔC) to obtain $\beta_c \Delta E$.

6.2 Outline of thesis

The thesis comprises three parts.

Part One provides background discussion on **the political economy of new drugs**, pharmaceutical innovation and its clinical and economic value. The thesis starts with a discussion about political economy and its relevance to price of a new drug and the economic research that addresses this critical policy choice (Chapter 2). Chapter 3 presents a review of the "bottom line" empirical evidence supporting the current framing of the PEND: i) the high rate of return (in health gains) to investment in pharmaceutical R&D; and ii) increasing pharmaceutical R&D and new drugs as a major driver of the ten year gain in average life expectancy at birth of the US population over the period 1950 to 2009. The definition of the clinical value of innovation is clarified and distinguished from the term "pharmaceutical innovation", which applies to any new drug, regardless of its clinical advantages compared to either placebo or the best alternative therapy. Two additional types of pharmaceutical innovation are identified (Chapter 4). Then the significance of using a shadow price rather than a maximum Willingness to Pay (maxWTP) to provide an economic value more generally is demonstrated. A conventional method to derive the shadow price of an input or output when the market fails to provide a price is illustrated (Chapter 5).

Part Two is concerned with **the health economics of the choice of a threshold price** for the reimbursement decision. The concepts of β_c and PEA are introduced. Part Two starts with the derivation of β_c for the special case of an economically efficient budget that is expanded to accommodate the additional cost of a new drug. PEA is introduced in Chapter 6. It is as a method used to characterise and quantify the relationship between price and population health outcomes. The capacity of β_c to capture information about variations in allocative and technical efficiency in the health budget and sub-optimality in displacement is demonstrated. In particular, its capacity to capture information about the strategy of improved allocative efficiency financed by optimal displacement as the best alternative strategy to reimbursement in an allocatively inefficient health budget is illustrated (Chapter 7). A simple applied game theoretic model is used to demonstrate the endogeneity of new drug price to the reimbursement process. This endogeneity concerns the relationship between new drug price and the institution's choice of decision threshold. This model predicts that as the threshold increases, so will a strategic profit-maximising firm's choice of the offer price per effect of the new drug (Chapter 8).

Part Three focuses on **the pharma-economics of new drug price**; in particular the question of whether the fact that the relationship between price and innovation is not captured by β_c means that the threshold price of the health effects of a new drug should be higher than β_c . Part Three starts with the results of an analysis of two cases for the *FPP* within the prevailing PEND. The following possibility is raised: these arguments for the *FPP* do not consider the implications of fixed health budgets and alternative methods to improve future health on the economic value of pharmaceutical innovation. Then, two additional cases for the *FPP* are framed as specific threats and analysed within a game theoretic model and the PEA framework. Both of these threats are about how a price below the *FPP* is against the interests of the institution because it lowers the population's health. The two threats differ in terms of the mechanism underlying this claim. The first specific threat is a line of reasoning that links drug price and R&D funding via the failure of the capital market. Specifically:

Firms rely on internal funds generated by above marginal cost pricing of new drugs because the capital markets fail to finance risky R&D. Hence without economic rents from higher prices it will not be possible to finance R&D.

This Game is called "The pharmaceutical R&D financing Game" (Chapter 9). The second specific threat is:

Unless the decision threshold price of new drugs is given a premium over that applied to non-pharmaco-therapy, there will be less health in the future. Buying new drugs buys both current health and future health gain via innovation and the decision threshold must accommodate this.

This Game is called "The new drugs need a premium Game" (Chapter 10).

The Conclusion (Chapter 11) presents a case for health economists to support the adoption of β_c as the decision threshold for the new drug reimbursement process. This case builds on the following observation: health economists have long questioned the practicality of using the opportunity cost of the additional cost of a new drug as the decision threshold price, primarily because of the absence of evidence of the opportunity cost. The starting point of an alternative approach to the political economy of the decision threshold is to ask why we do not have evidence of the best alternative strategy to new drug reimbursement and to identify β_c as a solution to this problem:

*In providing incentives for and rewards to firms to develop evidence of the cost and effect of patented innovation and technologies, institutions have failed to correct for the failure of the market to provide evidence of the cost and effect of unpatented or unpatentable health technologies and services. Using the β_c will provide an incentive for the institution to develop evidence of **both the least and most cost effective** of currently funded programs and hence correct for this market (and institutional) failure.*

6.3 The main result

The thesis concludes with a summary of how a rational institution should respond to the general form of the Threat: "Lowering prices is against the interest of health funders because it will reduce a population's future health". There are certain very restrictive conditions under which a population health maximising institution has an incentive to respond to this Threat by increasing the threshold price of a new drug above β_c . The promise of clinical innovation from a future drug is found to be neither a necessary nor sufficient condition for a benefit to the population from higher prices and more future NMEs. A necessary condition is that the institution must contract with the firm to ensure that the institution can recoup the additional expenditure today through higher prices that will be invested into R&D by the firm. These funds are recouped through a discounted price of the future drug. It is highly likely that such a contract would be incomplete and unenforceable and hence it is uncertain whether the institution will reap the benefits in the future (more health gains than otherwise possible) of its investment today (less health effects from today's budget). This highly unlikely future benefit to the institution (and certain current net cost) is in contrast to the certainty that the firm will benefit from increased economic rent today. This benefit to the firm (more economic rent today) occurs regardless of whether this contract is enforced or the promise of a low cost future drug is an eventuality.

The most certain and significant consequence of a lower price today is a reduction in firm's economic rent today. I conclude that, when the conditions are created for the institution to have an incentive to contract with the firm, it is in the interests of the firm to borrow from the capital market rather than the institution, if the former has a stronger preference for risk than the latter.

7 Trust, constraints and the counterfactual

This thesis is about reframing the prevailing PEND by considering three elements of the political economy: trust, constraints and the counterfactual. These three elements are the central principles of PEA. They guide the development of models that are used to analyse the highly charged question of new drug price.

7.1 Trust

Trust that rational Pharma acts strategically. Currently, economists use non-strategic (decision analytic) models to inform the new drug reimbursement process. Most pharmaco-economists would

accept that there is a certain element of strategy involved in developing a pharmaco-economic model. The objectives of such strategies are to specify models so as to either minimise or maximise the estimated ICER of a given new drug generated by that model.¹⁵ The process of critical review of pharmaco-economic models in all reimbursement processes that use economic evaluation is about working within this strategic dynamic to achieve the best estimates of additional cost and effect. The rules to this process are contained in guidelines and the peer reviewed methods literature on topics that range from meta-analyses of clinical trials to extrapolation of clinical trial results.¹⁶ However there is a second level at which strategic behaviour works within the reimbursement process and this aspect cannot be explored within the rules for pharmaco-economic simulations. For example, how does the institution's choice of threshold influence the firm's choice of offer price? Or, when firms and US pharma-economists say they have shown that it is in the interests of the population's health not to price new drugs below the *FPP*, should the institution accept that these claims are based on rigorous and non-strategic evidence? Should we accept industry funded pharma-economic literature if it is published in peer reviewed journals or should these studies be placed under a strategic microscope? Do we need to prove empirically and rigorously that firm's act strategically as part of the reimbursement process, or is it sufficient to establish incentives and opportunities for strategic play and to build on the rich but private domain experiences of participants in these processes?

7.2 Constraints

Resources are constrained; if a new drug is reimbursed at an additional financial cost to the health budget, something, somewhere, will need to be displaced to finance it. It is likely that no health budget can be expanded to accommodate all purchases that are considered "value for money" in the lay sense of the term.¹⁷ Something, somewhere, needs to be displaced. It could be a respite care program that was going to be extended to other regions, but at the next budget, these proposals are

¹⁵ This statement is difficult to support using public domain evidence, but the National Institute of Clinical Excellence (NICE) commentary on the reasons for differences in the ICER for trastuzumab estimates by Roche (the patent holder) with an estimate of £5,687 per QALY and the NICE independent reviewers (£18,000 per QALY) provides a number of examples of how these potential biases are generated in pharmaco-economic models. (See Section 3.6 in the NICE Technical Report TA107, Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer, 2006) Experience of most members of committees that receive HTAs/CEAs from firms in support of the decision to subsidise a drug at the *FPP* is that the process of review of the models typically involves the revision of assumptions that overestimate benefits and underestimate the incremental costs of a new drug, as estimated by the firm. The point made here is simply that this behaviour is consistent with the actions of a profit maximising firm. If there were no reason to believe that firms have an incentive to underestimate the ICER of new drugs, then the review process could well be very different. It is also likely that firms would make the same criticism of institutions; they have an incentive to underestimate effect and overestimate incremental costs in order to achieve a lower price for the drug at a given threshold.

¹⁶ For example, the Guidelines prepared for firms submitting HTA/CEAs to the Australian PBAC (Pharmaceutical Benefits Advisory Committee 2008).

¹⁷ Without evidence of ICERs of all the health programs and technologies, this statement is difficult to prove. Certainly there are services that can be considered "cost ineffective" that are currently funded and could be disinvested. There are also other services that are cost effective and that could be funded (Weinstein 2008). My point is simply that we cannot act as if health budgets are unconstrained, or are constrained only by some lay measure of "value for money" which is typically insensitive to changes in competition in the market for health inputs (See Chapter 3). Furthermore, an important theme in this thesis is that the choice of price by a firm that is a patent holder and has some monopoly power is endogenous to the choice of threshold; if a given threshold is imposed, firms with technologies that have ICERs greater than this threshold have the option to lower their price in order to make them "cost effective". Therefore, technologies with ICERs greater than a given threshold will not necessarily remain unfunded if that threshold is imposed. (See Chapter 6) And finally, choice of a threshold needs to involve recognition of the budget constraint. Weinstein (2008) summarised the US's preference for not applying CEA and decision thresholds and hence the absence of demand for evidence of the value of a QALY: "Until Americans come to terms with the fact that they are not willing or able to pay the cost of providing all citizens with all effective health care services, there will be no explicit need for a benchmark dollar value of a QALY."

reversed. It could be the expansion of a program of disability services that was going to be financed by an expanded disabilities budget, but instead this increased budget is transferred to health. The results of analyses that assume budgets are unconstrained are limited in their generalisability to countries that recognise these constraints.

7.3 The Counterfactual

It is in the population's interest to address the failure of markets and institutions to develop evidence of the counterfactual to reimbursement and higher drug prices. If we accept that budgets are constrained and probably inefficiently allocated, then the counterfactual to reimbursing a new drug at an additional cost to the health sector matters. Economics is about understanding the counterfactual of interest as not just any alternative strategy, but the opportunity cost of a nominated strategy. This is the counterfactual that signals the maximum benefit foregone by selecting a nominated strategy. The opportunity cost of reimbursement is not what is physically displaced to finance the additional cost (an operational issue) it is the best alternative strategy (optimal adoption and optimal financing) to reimbursement (adoption and financing). A key argument against adopting the core economic principle of opportunity cost to define the maximum economic value of a given strategy is the lack of evidence of the counterfactual; if we have no evidence of the incremental cost and effect of all strategies, how can the most cost effective alternative be identified? Maybe, one day, cost effective but unpatentable programs or publically funded innovation that the government chooses not to impose intellectual property rights over, will no longer be the counterfactual; they will be the factual. However, the failure of markets and institutions to provide an incentive to develop evidence of the counterfactual needs to be addressed before these programs can be financed. Furthermore, there is an imperative to address the long run implications for allocative inefficiency (and probably equity)¹⁸ of providing financial incentives to new patented technologies without addressing the market failure in relation to financing unpatented programs.

¹⁸ One possibility raised in this thesis is that the inequity that we observe in access to health care could be related to a systematic bias towards patented technologies and away from health care for which the market and institutions fail to provide advocacy and evidence and protection from displacement.

Part 1: The political economy of new drugs and the value of pharmaceutical innovation

The political economy of new drugs (PEND) is about defining the share of the value of pharmaceutical innovation that should be appropriated by a new drug's patent owner as profit. The political economy defines the rules by which a given share can be rationalised in a world that increasingly requires evidence rather than sheer purchaser and seller power to determine a price.

In Part 1, four concepts that are fundamental to understanding PEND are clarified:

- 1) How does PEND define the rules by which policy on new drug price can be assessed in an evidence based policy framework? (Chapter 2)
- 2) Is it reasonable to rely on empirical evidence of the historic rate of return on pharmaceutical innovation as the central piece of evidence guiding policy on the choice of a decision threshold? (Chapter 3)
- 3) What is the clinical value of pharmaceutical innovation? (Chapter 4)
- 4) What is the difference between a monetary and economic value of a good? (Chapter 5)

Chapter 2: Reframing the political economy of new drugs

The global PEND is driven and shaped primarily by the US; its pharmaceutical industry, its government via trade-negotiations with the OECD, and the US academic pharmacoeconomists and the evidence they generate. However, as the US starts to address issues such as whether it should use evidence of cost effectiveness to make decisions about drug reimbursement, the capacity of the prevailing political economy to accommodate a mechanism such as the decision threshold is tested.

In Chapter 2 we explore questions about the political economy of new drugs in the context of this changing landscape. We ask:

- 1) What is the political economy of new drugs?
- 2) How does it influence the research agenda?
- 3) Does it change over time?
- 4) What is the value in reframing the prevailing political economy to accommodate developments such as the use of economic evaluation of new drugs to inform reimbursement decisions?

1 The political economy of new drugs

The term “Political Economy” is a former name of the discipline of economics. Today it is used in a number of senses, and its usage continues to change. Common to most of these modern interpretations is the economic analysis of tension in policy choices in a context that recognises both the political and economic influences (Groenewegen 2008). In this thesis, the political economy of new drugs (PEND) is defined following the precedence set by Comanor in his 1986 paper: “The Political Economy of the Pharmaceutical Industry”. While Comanor did not explicitly define his use of this term, it can be inferred from his paper that the political economy of the pharmaceutical industry concerns the economics of the critical choices governments need to make about the pharmaceutical industry and its regulation.

Economics is a practical science. Since its inception as an independent discipline, it has probed the major policy issues of the day. The topics that aroused the interest of its practitioners have generally been those that presented government officials with critical choices. The modern literature on the pharmaceutical industry is no exception. (Comanor 1986 p. 1178)

Of particular interest to Comanor was the relationship between the economist’s research agenda and the politics of pharmaceutical regulation; he found that the political economy framed the research and as the political debate changed, so did the research.

In this thesis the focus is “the political economy of new drugs”: the factors that influence how any surplus associated with a new drug or a future drug is allocated across stakeholders, including consumers, purchasers, budget holders and firms.¹⁹ The relationship between the economic research agenda and the political process identified by Comanor is also a central issue in this thesis. The focus in this thesis on the political economy of new drugs rather than the pharmaceutical industry reflects the increased role of cost effectiveness analysis and the capacity to quantify the innovation associated with new drugs.

One way that the pharmaceutical industry seeks a share of the surplus is through lobbying. Lobbying plays an important part in the allocation of surplus associated with patented innovation in any sector of the economy. In the case of new drugs, this lobbying tends to focus on the question of an appropriate price for new drugs, given the health generating potential of that drug and future innovation. The associated policy choices include: i) whether new drug price should be regulated; ii) the choice of a decision threshold price in a reimbursement process; and iii) whether bilateral Free Trade Agreements (FTAs) with the US should be used to prevent partner countries from regulating the price US firms request for their new drugs.

In the broader economy, lobbying by patent holding firms is characterised as rent seeking or rent protection.²⁰ In the prevailing PEND, lobbying for higher new drug price is instead characterised as providing incentives for investment into further research and development (R&D). This way of framing the impetus for lobbying links increased price to increased profits as well as increased future health outcomes, hence creating an apparent win-win situation for firms and consumers. These claims of the relationship between new drug price and future health are supported by peer reviewed research

¹⁹ A UK example of the political economy of new drugs and the appropriation of surplus is from a commentary on proposed changes to the UK pricing scheme (Towse 2007) “*The more of the surplus that accrues to the innovator, the greater the incentives for future innovation and health gain. However, the greater the surplus that accrues to the NHS, the greater the immediate health gain. Evidence suggests that the societal gains from pharmaceuticals and other health technologies have been high.*”

²⁰ The term “rent seeking” was coined by Kruger and her original paper remains a significant milestone in the economics of lobbying and the associated deadweight social loss. (Krueger 1974)

and government studies (Comanor 1986; Scherer 2000; International Trade Administration 2004; Vernon, Goldberg et al. 2009). This evidence base supports the claim that the relationship between price and R&D investment is positive and that new drugs are a key driver of improved longevity (life expectancy).²¹ The claims that firms rely on non-capital market funded R&D rather than capital market borrowings due to the riskiness of this investment is supported by the pharma-economic literature.²² The claim of and evidence for a win-win outcome to the policy of higher prices for new drugs is critical to the success of lobbying by US Pharma.

2 The rate of return on investment in pharmaceutical R&D and the political economy

Comanor argued that the political economy of the pharmaceutical industry shaped the economic research agenda, most notably the premise that there is a trade-off between savings today and health tomorrow: society can have more of one and less of the other but not more of both. Comanor noted that the literature did not question whether this trade-off exists. Instead the research agenda prioritised an estimate of this trade-off, in the form of the ratio of the return (future health) on the original investment. Comanor identified three potentially relevant rates of return: the return to the firm in terms of economic rent from their investments; to the industry overall; and the social return where return is measured as the increase in social welfare (economic rent and consumer welfare).

Comanor found that the focus on evidence of these rates of return was the single issue common to the disparate economic literature on the pharmaceutical industry. He also found that, at the time of his review, no reliable estimate of the social rate of return on R&D had been published in the peer reviewed literature.²³ Comanor concluded that it could be possible to increase competition (lower price) without having a loss in future innovation, but the current political economy excluded this possibility from the research agenda. Consequently, the evidence that could test this hypothesis (the possibility that there is no trade-off) was not available.

3 Is the political economy of new drugs constant?

Comanor observed that over the period 1959 to 1985, the political economy of the pharmaceutical industry was reframed at least twice in response to changes in the political debate. The focus went from questioning whether the industry did in fact experience monopoly rents, to accepting that they did and then considering the impact of regulation and identifying optimal regulation on these rents and the incentive for R&D. Comanor also noted that the adversarial nature of the political debate was reflected in the economic research.

Particularly at the start, there was too little attention paid to the critical trade-offs essential for the development of effective public policy. One side presumed that substantial restrictions on

²¹ While improved quality of life is also an outcome of improved pharmaco-therapy, the US literature and lobbying is dominated by the evidence supporting the claims of improved longevity at the population level. This situation is probably a consequence of the preference in the US economic literature for population based analysis of the benefits of pharmaceutical innovation rather than CEAs of individual new drugs. The complexity of measuring quality of life at the population level, without a control group, is far greater than that of measuring quality of life in a controlled clinical trial.

²² “Non-capital market funded R&D” is a term used in this thesis to refer to the strategy by pharmaceutical firms of funding their investments in R&D through “internal funds” (economic rent) and publically financed health research such as the NIH (Vernon 2003; Keyhani, Diener-West et al. 2005; Santerre and Vernon 2006). This term distinguishes this strategy from the strategy of funding R&D by borrowing from the capital market.

²³ Comanor identified one study that estimated this return for three drugs but he found that the author had inflated this return by estimating the total social welfare from a given drug rather than the incremental social welfare from the innovation of this drug.

competition were required for innovation, and that the former was far more essential for social welfare, while the other largely ignored any relationship between competition and innovation. Neither approach was sufficient. (Comanor 1986 p. 1180)

In the 25 years since Comanor's 1986 review of the political economy of the US pharmaceutical industry, the following have continued to grow: the US pharmaceutical industry²⁴; US expenditure on pharmaceuticals and health as a percentage of Gross Domestic Product (GDP)²⁵; the number of new drugs in the US development pipeline²⁶; and the average longevity of the US population.²⁷ Studies have provided further evidence that the following relationships are positive: new drug price and R&D investment by firms (Vernon 2005); R&D investments and New Drugs as summarised by the costs of bring a new drug to market (DiMasi 2001); and new drugs and longevity (Lichtenberg 2006). And other evidence suggests that the costs of bringing a new drug to market continues to increase as does society's demand for new drugs, particularly in relation to chronic diseases for which obesity is a risk factor (Grabowski, Vernon et al. 2002; DiMasi, Hansen et al. 2003).²⁸ The evidence supporting the case for higher new drug price appears to have strengthened, but the focus of evidence development has not broadened; the landscape of this political economy appears to have intensified but not shifted.

Also since 1986, there have been three main developments in the global pharmaceutical economy. First, institutions throughout the Organisation for Economic Cooperation and Development (OECD) started using formal processes such as Health Technology Assessment/Cost Effectiveness Analysis (HTA/CEA)²⁹ to assess the incremental costs and benefits of new drugs compared to the best existing therapy.³⁰ The results of HTA/CEA are then used in conjunction with a decision threshold and other information to assess whether the population will be better or worse off if the institution reimbursed the drug at the firm's offer price. Hence, the policy debate throughout much of the OECD is increasingly broader than that of the US debate. The latter is primarily concerned with policies around

²⁴ To the extent that the almost 50% increase in expenditure on pharmaceuticals as a % of GDP reflects growth in the US sector (see following footnotes), it is reasonable to surmise that the role of the US pharmaceutical sector as a % of GDP has also increased since 1986. But how big was it in 2009? In 2009 an input output analysis of the US pharmaceutical sector prepared by consultants (Battelle Technology Partnership Practice) for the PhRMA (an industry lobby group) found that the output of the US biopharmaceutical sector represented 917B annually, with \$382B in direct contribution (a multiplier of 2.4). Given that the US GDP was estimated at \$14,043B this suggests that the pharmaceutical sector contributes (directly and indirectly) around 6.7% of the total GDP and around 2.3% for its direct contribution. It is in the interests of lobby groups to overestimate the role of their sector to the economy. For example, the authors write that: "A \$10 billion change in US biopharmaceutical revenues would have the following effect on the U.S. economy: \$29.7 billion in total output; 130,000 total jobs; \$9.2 billion in personal income." Source: "The biopharmaceuticals sector: The economic contribution to a Nation" July 2011. Available on www.PhRMA.org (Accessed 26-12-2012)

²⁵ Total pharmaceutical expenditure increased from 8.8% in 1986 to 12% in 2009 Total Health expenditure increased from 10.6% in 1986 to 17.4% in 2009, Source: OECD health statistics, Frequently requested data, www.oecd.org Accessed 26-12-2012

²⁶ From around 1300 in 1997 to 2995 in 2010 Source: <http://www.phrma.org/us-market-drives-global-development-medicines> (Accessed 26-12-2011)

²⁷ Life expectancy increased from 74.7 years at birth in 1986 to 78.2 in 2009 Source: OECD health statistics, Frequently requested data, www.oecd.org Accessed 26-12-2012

²⁸ The proportion of the population who are obese, in the US increased from 23.3% in 1991 to 33.8% in 2008. These proportions are based on measured height and weight, not self-report, which tends to be lower. Obesity is defined as a BMI > 30 kg/m² Source: OECD health statistics, Frequently requested data, www.oecd.org Accessed 26-12-2012

²⁹ In the words of Chandra, Jena et al. (2011), Cost effectiveness analysis is the half sibling to comparative analysis. The latter term appears to be used in the US in the same sense that HTA is used throughout countries that use economic evaluation.

³⁰ A summary of the range of OECD institutions that used economic evaluation in the mid 2000's is presented in ITA (2004). All countries have offices or institutions that place their local conventions in the public domain.

discounts to large purchasers, whether there should be universal access to drugs, whether HTA/CEA should be used and prices regulated. The rest of the OECD is additionally concerned with the choice of decision threshold and the type of information that should be included in an assessment of costs and benefits of new drugs.³¹ However, the imperative to maximise the benefits of pharmaceutical and biotechnology innovation remains a significant part of OECD-wide research on pharmaceutical policy.³²

Second, there has been a significant development in the quantity of evidence about the relationship between: i) price and innovation; and ii) new drugs generally and health.³³ However, it was only recently that the US pharma-economic literature provided two estimates of the ratio of the social return on consumers' investment in higher drug prices in the US. Lichtenberg's 2004 estimate of the social return on additional investment in new drug R&D is in the order of 160 to 1. Santerre and Vernon's (2006) estimate of a return on consumer's investment via higher prices over the period 1960 to 2000 in terms of the value of the additional health benefits from additional drugs is in the order of 28 to 1.

Third, the US pharmaceutical industry now has two additional avenues to take the PEND to the rest of the OECD: i) the formal reimbursement process for individual new drugs (lobbying for choice of decision threshold) (Vernon, Golec et al. 2010); and ii) the bilateral FTAs between the US and OECD countries (lobbying to prevent trading partners from regulating new drug price) (Harvey, Faunce et al. 2004).

US pharma-economists have sought to adapt the original US political economy and research agenda to accommodate some of these changes. For example, Vernon et al. (2009) chose to define the socially optimal threshold from the perspective of optimal innovation. The authors started with the premise that socially optimal decision investment in R&D occurs when the firm can appropriate 100% of the associated social surplus. Vernon et al. argue that this result occurs when the incremental cost per Quality Adjusted Life Year (QALY) of a new drug is the same as the cost per QALY of the least cost effective of currently funded services. The authors argue this reference is the provision of dialysis at a cost per QALY of \$129K. Other authors have argued that setting a price threshold of i ³⁴ and comparing the results of CEA against this threshold of i is price control under another name and its result is the same: pricing below the free market price will lead to a deadweight social loss.³⁵ Jena and Philipson have published a number of papers about the inclusion of dynamic welfare considerations in the decision threshold (Jena and Philipson 2007; Jena and Philipson 2008). Originally they argued that this threshold should be the maximum Willingness to Pay (maxWTP), just as Vernon et al. have

³¹ Research such as that presented in Lakdawalla et al. (2009) is a good example of how the pharmaceutical policy issues faced by the US are far removed from the methodological debates that occupy countries such as the UK and the associated institutions such as NICE. The commentary on this piece by the eminent pharma-economist Scherer (2009) should be read in conjunction with that study; it summarises the technical reasons why their estimate of the health gains from new drugs are likely to be overestimates. The opinion piece by Weinstein (2008) shows how the US is still struggling with the question of whether or not they should use a CEA **at all** in decision making. Weinstein was a co-author of one of the seminal papers that sought to formalise CEA (Weinstein and Stason 1977). More than thirty years later, Weinstein observed that *"Until Americans come to terms with the fact that they are not willing or able to pay the costs of providing all citizens with all effective health care services there will be no explicit need for a benchmark dollar value of a QALY."*

³² For example: "The Bioeconomy to 2030: designing a policy agenda" at the OECD Science, Technology and Industry Working Papers Series all available at www.OECD.org Accessed 26-12-2011

³³ Sloan and Hsieh provide a comprehensive summary of this literature. (Sloan and Hsieh 2007)

³⁴ For example, \$75,000 per incremental QALY

³⁵ For example, the report on OECD price controls prepared by the US International Trade Administration. (International Trade Administration 2004)

claimed. Their rationale included that “technology adoption through cost-effectiveness is a price-control policy in disguise and might therefore have many of the properties of such policies.” But in the later paper, they recognised a number of factors that supported the case for it to be lower than the maxWTP, including budget constraints and the contribution by public sector research funds to pharmaceutical R&D. Jena and Philipson did not specify exactly what this price should be, only that it should be higher than the threshold applied to non-pharmacotherapies.

One key aspect of the political economy has remained constant, despite these developments: the trade-off between savings today and health tomorrow remains the central premise.³⁶ The possibility that increased competition (lower prices) could lead to more health in the future as well as today is not part of the research agenda. Furthermore, it is a possibility that continues to be excluded from the prevailing political economy.

4 Reframing the political economy

The starting point for this thesis is the following set of questions.

- 1) Is it possible to reframe rather than adapt the prevailing PEND to accommodate the developments in drug reimbursement and HTA/CEA?
- 2) Could this reframed political economy include the possibility that each of the following can be simultaneously improved: competition; current health; and future health?
- 3) This reframed political economy would focus on the central policy decision by a reimbursing institution: Which decision threshold will maximise the npvPH?

The first step in this research was to develop a formal model to define the political economy of new drugs in the context of policy choice and research. Then the model was used to specify both the current and alternative frame for the political economy.

4.1 Architecture of evidence based policy

The relationship between the PEND and the research agenda is characterised using an adaption of Grüne-Yanoff and Schweinzer's Architecture of Game Theory (Grüne-Yanoff and Schweinzer 2008) with additional elements derived from Roe (1991) and Comanor (1986). The adaption is described in Appendix 1 and illustrated in Figure 1 p.39 . Amongst other advantages, this framework identifies the line of reasoning that leads to certain possibilities being excluded from the prevailing research agenda. For example, by defining the key trade-off as between more health tomorrow and more savings today, the possibility that both competition and population health can be improved is excluded. Consequently, this framework identifies that there is a requirement to redefine the evidence based policy framework that shapes the current research agenda and suggests some mechanisms by which this could be achieved.

³⁶ This is also expressed as the trade-off between access today and health tomorrow (Scherer 2000) and: “the key trade-off inherent in research and development: the decreased welfare of current patients as a result of higher prices versus the increased welfare of future patients as a result of the incentives for innovation that such prices provide.”(Jena and Philipson 2007)

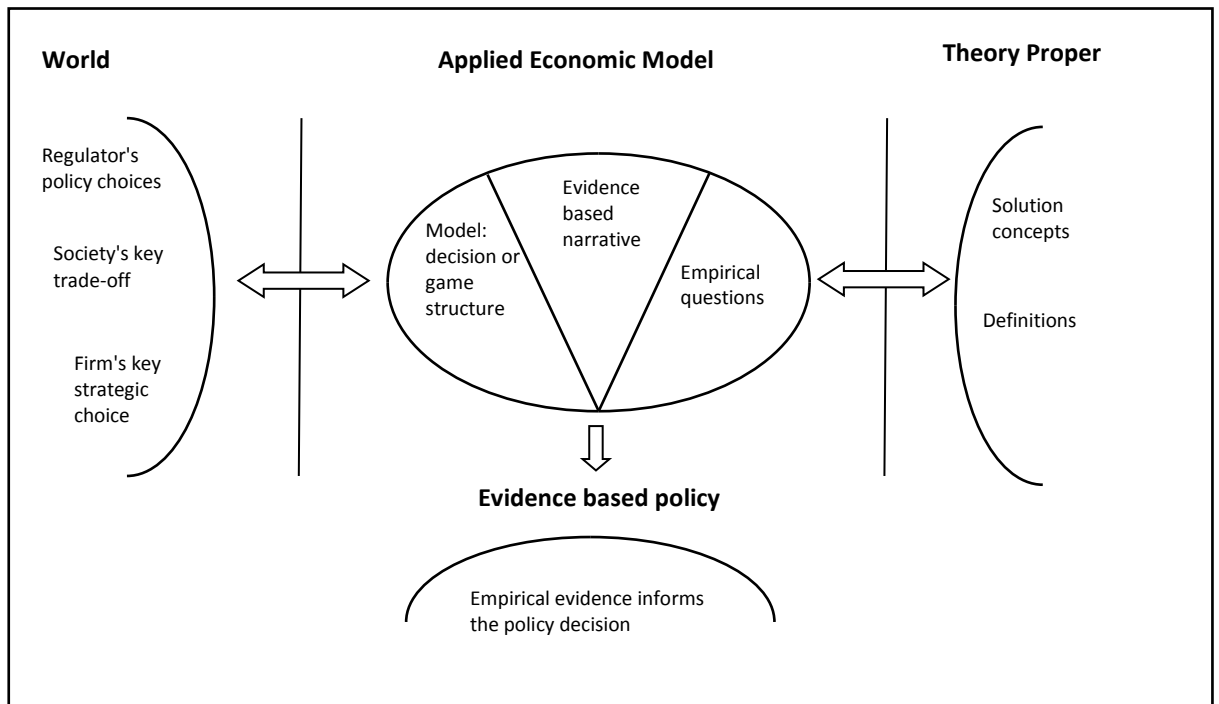


Figure 1 Architecture of political economy of evidence based policy: Adapted from Grüne-Yanoff and Schweinzer's Architecture of Game Theory

4.2 Prevailing political economy

The key **trade-off** is between savings today and health tomorrow, for example:

*If the price of today's new drug is reduced below the firm's preferred price (FPP), there will be financial savings for **some** today but this is at the cost of access to more drugs for the **whole population** in the future.³⁷*

The key **decision by the firm** is how much to invest in R&D and the key **policy choice** is whether or not to regulate or control the new drug price. This particular framing inspires **research questions** such as:

- 1) What is the relationship between today's price of a new drug, pharmaceutical R&D and future innovation? (Vernon 2005; Abbott and Vernon 2007; Vernon, Goldberg et al. 2009);

³⁷ An excerpt from the Joint Hearing of the Finance Committee of the US Senate in April 2004 is reproduced in Attachment 2 and contains a number of variations of this theme. This characterisation is a synthesis of the extensive literature on this topic, much of which is summarised in Comanor (1986) and Scherer (2000). Specific examples include: “*Greater access to today’s medicines could be obtained through drug price controls in the U.S., but this will come at a cost: lower R&D investment and fewer new drugs in the future. Understanding this tradeoff is imperative for sound public policy.*” (Vernon 2004). Another example is Vernon et al.’s (2006) analysis of a change in pricing policy in the US. “*Possibly the biggest economic concern over S.334 is that its objective, if achieved, would impart significant costs to future generations of Americans through delayed and reduced medical and pharmaceutical innovations (as a result of reduced levels of investment in R&D). This is something we have shown empirically. Given recent estimates on the productivity and value of pharmaceutical and medical R&D it is critical that the debate of price regulation and importation also consider the costs such policies are likely to entail. It is important to note that our analyses do not measure the relative costs and benefits of pharmaceutical importation (or price regulation). Instead, we acknowledge the obvious potential benefits and measure the more hidden potential costs. **The policy debate needs to focus on this trade-off.** Finally, since the debate is really about lowering drug prices in the U.S., it is precisely this debate that Americans should be having.*”

- 2) What is the incentive for purchasers to maintain prices at the *FPP*? (Lichtenberg 2004; Santerre and Vernon 2006).

This frame excludes empirical questions about the direction of the relationship between: i) new drug price, R&D, number of new drugs; and ii) future health of the population. This relationship is assumed to be positive under all conditions. The **critical piece of information** that will inform the regulator is the return on this investment in R&D (financed via higher prices and public investment), where this return is measured as the additional health gains possible from additional future drugs. If the health effects are monetised, for example using an estimate of the value of an additional year of life, then the return can be compared to the investment as a ratio. If this ratio is high then increased prices today represent a good evidence based policy choice. If this ratio is less than one, then there is a net loss on the original investment.

The **evidence based policy narrative** takes the following or a related form:

New drugs have been shown to be the key driver of historic gains in life expectancy for the US population. In order to achieve sustained increases in life expectancy, more new drugs are needed in the future. Pharmaceutical innovation is driven by R&D investments by firms. R&D investments are driven by higher new drug prices, acting as both an incentive and a funding source for ongoing R&D. The value of the possible health gains far outweigh the financial costs of R&D, therefore higher (unregulated) prices represent good policy.

4.3 An alternative political economy of new drugs

The impetus for this thesis is the possibility that an alternative framing of the prevailing PEND will open fresh paths for research and different critical research questions. There are many ways that the political economy could be reframed. The frame used in this thesis is summarised as follows.

The key **trade-off** is between savings for health purchasers today and firms' profits. The evidence for this trade-off is twofold. First, a firm would not lobby for a higher price unless this strategy increased its profits in the current period. Second, an institution would not reject a higher price of new drugs if it also decreased costs of providing the same health benefits from today's budget. Therefore the existence of this trade-off is a reasonable premise.

The key **decision by the firm** is how to maximise profits today and tomorrow. One strategy available to the firm is to minimise the R&D costs borne by the firm by creating an incentive for institutions to subsidise these costs. One mechanism by which this is achieved is to increase the price of current drugs, without reducing quantity sold (for example, increase the decision threshold). The key **policy choices** for the institution are: i) what should the decision threshold for the health effects for new drugs be; and ii) should this threshold be altered given that there is a relationship between new drug price today and future population health. This particular framing inspires **research questions** such as:

- 1) Given that budgets are constrained or fixed, under what conditions will increased pharmaceutical R&D today necessarily lead to increased population health in the future?;
- 2) What about the impact on the population's future health due to less resources being allocated to health care today?; and
- 3) How should institutions respond to Pharma's strategy of lobbying to increase the decision threshold?

The **critical pieces of information** for the institution are: i) what is the maximum acceptable price for new drugs; and ii) how does this maximum price change if there is a relationship between price and the npvPH. And the **evidence based narrative** takes the following or related form:

*Higher prices today mean increased economic rent for Pharma otherwise they would not lobby for them. It is in Pharma's interest to protect and seek these economic rents. Whether higher prices and more R&D today increase future health remains an empirical question. If higher prices also mean a higher **net** present value of the population's health, then it is in the Institution's interest to increase prices. Given the institution's objectives, the most effective strategy a firm can use to protect these rents is "**the Threat**": **lowering prices is against the interest of health funders because it will reduce a population's future health.***

This alternative framing would expand the market within which pharmaceuticals compete to include any health input, including unpatented programs and technologies. Competition for pharmaceutical R&D funds would include investments in other forms of medical and health innovation, including those that cannot be patented, and research on workforce and service delivery. The reframed political economy also recognises that there is a failure by markets to provide evidence of the cost effectiveness of unpatented and unpatentable programs. It recognises firms' rent seeking motives, accepts these as rational and explicates the increased rent available to firms as a consequence of lobbying. And finally, it includes both of the following possible scenarios, not just the first (as is the case with the prevailing political economy):

- 1) new drug prices increase and the future health of the population **improves**; and
- 2) new drug prices increase and the health of the current and future population **decreases**.

Consequently, the following two central premises of the prevailing political economy become testable hypotheses under this alternative framing:

- 1) Higher drug prices, more R&D and more new future drugs will always increase future health of the population; and
- 2) There is a trade-off between savings (and additional health from improved access) today³⁸ and health tomorrow.

4.4 Comparison of prevailing and proposed frames

The prevailing and alternative frames of the political economy are compared in Table 5 Table 5 (p. 43). Only the alternative frame accommodates the possibility that the health of the future population either increases or decreases as a consequence of lower drug prices today. It is designed to find the solution to the policy problem of the choice of a decision threshold price for new drugs that accommodates a range of characteristics of the health budget, and the relationship between price today and future innovation. This objective is in contrast to the prevailing frame, which, as demonstrated in Chapter 3 and Appendix 7, is specified so as to fit a solution, namely that threshold prices below the

³⁸ The reference to reduction in health today as a consequence of increased expenditure on more costly drugs was originally part of this trade-off. Typically this was expressed as the trade-off between access (lower priced drugs so that everyone, particularly the uninsured could afford them) and more health in the future. See for example Scherer (2000). However, increasingly the US literature expresses this as a trade-off between savings today and health in the future. For example, see Santerre and Vernon (2006). The critical question then is to compare the financial value of future health effects against these savings. For reasons discussed in Chapter 1, this particular framing results in a higher ratio of the gains in the future compared to the loss today. See also Footnote: 36

firm's preferred price or the maxWTP are not in the interest of an institution seeking to maximise the population's health.³⁹

One issue that is addressed in this alternative political economy is that it is not possible to calculate the critical ratio of costs to benefits of lower prices without evidence of the counterfactual. The counterfactual to higher drug prices becomes relevant when the budget is assumed to be either fixed or constrained (that is, not unconstrained). (See the discussion of these terms on page 48) However, without evidence of the alternative uses of these funds, it is not possible to determine whether or not a country such as the US could have done better by investing in alternative technologies (perhaps with a low incremental cost per QALY (ICER)) or in unpatented programs. This issue is also relevant to countries that do use HTA/CEA to inform new drug adoption decisions. The pharma-economic literature is strong on the requirement to use patents to generate a financial incentive for investing in the R&D for new drugs. However, as Arrow (1962) and Tirole (1988) both conclude, the failure of the market to provide an incentive to invest in innovation where that innovation cannot be patented is an economic case for public sector investment. The failure of the market to provide an incentive to invest in developing evidence of unpatented programs and technologies is not provided the same attention by pharma-economists as the potential failure to protect the results of patentable, pharmaceutical R&D (Sloan and Hsieh 2007). The issue of absence of evidence of the counterfactual is a barrier to testing the key empirical question under the prevailing frame. In the alternative frame, the absence of this evidence is a characteristic of economic context; the failure of the market to provide evidence of the unpatented counterfactual to higher prices.

5 Conclusion

The political economy shapes the pharma-economic research agenda. The key question faced by today's US researchers is how this political economy should be adapted to accommodate the rise of HTA/CEA as a determinant of new drug price. But how should the political economy and research agenda be reframed so as to accommodate the critical policy issues faced by institutions outside the US? There is more than one way that this political economy could be reframed. The frame proposed in this chapter and used throughout this thesis has a number of features that distinguish it from the prevailing political economy. One of these features is that it recognises that there is competition in the market for health inputs, including competition from unpatented and unpatentable technologies and inputs. The critical piece of evidence is a qualitative value (equation) of a health shadow price that reflects the competition in the market for health inputs.

The evidence of the historic rate of return on consumers' investment in pharmaceutical R&D via higher prices is no longer the key piece of evidence that informs policy. However, if the evidence that it is very high is correct, then it would seem that the value of an alternative political economy that also identifies the possibility of an increase in current and future health from lower prices has limited value; it will not change a policy decision.

In the following chapter, I show that despite the US evidence of a very high ratio of social return on pharmaceutical R&D, it is both possible and plausible that, had prices of new drugs in the US been lower over the past 50 years, that the health of the population could have been higher. A high return, as calculated in the US literature, does not exclude the possibility that lower prices can improve current and future health.

³⁹ The distinction between framing a problem to find rather than fit the solution comes from Birch and Gafni (1993).

Table 5 Reframing the political economy of new drugs

		Framing the problem to FIT the solution	Framing the problem to FIND the solution
World	Trade-off	Savings today vs. more health in the future population.	More economic rent today vs. more health (or more savings) today.
	Firm strategies	<ul style="list-style-type: none"> How much to invest in the R&D for new drugs? What is the price at which R&D is optimised? 	<ul style="list-style-type: none"> How much to invest in lobbying for a higher price? What is the most effective way to increase and protect economic rent?
	Regulator policies	<ul style="list-style-type: none"> Should the new drug price be controlled? How much should the public sector invest in R&D? How should FTAs accommodate pharmaceutical pricing? 	<ul style="list-style-type: none"> What is the decision threshold (shadow price) for the additional health effect a new drug? How much to invest in the development of evidence of counterfactuals? How to respond to the threat that lower prices are not in the population's interest?
Applied economic model	Evidence based narrative	Improved longevity is driven by Pharma R&D. To continue to improve longevity we need to continue invest in R&D via higher prices and more public research funds.	Less than 30% of the economic rent from higher prices is allocated to NME R&D. Firms have an incentive to generate and protect these rents. The most effective threat is to claim that the higher prices are in the interest of the population's health.
	Model structure	Decision theoretic, uncertainty but no private information and new drug price is exogenous to the reimbursement process.	Game theoretic, assuming that there is strategic response, new drug price is endogenous to the reimbursement process and firms hold private information (information in their private domain).
	Research questions	<ul style="list-style-type: none"> What is the health value of historic R&D decisions? What is the response of R&D to new drug price? What is the health return on consumers' investment in R&D? 	<ul style="list-style-type: none"> What is the economic value of the clinical innovation of new drugs? How much to invest in developing evidence of counterfactuals to Pharma R&D? Under what conditions will a price above the shadow price increase the npvPH?
Theory	Theory proper	Firms require the full surplus associated with the drug in order to achieve socially optimal levels of R&D. Price control leads to a deadweight social loss and pharmaceutical price control is no exception to this basic economic fact.	Shadow price of new drugs should accommodate existing inefficiencies and all alternative investment opportunities by the public sector. Firms have private information. There is a failure of markets to develop evidence of unpatentable health innovation.
Evidence based decision	Evidence	New drugs have contributed significantly to improvements in US longevity that would not have occurred without this R&D. There is a return of 28 fold in health benefits from every dollar invested in R&D raised through higher new drug price.	The improvements in longevity experienced in the US are below those experienced in other countries such as Canada, UK and Australia. (Appendix 3) These other countries have not corrected for the failure of the market to provide evidence of the counterfactual but they have provided incentives to develop evidence of the cost and effect of new drugs.
	Policy decisions	<ul style="list-style-type: none"> Do not regulate new drug price. Increase public subsidy of private Pharma R&D Use FTAs to control regulation in other countries 	It could be that there is a price above the shadow price that is better for the npvPH. If this is the case, this price should be adopted. Otherwise the shadow price should be applied. How much should be invested to correct for the markets failure to generate evidence of unpatented and unpatentable services, technologies and programs?

Chapter 3: The social rate of return on investment in pharmaceutical R&D

The central justification for the continued investment in new drug R&D via higher prices and public sector research funds is the return on this investment in the form of additional health for the population. If this rate of return is significantly greater than 1, then this is high enough to justify ongoing investment. In the prevailing political economy of new drug price (PEND), this ratio it is assumed to never be less than 0; there is never a loss in the population's health as a consequence of more pharmaceutical R&D. This assumption is consistent with a critical premise of the prevailing PEND; the relationship between more New Molecular Entities (NMEs) and the change in the population's health in the future is always positive.

In this chapter I show that the positive relationship between more NMEs and future health for the population is not axiomatic; it is a testable hypothesis and the direction of this relationship depends on the economic context of the health budget. I present a general expression for the estimate of a return on increased drug prices and public funding for private pharmaceutical R&D. I distinguish between three types of health budget constraints: i) a fixed budget that cannot be expanded; ii) a constrained budget that can be expanded incrementally, but expansion involves foregoing the best alternative strategy; and iii) an unconstrained budget that expands to fund every program that is "cost effective" in the lay sense of the term.

I use the general expression of a return on consumers' investment to show that the estimate of the 28 fold return on this investment in Pharma R&D via higher prices (Santerre and Vernon 2006) is consistent with maximising future population health only under the special case of a unconstrained budget. If the budget is constrained or fixed, then a return of 28 to 1, while high, does not exclude the possibility that, had prices and R&D been lower in the past, today's health could have been better.

1 Reimburser's problem

A country with a universal health care system and a fixed budget is negotiating a Free Trade Agreement (FTA) with the US. During the negotiation a US senator visits the country and explains that, even though he is advocating on behalf of the US government, he also has the interest of the citizens of this country at heart. He argues that the evidence is clear; increased life expectancy is driven by new medicines and new medicines are driven by more pharmaceutical R&D, which is in turn driven by not regulating the firm's Preferred Price (the *FPP*). Citizens in all countries would be better off if countries like this one stopped regulating the *FPP*. The short term gain of financial savings was at the cost of the population's longer term health; higher prices mean more health.

The Minister for Health and the Minister for International Trade ask the Reimburser her opinion on whether applying a decision threshold price per effect for new drugs that is lower than the *FPP* will lead the population's health to be worse off in the longer run. (The Reimburser makes the final decision regarding the adoption of a new drug at its offer price based on evidence of its additional cost and effect.) The Reimburser is provided with evidence of the gain in average life expectancy at birth in the US; a gain of a full decade over the sixty years 1950 to 2009. She is also provided with a summary of the peer reviewed evidence of the significance of new medicines contribution to this gain (PhRMA 2011). This report suggests that the contribution of new drugs to increased life expectancy in areas such as HIV and cardiovascular disease is in the order of 50% to 80%.

The Reimburser is also presented with a study that estimates that the health return on consumer investment in R&D via higher prices (foregone consumer surplus) in the US over the period 1960 to 2000 is in the order of 28 to 1 (Santerre and Vernon 2006). A study by Lichtenberg estimates that the social return on pharmaceutical R&D is in the order of 160 to 1 (Lichtenberg 2004). Furthermore, in the concluding chapter of a recent text on the topic of pharmaceutical innovation with contributions from a range of eminent pharma-economists, the editors state that:

With the rates of return of 10 to 1 based on measures of increased life expectancy alone, not even considering improvements in the quality of life, pharmaceutical research has successfully provided developed countries with better health at a cost that has been far exceeded by the value of improved longevity. (Sloan and Hsieh 2007 p. 273)

And finally, the Reimburser is given a study by Lichtenberg that explores the relationship between drug vintage (the years since patent granted) and Australian improvements in mean age at death (and other variables). This study concluded that:

"During the period 1995-2003, mean age at death increased by about 2.0 years, from 74.4 to 76.4. The estimates implied that, in the absence of any increase in drug vintage, mean age at death would have increased by only 0.7 years. The increase in drug vintage accounts for about 65% of the total increase in mean age at death." (Lichtenberg and Duflos 2008 p. 14)

As intuitively appealing as this line of reasoning is, the Reimburser is unsure whether it is sufficient to justify a policy of increased prices of new drugs via a higher threshold. She has these concerns, even though the purported objective of such a policy is the same as the Reimburser's objective; increasing the population's health. She performs a back of the envelope estimate of the additional financial cost to the pharmaceutical budget of the proposed increase in price for new drugs for the next year; a 10% increase in the pharmaceutical budget. The Reimburser then realises that the additional financial cost to the pharmaceutical budget permanent; it is not a one-off increase in prices but a policy that would lead to all future pharmaceutical budgets being higher than would otherwise be the case. Furthermore, the policy is expected to lead to more new drugs than would otherwise be the case and they will all be at this higher new price. These additional costs will need to be financed

somehow; the current fiscal climate is one of restraint and other programs will need to be displaced. While there might be \$28 worth of health benefits to certain **patients** for every additional dollar invested in R&D via higher prices, the ratio of additional **population** health to additional R&D dollars could be much smaller; even negative.⁴⁰ Even if the budget is increased to accommodate these additional costs, other programs, including the extension of existing programs, will be foregone. Lichtenberg's claim that the average longevity of a population would not have improved without the new drugs is difficult to accept unless there is no alternative use for the additional costs of the new drugs.

The Reimburser reviews the US evidence. It seems to her that the basis upon which this return on R&D is estimated makes no reference to these foregone opportunities.⁴¹ Can the US pharma-economists and regulators conclude, as they routinely do, that the US population would have been worse off with lower drug prices, without considering the evidence of foregone benefits – the counterfactual? If this evidence is shown to have limited relevance to US new drug price policy, can the US trade negotiators claim that all countries will be better off with unregulated (higher) drug prices? The Reimburser wonders if her intuition about the limitations of this evidence has an economic foundation.

The Reimburser asks her Health Economic Adviser:

Does the US estimate of a 28 fold health return on pharmaceutical R&D financed by higher drug prices exclude the possibility that at lower prices and less NMEs the US's population's longevity would now be even higher?

2 A closer look at the evidence supporting Pharma's lobbying

2.1 Why is return on consumers' investment in pharmaceutical R&D important?

US Pharma sources the majority of its funds for R&D from non-capital market funding: from purchasers (via higher prices) and public and private not-for-profit research institutes (Joint Economic Committee 2000; Lichtenberg 2004; Giaccotto, Santerre et al. 2005). Therefore, US Pharma must lobby (rather than contract with the capital market) to ensure that these funds are ongoing, if not increasing. While there is no doubt that increased economic rent for Pharma is an objective of this lobbying for higher price, it is not an acceptable justification for non-capital market investment. In simple terms, Pharma cannot lobby using the following justification: "increase prices because, even though it will increase your organisation's costs, it will increase our profits". Instead Pharma must lobby on the basis that there is a return to the funder of this additional R&D, namely, an increase in the population's future health.

Comanor (1986) observed that the single feature uniting the disparate US pharma-economic literature from the 1959 Kefauver Committee⁴² to the publication of Comanor's paper in 1986 was the recognition that the most critical piece of information in the current political economy was an estimate of the return on this investment in pharmaceutical R&D. Comanor also noted three ways in which this return on R&D was defined: the return to the individual firms, the return to the industry and the social return in terms of improved health. It is the last of these three that is of particular interest to the

⁴⁰ This would be the case if the additional services displaced to finance the additional new drugs had a lower ICER compared to the ICER of the new drugs.

⁴¹ A review of this literature is presented in Appendix 2. The summary presented in this chapter is primarily concerned with evidence of the social return to consumers' investment in Pharma R&D via higher prices.

⁴² See Footnote 2, Page 20

Reimbursers and other purchasers and public health research funding bodies as providers of funds to finance the R&D.

At the time of Comanor's 1986 publication, no estimate of the social return existed. Comanor reported that one study (Wu and Lindgren 1984) had found social rates of return on three specific new products' R&D of 65%, 169% and 69%. However, Comanor noted that the study had not deducted "the consumer and producer surpluses obtained from predecessor products" and that "this lead to inflated values".⁴³

Comanor also noted a practice by US pharma-economists of inferring that the costs of regulation outweighed "any prospective benefits at the regulatory margin". In simple terms, when some economists identified that there was unintended negative consequence of increased regulation, they would infer (not prove) that this cost outweighed the benefits of that regulation. For example, increasing the amount of evidence about a new drug that needs to be reviewed by a regulator such as the FDA will have the intended consequence of improving safety, but the unintended consequence of forgone health effects due to the delay in for time new drugs to reach the market (International Trade Administration 2004 p. 6). Therefore, some pharma-economists might infer that this leads to a net social loss. In Comanor's words:

While that (the unintended consequence) may be so, there is nothing in these findings that estimates the net social value of the drugs delayed or prevented by regulation. (Comanor 1986 p. 1207)

If the evidence of the social rate of return, the major justification of ongoing non-capital market investment in R&D, was not available in 1986, when did it become available?

2.2 What is the evidence of the return on consumer's investment?

2.2.1 A review of the literature

Numerous US pharma-economic studies published over the period 2000 to 2010 conclude or infer that the result of their study supports the policy of allowing drug companies to price without regulation because society's return on increased pharmaceutical R&D is high and therefore a population's future health will be worse if the price of drugs is lowered. However, a detailed review of these studies⁴⁴ reveals that only two published studies attempted to provide the evidence that is required to inform this policy choice; the return from pharmaceutical R&D estimated as a social return on non-capital market investment: Santerre and Vernon (2006) and Lichtenberg (2004).

A review of the full literature is summarised in Appendix 2. The remaining studies included in this review were classified into three types. The first group, which included most of the remaining studies, provide evidence that supports the "policy narrative", but not the policy choice. The evidence that supports the policy narrative is wide ranging. Some studies provide evidence that if profit increases, investment in R&D increases (Vernon 2004). Other studies provide evidence of the high and increasing present value of the costs of bringing a new drug to market (DiMasi, Hansen et al. 2003). One study provided evidence that even the threat of price control in the US was sufficient to reduce R&D investment (Golec, Hegde et al. 2005). The second group of studies provided evidence of rate of return estimates for the purchase of new drugs (not drug R&D). For example, they provide evidence from retrospective analysis of historic data that the increased expenditure on new drugs leads to a

⁴³ This is analogous to calculating the clinical value of innovation by comparing it to placebo rather than the best available existing care. This approach results in an overestimate of the clinical innovation of a new drug, where this overestimate increases as the clinical innovation of the comparator increases. (See Chapter 2)

⁴⁴ This review is presented in Appendix 2.

health benefit with a monetary value greater than the additional cost of these drugs (Cremieux, Jarninen et al. 2007).⁴⁵ The third group comprised three studies which could, under very restrictive conditions be interpreted as providing evidence of the social rate of return, but these conditions are very unlikely to occur.

2.2.2 The two estimates of the social return

The two studies (2000 to 2010) over this period that estimated a return on the ongoing non-capital market investment in pharmaceutical R&D found a very high return on historic investments of consumer surplus in pharmaceutical R&D via higher prices; in the order of 28 fold from Santerre and Vernon’s study and 160 fold from Lichtenberg’s study. These estimates of return are a powerful piece of evidence supporting continued and increased investment in pharmaceutical R&D via non-capital market sources. With returns this high, why would a rational institution respond to Pharma’s lobbying in any way other than continuing and possibly increasing this non-capital market funding?

The expression underlying Santerre and Vernon’s estimate is generalised to the following form.

$$r = \frac{k\Delta L^P}{\Delta \mathcal{R}} \quad \text{Equation 1}$$

where k is the maxWTP for an additional year of life (and assumed to be constant regardless of the investment in R&D) and ΔL^P is the additional life years possible from new drugs and $\Delta \mathcal{R}$ is the additional investment in R&D, which leads to the additional drugs. Hence, a 28 fold return on consumers’ welfare means that for every dollar of revenue from higher prices (foregone consumer welfare) the additional life years from the additional new drugs had a monetary value of \$28. This general expression is the measure of rate of return that is consistent with the prevailing political economy: the cost of increased savings (reduction in \mathcal{R}) is less life years in the future (reduction in L^P).

The policy narrative states (with supporting evidence) that: i) increased R&D will lead to more drugs; and ii) drugs have an average impact on life expectancy that is greater than or equal to zero. Therefore, if prices and R&D go increase, so must the population’s future health. (See Appendix 2) If the policy narrative is accepted, then it is reasonable that this expression of rate of return excludes the possibility that reduced R&D will improve the population’s health. Therefore the central premise of the prevailing political economy (that the trade-off exists) is not tested by the empirical research. This is consistent with the observation by Comanor (1986) that the possibility that improved competition (lower prices) today and improved future health could both occur, but is not considered in the research agenda.

A more general expression of this return on non-capital market investment in pharmaceutical R&D would accommodate the possibility that policy can both improve competition (lower prices) and improve the population’s health (today and tomorrow). But before such an expression can be developed, the critical implicit assumption in the US pharma-economic literature needs to be explicated. This assumption concerns the nature (and/or the existence) of the budget constraint.

3 Fixed, constrained and unconstrained budgets

In the simplest sense, budget constraints can be fixed, absent or something “in between”. To explore the question of “in between” we need a formal distinction between different types of budget constraints. Such a distinction is proposed by Claxton et al. (2000b.). In the context of a discussion

⁴⁵ For countries that use CEA to inform drug reimbursement decisions, there would appear to be little value in retrospective uncontrolled studies such as these to inform pricing decisions on future drugs.

about the shadow price of the budget constraint⁴⁶, Claxton et al. raise the idea of two types of budgets for health. The magnitude of the first is defined by some decision maker external to the health sector. For the purpose of this thesis, one such decision maker could be a Treasury Department official who takes into account the constraints in government spending. This budget is set at a fixed amount and cannot be expanded. The second type of budget has a size that is defined by a decision about the maxWTP for a health effects. Any program that meets the defined threshold can be financed. All programs that meet this criterion are financed if the health sector is economically efficient. The budget expands to accommodate any program that meets this criterion.

3.1 Four type of budgets

In an adaption of Claxton et al., the following formal definitions of budget constraints are proposed and used throughout this thesis.

- 1) A **fixed budget** cannot be expanded and any additional purchases can be funded only if existing activity is displaced.
- 2) A **constrained budget** can be expanded by a trigger such as the decision to finance a new drug but there is a foregone benefit to that expansion; other health and non-health programs or investments in R&D for unpatented programs could instead have been expanded or implemented.
- 3) An **unconstrained budget** is one that is expanded to accommodate any purchase that has an ICER at or below the maxWTP, where this maxWTP is defined by the social decision maker as in the endogenous budget from Claxton et al. (2000b). The corollary of this definition of a budget is that there is no foregone benefit, within or external to the health sector, to any purchase with an ICER at or below that threshold. The price of a new drug is relevant in that it must not be above the maxWTP.
- 4) **No budget** means that there is no constraint on health expenditure. The price of a new drug is not relevant to the new drug adoption decision in this context.

3.1.1 Why is it useful to have four classifications of budgets?

The important point about these distinctions is their implication for interpreting the benefit of new drugs. The US pharma-economic literature generally implicitly assumes that the health budget is unconstrained. In this context it is reasonable to conclude that if new drugs can be shown to have contributed to improved health of target patients, then less new drugs will reduce the population's future health.

An example of the application of this assumption in the peer reviewed literature is Lichtenberg et al. (2008) who state that an empirical finding that 65% of a two year increase in life expectancy can be attributed to new drugs means that if these new drugs were not available, the life expectancy of Australians would have been 35% of this amount, namely 0.7 years. This assumes that there is no other opportunity to improve the patient's health, other than new drugs. However, the only condition under which this claim can be made is if we assume an unconstrained budget; all other opportunities

⁴⁶ Claxton et al. (2000b) distinguish between a shadow price of a budget constraint that is determined from a positive empirical question and a normative decision by a social decision maker. The exogenous shadow price is derived in a situation where the health budget is defined by a policy maker exogenous to the health care system and the shadow price of the budget constraint is defined as the marginal benefit (additional QALYs) from marginal expansion of the budget. However, when the health budget is able to be expanded, the authors argue that "there is no reason to regarding existing budgets for health care as fixed." In these cases the budget is expanded to fund all services that have a net benefit of zero or more and hence the budget can be defined as endogenous.

are already funded because they meet the decision threshold. Under a constrained or fixed budget, the resources allocated to the additional cost of new drugs could have otherwise been allocated to other programs. The counterfactual to additional expenditure on new drugs would have been a world in which other services were purchased, resulting in health benefits that were either better than, less than or no different to those from more new drugs. In the context of the unconstrained budget, this counterfactual is irrelevant; if the counterfactual had an $ICER \leq \max WTP$, then it would have already been funded, and its funding would not be dependent upon the expenditure on new drugs.

Using these distinctions between types of budgets we can now prove that Santerre and Vernon's result of a 28 fold return on consumer investments via higher prices only excludes the possibility that the US could have done better with lower prices if there is an unconstrained budget. But first we start with a general expression for rate of return that accommodates all of these budgets.

4 Accommodating the budget constraint in the return on R&D

There is more than one possible expression for a return on R&D funded by non-capital market funds, and a number will include the benefits of foregone activity, which, if it is the best alternative activity, is the opportunity cost. One general expression that accommodates the possibility that more drugs could either increase, decrease or not impact on a population's future health is presented. Then I show that the conventional measure of the rate of return, r , is a special case of the general expression, where the budget is unconstrained. Finally, I derive the conditions under which the population's future health increases if prices and future NMEs decrease.

4.1 A general expression for a rate of return on consumer investment in pharmaceutical R&D

One general expression for return on non-capital market sourced investment in Pharmaceutical R&D is:

$$e = \frac{\Delta L^P - \frac{f}{d_t} \Delta L^P}{\frac{1}{d_0} (\omega \Delta \mathcal{R} + \Delta H)} \quad \text{Equation 2}$$

where:

- 1) ΔL^P is the additional health effects possible from the additional new drugs;
- 2) $\Delta \mathcal{R}$ is the additional investment in pharmaceutical R&D for new drugs;
- 3) ω is the ratio of every dollar that needs to be raised by higher prices in order to finance one additional dollar of NME R&D⁴⁷, where $3 < \omega < 5$;
- 4) ΔH is the increased investment from the public and private not-for-profit medical research funds;
- 5) d_i is the average incremental cost per effect of services displaced to finance the additional cost of the additional new drugs, at either the current period ($i=0$), or the future period when the new drug is marketed, ($i=t$);
- 6) f is the weighted average incremental price effectiveness ratio (*IPER*) of these additional new drugs.⁴⁸

⁴⁷ The evidence for this adjustment is that around 20% to 30% of the additional profit from a higher price with constant quantity purchased will be invested into R&D for new drugs hence $\frac{1}{0.3} < \omega < \frac{1}{0.2}$. (ITA 2004 p. 30)

This return e has four main characteristics that distinguish it from the conventional return r , as expressed in Equation 1.

- 1) The denominator captures the full financial value investment.
- 2) The financial cost of investment is translated into a health loss.
- 3) The financial cost to the health budget of purchasing the new drugs is included.
- 4) The financial costs of the new drugs are converted to health effects.

Each of these is reviewed in detail below.

4.1.1 The denominator captures the full financial value investment.

The denominator captures the full change in investment made by the non-capital market investors ($\omega\Delta\mathcal{R} + \Delta H$) not just the resultant increase in investment by the firm ($\Delta\mathcal{R}$). This investment by the non-capital market funders comprises:

- 1) the increase in investment from the public and private not-for-profit medical research funds, for example, the National Institute of Health (Joint Economic Committee 2000)); and
- 2) $\omega\Delta\mathcal{R}$, the total increase in expenditure by the purchaser as a consequence of the higher prices, only a portion of which is invested into pharmaceutical R&D for new drugs.

Why is it useful to define the investment against which the return is being assessed as the full investment by consumers via higher prices and public sector research funding ($\omega\Delta\mathcal{R} + \Delta H$), rather than $\Delta\mathcal{R}$, the changed investment by firms into R&D? The reason is that it prevents an overestimate of the return on the investment by consumers and the public sector, where this return is in the form of the number of additional new drugs in the future. In simple terms, $\Delta\mathcal{R}$ underestimates the investment required by consumers to achieve an additional drug and by using $\Delta\mathcal{R}$ as the denominator, the return to consumer investment is overestimated. This issue is discussed in more detail in Appendix 2, Section 6.2, p.205.

4.1.2 The financial cost of investment is translated into a health loss.

The financial cost of the investment, $\omega\Delta\mathcal{R} + \Delta H$, is translated to a loss in potential health benefits (a health rather than financial cost) to the population as a consequence of the services displaced to finance the additional expenditure.

In this example, this loss in health effects is derived by dividing the additional financial cost to the public sector and purchasers by d_0 the average ICER (aICER)⁴⁹ of the services displaced to finance these additional costs. This displacement occurs because the budget is assumed to be fixed. If the budget were constrained rather than fixed, the aICER of the services that could otherwise have been financed with the expanded budget would be used. Hence, the health cost to the population of higher prices and additional public sector funding of research is defined as the foregone health effects of the investment in non-capital market funded R&D which under a fixed budget is given by the expression:

$$\frac{\omega\Delta\mathcal{R} + \Delta H}{d_0}$$

⁴⁸ The *IPER* is arithmetically identical to the ICER and therefore includes adjustments to account for any net additional costs or savings elsewhere in the health system. Conceptually the *IPER* recognises the endogeneity of price of new drugs to the reimbursement process. Unlike the ICER of say a smoking cessation program where the only costs are the salary of a counsellor, the *IPER* of a drug behaves more like the price in a bilateral monopoly – it is the product of negotiation.

⁴⁹ The average ICER is an average of the average.

4.1.3 The financial cost to the health budget of purchasing the new drugs is included.

The numerator:

$$\Delta L^P - \frac{f}{d_t} \Delta L^P$$

accounts for the financial costs to the health budget of additional future drugs:

$$f \Delta L^P$$

New drugs are not provided free of charge by companies. It is clear to US pharma-economists that the cost to firms of manufacturing new drugs should be netted off the sales in order to estimate the rate of return to the firms of their investments in R&D. Vernon (2003) is an example of the numerous studies that examine the relationship between firm profit as a return on pharmaceutical R&D, not firm revenue. It seems reasonable then to assume that the additional net cost to the health sector of the new drug should also be included in the rate of return to that sector from its investments in higher prices.⁵⁰

The additional net financial cost to the health sector of the new drugs is represented by ΔC in HTA/CEA and by $f \Delta L^P$ in this ratio, where ΔL^P is the additional health effects from the new drugs and f is the weighted average *IPER* of these new drugs.

4.1.4 The financial costs of the new drugs are converted to health effects.

We assume, initially, that the net additional financial cost of the future new drug needs to be financed from within a fixed budget. Services need to be displaced to finance the additional financial cost to the health sector of adopting the future new drug. The aICER of the displaced services in the future (time = t) are given by d_t . Hence, the numerator, ΔL , the net effect of more R&D today on the population's future health is:

$$\Delta L = \Delta L^P - \frac{f}{d_t} \Delta L^P$$

This represents the health gain to the target patients for the new drug, ΔL^P , less ΔL^D , the loss in health to other patients in the population due to the financing the additional cost of the future new drugs by displacing programs with an aICER of d , where:

$$\Delta L^D = \frac{f \Delta L^P}{d_t}$$

Assume for simplicity that the cost per effect of displaced services is constant over time.

$$d = d_0 = d_t$$

Then Equation 2 is rearranged to provide one alternative estimate of the return on the non-capital market investment:

⁵⁰ The question of whether the economic rent to the firm should be included in the estimate of the impact of new drug R&D is discussed in detail in Chapter 10. In this chapter the question is: what is the return to the consumer of their investment in new Drug R&D via higher prices?

$$e = \frac{\Delta L^P (d - f)}{(\omega \Delta \mathcal{R} + \Delta H)}$$

This equation is saying that the return on consumers and the public sectors' full investment into more future drugs is the additional health effects from that drug with a monetary value given by the difference between the ICER of the health effects displaced and the *IPER* of the health effects from new drugs. The drivers of the return e include four parameters not identified in the conventional measure r : d , f , ω , and ΔH . The aICER of displaced services, d is relevant because it signals the health value of the additional resources used to finance higher prices. The higher the aICER of displaced services, the less health effects can be purchased from the additional savings available to consumers with lower prices. The *IPER* of the new drug, f , is relevant because the higher it is, the higher the additional costs of the future new drugs and the more health effects need to be displaced (health programs contracted) to finance the new drugs. The proportion of additional funds raised by higher prices that is invested in NME R&D (ω) is relevant because the higher this proportion is, the smaller the number of future NMEs per dollar of higher prices. Finally, it is not only higher prices that finance pharmaceutical R&D. A significant share is financed by health research institutes, both private-not-for-profit and public (ΔH).

Unlike the conventional US estimate r , e is not a function of the choice of the maxWTP, k . This situation is a consequence of converting the financial costs of additional financial expenditure today and in the future, into foregone health effects.

In summary, this alternative rate of return captures the net effect on the population's health of the non-capital market funded investment in increased R&D by firms financed by non-capital market funds. Significantly, this method prevents the following error:

- 1) the loss to consumers measured as financial savings compared to the financial value of additional health gains from future drugs (underestimates the loss relative to the benefit);
- 2) the additional health effects that could have been purchased being compared to the additional health effects from the drugs.

The general expression presented in this section is one of a number of possible general expressions. Other possible expressions include using an opportunity cost rather than a simple net population benefit. (See Chapters 6 and 7)

Now we compare Equation 1

$$r = \frac{k \Delta L^P}{\Delta \mathcal{R}}$$

and Equation 3

$$e = \frac{\Delta L^P (d - f)}{(\omega \Delta \mathcal{R} + \Delta H)}$$

This comparison illustrates why r is a special case of e . The former assumes that there are no health effects foregone in order to achieve the additional benefits of the new drugs, either in terms of higher prices today or more expenditure on more drugs tomorrow. While this situation could apply in the US, at least in the minds of decision makers and consumers (Weinstein 2008), it is unlikely to apply in other countries throughout the OECD and it certainly does not apply in the country in which the Reimbursing makes decisions. It is a special, rather than a general, case.

We now address this situation formally.

4.2 Conditions under which more future NMEs means less future health

Now we return to the central premise of the prevailing political economy: the increased health of the population is positively related to the number of additional NMEs in the future and hence positively related to higher prices. Is it possible for there to be a net increase in the future health of the population as a consequence of reduced investments by the non-capital-market sources, even if the conventionally measured return on this investment is estimated to be 28 to 1?

The net effect on the population's health of more new drugs in the future is given by the numerator of Equation 2.

$$\Delta L = \Delta L^P - \frac{f}{d} \Delta L^P$$

If the net effect on the population is negative (there is less health as a consequence of more future new drugs) then:

$$\Delta L = d\Delta L^P - f\Delta L^P < 0$$

where

$$\Delta L^P, d > 0$$

$$\Rightarrow d - f < 0$$

$$\Rightarrow 0 < d < f$$

Equation 4

This result simply says that if the aICER of the services displaced to finance the new drug is less than the *IPER* of the new drug, then the effect of purchasing the additional new drug in the future is a net reduction in the population's health. The conventional rate of return:

$$r = \frac{k\Delta L^P}{\mathcal{R}}$$

is constant regardless of the relationship between d and f . It is also constant regardless of the price of the new drug. Therefore it is possible that $r \gg 1$ and the health gains for one group of patients is very significant, but there is a net loss in health effects for the population, compared to the current population health $\Delta L < 0$.

The corollary of this result is that had new drug prices been lower, and the services not displaced, it is possible that health effects could also have been lower if $d > f$ or been higher if $d < f$.

Is the condition $d < f$ plausible? Is it possible that the aICER of the services that are displaced are lower than the aICER of the health effects of the new drug? It is plausible in the context of a decision to adopt a specific new drug, when budgets are fixed. The case of health budgets across the UK being required by law to purchase Herceptin for eligible patients because it was established by NICE as being a "cost effective" drug is an example of how this situation could arise. The significant additional financial costs of Herceptin needed to be financed by displacing other cancer drugs and therapies for

which there was no legal requirement for them to be reimbursement by the funder. If these other programs were more cost effective than the new drug, then the net effect would have been a reduction in the health of the population (Barrett, Riques et al. 2006). It is also possible that institutions such as NICE and PBAC, in providing incentives for evidence development of patented inputs without addressing the failure of the market to provide evidence of unpatented inputs, have increased the probability that $d < f$.⁵¹

It can be concluded that, if the health budget is unconstrained, a positive relationship between more NMEs and more population health can be inferred from the result of the conventional rate of return of around 28-fold. In this case there is no health loss to either the additional costs of R&D or the additional costs of the future drug hence the entire benefit of the additional drugs is appropriated as additional health effects. However, if the budget is fixed, then this assumed relationship and hence the central premise of the current political economy is an empirical question. The direction of the net effect of more NMEs on the population health depends upon the relationship between the *IPERs* for the new drug and *aICERs* of the displaced services. In turn this relationship depends upon a range of institutional and market arrangements and incentives, particularly the differential impacts of incentives and reimbursement decisions on patented, compared to unpatented, technologies and programs.

What about the case of the constrained budget where services do not need to be physically displaced and the budget can be expanded, but there are competing uses of the expanded budget?

5 The conventional rate of return and the constrained budget

What are the conditions under which lower prices in the past for drugs could have led to better health today, if budgets are constrained (rather than fixed, or unconstrained)? This possibility for better health today if prices were lower is discussed in this section in the context of the US rather than another country, for three reasons. The first reason is that the US is the only country for which there is an estimate of a return on increased price of new drugs. Second, the possibility that the US could have done better had it not maintained higher drug prices and instead invested in other technologies or improved access to all health care is not even considered as a possibility in the prevailing US political economy of new drugs. Third, relative to other countries such as Australia, Canada and UK, the US budget is constrained rather fixed. Over the period 1990 to 2010, the US had the greatest increases in the percentage of the GDP that is expended on either health or pharmaceuticals.⁵² The US health

⁵¹ Significantly, institutions such as NICE, PBAC and the MSAC with their preference for financing programmes and technologies that have demonstrated cost effectiveness could be increasing the probability that $d < f$.

First, the availability of evidence of cost and effect is biased towards programs for which the market and institutions provide incentives for an evidence base. A focus on HTA/CEA generated evidence to inform decisions can be justified as consistent with Evidence Based Medicine (EBM). However, EBM does not recognise the failure of markets and institutions to provide incentives for the development of evidence for non-patented or unpatentable technologies. Hence, it is likely that there are programs that are cost effective, but are not funded because the market has failed to provide incentives to develop evidence of cost and effect.

Second, the process of displacement to finance new drugs is biased towards programs that have not been approved as part of formal evidence based reimbursement process. If a program is recommended or reimbursed via an EBM decision process, then the capacity of the system to displace this program in order to access the funds for a newly reimbursed service is limited. This is particularly relevant if there is a financial incentive to prevent this displacement (a patent for example). Additionally, a program for which there is no evidence of cost and effect can be displaced more easily than one for which there is evidence of “cost effectiveness”.

Therefore, to the extent that increased probability of being displaced is correlated with less available evidence rather than the underlying cost effectiveness of the program, it is feasible that there are situations where $d < f$ and hence the net effect of reimbursement on a population is negative.

⁵² See Figure 15 (Appendix 3 page 225) and Figure 16 (Appendix 3 page 225)

budget is not unconstrained though. If the health budgets were unconstrained, the US could have had both higher prices to the producer today and subsidised the price of drugs to consumers (improved access), both of which would have represented an additional cost to the US health budgets. Essentially, the idea of the trade-off between savings (or improved access) today and health tomorrow, which is a central theme of the US policy narrative, would not be relevant in a society that had an unconstrained health budget.⁵³

5.1 The conditions under which less future NMEs and more future health is possible

The following condition in a constrained budget would lead to the possibility that at lower prices and less new NMEs in the past, the population's health could be better off today, despite less additional health effects from new pharmaceuticals:

The availability of an alternative option to the investment of $\omega\Delta R$ in new drug R&D, for example the extension of an existing program or a unpatented medical innovation, where the resultant health effects have a lower cost compared to those of the new drugs.

Consider the case of a constrained budget; it can be expanded to accommodate the additional financial costs of the new drug but as a consequence of this expansion, the benefits of other services that could also have been adopted are foregone. In this situation the net impact on the health of the population is the same as the effect on the target patients. Furthermore, it is reasonable to assume that the expected net effect of adopting a new drug for a patient group is positive because the drug regulation process is intended to minimise the risk of a net negative effect on patients health from new drugs, even though some authors argue that this regulation in fact unnecessarily delays new drug approvals (Philipson, Berndt et al. 2008; Vernon, Golec et al. 2009).

However, if the counterfactual to purchasing new drugs with additional funds were a more cost effective strategy, then there is a net economic loss from the strategy of more NMEs, even if there is a net increase in population health. Furthermore, alternative investments in R&D in technologies apart from new drugs could have resulted in more cost effective new technologies. In short, it is possible that a country such as the US could be better off today had it had lower drug prices in the past, if it had a constrained budget and/or options other than additional expenditure on new drugs to improve health.

This result (lower prices, less drugs and more health) is possible, even if the estimate that there is a 28 to 1 return from investment in pharmaceutical R&D via higher prices is accurate, for at least two reasons. First, the return in terms of additional possible health effects from alternative investments could be the same, but the return to consumers could be higher, simply because the price of the future health effect is lower. Second, the costs of achieving given innovative health effect could be much lower, simply because the associated investment is lower.

This result simply reinforces the fundamental principle of economics; opportunity cost. If we are selecting the strategy that maximises health, then this is also the selection that minimises the opportunity cost. If the opportunity cost of the action is greater than the benefit of the action then the population would have been better off by funding that alternative action instead.

But the point remains that the US has had a dramatic ten year increase in longevity since 1960 and retrospective analyses seem to suggest that much of this health gain can be explained by new drugs.

⁵³ The US pharma-economic literature is not consistent in this position. Much of the US pharma-economic analysis implicitly assumes that the budget is unconstrained.

Given this evidence, is it plausible that the US, with its focus on rapid uptake of new technologies, could have done better with lower drug prices and less new drugs?⁵⁴

5.2 Is it plausible that the counterfactual world could have been healthier?

If the evidence of the aICER of the counterfactual could be compared to the Incremental Price Effectiveness (*IPER*) of new drugs, then it would be possible to test empirically this question of whether the US could have done better with lower prices. Unfortunately, as is the case with much of the rest of the OECD, there is comparatively less evidence on the counterfactual to increased expenditure on patented technologies; for example, unpatented respite care programs. The reasons for this include the failure of the market to provide evidence of unpatented programs and the failure of institutions to address this market failure. This point is a major theme throughout this thesis.

In the absence of evidence of the counterfactual to current drug prices in the US, there is an alternative option available to assess this question. When we look at the evidence beyond the US, the possibility that its population could have done better becomes apparent, and the absence of evidence of the counterfactual in the US is no longer a barrier to determining whether it is reasonable to exclude the possibility that the US could have done better with lower drug prices and less NMEs. This evidence is discussed in detail in Appendix 3. In summary, the increase in longevity experienced by the US over the period 1960 to 2008 could be significant at 10 years (PhRMA 2011) however, this literature does not refer to the increase in average longevity of the US population relative to the rest of the OECD. For any two points in time over the period 1960 to 2008, the US population's longevity increased less than that of countries such as Australia, Canada and the UK. In 2009, the life expectancy of a male at birth was estimated at 80 for an Australian male and 76 for a US male. (Section 4, p. 226, Appendix 3) This represented an improvement of 6 and 4 years in life expectancy since 1990 for an Australian and a US male, respectively. Hence the gain in average life expectancy at birth for a US citizen was two thirds of that of the gains for an Australian citizen.

This evidence is not sufficient to prove that the US could have done better had they lowered prices and instead invested in other health programs, in workforce and improved access to health care for the uninsured. It simply raises the evidence missing from the current US policy narrative that could convince decision makers that while new drugs could have contributed to 60% of the ten years of growth in life expectancy in the US, this does not mean even more drugs are essential for continuing improvements in life expectancy. Perhaps looking beyond the backyard of the US to consider the options taken by other countries should be part of the policy choice set.

From the perspective of this thesis and its focus on the political economy of new drugs, the omission of the evidence of the US life expectancy gains relative to the rest of the OECD from the US policy narrative is significant. It excludes consideration of the possibility the US could have achieved more with lower drug prices and more expenditure on other areas, including improved access to new drugs. Had US Pharma introduced this issue into the policy narrative, they would have had to consider the possibility that the health of the US could have been better than it was today, despite the significant increases over the previous 50 years.

6 Discussion and conclusions

6.1 The Reimbursers' questions

The Reimbursers reviews her question.

⁵⁴ A number of studies have shown that the US has shorter delay times for new drug adoption. (Danzon, Wang et al. 2005)

Does the US estimate of a 28 fold health return on pharmaceutical R&D financed by higher drug prices exclude the possibility that at lower prices and less NMEs the US's population's longevity would now be even higher?

The gain in average life expectancy at birth in the US since 1960 and the contribution of new drugs is an important theme in the US policy narrative. The evidence that there is a 28 to 1 return could have some influence in the US as part of the strategy to lobby to maintain higher prices. This evidence is not sufficient to persuade the rest of the OECD that increased prices will lead to better outcomes for these countries. One reason is that this result does not exclude the possibility that had US health budget holders made other investments in the past, health today would have been better. Furthermore, it is not just the estimate of return on pharmaceutical R&D derived using **Equation 1** that excludes the possibility that the US was worse off with higher prices: the prevailing political economy of new drugs excludes the possibility of increased prices today and worse health tomorrow. The omission of the evidence of the US life expectancy gains relative to the rest of the OECD from the US policy narrative is a significant advantage to the US policy narrative. It means that pharma-economists do not need to explain whether the US could have achieved more with lower drug prices and more expenditure on other areas, including improved access to new drugs. In simple terms, the prevailing political economy of new drugs can accommodate variation in the size of the costs compared to the benefits of lower drug prices ($0 < r < 200$), but it cannot accommodate the possibility that lower prices leads to more health, that is, $r < 0$.

6.2 Conclusion

The Reimburser reflects on the situation. Twenty years of application of economic evaluation and a decision threshold to new drug reimbursement decisions has improved the information available to the new drug reimbursement process. This long term use means that her country does not need to rely on the results of retrospective studies to justify the uptake of new drugs such as those the US regulators are apparently informed by, if the following is correct:

*Benjamin Franklin once remarked, "In this world nothing can be said to be certain, except death and taxes." Spokespersons for the pharmaceutical industry might be inclined to argue that the benefit-generating capability of prescription drugs also belongs in this exclusive category. They could make a compelling case: **recent studies suggest** that pharmaceutical products increase longevity, improve quality of life, and often result in medical cost savings. (Giacotto, Santerre et al. 2005)*

The use of economic evaluation also improved the confidence with which a government can defend a decision to finance a new high cost drug; it might have a significant additional financial cost to the drug budget, but at least it is "value for money".⁵⁵ But did the strategy of a threshold price for new drugs result in reimbursement decisions that increased the population's health? Or were the programs displaced to finance new drugs more cost effective than the new drugs? Did this strategy of using HTA/CEA ensure that the best use was made of the entire health budget? Or did it create a system that programs that were unpatented or unpatentable could not access or compete against because there was a failure in the market to provide evidence of their cost and effect? Did the attempts to correct the failure of the free market to generate evidence of the incremental cost and effect of new drugs generate other problems? In the words of Arrow (1963):

The social adjustment towards optimality thus puts obstacles in its own path. (p. 947)

⁵⁵ The Health Minister said this to the Reimburser after she approved a very high cost drug with a significant additional cost to the health budget. The Health Minister expressed his relief at being able to provide Treasury with a "solid economic rationale" for this unexpected increase in the drug budget, namely that it was "cost effective" and "value for money".

The Reimburser is concerned that she has a long journey ahead to answer the Ministers' question: How should she respond to the claim that a decision threshold that is below the *FPP* is worse for the population? She is clear of the next step; an understanding of exactly what Pharma is claiming there will be less of, if new drug prices are lower. The value of the desired outcome of R&D - clinical innovation - is the subject of the next chapter.

Chapter 4: The clinical value of innovation

The term "innovation" is used in a number of different ways in pharmaceutical regulation processes. This chapter addresses the question of what is meant by the term "innovation" in the context of the debate on new drug prices. First, this chapter draws the distinction between some of the lay and medical uses of the terms "innovation" and "innovative": i) innovation (the process); ii) an innovative drug (a new drug); iii) a clinically innovative new drug; and iv) the value of clinical innovation. Second, the three types of pharmaceutical innovation in the economic sense (the potential to generate a social surplus) are identified.

- 1) **Clinical innovation:** The definition of the clinical value of innovation used in Health Technology Assessment/Cost Effectiveness Analysis (HTA/CEA) is proposed as the most appropriate: *The estimated present value of the long term gain in health effects compared to best existing therapy for a well specified group of patients and clinical protocols.* This definition is the "incremental effect", ΔE , used in CEA. A new drug with no clinical benefit compared to the best alternative therapy has no clinical value of its innovation ($\Delta E = 0$), even if such a drug is sufficiently different from other drugs to be defined as "innovative".
- 2) **Resource innovation:** An example is innovation in the resources involved in supplying a given clinical benefit by developing an oral version of an intravenous (IV) drug. Resource innovation is captured in HTA/CEA via a negative ΔC (where the additional financial costs of the new drug are excluded).
- 3) **Developing and manufacturing innovation** An example is innovation in the methods of manufacturing drugs by for example, refining the processes used to develop large molecules such as trastuzumab.⁵⁶

An analogy between clinical and economic concepts of value is noted. Clinical value of innovation, like economic value, is constrained by the best alternative strategy. The clinical value of a new drug's innovation is its gross clinical effect (compared to no care) constrained by the opportunity cost (foregone health benefit) to the patient of not using the best existing therapy.

⁵⁶ For a discussion of the technicalities of developing such a drug and the opportunities for innovation and change in this process refer to a discussion on its production prepared for the European Medicines Agency as part of their approval process. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000278/WC500049816.pdf Accessed: 21-02-12

1 The Reimburser's problem

The US International Trade Delegate is arguing that pharmaceutical regulation needs to “reward innovation” and that the pricing system in the country of interest does not achieve this. The Reimburser is aware that a recent decision about a new drug was controversial because the Reimburser refused to pay more for that drug (on cost per course basis) compared to a drug that had been off patent for at least five years; a generic. The reason for her decision was that the new drug was shown in clinical trials to be no more effective than the existing generic drug. The new drug was innovative in that it had a different molecular structure from any existing drug, and it was even the lead drug in a new therapeutic sub-class,⁵⁷ however the new drug did not provide a clinical advantage over the standard therapy for this condition. The International Trade Delegate argued that a significant investment had been made into researching and developing this innovative drug and hence the price needed to reward this investment in innovation. The International Trade Delegate points out that the firm that took this risk and invested would have been better off if it had simply produced the generic. Where is the incentive for innovative firms to take risks if they are rewarded no more than generic firms that take no risks? He argues that it does not make economic sense for this investment in the innovation process to remain unrewarded.

The Reimburser is concerned about the concepts of innovation revealed by the discussion with the US International Trade Delegate. From a clinical perspective, the value of innovation is about the clinical benefit of the new drug, not about the characteristics of the molecule or the type of risks taken by the firm. However, the Health Economic Adviser points out that a new drug could be no more effective than an existing drug but delivered in a way that does not require a hospital admission, hence reducing the cost associated with administering the drug. Hence the innovation in this case is not about clinical benefit; it is about resource benefit.

Is there a fundamental difference between how economists and clinicians understand the value of pharmaceutical innovation? The Reimburser asks her Health Economic Adviser:

"Is there a way of defining the value of pharmaceutical innovation that makes sense from both an economic and clinical perspective?"

2 Innovation: lay, regulatory and medical concepts

2.1 Innovation and the regulatory process

The term “innovative” is used to distinguish between generic firms (that do not invest in pharmaceutical R&D and only produce generic drugs) and innovative firms (that do invest in pharmaceutical R&D).⁵⁸ If an innovative firm develops a new molecule, it only needs to establish a sufficient degree of physical difference from an existing technology to be defined as an: "innovation"

⁵⁷ An example of a new therapeutic subclass is the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the early 1990's. SSRIs are anti-depressants that were considered a separate therapeutic subclass from the existing tricyclic anti-depressants (TCAs). Fluoxetine was the first SSRI (innovative) and then others (“me-toos”) followed (e.g. sertraline). The introduction of venlafaxine in the late 1990's was considered to be a new therapeutic subclass, the serotonin–norepinephrine reuptake inhibitors (SNRIs). (DeVane 1994; Pekarsky 2010)

⁵⁸ This characteristic of a firm, investment in pharmaceutical R&D, is a necessary condition for membership in the PhRMA: *"The Pharmaceutical Manufacturers Association was founded in 1958. Its name was changed to the Pharmaceutical Research and Manufacturers of America in 1994 to underscore the extraordinary commitment of member companies to research. Headquartered in Washington, D.C., PhRMA represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier and more productive lives."* www.phrma.org/about/phrma Accessed: 21-02-12

or "invention". For example, a New Molecular Entity (NME) can be awarded a patent provided it is a different molecule to any existing molecule. Whether it is more or less effective or equivalent to placebo is not relevant to the decision to define it as "innovative" or an "invention" for the purpose of a patent. Consequently, each year there are many more molecules patented and tested in Phase 1 trials than there are NMEs registered (approved for therapeutic use).^{59,60}

For a firm to be provided with a licence to market that drug, it requires evidence of the clinical value of this innovative molecule, typically evidence of its safety and efficacy.⁶¹ In most jurisdictions, the minimum evidence of clinical value of innovation is obtained by controlling (constraining) the effect of the new drug by some alternative therapy. For the firm to obtain a licence to market a new drug in the US it requires evidence of its performance against placebo, preferably derived from a double blind randomised control trial (RCT). The evidentiary and performance demands on a licenced drug (one that is approved by an agency such as the US Food and Drug Administration (FDA) in addition to being patented) are therefore much higher than those of an innovative molecule (one that is awarded a patent). Some new drugs that are approved by the FDA are referred to as "innovative" to distinguish between first in class (innovative or lead) and follow on (or me-too) drugs (Pekarsky 2010). But not all drugs that are approved for use or described as "innovative" necessarily have a clinical value in the underlying innovation. So what is clinical innovation?

2.2 Clinical innovation

Health Technology Assessment/Cost Effectiveness Analysis (HTA/CEA) informs the so called "fourth hurdle" of regulation where the quantification of the new drug's clinical innovation is the primary objective of the analysis.⁶² The regulatory imperative of reimbursement decisions is to assess the appropriateness of changed, additional or substituted therapy. Therefore, reimbursing institutions are interested in the clinical value of innovation for a group of patients for whom a subsidy for the cost of the drug is being proposed. A common definition of the clinical value of innovation of a new technology is the best estimate of the additional clinical effect (or effects) of the new technology

⁵⁹ For example, in the Pfizer 28 February 2011 Pipeline Report, the company reported 93 NMEs in the pipeline of which 4 were in the Registration phase and 13, 28 and 49 of which were in Phase 3, 2, and 1 respectively. It is not possible to determine the number of NMEs with Pfizer patents on this date, but not yet in Phase 1, from this report.

http://www.pfizer.com/files/research/pipeline/2011_0228/pipeline_2011_0228.pdf Accessed: 21-02-12

⁶⁰ A search of the Australian patent data base on February 28 2011 of patents where the applicant's name contains the word Pfizer contains 2,513 results, not all of which are NMEs. <http://pericles.ipaustralia.gov.au/ols/auspat/>

⁶¹ The US Food and Drug Administration details the requirements for approval on <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm> Accessed: 21-02-12

⁶² A paper by Cohen et al. (2007) describes the fourth hurdle and also describes some of the limitations of not considering the opportunity costs of decisions.

compared to the best existing therapy for the group of patients for whom its use is being assessed.^{63,64} This definition requires specificity in the assessment of the "clinical value of innovation" of a new technology. For example, an HTA/CEA assessor is unlikely to ask the question: "Is this new drug clinically innovative?" Instead he might ask: "If current best therapy is replaced by this new drug for this patient group, using this clinical protocol (tests, dose and duration of therapy) what is the expected incremental effect as measured by this set of clinical endpoints?"

HTA/CEA typically involves meta-analyses of the evidence of effect from RCTs and the extrapolation of this evidence to longer time periods, additional patient groups and clinical end points by way of pharmaco-economic models. Uncertainty is characterised and analysed using deterministic and probabilistic sensitivity analyses. The net financial implication to the health budget of adoption, ΔC is also estimated. (See the discussion about resource innovation in the following section.) The incremental financial cost, ΔC , and incremental effect, ΔE , of the new drug compared to the best alternative therapy are summarised as either an incremental cost effectiveness ratio:

$$ICER = \frac{\Delta C}{\Delta E}$$

Or a net benefit metric:

$$NB_i = i\Delta E - \Delta C$$

where i is some monetary value of the clinical effect.⁶⁵ (See Appendix 4 for a discussion of this terminology.)

This information is then used in conjunction with a range of other evidence to inform the decision to reimburse that drug.⁶⁶ While HTA/CEA methods vary across jurisdictions, there is a key common element; the focus on the estimate of ΔE for a specific clinical context (comparator, patient group and

⁶³ In 1993, the Australian Pharmaceutical Benefits Advisory Committee (PBAC) published the first Guidelines for the use of HTA/CEA to inform a drug reimbursement process. The most recent version of these can be found at <http://www.pbs.gov.au/info/industry/listing/elements/pbac-guidelines>. Accessed: 210212 These Guidelines illustrate the rigour and specificity HTA/CEA requires for Industry submissions to PBAC for reimbursement of new drugs.

⁶⁴ The US has only recently started to consider the idea of comparative effectiveness as a way of understanding the benefits of a new drug. In recent years the US has focused on evidence of performance against placebo rather than an alternative active therapy as an indicator of the value of a new drug. In the words of the FDA: "*FDA's experience with comparative effectiveness claims is relatively limited. Our enabling law (FDC Act, as amended in 1962) does not require assessment of comparative assessment and the legislative history made it very clear that there is no relative effectiveness requirement. A new drug does not have to be better than or even as good as existing treatment.*" Source: Comparative Effectiveness Research a PPT by R. J. Temple. Available as a download at www.FDA.gov Accessed 12-12-2011 This statement suggests that the US decision makers conflate the idea of having to be proven to be more effective than existing therapies in order to be approved by the FDA and having to provide evidence of comparative effectiveness as part of the new drug approval for uptake on the formularies. Comparative effectiveness analysis also concerns the review of data bases such as cancer registries and longitudinal data bases held by Medicare and Medicaid to develop evidence of comparative effectiveness. For an example of some of the infrastructure investments by the US in relation to comparative effectiveness see the Fact Sheet: "American Recovery and Reinvestment Act Investments in Comparative Effectiveness Research for Data Infrastructure" Available at www.FDA.gov Accessed 12-12-2011.

⁶⁵ The ICER does not appropriately accommodate the situation where either or both of the incremental cost and effect are negative. Hence the NB_i is considered preferable. However, in this thesis the situation of interest is where there is both an additional cost and an additional effect.

⁶⁶ The references and guides for pharmacoeconomics and HTA/CEA are extensive. The following three articles are examples of the contributions made by economists to the HTA/CEA process. (O'Brien 1996 ; Briggs and O'Brien 2001; Briggs, O'Brien et al. 2002)

clinical protocol). A drug might be described generally as clinically innovative, but the estimate of value of clinical innovation is specific to a clinical context.

3 Non-clinical pharmaceutical innovation

The focus on clinical innovation (ΔE) as the main tangible outcome of pharmaceutical innovation is consistent with the narrative around medical research more generally: it is about developing cures and treatment for diseases and improving life expectancy and quality of life for patients.⁶⁷ However, pharmaceutical innovation (the product of pharmaceutical R&D) can take at least two other forms and still potentially impact on population health, without having any clinical innovation content in the new drug. The first is in relation to the implications for health resource use generally and the second is innovation in the drug manufacturing process.

3.1 Resource innovation

The incremental impact of a new drug on resource use is:

- the conventional ΔC (the net financial impact of adopting the new drug compared to existing therapy);
- less the share of that additional financial cost that is attributed to either:
 - the difference in the financial cost of the new drug compared to the drug that it substitutes for; or
 - the financial cost of the new drug if it is added to existing therapy (no substitution).

We start with an example of pure resource innovation: a new formulation of a drug that allows the drug to be taken orally at home rather than intravenously as part of a hospital admission. There is an R&D cost associated with this development. This innovation could result in a reduction in the non-drug costs of \$250 per course of the drug. In this case, the difference in resource use is captured in the ICER or NB_i via ΔC . From an economic perspective, this innovation can be valued in terms of increased population health, for example if the additional financial savings are allocated to other health services. However, if the firm prices so as the additional savings are entirely offset by the additional cost of the drug, then the entire value of the resource innovation is appropriated by the firm.⁶⁸ For this reason, ΔC only captures “resource innovation” if the net additional cost of the new drug relative to the existing substituted drug are excluded.^{69, 70}

⁶⁷ The American Pharmaceutical Research and Manufacturer’s Association website www.phrma.org is rich in examples of this narrative, for example the statement that: “2011’s New Medicines Fought Wide Range of Diseases, Conditions” Accessed: 21-02-12

⁶⁸ The endogeneity of new drug price is discussed further in Chapter 6.

⁶⁹ Why should the resource innovation be considered in terms of the incremental cost net the effect of the incremental cost of the drug itself? The incremental cost includes a term relating to the net financial effect of adoption on other resources, as well as the additional cost of the new drug compared to the existing drug (if it is a direct substitution.) However, as first discussed in Chapter 6, while differences in resource use and the associated costs can be estimated empirically in a clinical trial, the price of the drug and its associated cost is determined endogenously to the Reimbursement process. What this means is that a new drug could be innovative in terms of preventing the need for an admission to deliver the drug IV, however, the incremental cost will not reflect this if the firm prices the drug so as to appropriate the full value of that surplus or resource innovation. That the price of the new drug is the mechanism by which clinical and resource innovation are appropriated by the firm, a point well understood by pharma-economists, for example Vernon et al (2009).

⁷⁰ Technically we could consider an incremental cost as resource innovation (albeit undesirable) – for example, two additional consultations with a GP are required.

3.2 Manufacturing innovation

Another form of non-clinical innovation is in the manufacturing process. Typically the variable costs of producing drugs is argued to be low relative to the cost of R&D, however, there remains scope to reduce the manufacturing costs.^{71,72} Reduced cost of manufacturing is the source of innovation used by Tirole (1988) to illustrate the “pure value of innovation.” Tirole shows how if the firm is a monopolist in its output market it can maintain a price per unit of the good following innovation in manufacturing and the entire surplus is appropriated by the firm. In more competitive situations financial savings will be shared with purchasers. This example of innovation in manufacturing is expanded in Chapter 10 in terms of its implications for pricing of drugs today in order to gain innovation in the future.

4 Discussion and conclusion

4.1 What did the AUSFTA conclude?

The confusion in the US between innovative drugs and clinically innovative drugs could be a consequence of the US imperative to distinguish between the generic and the innovative sectors of the pharmaceutical industry; the latter does need to invest in pharmaceutical R&D whereas the former does not. However, the prevailing political economy of new drug price (PEND) is unequivocal: the primary value of pharmaceutical R&D is in its impact on a population's health; the ability to cure and treat disease and improve or extend quality of life (Chapter 1 and Appendix 2).

Despite the confusion in the US Congress and Senate about the distinction between innovative drugs (non-generic drugs) and clinically innovative drugs, the AUSFTA ultimately made this distinction. From Annex-2-C-Pharmaceuticals comes the following statement:

*(d) the need to recognize the value of innovative pharmaceuticals through the operation of competitive markets or by adopting or maintaining procedures that appropriately value the objectively demonstrated therapeutic significance of a pharmaceutical.*⁷³

In other words, according to the AUSFTA, the value of innovative drugs is derived from their therapeutic significance, not simply that they are a molecularly distinct drug that is the result of investment in pharmaceutical R&D. Given the significance of clinical innovation in the PEND, this outcome might come as no surprise.

4.2 Other results of pharmaceutical innovation

The identification of three aspects of pharmaceutical innovation, all of which are products of pharmaceutical R&D, is a reminder that the economic concept of pharmaceutical innovation is broader than the pure clinical concept. The clinical and resource innovation are consistent with the policy

⁷¹ DiMasi's study (2002) highlighted a range of factors that could be addressed to improve productivity of drug development processes, including both regulatory and business decision making. He concluded: “*Whether faster development times, quicker termination decisions or higher success rates derive from public policy initiatives, better management, or new technologies, the impact on R&D costs can be substantial. Ultimately, the increased efficiency could result-in more innovation and new therapies reaching patients sooner.*”

⁷² There are numerous businesses offering innovative solutions to pharmaceutical manufacturers to improve their efficiency. A quick look at an industry journal such as the Pharmaceutical Manufacturing magazine highlights that pharmaceutical manufacturers are like every other industry – they welcome innovation in the manufacturing process. <http://www.pharmamanufacturing.com/> Accessed: 21-02-12

⁷³ http://www.dfat.gov.au/fta/ausfta/final-text/chapter_2.html Accessed: 21-02-12

narrative about the benefits of investing in more drugs; the advantages are not just more health but also more medical savings (Giacotto, Santerre et al. 2005). The idea that new drugs generate savings is an increasingly important part of the global policy narrative. Personalised medicine is a current example of the imperative for resource innovation. Advocates of targeting by pharmacogenomic markers highlight the promise of innovation leading to improved sustainability of the health care sector (Davis, Furstenthal et al. 2009; Personalized Medicine Coalition 2010). Innovation in manufacturing is a source of improved profitability for firms. One of the limitations of HTA/CEA is that while it isolates clinical innovation, ΔE , it does not isolate the resource innovation (this is integrated with the price of the new drug in ΔC) and completely ignores manufacturing innovation. Pharmacogenomics is also argued to contribute to manufacturing innovation (Cook, Hunter et al. 2009).

4.3 Opportunity cost and clinical value of innovation

The methods developed in HTA/CEA have important implications for how we understand the process of quantifying the "objectively demonstrated therapeutic significance of a pharmaceutical". These methods highlight that if the Reimbursing body wants to assess the decision whether or not to replace an existing technology with a new innovative technology, she needs to define the clinical value of innovation of an NME in terms of specific clinical context. Characteristics that define this context include: patient groups (e.g. a positive result on a particular test); conditions of use (e.g. dose and duration of therapy) and a specific therapeutic context (e.g. first or second line). Furthermore, in order to define the clinical value of innovation, the estimate of effect of the new drug for the specific clinical context needs to be constrained by the **opportunity cost to the patient** of using the new therapy; the foregone benefits of the best alternative therapy.

4.4 Conclusion

Achieving agreement on the clinical value of innovation is only the starting point in the issue of pricing new drugs. The excerpt above from the AUSFTA refers to the need to "**appropriately** value the objectively demonstrated therapeutic significance of a pharmaceutical". HTA/CEA can provide an objective value of therapeutic significance for a clinical context (ΔE). It can also provide an objective value of the financial significance of that new drug for a health budget ΔC , at a particular price (the offer price) of that drug. However, the appropriate value of that new drug in the context of a market transaction, the economic value or shadow price, cannot be derived from the methods developed for HTA/CEA. The concept of shadow price is the subject of the next chapter.

Chapter 5: The shadow price, λ

For some non-economists, the idea of a monetary value and an economic value of a good are synonymous. However, the difference between an economic and a maximum willingness to pay (maxWTP) valuation of a good is a critical concept in economics: the former necessarily captures information about the forgone benefit of a purchase whereas the latter might or might not. If a decision maker had only one piece of information about the value of any good to compare to its offer price, and had limited resources, she would prefer its economic to its maxWTP value. The shadow price is one way that economists capture economic value, but the definition of the shadow price and its derivation varies across disciplines.

Three examples of shadow price are reviewed. The **shadow price of the budget constraint** λ is an important concept in economics and operations research; it values the action of relaxing (or tightening) a resource constraint by one unit as the maximum possible gain (or minimum possible loss) from this action. In the context of Cost Benefit Analysis (CBA), the **shadow price of an input (or output)** is derived from available information and is intended to correct for the failure of the market to provide market prices. The **average shadow price** is a term used to define a decision threshold for the adoption of inputs in the case of inputs that are not infinitely divisible.

These terms all relate to the same concept: valuation of an action with reference to its minimum possible loss or maximum possible gain. The advantages of valuing an input with no market price with reference to its incremental effect or benefit valued at any shadow price rather than the maxWTP are demonstrated. These benefits exist because unlike the maxWTP, the shadow price is sensitive to alternative methods of achieving these incremental effects. Hence, the situation where an input with market power can appropriate the full surplus associated with its incremental effect can be avoided.

These advantages over the maxWTP apply to all types of a shadow price. However, there are situations when it is preferable to use the CBA style shadow price to value an input (via the shadow price of its incremental effect) rather than the shadow price of the budget constraint. Models from which λ is derived typically assume that the budget is (resources are) currently economically efficient and that the prices of inputs are set in perfectly competitive markets. In contrast, a health budget holder faces a health budget that is not economically efficient. Furthermore, the inputs for which this valuation is being sought will typically have market power, for example a patented drug. In such contexts the derivation of a shadow price for an input from existing information about the economic context (CBA style) is a more appropriate approach than using the shadow price of a budget constraint, λ . A general method of deriving a CBA style shadow price for an input is illustrated.

"In fact the real cost of any programme is not the number of dollars appearing on the programme budget, but rather the value of the benefits achievable in some other programme that has been foregone by committing the resources in question to the first programme. It is this opportunity cost that the economic evaluation seeks to estimate and to compare with the programme benefits."

(Drummond, Sculpher et al. 2005 p. 9)⁷⁴

"Everyone knows umbrellas cost more when it rains." Tom Waits from "Talking at the same time" 2011⁷⁵

1 The Reimburser's problem

How should the objectively determined therapeutic significance of a new drug, its clinical innovation, be valued for the purpose of a market transaction?

The Reimburser recently read a paper by US pharma-economists that said that the economic value of new drug innovation was indicated by the Payer's maxWTP as revealed by the aICER of the least cost effective of funded programs, for example, dialysis (Vernon, Goldberg et al. 2009). Back of the envelope calculations suggest to the Reimburser that if all new drugs were paid the aICER of programs such as dialysis, there would be a significant expansion of the current drug budget and health services that are more cost effective than the new drugs would need to be displaced to finance these additional costs from a fixed health budget.⁷⁶

Then the Reimburser reviews a series of papers that refer to the use of the maxWTP as an appropriate value of the health effect, in the absence of evidence of the shadow price of the budget constraint (Johannesson and Weinstein 1993; Stinnett and Mullahy 1998). She also reads a paper by Weinstein (2008) that describes multiple ways to understand the value of a QALY in the context of the US. Weinstein clearly links the imperative to find a value for a QALY to the recognition by the US population that resources are limited.

Until Americans come to terms with the fact that they are not willing or able to pay the costs of providing all citizens with all effective health care services there will be no explicit need for a benchmark dollar value of a QALY." (Weinstein 2008 p. 345)

Five years ago the Reimburser was involved in the decision to award a significant grant to a group of academics who surveyed over 1000 people to estimate the maxWTP for a QALY.⁷⁷ At the time she was convinced by the argument that because there was no perfectly competitive market for health effects, health tended to be undervalued by the market and therefore it was necessary to survey society to find a value. The Reimburser provides the result of this study (maxWTP per QALY = \$75,000) to her Health Economist as a guide to the economic value of the health effects of a new drug. The Reimburser is confused when the Health Economist states that this information is not what he needs. The Health Economist uses this example to illustrate the issue:

A Consumer asks her Agent to purchase a particular new bicycle on her behalf. Which of the two following pieces of information should she give her Agent? The maximum price she is willing to

⁷⁴ The text from which this quotation is sourced does not provide a method whereby this opportunity cost can be estimated, however, it does detail how the maxWTP for a QALY can be estimated.

⁷⁵ Just a reminder - the maxWTP can also change as the context changes.

⁷⁶ Section 4, Appendix 7, starting from p. 258 discusses the issue of choice of the aICER and full value price in more detail.

⁷⁷ The inspiration for the study was one very similar to that described in Donaldson et al. (2011).

pay for the bicycle (\$5,000) or the lowest price that bicycle is available for, according to the results of an online search (\$1,250)? The latter is the shadow price of the bike, the former is the maxWTP.

The Reimburser is inclined to say the shadow price is the price the Consumer should give her Agent. In fact, if the market for this type of bike were perfectly competitive, then it would not matter which of these two prices the Consumer gave her Agent. In this case the price at every shop would be \$1,250 and hence the price the Agent pays for a new bike would be \$1,250, regardless of the information the Agent is provided with and regardless of the Consumer's maxWTP. However, if the local market were a monopoly and the online price were from a competitive market, then it would matter which price she gave her Agent; the monopolist could be pricing at average rather than marginal benefit and hence the purchase price could be higher than the online price from a competitive market. The potential loss resulting from providing the wrong piece of information to her Agent would be maximised under the following scenario.

The local monopolist bike shop owner does not provide price tags for her new bikes. Instead she asks the Agent, what is the maximum you are willing to pay for a bike? Then, after receiving this information she writes a price tag for that bike and offers it to the Agent. In this case the Agent would pay \$5,000 for the bike if the only information that was provided to the Agent was the maxWTP. The loss of surplus to the Consumer would be \$3,750 (= \$5,000 - \$1,250). If the Agent were provided with the information about the shadow price, and the local monopolist bike shop owner knew the Agent could take her business elsewhere (not such a monopoly after all), she would have reduced this price.

This example makes the intended point, but it just does not seem "technical enough" to the Reimburser. There is no "online price" from a competitive market for a new drug that she can benchmark the new drug price against. The Reimburser asks her Health Economist:

- 1) *Why is it that the maxWTP is not an economic value?*
- 2) *Which shadow price should she use?*

2 Why is the shadow price preferable to the maxWTP?

The key difference between the shadow price and the maxWTP is that the former acts as a conventional price by capturing the information about the economic context whereas the maxWTP captures only one aspect of the economic context, the consumer's preferences. If there is increased competition in the market for a good and the price is reduced, the maxWTP for the item does not change, whereas the shadow price will reduce.

A hypothetical application of shadow prices to a real world problem (the non-excludability and non-rivalry of the outputs of dung beetles) illustrates this issue. The method is an adaption of those described by Mishan and Quah (2007) and McKean (1972).

2.1 Dung beetles, flies and outdoor dining in Canberra

When the number of flies in Australia were reduced by the introduction of dung beetles by the Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO) in the 1980's, outdoor dining in places in Australia such as Canberra became possible, apparently for the first time. There is no dung beetle market in Australia, despite their tangible and significant value to the Australian economy (Commonwealth Scientific and Industrial Research Organisation 2006). The output of a program to introduce dung beetles is both non-rival in consumption and non-excludable; such a program is a public good. So how can we derive a price for the main input into this program;

the dung beetle? (While the role of dung beetles in reducing flies in Canberra is true, the following story about the bidding process and competition is completely fictional.)

Assume for simplicity that the only output of the dung beetle program is: fly free outdoor dining in Canberra (FFODC). Assume that there are three inputs in this program, two of which are priced at their marginal cost of production (transport and labour) and one of which does not have a price (the dung beetle). Now assume also that there is an alternative method for achieving FFODC and there is a functioning market for this good (outdoor fly screens). The evidence of the value in exchange of FFODC is revealed in the functioning market of outdoor fly screens.

This story is set out in Table 6. The Canberra Council, who will finance this Dung Beetle Program, wants to know about its costs. CSIRO is the only group in Australia to have a licence to import dung beetles and there is no other way for the Canberra Council to obtain them.

Part 1: From the first column we see that the labour and transport costs for the Dung Beetle Program are \$100K and \$10K respectively. CSIRO has not told Canberra Council how much it costs for the 1,000 dung beetles. CSIRO has also financed a rigorous study that estimated the maxWTP by the Canberra population for the goal of FFODC and found this was an amount of \$20M. The Council asks CSIRO the costs of the dung beetles. They reply that it is \$19,890 per beetle or \$20M for the overall cost of the program. This is exactly the maxWTP for FFODC. The owners of the Outdoor Fly Screen Company make an urgent submission to Canberra Council. They say they can achieve the same result (FFODC) with a different program for \$1.15M. Clearly, even though the costs of the Dung Beetle Program are the same as the benefits, there is a more cost effective option. The Canberra Council decides to use the Outdoor Fly Screen Program.

Part 2: CSIRO comes back to the Council and says they have revised their costs. They can now provide Dung Beetles for \$1,040 each. The costs of the Dung Beetle Program are now the same as the Outdoor Fly Screen Program: \$1.15M.

This simple example illustrates the following point. If there is only one situation in which dung beetles are an input, and there is a failure of a dung beetle market to function, then provided that there are multiple inputs and methods of production that can be used to achieve the same output, FFODC, then a shadow price of dung beetles that takes into account this competition can be calculated. The dung beetle is valued at \$19,890 but its shadow price is \$1040.

Table 6 What is a dung beetle worth? What is its market price?

	Part 1	Part 2	Scenario
	Max WTP output	Shadow price input	Max WTP output (higher costs of manufacture)
Dung Beetle Program			
Labour	\$100,000	\$100,000	\$2,000,000
Transport	\$10,000	\$10,000	\$30,000
Subtotal	\$110,000	\$110,000	\$2,030,000
Dung beetles - patented so no market price			
1000 beetles	\$19,890,000	\$1,040,000	\$17,970,000
per beetle	\$19,890	\$1,040	\$17,970
Program total cost	\$20,000,000	\$1,150,000	\$20,000,000
Outdoor fly screens program			
Labour	\$100,000	\$100,000	\$100,000
Transport	\$50,000	\$50,000	\$50,000
Fly screens	\$1,000,000	\$1,000,000	\$1,000,000
Program total cost	\$1,150,000	\$1,150,000	\$1,150,000
Output			
Outdoor dining in Canberra is possible			
Max WTP	\$20,000,000	\$20,000,000	\$20,000,000
Select dung beetle program			
Cost of dung beetle program	\$20,000,000	\$1,150,000	\$20,000,000
Surplus (MaxWTP less cost)	\$19,890,000	\$19,890,000	\$17,970,000
Dung beetle patent holder	\$19,890,000	\$1,040,000	\$17,970,000
Consumer surplus	\$0	\$18,850,000	\$0
Deadweight loss	\$0	\$0	\$880,000
Select outdoor fly screen program			
Cost of outdoor fly screen program	\$1,150,000	\$1,150,000	\$1,150,000
Surplus (MaxWTP less cost)	\$18,850,000	\$18,850,000	\$18,850,000
Consumer surplus	\$18,850,000	\$18,850,000	\$18,850,000

So why is it that there is an advantage to the Canberra Council in using the shadow price? The first advantage is that if outdoor fly screens are a more cost effective way to achieve the intended output of outdoor dining, Canberra's Council will recognise that they can achieve the same result at a much lower cost. The maxWTP considers only the preferences for outdoor dining and not alternative method of achieving this; it values the output not the specific input.

The second advantage of this approach is that it maximises consumer welfare. CSIRO knows the maxWTP for the benefits of the program; it did the study to estimate it. If the CSIRO knew that the competition (fly screens) was not recognised, then it would be possible for the CSIRO to appropriate the entire surplus associated with the reduction in flies in Canberra by pricing its input such that the total cost of the program is the same as the maxWTP. At the shadow price, the surplus is appropriated by the consumers. The point is that not only does the shadow price capture information about the economic context – the competition in the outdoor dining market – it also has the potential to reduce the risks associated with other distortions that could arise as a consequence of, for example, market power due to patents.

The third problem this method overcomes is the deadweight loss⁷⁸ that can arise when the maxWTP for the output is used to derive the price of an input with market power and the competition of the alternative input is neglected. The Scenario column from Table 6 is an example where the actual costs of labour and transport for the dung beetle program are higher than the total costs of the Outdoor Fly Screen Program. Even if the benefits outweigh the costs of the Dung Beetle Program, for example it could be priced at \$15M, there could still be a deadweight loss of \$880,000 compared to the best alternative strategy, the Outdoor Fly Screen Program.

The observable difference between a value for the dung beetle calculated using the maxWTP for FFODC rather than a shadow price for that effect is as follows. The maxWTP for output derived value of the dung beetle as an input remains constant, regardless of how much competition there is to produce that output. The method can tell us what the dung beetle is worth from a lay perspective, but not its economic value. In contrast, the shadow price for that dung beetle (derived from the shadow price for the output, which is in turn derived from a functioning market) is defined by the economic environment, and will change as competition in the input markets change. It tells us what the Canberra Council should pay for a dung beetle given the competition in the market. It also maximises consumer surplus and prevents deadweight losses in social welfare.

The shadow price for the dung beetle is **endogenous** to the economic context (the market for reduction in number of flies in outdoor dining areas). The value of the dung beetle derived using the maxWTP is **exogenous** to the economic context; it only reveals the consumer's preferences which are not subjected to the constraints of alternative methods of producing the outcome of reduced flies. The shadow price of that input, unlike its maxWTP,⁷⁹ internalises the economic conditions, albeit with varying degrees of consistency between the specified economic context and the real world economic context.

We can conclude that shadow prices are preferable to maxWTP to value an input, particularly when there is competition in the market for inputs and the input being valued has market power. However, there is more than one type of shadow price. So which shadow price should be used in the context of the economic value of pharmaceutical innovation?

3 Shadow prices

The key concept of a shadow price is that the value of a resource allocation action is defined objectively by reference to its minimum possible loss or maximum possible gain. In the case of the dung beetles, the shadow price is defined with reference to the best alternative fly reduction strategy and will increase and decrease as the costs of the alternative change. However, there is more than one type of shadow price referred to in the economic literature. In the most recent edition of the 1971 classic text on Cost Benefit Analysis (CBA) (Mishan 1971), Mishan and Quah (2007) identified two usages of the term shadow price in the context of general economics and these are discussed below. Other authors have discussed the issue of finite divisibility of programs and the implications for shadow price and decision rules and hence a third usage of the term "shadow price" by Kim and Cho (1988) is also discussed.

⁷⁸ There is a reduction in social surplus, not just a redistribution of surplus; even if one subgroup is better off, the entire group is worse off.

⁷⁹ The maxWTP is not immune to changes in context. "Everyone knows that umbrellas cost more when it rains" Tom Waits, from "Talking at the same time." An instructive ditty appearing on Bad as Me, 2011.

3.1 Three shadow prices

The first usage of "shadow price" identified by Mishan and Quah (2007) is in the context of optimisation techniques and it differs slightly in its definition in economics compared to operations research. In operations research, the shadow price is the **minimum** loss in effect that occurs when one unit of a continuous resource (or constraint) is **withdrawn** (Takayama 1994). In economics, it is the **maximum** additional units of maximand or effect gained as a consequence of **relaxing** a constraint by one unit at the margin. The value of the Lagrange multiplier, λ , at optimisation is an example of this type of shadow price (Mas-Colell, Whinston et al. 1995).^{80,81} The shadow price, λ , in this context is also referred to as the shadow price of the budget constraint and is the sense in which the term is used by a number of health economists.⁸²

The second usage identified by Mishan and Quah is in the context of a cost benefit analysis (CBA). The definition proposed by Mishan and Quah is the appropriate price for an input or output in the context of CBA when the market price does not reflect the true social cost or benefit. One example is when the market price is systematically failing to include some aspect of the cost or benefit of the production or consumption of a good or service, for example the externality of pollution. Shadow prices are also used when there is no apparent market for a particular input or output. An example of the use of shadow price in this sense is the valuation of volunteer or carer time in a HTA/CEA.^{83,84}

In addition to the two uses identified by Mishan and Quah, shadow price has particular meaning in operations research and decision analysis in cases where the inputs are integer or discrete rather than continuous (Kim and Cho 1988). In the words of Mukherjee and Chatterjee: "*A shadow price for integer programming with valid economic interpretation eluded researchers, until Kim and Cho (1988) introduced the concept of average shadow price.*" (Mukherjee and Chatterjee 2006 p. 13).

The concept of an average shadow price as a critical price above which there is no incentive to purchase a discrete input is of relevance to health economics; in a universal health care system, decisions regarding new technologies tend to be in relation to financing the technology for no-one or all patients in a particular target group. Kim and Cho's definition of a shadow price is in the same units as the CBA shadow price (cost per unit output rather than units of output as in the optimisation context), however its application to decision making is different. In this case it is applied as a threshold or critical price in the context of a decision by a firm to acquire a discrete input rather than

⁸⁰ The shadow price can also be defined in an examination of the first order conditions required for Pareto optimality. It can be defined as the multiplier derived from the Kuhn-Tucker theory at optimality – it is the additional utility to a consumer as a consequence of relaxing an endowment constraint. See for example (Mas-Colell, Whinston et al. 1995) page 563

⁸¹ If there were decreasing marginal returns to additional inputs or resources we would expect that a shadow price that was derived using the operations research definition would be greater than that derived using the economic definition.

⁸² See for example Stinnett and Mullahy (1998) and Sendi et al. (2002).

⁸³ See for example Drummond et al. (2005) pages 58 to 59.

⁸⁴ Sculpher et al. (2005) appear to characterise shadow pricing as exclusively defined within and applying to a first best world and hence the limits on using shadow pricing can be inferred as equivalent to the limits of assuming a first best world. The authors argue that neoclassical welfare economic theory is an "application to a presumed nirvana of a first-best neoclassical world, where market prices represent the social value of alternative activities (and, when they do not, they can be shadow-priced assuming a first-best world)" and "only fits with a narrow and rarefied view of the world." The authors use this argument as a justification for their preference for a social decision making rather than neoclassical welfare economic theory as a foundation to economic evaluation of health care technologies. The capacity to develop a shadow price for a good within welfare economic theory and attempt to take into account market failure is not explored by these authors. It is likely (but not certain) that the authors' argument is an extension (or characterisation or application) of the debate between Mishan and Williams, one side of which is expounded in Mishan (1982). It would be useful to reduce the uncertainty surrounding the rationale of their decision to use this as a justification.

as a shadow price of a given input or output to be used in a CBA and an associated metric such as a Cost Benefit ratio. In this way it has the potential to become a signal to the owner of that input, instead of the more passive⁸⁵ approach to costing inherent a CBA.

It would appear that when CBA methods use the concept of a shadow price of an input, it is being used to refer to an average shadow price rather than a marginal shadow price; projects valued by CBA and therefore their inputs are often discrete rather than continuous. But the use of the term “average shadow price” rather than a marginal shadow price can lead to some discomfort for economists. Why? And does it matter?

3.1.1 Why should we be as comfortable to use an average as a marginal shadow price?

In the context of new drug reimbursement policies, which are discrete, the concept of an average shadow price is more appropriate than a marginal shadow price.⁸⁶ However, the concept of a marginal shadow price dominates the literature, and the term shadow price tends to be interpreted by economists as a marginal concept. Is it because marginal is the “correct” concept and average is “incorrect”?⁸⁷ Is it the case of an expanding margin? Or is it because the marginal shadow price is derived from a model that has good properties for theory but not for applied economics? Is it legitimate to rely on an average rather than marginal shadow price in the context of the reimbursement decision?

The key role of a shadow price is to put a price on any constraint by referencing this to the potential gain or loss from changing this constraint. The simplest models from which a shadow price can be derived as part of the optimisation problem are those that are continuously differentiable and hence all inputs and outputs are continuous (infinitely divisible). In this way, first order conditions and a unique solution (if there is one) to the optimisation problem can be identified. The theoretical advantages of a continuously differentiable function are well appreciated.⁸⁸ However, one only needs to look at the extraordinarily strict conditions that need to be met in order to have well behaved utility functions to be reminded of the key trade-off in a theoretical model: the better behaved the model, the less relevant to the real world.⁸⁹

The linear programming problem with continuously differentiable functions is the operations research equivalent of a well behaved utility function with neat solutions. One real world adaptation of the simple linear programming problem is the introduction of discrete inputs. When the inputs are discrete, the function(s) is no longer continuously differentiable. The relevance of integer or mixed

⁸⁵ In the health economic literature, the cost in a CBA is generally accepted as a given or an attempt is made to adjust it to reflect a social opportunity cost, but it is not seen as a signal to the producer of the value in exchange of that input. For example, see Chapter 7 in Drummond, Sculpher et al (2005)

⁸⁶ Weinstein and Stason (1976) seems to be the earliest reference used in the health economic literature to refer to the discrete properties of health programs and the implications for optimal allocation of health resources. Birch and Gafni (1992) is probably a better known reference and discussed the implications for shadow prices and budget constraints.

⁸⁷ My first attempt to present these results to a mainstream Economics Department resulted in the following message: shadow prices are marginal not average so go back to square one. The message was very loud and very clear: there is no such thing as an average shadow price. With hindsight, the audience’s response was possibly a consequence of a lack of exposure to applied economics rather than an error on my part.

⁸⁸ For example, many neoclassical macroeconomic problems start with the Inada conditions about a production function of a firm. These conditions are necessary to ensure that in a neoclassical growth model, the growth path is stable. There are six conditions, one of which is that the function is continuously differential, which in turn implies that the inputs are continuous and not “lumpy” (Hahn 2008). Cobb Douglas production functions also meet the condition of being continuously differentiable (Brown 2008).

⁸⁹ Most advanced microeconomic text books will detail these conditions. See for example Jehle and Reny (2001) Section 1.3, the Consumers Problem in particular, Theorem 1.4 on the sufficiency of the consumer’s first order conditions.

programming in health economics was identified in Birch and Gafni (1992).⁹⁰ As Kim and Cho (1988) demonstrate, the process of finding the optimal allocation of resources becomes much more complex when discrete inputs are introduced (but the leap in complexity is probably less of an issue given the improvements in computational tools since 1988). With developments in software and processing power, the complexity of solving problems is reduced, but the information requirements for using integer programming to solve resource allocation problems for entire budgets remain significant. However, the constraint placed on the set of optimal solutions by removing the condition of a continuous function is a necessary characteristic of a model that captures this significant real world characteristic.

The dung beetle example adds one additional layer of complexity to this mixed programming problem: prices are not available for one input and there is the potential for market power. If the problem were to allocate all of Canberra Local Government's resources across every opportunity to improve the welfare of its citizens, then the task would be prohibitively complex, regardless of whether linear or integer programming were used. However, by partialising the problem to the objective of reduction of flies in Canberra, the constraint that provides the shadow price is the best alternative use of resources to achieve this outcome. However, the shadow price in this case is an average shadow price because even though we can choose to use outdoor fly screens at one or 100 outdoor restaurants, the dung beetle program has discrete properties; it is either implemented or not and if implemented requires a minimum number to become a self-sustaining program. The decision is not how big the program should be; it is how much the Council should pay for it.

In conclusion, whether an average or marginal shadow price is the most appropriate solution concept for a problem is a characteristic of the structure of the problem. The average shadow price is the best way to price a constraint in problems such as those described by Kim and Cho and the fly reduction problem. It is possible that the marginal shadow price is the dominant concept in the economic literature as a consequence of theoreticians' and teachers' rational preference for a continuously differential function in order to demonstrate a key economic principle; the necessity of defining an opportunity cost in order to achieve optimisation. When discrete inputs are introduced, the overall optimisation problem becomes more complex, but the fact that the shadow price is average not marginal is the inevitable result of the structure of the problem, not a methodological choice.

3.2 How does the value of a given shadow price respond to economic contexts?

One difference between shadow prices is their relevance in a context of economic inefficiency, market power and the resultant price distortions. If the budget is not economically efficient then the shadow price of the budget constraint is not necessarily representative of the (full or potential) economic value of an expanded or contracted budget. Consider the example of a budget for public transport. Assume that the least cost-effective currently funded mode of transport (e.g. diesel buses costing \$100 per 100km) is less cost effective than the most cost-effective unfunded mode of transport (e.g. electric buses at \$50 per 100km). There is an opportunity to improve the output for a given budget by reallocating funds from the funded to the unfunded program. In this case, if the shadow price of contracting the existing budget were calculated before achieving economic efficiency, it would yield a lower economic value of the budget (1km lost per reduction in budget of \$1) than if calculated after achieving economic efficiency (2km lost per reduction in budget of \$1). This situation is analogous to the bias that would occur if the clinical value of innovation were defined by using the

⁹⁰ Without this paper I am not sure where I would be. It opened my eyes. It was the first step in the line of thinking that led me to the health shadow price.

opportunity cost of forgoing the least effective available alternative therapy instead of the foregone benefits of the most effective alternative existing therapy.

Significantly, in CBA, the use of the concept of "shadow price" as a price for an input is intended to be a solution to the problem of valuing inputs and outputs in a way that reflects economic constraints in a situation where there is market failure that leads to inefficiency. In many cases this market failure is the motivation for using CBA.⁹¹ The use of the shadow price in this context requires that the analyst understands the many sources of market failure in the current situation. In contrast, the shadow price as the marginal unit lost or gained when the budget is tightened or relaxed in a linear programming problem is only relevant when the budget is economically efficient and the markets are perfectly competitive.⁹² It does not require that the analyst explore sources of market failure because it assumes there are none.

3.2.1 Derive the input price from the maxWTP or the shadow price for the output

There are two ways a price for an input without a market price can be derived and applied. First, we could derive the input's value from a maxWTP for that output. Second, we could derive the input's price from the shadow price of the output. These options correspond to Parts 1 and 2 from the Dung Beetle Program example. They also correspond to a choice by the Reimbursing: should the price for the new drug be derived from the maxWTP for the output or the shadow price for that output? Hence we ask: which of these two methods achieves an "appropriate" economic value of the clinical innovation of a new drug? Clearly, if a new drug had a competitive market price then we would not need to have an annex to the AUSFTA to set the parameters for such a price. Also, market power is an important feature of the market for new drugs. Furthermore, budgets are fixed or constrained and there is significant competition in the health input market. Hence the derivation of an appropriate price for the new drug in the context of the market transaction called "reimbursement" is most appropriately generated from a shadow price for the least cost way of achieving health gains with alternative health inputs. And finally, as demonstrated in the Dung Beetle example, the appropriately derived shadow price of the output can be used as a signal to firms supplying inputs, hence the shadow price for that input can be derived by the supplier and the average shadow price of the output becomes a decision threshold for the purchaser.

Do health economists use shadow price in this way to value a new drug? No, not at this stage, but they do use shadow price, in a number of ways.

4 Shadow price and health economics

The majority of the health economic literature on the topic of the shadow price and the associated areas of CBA and decision thresholds appears to have its origins in Sugden and Williams (1978) and the seminal paper from Weinstein and Zeckhauser (1973). The reliance on this stream of literature is logical given the significant roles that Williams and Weinstein played in the development of health economics in the UK and the US respectively. However, these authors have very little overlap with the stream of literature that applies shadow price in the CBA context using methods described by Mishan

⁹¹ So why is there a preference for maximum willingness to pay as a way of valuing the benefits in a CBA? (For example see Sugden and Williams (1978) and Drummond et al. (2005).) The dung beetle example presented in this Chapter shows how if the maxWTP is used to value the output of the dung beetle and then to price the dung beetle, particularly when there is market power, and there is competition in means of producing the output. Essentially we can separate out the valuation of the surplus from the question of the allocation of that surplus across producer and consumer by introducing the competing use of resources, the outdoor flyscreens. This issue seems to me to be one of the sources of tension between Williams and Mishan as described by Mishan (1982).

⁹² This situation is explored in detail in Chapter 5.

and Quah (2007) and McKean (1972).⁹³ Possibly as a consequence of these origins, and its close association in operations research methods,⁹⁴ the health economic literature generally uses the term “shadow price” to refer to the shadow price of the budget constraint (Stinnett and Mullahy 1998) or to refer to the valuation of an input such as voluntary carer time, for which there is a supply but no market price (Coupé, Veenhof et al. 2007). There is some discussion about the shadow price of capital and its relationship to the discount rate (Drummond, Sculpher et al. 2005). There is also a significant literature on the question of the valuation of health gains for the purpose of a CBA. This valuation tends to be based on consumer or social preferences for health, and does not take into consideration competing means of producing these.⁹⁵

Most authors recognise that the practical limitations of using the shadow price of the budget constraint as a decision threshold for new drugs or any other program. The challenge has become to find a reasonable substitute. For example, in a paper that argues for the routine use of a second best rule to opportunity cost in assessing decisions about programs, Sendi et al. (2002) identify the shadow price as having a relationship with the decision threshold and as an indicator of value in the absence of a market: *The threshold value λ reflects the shadow price per unit effectiveness (e.g. dollars per life-years saved) in the absence of a market.* The authors then go on to discuss a number of factors that could constrain the use of this shadow price as the threshold in program adoption, including: if the budget constraint is not defined from a societal perspective, then λ cannot be quantified; the finite divisibility of health resources and programs; and the stochastic nature of the evidence of the marginal program and hence the shadow price. The authors then go on to advocate the use of the average ICER⁹⁶ of displaced services as a second best alternative to the shadow price of the budget constraint, with a particular emphasis on the point that the average ICER of the service displaced is a function of program size.

Some authors have developed shadow prices, in the sense of valuing a good or service for which there is no market. Van den Berg used multiple methods to value informal care, including contingent valuation and willingness to pay and accept. He also explored the psychological effects of monetisation of informal care (Van den Berg 2005).

The idea that charges for services do not necessarily represent their “cost” has a long history.⁹⁷ This debate is typically made with reference to internal prices set by organisations and there is an extensive discussion in Drummond et al. (2005) in relation to the question of costing non-market inputs in the absence of a market price.

⁹³ A paper by O’Brien and Gafni (1996) does apply Mishan’s methods of contingent valuation to the health outputs of a health program, however it does not address the issue of valuing inputs with market power. It does address the issue of analysing the relationship between price and demand in a private market for health services as a way of valuing health.

⁹⁴ Pharmaco-economic models are often developed by operations researchers (applied mathematicians) in conjunction with economists. See for example the Sheffield decision analysis group <http://www.shef.ac.uk/scharr/sections/heds/modelling> . Accessed: 21-02-12

⁹⁵ For example, see Chapter 7 in Drummond, Sculpher et al (2005)

⁹⁶ The concept of an average ICER for displaced services takes into account the fact that if the amount of services that are displaced changes, then the aICER could change if there are increasing or decreasing marginal costs.

⁹⁷ McNeil et al. (1975) is an example of this history. While there were some earlier discussions about this issue in the literature, this discussion of the issue is particularly eloquent. The paper makes no reference to the question of market power of the patent holders of the new technology; an omission typical of most cost effectiveness analyses. The paper does refer to the idea that even if the new technology is cost effective that this is not sufficient information to justify its adoption because budgetary implications also need to be considered. That particular edition of the New England Journal of Medicine was a microcosm of the critical issues in health economics and Bayesian statistics at that time.

However, there appears to be a reluctance to consider the implications of using a price that is set in a market where there is significant market power, for example specialists and medical technologies. Drummond et al. (2005) indicates that the issue of the difference between market prices of inputs and their opportunity cost is well known amongst health economists. In a discussion of the question of whether or not the price of an input should be accepted even though in cases such as a new drug it is unlikely to be indicative of its social opportunity cost, the authors conclude that:

".. health economists recognize that market imperfections exist in health care, unless they are undertaking an economic evaluation! In order for analysts to attempt to adjust market prices they should be convinced that:

- 1) *to leave price unadjusted would introduce substantial bias into the study*
- 2) *there is a clear and objective way of making the adjustment."* (Drummond et al 2005 p. 58)

The authors do not go on to propose a rigorous method whereby this adjusted price could be derived.

In conclusion, most health economists are familiar with the idea of a shadow price, however, it seems that they are less likely to be familiar with its application in CBA as described by Mishan and Quah (2007) and McKean (1972) than they are with the applications by Sugden and Williams (1978) and the seminal paper from Weinstein and Zeckhauser (1973). This asymmetry in understanding limits the historic application of shadow pricing in health economics, but it also highlights an opportunity for further development.

5 Discussion and conclusion

Health economists always recognised the significance of a shadow price of a budget constraint as the ideal decision threshold against which the results of economic evaluations (the ICER) can be benchmarked and the decision to allocate resources to a program informed. The impracticalities of using the shadow price of the budget constraint are also widely recognised. Health economists have been quick to point out situations where the market price fails to accommodate the full value of health benefits and there is a long tradition of valuing health outcomes using the maxWTP. However, as shown in the example of the Dung Beetle Program, the use of maxWTP for an output to derive a value for an input, when that input has market power, can have significant implications for consumer surplus and for a potential deadweight loss.

Health economic textbooks indicate a need for methods to value inputs appropriately but do not propose "*clear and objective ways of making the adjustment*" to a market price where this market price is likely to reflect market power. The welfare economic literature does provide a suitable starting point. Examples of general methods to derive the shadow price of an input are set out in Mishan and Quah (2007) and McKean (1968).⁹⁸ The key issue is to recognise that the constraint to the adoption of this input (for example the dung beetle) is the best alternative input (the outdoor fly screens) and that the shadow price represents this constraint.

In summary, the health economic focus on the shadow price of the budget constraint as THE shadow price relevant to health care decisions can lead to the following Catch 22: we can't find this shadow price until economic efficiency is achieved and we can't improve economic efficiency until this price is found. Chapter 6 introduces a method, Price Effectiveness Analysis (PEA), whereby such a shadow price can be developed in the context of a reimbursement process. The imperative of PEA is to find a shadow price for health effects that will improve economic efficiency rather than one that is

⁹⁸ In pages 135 to 139, McKean sets out three methods to derive the shadow price of an input by using information available from other decisions and other "price relationships observed in other markets for similar items." (McKean 1972)

conditional on economic efficiency, for example λ . This is consistent with the role of a shadow price in the welfare economic literature in the tradition of Mishan and McKean.

Part 2: The new drug decision threshold

Part 1 introduced the rationale for an alternative PENDING and clarified two concepts:

- 1) the clinical value of innovation - the objectively demonstrated therapeutic significance of a pharmaceutical; and
- 2) the economic value or shadow price – and how this differs from the maxWTP.

In Part 2 we develop the case for a new drug decision threshold, the health shadow price β_c .

The health shadow price is the Incremental Price Effectiveness Ratio (*IPER*) of the new drug such that the Reimbursing Party is indifferent between the decision to adopt the new drug and the best alternative strategy (Chapter 6). The health shadow price is shown to be sensitive to the economic context of the health care budget (Chapter 7). The framework used to develop β_c and the associated concepts is Price Effectiveness Analysis. This framework is then expanded to incorporate strategic behaviour by firms (Chapter 8).

In this chapter, five concepts central to this thesis are introduced: opportunity cost in the context of an institutional decision; price effectiveness analysis (PEA); reimbursement as adoption and financing; the health shadow price β_c ; and the economic value of clinical innovation, *EVCI*.

- 1) **Opportunity cost of a strategy** in an institutional setting does not necessarily imply that the decision maker is physically choosing between these two strategies and their corresponding end state alternatives. Instead, it means that the decision maker is valuing all states of the world that could emerge under different allocations of resources (Buchanan 2008).
- 2) **Price effectiveness analysis** is a method of assessing the decision to reimburse a new drug by testing the relationship between the *IPER* of the new drug and the population's health.
- 3) The **strategy of reimbursement** comprises the actions of adoption and financing.
- 4) The **health shadow price, β_c** , is the *IPER* of the health effects gained by the target patients as a consequence of the strategy of reimbursing (adopting and financing) the new drug with clinical innovation ΔE^P and additional financial cost ΔC^P such that the funder is indifferent between the strategy of reimbursement and the best alternative strategy available to the funder also using the resources ΔC^P .
- 5) The **economic value of clinical innovation, *EVCI***, is the gross clinical benefit of the new drug, constrained twice: by the clinical opportunity cost (the best alternative therapy to the new drug) to obtain ΔE^P and the economic opportunity cost (the best alternative use of resources ΔC^P) to obtain *EVCI* ($=\beta_c \Delta E^P$).

The derivation of the parameters β_c and *EVCI* is illustrated using the special case of the decision to reimburse (adopt and finance) a new drug where the additional financial cost ΔC^P is financed by the expansion of an economically efficient health budget and there is no strategic play by the firm. The terminology for the associated decision rules and summary metrics for the decision to reimburse are identified.

1 The Reimburser's problem

The Reimburser understands that the choice of the decision threshold for a new drug is a complex one; both technically and politically. She also understands it is related to the idea of the appropriate valuation in a market context of the objectively determined therapeutic significance of a new drug. After discussions with her Health Economic Adviser about clinical innovation and the shadow price she decides that what she needs is an (average) shadow price for the health effects from the new drug, which is expressed as a decision threshold and is calculated with reference to the best alternative use of the incremental financial cost of the new drug, ΔC (Chapter 5). A firm can then use this information as a signal of the maximum acceptable Incremental Price Effectiveness Ratio (*IPER*)⁹⁹ of the new drug. But how should she arrive at such a measure? The Reimburser asks her Health Economic Adviser:

Is there a shadow price for the health effects of a new drug that:

- 1) is based on the opportunity cost of the best alternative way to produce health effects; and*
- 2) can be used as a decision threshold IPER for a new drug?*

2 The path to the health shadow price

The Health Economic Adviser provides the Reimburser with the path that he used to develop the idea of the objective value of the health effects of a new drug, the health shadow price. This path is illustrated in Figure 2. The Reimburser works her way along this path. Her starting point is the question of the appropriate value of “*the objectively demonstrated therapeutic significance of a pharmaceutical*”. (See p. 65). The Reimburser recognises that this is about the value of the clinical innovation in the context of an economic transaction, where the patent holder, the firm, has market power. However, as the large monopsonist purchaser, she also has some market power. In this situation she can choose to value the new drug using either an economic concept, opportunity cost, or a lay concept of value for money that does not recognise the economic context. The former is preferable to the latter in this context.

The opportunity cost is not what is physically displaced to finance the new drug; that is an operational issue. The opportunity cost is the best alternative strategy. Furthermore, as a member of an institution, she does not need to focus only on alternative strategies physically available to her. According to Buchanan (2008), in an institutional setting, the use of the term “opportunity cost to the decision” does not necessarily imply that the decision maker is physically choosing between these two strategies and their corresponding end state alternatives. Instead, it means that the decision maker is valuing all states of the world that could emerge under different allocations of resources, in this case, ΔC . This definition overcomes, at some level at least, the possible failure of the institution to include these alternatives in the physical choice set; in particular, unpatented services such as workforce strategies, respite care and training health workers.¹⁰⁰

⁹⁹ See the Glossary Table 3 page 11

¹⁰⁰ From the New Palgrave Dictionary of Economics is Buchanan's definition of opportunity cost in the institutional setting: “Results may emerge from the operation of some institutional process without any person or group of persons ‘choosing’ among end-state alternatives, and, hence, without any subjectively-experienced opportunity cost. Despite the absence of this important bridge between cost and choice in the ordinary sense, however, values may be placed on the ‘might have beens’ that would have emerged under differing allocations. The patterns of these estimated value losses, over a sequence of institution-determined allocations, may enter, importantly, in a rational choice calculus involving the higher-level choice amongst alternative institutional procedures for allocation. In this higher-level choice, opportunity cost again appears as the negative side of choice even if ‘choice’ in the standard usage of the term is not involved in the making of allocations, taken singly.”(Buchanan 2008)

The Reimburser does not need to know the shadow price of the budget constraint in order to understand the opportunity cost of reimbursement. In fact it is very likely that it cannot be defined given the current levels of inefficiency in the health budget. This shadow price should reference the average shadow price of the best alternative input (Kim and Cho 1988). In the context of the reimbursement process, the common reference point across alternative inputs is the amount ΔC , the incremental cost of the new drug at the offer price, the *IPER*. The opportunity cost of reimbursement is the maximum health effects foregone by allocating ΔC to the reimbursement of the new drug rather than alternative strategies.

The firm, and in some cases the purchaser, have market power; they are price makers not price takers. The patent owning firm can and must select a price for the new drug, unlike the case of a perfectly competitive market for a given drug, where the firm must take the market price. The Reimburser, she can use the decision threshold to provide signals to firms, and change this signal if she chooses, as the competitiveness of the market for health inputs changes. The issue of interest is the Reimburser's choice of the decision threshold. The principal suggested by Drummond et al. (2005) is to adjust the input price in a HTA/CEA to reflect its social opportunity cost.¹⁰¹ This method is not applicable in this situation; the new drug price problem is about the Reimburser providing a signal about the market for health inputs and the firm uses this signal to select an offer price. New drug reimbursement is not an extension of the problem of correcting a charge for an input in a CBA.

And finally, the Reimburser recognises that the initial choice is about the qualitative value (an equation) of the threshold, not the quantitative value.¹⁰² She notes that there appears to be more certainty regarding the quantitative value of NICE's threshold than its qualitative value.¹⁰³ She recognises that only a qualitative value can be assessed in a theoretical context. Furthermore, a given the qualitative value could provide a unique quantitative value for each decision at a given point in time, however, it is also important to accommodate the possibility that this threshold will be a function of a range of factors including competition in the market and hence vary over time and across decisions.

¹⁰¹ Drummond et al. (2005) provide guidance on how to deal with a non-market price. The authors argue that while there is a theoretical imperative to adjust the "market price" of an input in certain situations, in order to make such an adjustment it was also necessary for health economists to establish a likely benefit to decision making and to use a clear and objective method of making this adjustment. Using the approach suggested by Drummond et al., if there were an acceptable method of adjusting the drug price, the Reimburser could perform a CEA using this adjusted price instead of the firm offer price and then make a decision as to whether the drug was cost effective. The Reimburser needs to signal the value of the health effects of the new drug to the firm rather than decide of a price of the drug that reflects social opportunity cost.

¹⁰² The **qualitative** value of a decision threshold is its value referenced to an economic, financial or administrative concept such as the shadow price of the budget constraint, the maximum willingness to pay or the aICER of displacement. It is preferable to express it algebraically and with reference to economic theory, for example, the shadow price of the budget constraint. The **quantitative** value of a decision threshold is its numeric value, for example \$75,000 per QALY.

¹⁰³ The uncertainty in the qualitative value is suggested by Culyer et al. (2007) "*The threshold could represent the shadow price of the NHS budget constraint or a societal willingness to pay for health improvements; we cannot say what NICE thinks the threshold represents, since it denies that it has one and therefore does not discuss its origins.*" The relative certainty in its quantitative value (and debate as to whether it should be increased) is indicated by Raftery (2009) and also Towse (2009).

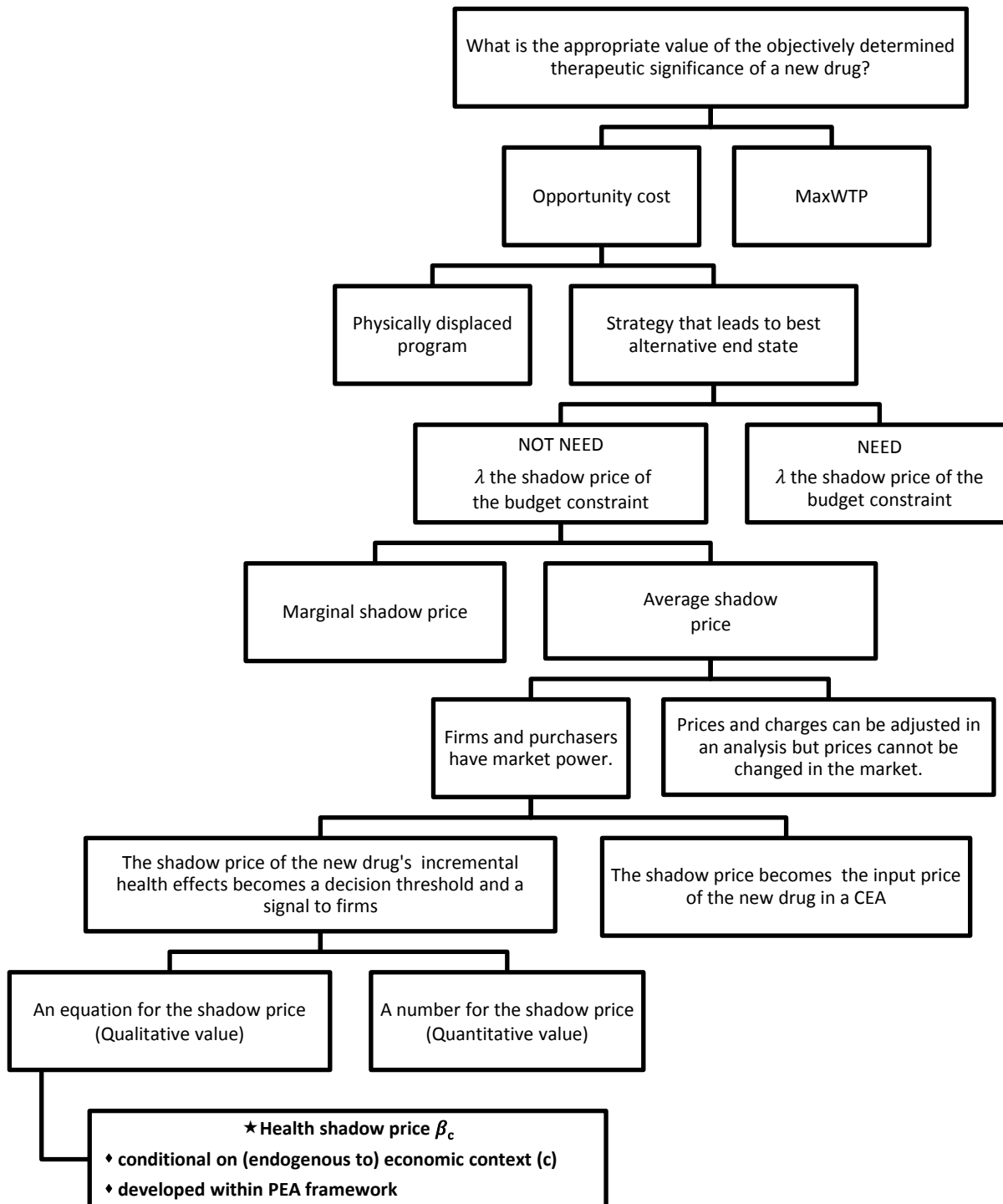


Figure 2 The path to PEA and the health shadow price

3 PEA, β_c and the economic value of clinical innovation

In a discussion on the significance of alternative methods to determine the unit cost that should be used in an economic evaluation, when both charges and costs are available, Drummond et al (2005) conclude that:

If the results of studies are relatively insensitive to the method used to approximate costs, should we be concerned about this issue? Only to the extent that when costs or cost-effectiveness ratios are compared across studies, the differences observed may be partly dependent upon the precise type of cost to charge adjustments. (p. 59)

Price effectiveness analysis (PEA) reframes how health economists understand the problem of a price for an input, where that input is patented. In PEA it is understood that even if the decision resulting from a HTA/CEA is not sensitive to the way that the unit costs are derived from, for example, charges, if the patent holder of this input has market power then the price used in a HTA/CEA in this way is providing a signal to the firm of a potential maximum acceptable price. If the decision that results from a HTA/CEA is not sensitive to the method of costing, and hence price, of one of the inputs, then this could be a signal to the owner of this input that the price can be increased. Furthermore, the maximum acceptable price for the input can be inferred from the value assigned by the Reimbursers to health effects via the decision threshold, (as discussed in Part 1 of the Dung Beetle story). It matters what price is assigned to an input either directly (via a unit cost in a HTA/CEA) or indirectly via a decision threshold because the patent holding firm can respond to this signal in ways that impact on both consumer welfare and social welfare. The implications of this strategic context are discussed in detail in Chapters 8 to 10. In this chapter, a method for determining a reference price, the health shadow price, is presented.

The starting point is that the problem of adjusting the price of an input in a HTA/CEA to reflect the input's social opportunity cost¹⁰⁴ is reframed in PEA as a problem of:

- 1) developing a clear, objective and theoretically defensible method;
- 2) identifying a qualitative value (equation) for the shadow price for the additional health effects of the new drug;
- 3) referencing the best alternative strategy; and
- 4) applying this as a signal (decision threshold) in the Reimbursement decision.

In this chapter I show that, used together, the following five concepts provide a clear and objective method of introducing the shadow price into the reimbursement process.

- 1) Opportunity cost as the strategy that leads to the best end state alternative. This strategy is not the physically displaced strategy (an operational issue) and not necessarily a physical option available to the Reimbursers.
- 2) Reimbursement is a strategy comprising two actions: adoption of the new drug and financing of its additional costs.
- 3) PEA is a method whereby the relationship between the price of a new drug and the population's health can be analysed.
- 4) The health shadow price, β_c , is the *IPER*¹⁰⁵ of a new drug such that the Reimbursers:
 - a. is indifferent between:
 - i. the strategy of reimbursing the new drug (adoption and financing); and
 - ii. the best alternative strategy for improving the population's health.
 - b. given:

¹⁰⁴ This approach is nominated by Drummond et al (2005). It appears to have its origins in Sugden and Williams (1978) and has two problems. The first is that the social opportunity cost appears to be calculated with reference to the maxWTP for the output. The second is that it does not recognise that if the producer has market power, then the price of the input is endogenous to the decision regarding the adoption or otherwise of a program. (See example of the Dung Beetle)

¹⁰⁵ In PEA, the price of a new drug is referred to as an incremental price per additional effect (*IPER*=*f*). Arithmetically, it is identical to the additional cost per unit effect of the new drug. The term "price" is used instead of the term "cost" to recognise that, unlike the ICER of a QUIT smoking counselling session (for example), the ICER of a new drug is endogenous to the decision to reimburse it.- it is a price that is up for negotiation.

- i. the economic context of the health budget (is it allocatively and technically efficient?); and
 - ii. the optimality with which adoption is financed from the health care budget.
- 5) The economic value of clinical innovation is the clinical value of innovation valued at β_c . This is the appropriate value of objectively determined therapeutic significance of a new drug, in the context of a market transaction.

3.1 The problem

To illustrate the concepts and define the terminology we initially assume an economically efficient budget **and** perfectly competitive input markets (no market power). These assumptions are relaxed in Chapters 7 and 8. The nominated strategy (reimbursement) is adoption financed by expansion of the budget (not by displacing existing services). Five parameters need to be defined to derive β_c and hence the shadow price of the new drug in this situation:

- 1) a maximand (the measure of effect);
- 2) a nominated strategy and its corresponding effect(s);
- 3) the constraints that define the set of strategies from which the best alternative strategy will be selected;
- 4) the set of alternative strategies; and
- 5) the best alternative strategy from this set.

A simple example of the decision to purchase a new drug and to finance its purchase with the expansion of a budget is used to illustrate these five elements.

- 1) The effect or maximand is health, measured in **QALYs**.
- 2) The nominated strategy (**R**) is **reimbursement**, which comprises the actions of **adoption** and **financing**:
 - a. Adoption
 - i. The adoption of a new Drug P is achieved by completely replacing Drug Q with Drug P for target patients.
 - ii. The effect associated with adopting Drug P is $\Delta E^P = 20 \text{ QALYs}$, the increase in health gains possible for the target patients following the adoption of the new Drug P compared to the best care they would otherwise receive (Drug Q).
 - b. Financing:
 - i. The new drug has an additional financial cost of $\Delta C^P = \$1000$, which consists entirely of the additional cost of the drug (there are no other financial implications);
 - ii. The additional cost of this new drug is financed by the expansion of the existing health budget by \$1000.
 - iii. The firm's offer price f of the new drug is expressed in terms of the *IPER*¹⁰⁶:

¹⁰⁶ The *IPER* (the incremental price effectiveness ratio) is used instead of the ICER (the incremental cost effectiveness ratio) because the additional cost of the new drug to the health system is a function of the price of the new drug, which is in turn the subject of negotiation not the empirical result of a clinical trial.

$$f = IPER = \frac{\Delta C^P}{\Delta E^P} = \frac{1000}{20} = \$50 \text{ per QALY}$$

- 3) The **constraints** that define the set of alternative strategies (comprising adoption and financing actions) are:
 - a. the additional financial cost of Drug P (\$1000) (that is, the alternative adoption action must have an additional financial cost of \$1000 and the financing action, in this case budget expansion, must raise this amount) ; and
 - b. the programs and technologies currently available to expand or adopt, or to displace to finance any additional cost of the new drug.
- 4) The **set of alternative strategies** defined by these constraints comprises adoption (or expansion) actions and corresponding financing actions (displacement or budget expansion). The action of adoption (or expansion) of these programs and technologies must be financed by an amount of \$1000. This set of alternative strategies excludes the mutually exclusive therapies for the group of target patients identified by the nominated strategy, reimbursement of Drug P. The best of the mutually exclusive actions relative to Drug P (Drug Q) is already included in the estimate of the incremental effect of Drug P. The incremental effect of each of the actions and pairs of actions (financing plus adoption is a strategy), given the strategies in the constraint set in Step 3) are assumed, in this example, to be known with certainty.
- 5) The **best alternative strategy (T)** is the strategy from this set of alternative strategies that has the greatest effect. This strategy comprises the adoption action with the greatest effect and the financing option with the minimum reduction in health. In this example there is only one financing option; budget expansion, which never results in displaced health effects. In this example, the best alternative strategy is expansion of Program S with an associated effect, $\Delta E^S = 25 \text{ QALYs}$ and an additional cost of \$1000 that is financed by expansion of the budget.

The reason that Steps 3) and 4) are separated is to allow the economic problem to be changed by either:

- 1) changing the constraints that defined the set of alternative strategies (for example, there is technological change that expands the number of new programs that could potentially be included, or the methods for financing change); or
- 2) changes in the alternative strategies (combination of actions) within this set for given constraints (for example, changes in the relative price of inputs).

Both of these types of changes will impact on the incremental cost and effect of alternative strategies, which would be recalculated in Step 4).

3.2 Summary measures

The following summary measures represent the concepts related to β_c and the associated economic value of innovation in the context of a perfectly competitive market and economically efficient health budget. The terminology is expanded for non-optimal initial conditions in Chapter 7.

The **net health benefit of Drug P:**

$$\Delta E^P = 20 \text{ QALYs}$$

is the incremental gain in health for the target patients from using Drug P instead of the best alternative therapy for these patients, Drug Q. In the case of a new drug, it is the effect size, preferably derived from an RCT of the new drug against the best available therapy, multiplied by the number of target patients in the population. It is also referred to as the **clinical value of innovation** (CVI) which emphasises the link between pharmaco-economics (derived from HTA/CEA and the incremental effect) and pharma-economics (which is motivated largely by the economics of pharmaceutical innovation). (See Chapter 4)

The net financial cost of adopting Drug P:

$$\Delta C^P = \$1000$$

is the additional financial cost of the nominated strategy compared to the best alternative therapy (assessed in clinical terms) for that group of patients. These are the additional financial resources that need to be sourced to finance the additional costs of the new drug from the health budget, at the offer *IPER*. In this example, the financing action is the expansion of the budget.

The net health benefit for the population of the strategy of reimbursement:

ΔE^R is the net effect on a population's health of reimbursement (adoption and financing). (In contrast, the net effect of the drug ΔE^P is the net effect of adoption for the patient group). In the case of financing by an expanded budget, no existing program needs to be displaced hence the net health benefit of Strategy R for the population is the same as that of the health effect for target patients from adoption of the new drug.

$$\Delta E^R = \Delta E^P = 20 \text{ QALYs}$$

If a program had to be displaced to finance adoption, then the net health effect of reimbursement would be the incremental effect of the new drug less the loss of health effects from displaced services. This issue is explored in Chapter 7.

The net health benefit for the population of the best alternative strategy T:

Similarly, the net health effect of the best alternative strategy T is the same as that of action S (expansion of Program S) because the additional costs are financed by the same action for both reimbursement and the best alternative strategy, namely budget expansion. If T comprised action S financed by the displacement of a second program rather than by budget expansion, the last term would not be “+0” but include the loss to the patients whose program was displaced.

$$\Delta E^T = \Delta E^S + 0 = 25 \text{ QALYs}$$

The net financial cost of the strategy of reimbursement:

$$\Delta C^R = \Delta C^P = \Delta C$$

where ΔC is the expansion of the budget. If the strategy is financed within a fixed budget the net financial impact of reimbursement on the total budget is 0 even though there is a reallocation of ΔC^P within the health budget. This issue is explored further in Chapter 7.

The **opportunity cost** expressed as benefit foregone of the nominated strategy, Strategy R (reimbursement, the substitution of Drug Q by Drug P financed by expansion of the budget) is the effect of the best alternative strategy, T (expansion of Program S financed by expansion of the budget); 25 QALYs.

Note: As stated before, these strategies, R (reimbursement) and T (best alternative), are not mutually exclusive for the group of target patients for the new drug.¹⁰⁷ However, they are mutually exclusive options for the population, where the budget is only expanded to finance one strategy.

This opportunity cost is a consequence of the definition of the set of alternative strategies, which in turn defines the opportunity cost in terms of the best alternative use of the fixed budget increment ΔC^P .

The **net economic benefit (health)** of the nominated strategy ($NEBh^R$) is the strategy R's impact on the population net the effect of the best alternative strategy (T):

$$NEBh^R = \Delta E^R - \Delta E^T = 20 - 25 = -5 \text{ QALYs}$$

Hence there is a net economic loss of 5 QALYs as a consequence of reimbursing the new drug at the offer price of f .

The **health shadow price**, β_c is the *IPER* (β) of the new drug in a specific economic context (c) at which the Reimbursing is indifferent between the two strategies of reimbursing the new drug and the best alternative strategy, T.

$$\begin{aligned} 0 &= NEBh^R \\ &= \Delta E^R - \Delta E^T \\ &= \frac{\Delta C^P}{f} - \Delta E^T \\ &= \frac{\$1000}{f} - 25 \end{aligned}$$

$$\Rightarrow f = \frac{\$1000}{25} \text{ per QALY}$$

$$\Rightarrow \beta_c = \$40 \text{ per QALY}$$

The **(average) shadow price of the budget constraint** is the maximum gain in health effects as a consequence of budget expansion, without the new drug.

$$\lambda^B = \Delta E^T = \frac{\$1000}{25} = \$40 \text{ per QALY}$$

The average shadow price of the budget constraint could also be expressed in terms of units of output (in this case QALYs). This approach is more common in operations research models than health economic models. In this case it would be 25 QALYs.

And finally, the **economic value of clinical innovation** is simply:

$$EVCI = \beta_c \Delta E^P = 40 \times 20 = \$800$$

This is the economic value of the objectively estimated therapeutic value of the new drug, as estimated for a market where there is competition for alternative ways to produce the health effect.

¹⁰⁷ The mutually exclusive alternative strategy to R for this group of patients is already accommodated in the definition of clinical innovation which is estimated against the best alternative mutually exclusive strategy for this patient group.

4 Discussion

A number of concepts were introduced in this chapter. Some of these concepts are intended to allow distinctions to be drawn between concepts that are currently used interchangeably. Others relate to concepts that are unique to PEA. Pairs of concepts are summarised in the following table.

Table 7 Summary of PEA concepts

Concept 1	Concept 2	Distinction
Adoption The clinical decision to substitute therapy A with therapy B or add therapy B to therapy A.	Reimbursement The decision to Adopt a new drug and Finance its additional cost from the health budget.	Conventionally, the terms adoption and reimbursement are used interchangeably. The characterisation of Reimbursement as two actions, adoption and financing, allows the decision of reimbursement to be related to the net effect on the population (rather than patients) and also allows the optimality of both the adoption and financing actions to be considered separately when defining the health shadow price.
ICER Incremental cost effectiveness ratio	IPER Incremental price effectiveness ratio	Arithmetically identical terms. The term <i>IPER</i> is used to distinguish inputs such as new drugs where the price is the subject of negotiation, strategy and market power. The price of the drug is selected by the firm, is not a given and it is not the result of a clinical trial.
ICER As above	aICER (weighted) Average ICER	Typically economists estimate the average ICER for a program and refer to it as the ICER. The term “average ICER” is used to allow for the possibility that if a service is expanded or contracted its aICER will be a function of the direction and the size of the budget change as a consequence of increasing or decreasing marginal costs.
ΔE^P The net health effect of adopting the new drug.	ΔE^R The net effect of reimbursement on the health of the population.	The incremental effect of the new drug is its clinical innovation compared to the best existing therapy. The health effect of reimbursement is the net effect of reimbursement on the population. It is a function of the clinical innovation of the drug (adoption) and the method of financing the new drug (displaced services or expanded budget).
NBh_i $= \Delta E^P - \frac{\Delta C}{i}$ The conventional net benefit. (See Appendix 4 for a discussion of this terminology.)	$NEBh^R$ $= \Delta E^P - \frac{\Delta C}{\beta_c}$ The net economic benefit of reimbursement	The conventional net benefit is sometimes referred to as the net economic benefit. It can be valued by a range of values of i (monetary valuations of health effects see Appendix 4) including k , n and d . However, strictly speaking, it is only the net economic benefit if it accommodates the economic context, for example, the competition in the market for health inputs and existing inefficiencies. Hence the net economic benefit is the conventional net benefit with β_c as the value of i .
λ^B Shadow price of the budget constraint	β_c Shadow price of the health effects of the new drug	In this case, the shadow price of the budget constraint is defined as the maximum additional effect or the additional cost per additional effect, of the expansion of the budget constraint. It is calculated without the new technology. β_c is <i>IPER</i> of the new drug such that, in the specific economic context c , the Reimburser is indifferent between the strategy of reimbursement and the best alternative strategy in terms of their impacts on the population’s health.

4.1 Key concepts expanded

4.1.1 The net economic benefit (health) for the population

The parameter $NEBh^R$ is the net economic benefit measured in health effects of the strategy of reimbursement. It is an economic value, quantified in health effects, of the precisely defined net health benefit (for the population) of the strategy of reimbursement (adoption and financing). There are a

number of ways to express this parameter in the example presented in this chapter, where the economic context is economic efficiency and financing occurs by expanding a budget constraint. In all cases, it is the last term in this equation that gives the $NEBh^R$ its distinctly economic flavour, not monetisation. This term, $-\Delta E^T$, is the foregone benefit to the population of the best alternative strategy for the **population**. For example:

$$NEBh^R = \Delta E^R - \Delta E^T$$

However, because the additional costs are financed by budget expansion, there is no net reduction in the health for the population, therefore:

$$\Delta E^R = \Delta E^P$$

That is, the incremental health gains for the population from reimbursing the new drug are the same as the incremental health effects of the new drug for the target patients.

$$\Rightarrow NEBh^R = \Delta E^P - \Delta E^T$$

The $NEBh^R$ defines the economic value of accessing the clinical innovation from Drug P (ΔE^P) in the context of reimbursement financed by an expanded budget. It defines the economic value in terms of how many additional health gains are available for the population due to reimbursement (ΔE^R), compared to health effects possible from the best alternative way to use the additional budget funds within existing technologies, ΔE^T .

One way of thinking about this metric is as follows. If there is a gain in the population's health from the new drug when it is adopted and the additional cost were financed by budget expansion, then the benefits to the population of expanding the budget needs to be netted from the benefits of the clinical innovation of the new technology. Hence the economic value of the new drug is the clinical innovation constrained by what could have been achieved by the same additional resources and existing technologies.

4.1.2 Value of the new drug

The **gross effect** of the new drug is E^P , the effect of the drug compared to (constrained by) placebo. The **clinical value of innovation** is the gross effect of the new drug constrained by the opportunity cost of the best alternative therapy for the same patient group. This definition is consistent with the HTA/CEA definition of the clinical innovation of a new therapy.

$$\Delta E^P = E^P - E^Q$$

The **economic value** of the new drug's clinical innovation is the clinical value of the innovation constrained by the economic context, including factors such as the following, which are discussed further in Chapter 7:

- 1) whether the budget is fixed or expandable;
- 2) the degree of competition in the market for inputs into health effects;
- 3) whether or not there is an initial condition of economic efficiency; and
- 4) the optimality or otherwise of displacement if the budget is fixed.

The **health shadow price** β_c is the mechanism by which the economic context is accommodated in the economic value of clinical innovation.

$$EVCI = \beta_c \Delta E^P$$

In the example given in this chapter, the $EVCI$ is the gross health benefit of Drug P, E^P , constrained twice: by both E^Q (the gross benefit of Drug Q, the best alternative therapeutic strategy for these patients) and ΔE^T (the incremental health gain of the best alternative use of resources, ΔC^P for the population). In the scenarios explored in the following chapters, it is also constrained by the optimality or otherwise of the process of displacement. Furthermore, the best alternative strategy is defined by the existing inefficiency in the health care system.

There is an instructive analogue here between the clinical value of innovation and the economic value of clinical innovation.

- The clinician needs information about both the new and the best existing strategy in order to determine the best action for the patient.

By using the clinical value of innovation rather than the gross effect of the new drug, HTA/CEA makes sure we do not attribute the clinical value of innovation of Drug Q relative to placebo to Drug P. This technique prevents the following scenario from occurring: a new drug is adopted because it has a clinical advantage compared to placebo, but it is less effective than an existing drug. Hence even though patients are better off using the new drug compared to no drug, they would be best off using the best existing therapy compared to the new drug.

- The fundholder needs information about the effect of both reimbursement and the best alternative strategy to reimbursement on the population's health to make the best decision for the population.

The economic value of clinical innovation of a new drug is calculated net of the incremental effect of the best alternative strategy to reimbursement. In the case illustrated in this chapter, we need to avoid the situation of attributing the increase in the population's health that is due to the budget expansion to the clinical innovation of the new drug. This technique prevents the following scenario: fundholders expand the budget to finance the new drug and justify this because the health of the population increases. However, if the health of the population would have increased more if we had adopted the most cost effective of existing strategies, then the fundholders have made a suboptimal decision; another strategy would have resulted in a greater increase in the population's health.

5 Conclusion

The Reimbursers then reviews her question:

Is there a shadow price for the health effects of a new drug that:

- 1) *is based on the opportunity cost of the best alternative way to produce health effects; and*
- 2) *can be used as a decision threshold $IPER$ for a new drug?*

PEA is a method whereby the relationship between price of a new drug and the population's health can be analysed. β_c is the $IPER$ of the new drug at which the Reimbursers is indifferent between expanding the budget to finance the new drug and financing the best alternative strategy. In the simple example presented in this chapter, where the additional cost of the new drug is financed by budget expansion, β_c is no different to the shadow price for the budget constraint, λ . Using β_c as the decision threshold appears no different than using λ . However, the difference (bias and economic loss) between CEA applied with a threshold of λ and PEA with a threshold of β_c arises in the following contexts:

- 1) when there is a fixed or constrained budget and economic inefficiency in that budget; and/or

2) when displacement to finance the additional costs of the new drug is suboptimal.

The ways in which β_c accommodates the economic context - and λ fails - are demonstrated in the following chapter.

Chapter 7: The health shadow price and the economic context

The value of clinical innovation of a new drug is specific to a particular clinical context; the patient group, the clinical protocol and the best alternative therapy. Similarly, the economic value of a given clinical value of innovation is specific to a particular economic context; the financial costs of the proposed and existing therapy, the method of financing the additional costs (budget expansion or displacing services), the efficiency of the existing allocation and the competition in the market for health inputs. In this chapter, the ways in which β_c and $EVCI$ capture the economic context of the health budget are illustrated. β_c is derived for four different economic contexts. Two strategy specific values for β_c are derived using the framework of PEA.

The first corresponds to the best alternative reallocation strategy: Strategy A, which is the transfer of amount ΔC^P from the budget of one currently funded program to a second currently or potentially funded program. I show that when the budget is fixed and allocatively inefficient:

$$\beta_c^\alpha = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

where, n is the aICER of the most cost effective existing technology or program (in expansion), m is the least cost effective of currently funded technologies or programs (in contraction) and d is the cost per effect of the services displaced to finance the additional costs, ΔC^P , of the new drug. Hence, β_c^α is a function of the optimality of displacement ($m - d$) and the level of allocative inefficiency in the health budget ($m - n$).

The second strategy specific value corresponds to the best alternative investment strategy; Strategy V, the investment of ΔC^P in a program of improvement (e.g. training the workforce) that reduces the future aICER of an existing program and hence improves the technical efficiency of a program in the future. I show that:

$$\beta_c^v = \left(\frac{1}{\mu} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

where μ is a parameter that summarises the aICER of the gains in health effects from a fixed budget obtained by the best investment of ΔC^P .

The health shadow price of the health effects of a new drug is the minimum of the two best alternative strategies (reallocation and investment)

$$\beta_c^* = \min\{\beta_c^\alpha, \beta_c^v\}$$

1 The Reimburser's problem

The Reimburser understands that β_c is derived within:

- 1) a strategy of reimbursement (adoption and financing);
- 2) an economic context that includes alternative ways to produce health effects; and
- 3) a health budget that may or may not be economically efficient.

The Reimburser also understands that the best alternative strategy to the strategy of reimbursement of the new technology need not be an actual physical option available to her. Following the definition of opportunity cost from Buchanan (2008) she understand that the best alternative strategy simply needs to represent the alternative resource allocation that maximises the payoff. Hence the choice of the alternative strategy to reimbursement can compensate, at some level at least, the failure of the institution to consider reimbursement of unpatented and unpatentable strategies.

The Reimburser also understands that a threshold *IPER* for a new drug derived from the health shadow price will accommodate the economic context, for example, the competition in the market to produce health effects. In contrast, a threshold Incremental Price Effectiveness Ratio (*IPER*) for the drug derived from a maxWTP for health effects will not accommodate the full economic context. However, the Reimburser does not yet understand how the health shadow price accommodates the characteristics of the health budget.

The Reimburser asks:

- 1) *How does β_c vary across different reimbursement strategies and economic contexts?*
- 2) *Why can PEA and not HTA/CEA accommodate the economic context?*

The Health Economist develops four scenarios that illustrate β_c and the EVCI under reimbursement, where adoption is financed in two different ways. The first scenario is an algebraic presentation of the case presented in the previous chapter. The remaining three scenarios illustrate reimbursement under a fixed budget and a range of economic conditions, including allocative inefficiency. These scenarios also illustrate situations of optimal and suboptimal displacement. The nominated strategies and economic conditions of each scenario are presented in Table 8.

Table 8 Four scenarios of nominated strategy "Reimburse a new Drug P"

Scenario	Nominated strategy: Reimburse a new Drug P	Economic conditions
1	Adopt a new Drug, P and finance the additional costs by expanding the existing budget.	<ul style="list-style-type: none"> • Economic efficiency • No price distortions other than that of new patented technologies • Expandable budget • No displacement
2	Adopt a new drug P and finance the additional costs by displacing an existing program	<ul style="list-style-type: none"> • Economic efficiency • No price distortions other than that of new patented technologies • Fixed budget • Displacement can be optimal or suboptimal
3		<ul style="list-style-type: none"> • Allocative inefficiency • No price distortions other than that of new patented technologies • Fixed budget • Displacement can be optimal or suboptimal
4		<ul style="list-style-type: none"> • Technical inefficiency • No price distortions other than that of new patented technologies • Fixed budget • Displacement can be optimal or suboptimal

Note: All analysis and discussion in this research is concerned solely with new drugs that have clinical innovation $\Delta E > 0$ and an additional cost $\Delta C > 0$. The limitations of the ICER under cases where one or both of these conditions is not met are recognised but not relevant to this discussion. Hence the $ICER_i$ and the conventional net benefit, NB_i are interchangeable as summary metrics of the decision to adopt a new drug.¹⁰⁸

2 Scenario 1: Adoption financed by expansion of an economically efficient budget

A Reimburser in a fictional country is **required**¹⁰⁹ to increase the health budget by an amount $\Delta C^P > 0$ and adopt a new drug, P. This requirement to purchase the new drug is a consequence of the new drug being clinically innovative, and in this fictional country, any drug that is clinically innovative must be reimbursed, regardless of the price of that drug. **New drug adoption financed by budget expansion** is the nominated strategy. The budget is currently economically efficient.

The new technology, Drug P, has an offer price expressed as an *IPER* $f > 0$ and an additional effect compared to the best alternative therapy (clinical value of innovation) for this group of patients of:

$$CVI = \Delta E^P = \frac{\Delta C^P}{f} > 0$$

¹⁰⁸ The definitions of $ICER_i$ and NB_i are presented in the notation glossary and in Appendix 4.

¹⁰⁹ The “operational” justification is that in this fictional country, the Reimburser is required to adopt the new drug based on consideration of its clinical innovation value only, that is, $\Delta E > 0$. From a methodological perspective, this assumption allows us to separate the question of the choice of the decision threshold (explored in Chapter 8 in a game theoretic model) from the question of the economic value of the strategy of reimbursement. It also allows us to exclude the possibility that the firm considers the decision threshold when it sets the price. See also the discussion in the Conclusion to this Chapter.

where $\Delta C^P > 0$ is the additional financial cost of the new drug.

The Reimburser also identifies the most cost effective (in expansion or adoption)¹¹⁰ of the existing programs; Program N at an aICER of $n > 0$. This is an opportunity to increase the health of the population by an amount:

$$\frac{\Delta C^P}{n} = \Delta E^N > 0$$

Expansion of Program N is the best alternative strategy.¹¹¹ It is the action with the maximum possible gain that also meets the condition of being financed by expanding the budget constraint by an amount ΔC^P . (See Chapter 6, Section 3, p. 84.)

This scenario is illustrated in Figure 3.

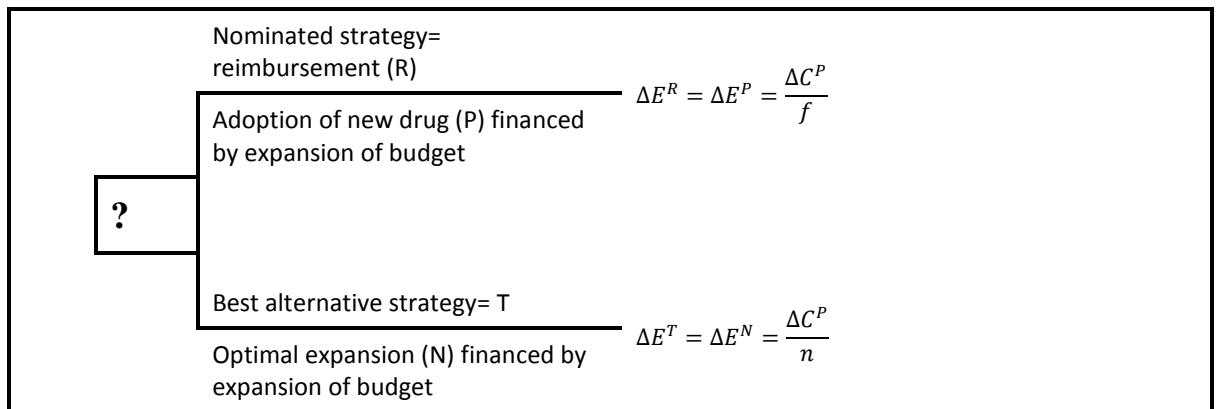


Figure 3 Payoffs to adoption with initial condition of economic efficiency

The shadow price (λ) of the budget constraint (B), defined in terms of expansion (e) and measured as an ICER is:

$$\lambda_e^B = \frac{\Delta C^P}{\Delta E^N} = n$$

This result is the aICER of the additional effects ΔE^N of the most cost effective program in expansion, where the additional cost of this program is financed by expanding the health budget by an amount ΔC^P .

The net financial cost of strategy R is:

$$\Delta C^P > 0$$

This is the additional financial cost to the health budget of reimbursing the new drug and it is financed by expansion of the budget.

¹¹⁰ The program that is the most cost effective in expansion is defined as follows. The incremental gain in health effect of expanding all existing programs by an amount ΔC^P is estimated. Then the program that gains the largest number of health effects as a consequence of expansion is the most cost effective program (in expansion). This Program is not necessarily the most cost effective of all programs. The average cost per effect of the whole program could be more than the cost per effect in expansion if the program has increasing marginal benefit or decreasing marginal cost or both. However there could also be another program or technology that is not yet funded and is only available if the budget is expanded. Hence the best alternative strategy set includes programs and technologies that are either currently funded or not currently funded.

¹¹¹ This is Strategy S from the previous Chapter.

The net health benefit of strategy R is:

$$\Delta E^R = \Delta E^P > 0$$

This is the net health gain to the population as a consequence of Reimbursement. This is the same as the gain to the target patients because in this scenario, no services need to be displaced to finance the additional cost of the new drug.

The *NEBh* of strategy R ($NEBh^R$) is:

$$NEBh^R = \Delta E^R - \Delta E^T$$

$$= \Delta E^P - \Delta E^N$$

$$= \Delta C^P \left(\frac{1}{f} - \frac{1}{n} \right)$$

Equation 5

This is the gain in health effects for the population as a consequence of strategy R ΔE^R constrained by the health effects ΔE^T of the best alternative use of the expanded budget, strategy T. (See Figure 4).

The health shadow price of the health effects, of the new drug is an *IPER* for the new drug such that the Reimburser is indifferent to the strategy R and the best alternative strategy, T, that is, the net economic benefit of reimbursement is zero:

$$NEBh^R = 0$$

$$\Rightarrow \Delta E^R - \Delta E^T = 0$$

$$\Rightarrow \Delta E^P - \Delta E^N = 0$$

$$\Rightarrow \Delta E^P - \Delta E^N = 0$$

Substituting in Equation 5

$$\Rightarrow \Delta C^P \left(\frac{1}{f} - \frac{1}{n} \right) = 0$$

$$\Rightarrow \frac{1}{f} = \frac{1}{n}$$

If $f = n$ then the net economic benefit (health) of reimbursement is 0, therefore the health shadow price is:

$$\beta_c = n$$

The key parameters derived in this scenario are summarised in Table 9 (p. 96).

3 Scenario 2: Adoption financed by displacement in an economically efficient budget

The Reimburser is **required** to adopt a new Drug P, financing its additional cost by displacement of an existing program. The health budget is fixed and currently economically efficient. The **strategy**

of reimbursement (R, the nominated strategy) comprises two actions: displacement followed by adoption. Adoption is financed by displacement of existing programs rather than expansion of the budget as in Scenario 1. This situation is a consequence of the fixed budget.

The Reimburser does not perform the action of displacement, which is carried out by a separate agency lead by the Displacer, who operates under rules that prevent him from displacing certain types of programs.¹¹² Program D is displaced. It has an aICER of $d > 0$ and hence displacement is at a health loss (or cost) of:

$$\frac{\Delta C^P}{d} = \Delta E^D$$

The Reimburser is **required** to use these additional financial resources ΔC^P to finance the additional a new drug that has:

- 1) an additional financial cost of $\Delta C^P > 0$;
- 2) an additional effect for the target group of patients $\Delta E^P > 0$; and
- 3) and an *IPER* of:

$$f = \frac{\Delta C^P}{\Delta E^P} > 0$$

The only criterion for reimbursement that has to be met by the new drug is that $\Delta E^P > 0$ and this new drug meets this criterion. Using PEA, the strategy of reimbursement is understood to comprise the actions of displacement and adoption. It is compared to the best alternative strategy (optimal displacement and optimal expansion) (Figure 4). The (non-economic) payoff to reimbursement, R, is the net change in the health of the population.

The Reimburser identifies the least cost effective (in contraction) of existing programs; Program M at an aICER of m . She also identifies the most cost effective of the existing programs (in expansion, **given previous contraction**¹¹³) and unfunded programs and technologies that are not currently funded; Program N at an aICER of n . Therefore the best alternative strategy (T) to the nominated strategy (R) is to displace an amount ΔC^P from the least cost effective Program (M) at a health effect loss of:

$$\frac{\Delta C^P}{m} = \Delta E^M$$

and use these funds to expand the most cost effective existing Program (N) at a health gain of

$$\frac{\Delta C^P}{n} = \Delta E^N$$

¹¹² The Displacer is not permitted to displace programs that are patented and approved as part of a legally enforceable reimbursement process. He can displace programs that are unpatented and can be contracted by small units, for example a respite care program that can be contracted by reducing the hours of care available by one or 100 hours.

¹¹³ How do we identify a program's cost effectiveness in expansion if there is a fixed budget? First the least cost effective of existing programs, M needs to be contracted. Then the most cost effective in expansion of remaining programs is funded. This is the most cost effective given previous contraction. This device allows for the possibility that the best alternative strategy under a fixed budget has no net health effect if the budget is currently economically efficient.

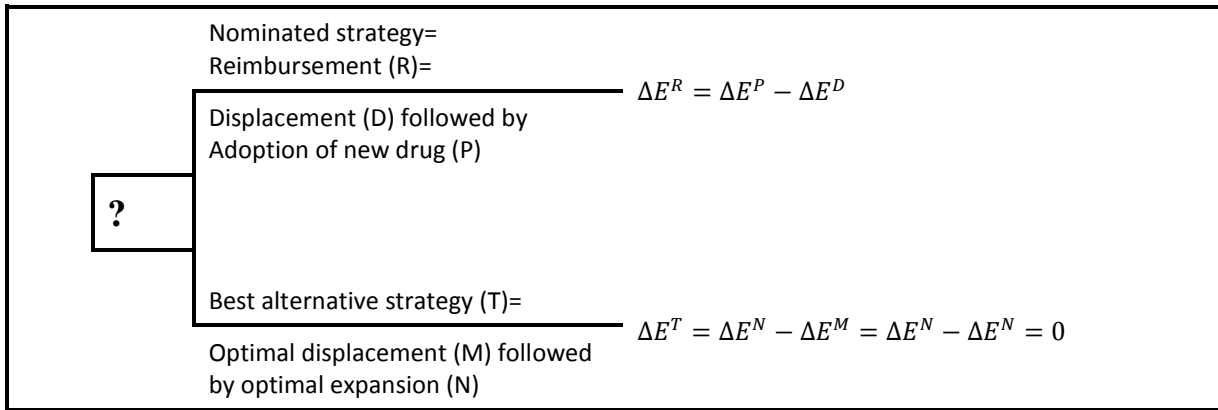


Figure 4 Payoff to reimbursement with initial condition of economic efficiency

The net health benefit of the best alternative strategy (T) is:

$$\Delta E^T = \Delta E^N - \Delta E^M$$

The health budget is currently economically efficient and reallocation is assumed to be costless. This implies that:

- 1) after optimal displacement, which is to displace the least cost effective (in contraction) of existing programs, Program M,
- 2) optimal expansion occurs when the same Program (M) is now refunded because it would then be the most cost effective (in expansion) of remaining programs.

If there were another more effective program that could have been expanded, it would already have been identified because the budget is economically efficient: there is no action that can be performed within existing funds and technologies that would increase the health output.

Hence, at initial condition of economic efficiency, the net effect of optimal displacement and optimal expansion is zero, $m = n$ and:

$$\Delta E^N = \Delta E^M$$

Therefore, the best alternative strategy (T) has a net financial cost and net health benefit of 0. This situation is a consequence of the current optimality of allocation ($\Delta E^T = 0$) of a fixed budget ($\Delta C^T = 0$). There is no strategy within current technologies and programs that can be implemented or expanded to increase the population's health.

The shadow price of the budget (in contraction) is:

$$\lambda_c^B = m (= n)$$

The shadow price of the budget (in expansion given previous contraction ($e|c$)) is:

$$\lambda_{e|c}^B = n = m$$

The nominated strategy of reimbursement (R) comprises two actions: displacement (D) and adoption (P).

The net financial cost of reimbursement is the net financial benefit of displacement and adoption:

$$\Delta C^R = \Delta C^P - \Delta C^D = 0$$

The net health benefit of Strategy R, ΔE^R , is the net effect of adoption and displacement:

$$\Delta E^R = \Delta E^P - \Delta E^D$$

The *NEBh* of reimbursement is:

$$\begin{aligned} NEBh^R &= (\Delta E^P - \Delta E^D) - (\Delta E^N - \Delta E^M) \\ &= (\Delta E^P - \Delta E^D) - (\Delta E^N - \Delta E^N) \\ &= \Delta E^P - \Delta E^D - 0 \\ &= \Delta E^R \end{aligned}$$

This is the net health benefit to the population of reimbursement ($\Delta E^P - \Delta E^D$) constrained by the net health benefit for the population of the best alternative use of funds ($\Delta E^N - \Delta E^M$). The reason that $\Delta E^R = NEBh^R$ is that the best alternative strategy to reimbursement in an economically efficient and fixed budget has a net health benefit of zero:

$$\Delta E^T = \Delta E^N - \Delta E^M = \Delta E^N - \Delta E^N = 0$$

The shadow price of the budget constraint, λ , could be defined in any one of three ways. First, it could be undefined as a result of budget being fixed; there is no point in defining the value of an expanded budget if that budget cannot be expanded and therefore it is not an action in the choice set of alternative strategies. Second, it could be defined as the loss if the budget is contracted¹¹⁴, which is in this case m , the aICER of the least cost effective of currently funded strategies. Third, it could also be defined as the gain if the budget is expanded by one additional unit. In this case, additional information apart from that available in the alternative strategy set is required in order to determine the shadow price of the budget constraint. Depending upon whether the most cost effective program in expansion has increasing or decreasing returns to scale, it could be greater or less than m .

The health shadow price is the *IPER* of the new drug such that the Reimbursers is indifferent between the strategies of R and the best alternative strategy (T , optimal displacement and adoption):

$$NEBh^R = 0$$

$$\Rightarrow (\Delta E^P - \Delta E^D) - (\Delta E^N - \Delta E^M) = 0$$

$$\Rightarrow \Delta E^P - \Delta E^D = 0$$

$$\Rightarrow \Delta C^P \left(\frac{1}{f} - \frac{1}{d} \right) = 0$$

So when $f = d$ the reimbursers is indifferent between the two strategies and hence the shadow price of the health effects from the new drug is d :

$$\beta_c = d$$

¹¹⁴ The shadow price when the budget is contracted by one unit is consistent with the operations research use of the term and when it is expanded, the economic use. (See Section 3.1 Chapter 3)

Therefore the economic value of clinical innovation is:

$$EVCI = \beta_c \Delta E^P = d\Delta E^P$$

The key parameters derived in this scenario are summarised in Table 9, page 105.

4 Scenario 3: Adoption financed by displacement in economically inefficient budget

As presented in Figure 5, Scenario 3 has only one difference to Scenario 2; the initial condition in the health budget is allocative inefficiency rather than economic efficiency. The nominated strategy is reimbursement of Drug P: adoption of the new drug financed by displacement of an existing program. Consider the set of alternative strategies identified in Step 4 in Chapter 6 (p. 84). This set contains many actions that are displacement and many actions that are adoption or expansion. It can be considered as the set from which the set of possible options identified in Program Budgeting Marginal Analysis (PBMA) is drawn.¹¹⁵

In terms of Figure 5, the best alternative strategy (T) is optimal reallocation (A) of ΔC^P from Program M (the least cost effective program in contraction) to Program N (the most cost effective in expansion, conditional on previous contraction) where $n < m$. Optimal reallocation comprises two actions from the set of alternative actions – contraction of Program M (financing) and expansion of Program N (adopting).¹¹⁶

Therefore, as a consequence of existing allocative **inefficiency**:

$$\Delta E^T = \Delta E^A = \Delta E^N - \Delta E^M > 0$$

Note: The distinction between ΔE^T and ΔE^A is that the former is the outcome of the best strategy, T , from the set of alternative strategies whereas the latter is the best of strategy a particular type of strategy (reallocation) from this set of alternative strategies. The best alternative reallocation strategy is always reallocation from Program M to Program N. However, if another type of strategy such as the investment in changed practice is included in this set then the best alternative strategy, T , from this set could change. (See Scenario 4, summarised in this chapter and reported in full in Appendix 5.

¹¹⁵ PBMA has a long history and its preeminent advocate in Health Economics is Gavin Mooney. The first text I read on this topic was “Choices for health care: a practical introduction to the economics of health provision.” (Mooney, Russell et al. 1986) I have also been fortunate enough to observe Gavin take a group through the process of PBMA. The set of all alternative actions in Step 4) of PEA is essentially a formalised version of identifying activity at the margin in PBMA.

¹¹⁶ Why is Strategy A, optimal reallocation, described as the best alternative strategy T ? Shouldn't the two actions of optimal displacement and adoption each be described as the best alternative? The important point is that pairs of displacement and adoption in such a set are about the strategy to reallocate, which, like the term reimbursement, describes two actions. Reimbursement is a qualitatively different strategy to the strategies of i) Reallocation, and ii) budget expansion and new Program adoption.

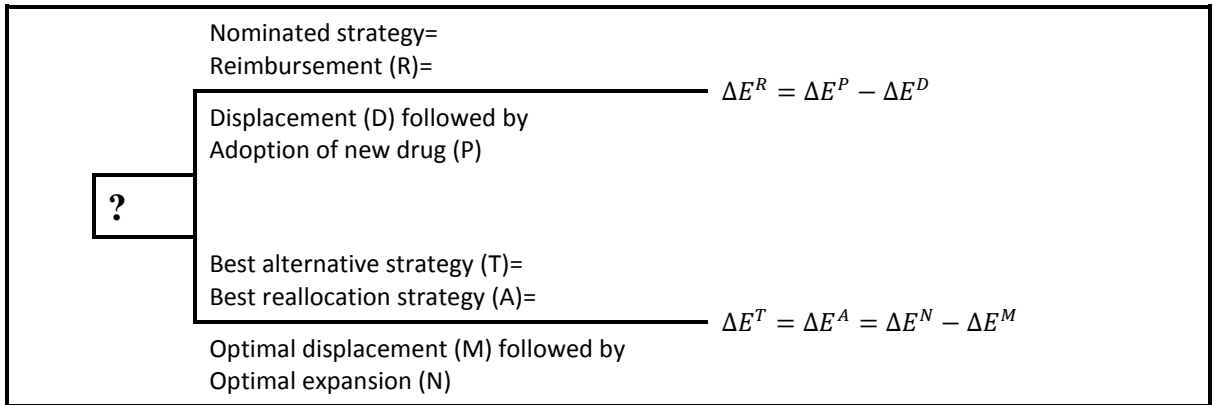


Figure 5 Payoff to reimbursement with initial condition of allocative inefficiency

The net financial cost of Strategy R is $\Delta C^P - \Delta C^P = 0$ and therefore the net financial cost of the best alternative strategy is also zero. This is the situation because the budget is fixed and therefore there is no net financial cost of either strategy. This is the case even though $\Delta C^P > 0$, that is the net cost of adoption is greater than 0.

The net health benefit for the population of Strategy R is $\Delta E^P - \Delta E^D$ and the impact of the best alternative strategy to R (reallocation, strategy A, which is optimal adoption and optimal displacement) is $\Delta E^N - \Delta E^M$.

The *NEBh* for Strategy R is:

$$\begin{aligned}
 NEBh^R &= \Delta E^R - \Delta E^T \\
 &= (\Delta E^P - \Delta E^D) - (\Delta E^N - \Delta E^M) \\
 &= \left(\frac{\Delta C^P}{f} - \frac{\Delta C^P}{d} \right) - \left(\frac{\Delta C^P}{n} - \frac{\Delta C^P}{m} \right) \\
 &= \Delta C^P \left(\frac{1}{f} - \frac{1}{d} - \frac{1}{n} + \frac{1}{m} \right)
 \end{aligned}$$

The health shadow price is the *IPER* of the new drug at which the net economic benefit of Strategy R is 0, that is, where the Reimbursers is indifferent between reimbursement and the strategy of optimal reallocation.

$$\begin{aligned}
 NEBh^R &= 0 \\
 \Rightarrow (\Delta E^P - \Delta E^D) - (\Delta E^N - \Delta E^M) &= 0 \\
 \Rightarrow \left(\frac{\Delta C^P}{f} - \frac{\Delta C^P}{d} \right) - \left(\frac{\Delta C^P}{n} - \frac{\Delta C^P}{m} \right) &= 0 \\
 \Rightarrow \Delta C^P \left(\frac{1}{f} - \frac{1}{d} - \frac{1}{n} + \frac{1}{m} \right) &= 0 \\
 \Rightarrow \left(\frac{1}{f} - \frac{1}{d} - \frac{1}{n} + \frac{1}{m} \right) &= 0
 \end{aligned}$$

$$\Rightarrow f = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

$$\Rightarrow \beta_c^\alpha = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

where the superscript α refers to this particular health shadow price as relating to the best alternative reallocations across existing programs. (In the following section, a set of alternative strategies that includes only investment strategies is used.)

The economic value of clinical innovation is the clinical value of innovation valued by its health shadow price.

$$EVCI = \beta_c^\alpha \Delta E^P = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1} \Delta E^P$$

The key parameters derived in this scenario are summarised in Table 9.

5 Scenario 4: Adoption financed by displacement in an economically inefficient budget (investment version)

Scenario 4 is presented in detail in Appendix 5. The key parameters derived in this scenario are summarised in Table 9, page 105. In summary, Scenario 4 demonstrates that if there is an option to invest ΔC^P today in changed practice that will reduce the aICER of a program in the future, then there is a parameter that can capture both the reduction in static efficiency today (for one year taking ΔC^P away from the least cost effective program) as well as the gain in dynamic efficacy that occurs because the future aICER of the program is lower than the current aICER. That parameter is μ . The superscript v on the health shadow price β_c allows the distinction to be drawn between the health shadow price derived from investment strategies β_c^v and the health shadow price derived from reallocation strategies β_c^α .

6 Results

The variation in both β_c and $EVCI$, across the four scenarios is presented in Table 9. The properties of these parameters are then discussed.

6.1 Parameters' Properties

We assume that all of the following parameters are greater than zero: f , m , d , n , ΔE^P and ΔC^P . We also continue to assume that the Reimbursers in this fictional country must reimburse the new drug, regardless of the offer price ($IPER$) of f , provided that new drug meets the condition that $\Delta E^P > 0$.

What are the properties of the following parameters as illustrated by the four scenarios?: ΔE^P , ΔC^P , ΔE^R , λ^B , β_c and $EVCI (= \beta_c \Delta E^P)$

Table 9 Summary of parameters across all scenarios

Parameter	Scenario 1: economic efficiency and financed by budget expansion	Scenario 2: economic efficiency and financed by displacement	Scenario 3: allocative inefficiency and financed by displacement	Scenario 4: technical inefficiency and financed by displacement
Clinical value of innovation (target patients) ΔE^P	$CVI = \Delta E^P$	$CVI = \Delta E^P$	$CVI = \Delta E^P$	$CVI = \Delta E^P$
Net health effects from reimbursement (population) ΔE^R	$\Delta E^R = \Delta E^P - 0 = \Delta E^P$	$\Delta E^R = \Delta E^P - \Delta E^D$	$\Delta E^R = \Delta E^P - \Delta E^D$	$\Delta E^R = \Delta E^P - \Delta E^D$
Conventional Net Benefit NB(k)	$NB_k = k\Delta E^P - \Delta C^P$	$NB_k = k\Delta E^P - \Delta C^P$	$NB_k = k\Delta E^P - \Delta C^P$	$NB_k = k\Delta E^P - \Delta C^P$
Net economic benefit from reimbursement (health) $NEBh^R$	$NEBh^R = \Delta E^R - \Delta E^N$	$NEBh^R = \Delta E^R - 0$ $= \Delta E^P - \Delta E^D$ $= \Delta C^P \left(\frac{1}{f} - \frac{1}{d} \right)$	$NEBh^R =$ $(\Delta E^P - \Delta E^D) - (\Delta E^N - \Delta E^M)$ $= \Delta C^P \left(\left(\frac{1}{f} - \frac{1}{d} \right) - \left(\frac{1}{n} - \frac{1}{m} \right) \right)$	$NEBh^R =$ $(\Delta E^P - \Delta E^D) - (\varphi \Delta E^G - \Delta E^M)$ $= \Delta C^P \left(\left(\frac{1}{f} - \frac{1}{d} \right) - \left(\frac{1}{\mu} - \frac{1}{m} \right) \right)$
Net financial cost of adoption (target patients) ΔC^P	ΔC^P	ΔC^P	ΔC^P	ΔC^P
Net financial effect of reimbursement (Population) ΔC^R	$\Delta C^R = \Delta C^P$	$\Delta C^P - \Delta C^P = 0$	$\Delta C^P - \Delta C^P = 0$	$\Delta C^P - \Delta C^P = 0$
Health shadow price λ	$\beta_c = n$	$\beta_c = d$	$\beta_c = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$	$\beta_c = \left(\frac{1}{\mu} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$
Shadow price of the budget in expansion λ_e^B	$\lambda_e^B = n$	Unknown / not defined	Unknown / not defined	Unknown / not defined
Shadow price of the budget in expansion conditional on initial contraction $\lambda_{e c}^B$	n/a	$\lambda_{e c}^B = n = m$	Unknown	Unknown
Economic value of clinical innovation $EVCI$	$EVCI = n\Delta E^P$	$EVCI = d\Delta E^P$	$EVCI = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1} \Delta E^P$	$EVCI = \left(\frac{1}{\mu} - \frac{1}{m} + \frac{1}{d} \right)^{-1} \Delta E^P$

d is the aICER of the services displaced to finance the additional cost of the new drug;

m is the aICER of the least cost effective service in contraction;

n is the aICER of the most cost effective service in expansion;

μ is the parameter that captures the gain in health effects for one program by investing in improved practice in terms of an aICER;

φ is the parameter that captures the NPV of additional health effects possible from changed practice in Program G

1) The clinical innovation of the new drug ΔE^P

The clinical innovation of the new drug ΔE^P is constant across these scenarios. The drivers of change in the clinical innovation of a given drug are not specified in this chapter. They include: the choice of comparator, the clinical protocol, duration of therapy and dose. These determinants of ΔE^P are accommodated by HTA/CEA methods. (See Chapter 4)

2) The additional financial cost of adoption to the health budget $\Delta C^P (=f\Delta E^P)$

The additional financial cost to the health budget, the amount that must be financed, ΔC^P is constant across these scenarios. The drivers of change in ΔC^P include all those factors that determine ΔE^P . The additional driver is the price (or unit costs) of resources such as diagnostic tests and the *IPER* of the new drug. In Chapter 8, the consequences of recognising that f and hence ΔC^P is a function of the Reimburser's maximum acceptable *IPER* are explored.

3) The conventional Net Benefit NB_i

The value of the conventional net benefit value remains constant regardless of the economic context and varies with the administrative choice of i , which, in Table 9, is k .

4) The net effect of reimbursement on the population's health ΔE^R

The net health effect for the population is less than 0 when the budget is fixed and the aICER of displaced services is less than the *IPER* for the new drug ($d < f$). The net effect on the population's health is a function of d . ΔE^R_{\max} for a fixed budget, given the requirement to reimburse the new drug at the price f occurs when d is maximised, that is, displacement is optimal and hence $d=m$.

5) The net economic benefit of reimbursement (health) $NEBh^R$

Assuming that adoption is a requirement, then the $NEBh^R$ is maximised when the health benefits of the new drug are greater than those of the best alternative strategy (adoption is optimal, $f < n$) and displacement is optimal ($d=m$). The conditions under which the $NEBh^R$ is positive are characterised and the limitations of alternative thresholds to the health shadow price are demonstrated in the following three inequalities.

Inequality one: reimbursement vs. improved economic efficiency

$$NEBh^R > 0$$

$$\Rightarrow \Delta C^P \left(\left(\frac{1}{f} - \frac{1}{d} \right) - \left(\frac{1}{n} - \frac{1}{m} \right) \right) > 0$$

$$\Rightarrow \left(\frac{1}{f} - \frac{1}{d} \right) - \left(\frac{1}{n} - \frac{1}{m} \right) > 0$$

$$\Rightarrow \left(\frac{1}{f} - \frac{1}{d} \right) > \left(\frac{1}{n} - \frac{1}{m} \right)$$

Equation 6

This inequality identifies the conditions under which the $NEBh^R$ is positive by comparing the strategy of reimbursement (on the LHS) and the strategy of reallocation to reduce economic inefficiency (on the RHS). From Equation 6, we observe that the $NEBh^R$ can be negative even if the net effect of displacement and adoption is positive ($\Delta E^R > 0$); the This occurs if there is sufficient allocative inefficiency ($m > n$).

Under the use of d as the decision threshold (CEA_d) the Reimburser would only adopt the new drug if $f \leq d$. The net health benefit of reimbursement (ΔE^R) is never negative in this case, however, the $NEBh^R$ will be negative even if the $\Delta E^R > 0$, if the best alternative strategy (optimal adoption and

displacement) is more effective than reimbursement. Hence even though the $\Delta E^R > 0$ under (d) , ΔE^R is not necessarily maximised.

If we use the aICER of the most cost effective of alternative strategies as the decision threshold, then we would adopt if $n \geq f$. In this case, the net benefit for the population will always be positive or equal to zero, because the aICER of the program that is displaced can never be more than the most cost effective of existing programs in expansion. Hence, because $n \geq f$ and $d \geq n$, then $d \geq f$ hence the net effect of displacement and adoption is always positive. However, if displacement is suboptimal ($m > d$) then there would be a net economic loss to reimbursement under n as a threshold, regardless of the net impact on the population.

Inequality two: optimality of adoption vs. optimality of displacement

Rearranging Equation 6 we have:

$$\left(\frac{1}{f} - \frac{1}{n}\right) > \left(\frac{1}{d} - \frac{1}{m}\right) \quad \text{Equation 7}$$

This inequality looks at the conditions under which the $NEBh^R$ is positive by comparing the degree of optimality of adoption (LHS) with that of the optimality of displacement (RHS). If displacement is suboptimal ($d \leq m$), provided that adoption is optimal, the net economic benefit could still be positive but not maximised. However, the reverse is not the case. If adoption is suboptimal then there will always be a net economic loss, because $d \leq f$.

Inequality three: price of new drug vs. health shadow price

Rearranging Equation 7 we have:

$$\frac{1}{f} > \left(\frac{1}{n} + \frac{1}{d} - \frac{1}{m}\right) = \frac{1}{\beta_c} \quad \text{Equation 8}$$

By definition, if the *IPER* of the new drug is β_c then the Reimbursers is indifferent between strategy R and the best alternative strategy. Hence, only under the health shadow price as the decision threshold is the $NEBh^R$ never less than zero and hence the health of the population maximised.

6) The shadow price of the budget constraint λ^B

The shadow price of the budget constraint is defined when the budget is constrained and economically efficient; it is the aICER of the most cost effective program in expansion, n . When the budget is fixed and economically inefficient, λ^B could be defined using the operations research definition, the minimum loss under budget contraction, in this case, the least cost effective program in contraction with an aICER of m . Alternatively it could be undefined.

7) The health shadow price β_c

The only case where β_c could be greater than n is when the health budget is fixed and economically efficient (Scenario 2). In this case, the opportunity cost of Strategy R is zero, and β_c is the aICER of the displaced program. If there is a constrained budget and existing economy efficiency (Scenario 1), β_c is n . If there is fixed budget and allocative or technical inefficiency (Scenarios 3 and 4), $\beta_{c_{\max}}$ is n .

Proof by contradiction:

If:

$$\beta_c > n$$

$$\Rightarrow \frac{1}{n} > \frac{1}{\beta_c}$$

$$\Rightarrow \frac{1}{n} > \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)$$

$$\Rightarrow \frac{1}{m} > \frac{1}{d}$$

$$\Rightarrow d > m$$

However m is the least cost effective of all programs in contraction, and d is the aICER of the displaced services (a contracted program) therefore, $m \geq d \forall m, d$. Therefore β_{cmax} is n . If there is allocative inefficiency and a fixed budget then β_c is maximised when displacement is optimal ($d=m$).

8) The economic value of the new drug's clinical innovation, *EVCI*

The economic value of the new drug's clinical innovation, $EVCI = \beta_c \Delta E^P$, varies across scenarios. As the competition from other ways of generating health effects increase, the economic value of the clinical innovation decreases. As the suboptimality of displacement increases, so does the economic value of Strategy R and hence the economic value (market price) of the new drug.

7 Discussion

What advantages does PEA offer over HTA/CEA? What are the differences between the two methods? PEA does not replace HTA/CEA, which estimates the consequences of the adoption decision, ΔE^P and ΔC^P .

- 1) PEA identifies the strategy of reimbursement (adoption and financing) whereas HTA/CEA identifies the action of adoption.
- 2) PEA quantifies the net health effect for the population of the reimbursement decision, whereas HTA/CEA quantifies the net health effect for target patients from the adoption decision.
- 3) PEA identifies whether there is an alternative strategy that is preferable to reimbursement whereas HTA/CEA only compares the actions of adopt or not adopt.
- 4) β_c is endogenous to the reimbursement decision (it captures suboptimality of displacement) and to the economic context (it captures the best alternative strategy including the strategy of improving inefficiency, technical or allocative).
- 5) PEA appropriately attributes an increase in the population's health following reimbursement to clinical innovation, rather than the strategies of increasing the budget or improving existing inefficiency. The $NEBh^R$ is always estimated net of the best alternative strategy.

7.1 The Reimburser's questions

- 1) *How does β_c vary across different reimbursement strategies and economic contexts?*

The economic context of reimbursement varies as a consequence of: the method of financing (budget expansion or displacement); the optimality of displacement; the availability of alternative strategies to improve the health outcomes of the budget; and existing inefficiency in the health budget. This is analogous to the net health benefit of adoption of a new drug for a patient group (its clinical

innovation) varying as a consequence of: the patient group; duration and dose of therapy; patient compliance with therapy; position of therapy in the clinical context (first, second or third line); and the best available alternative strategy for that patient group.

Unlike the maxWTP for the health effects of the new drug, β_c captures this variation in economic context; it is endogenous to the economic context. The reason this occurs is because:

- 1) β_c is solved by finding the *IPER* of the health effects of the new drug at which the Reimbursing Party is indifferent between the reimbursement of the new drug and the best available strategy, where this best alternative strategy includes reducing inefficiency;
- 2) the difference in the net health effects of the two alternative strategies captures the economic context of inefficiency and whether the budget is fixed or constrained; and
- 3) if the optimality of displacement varies, so will the net health effect of reimbursement.

The maxWTP for given health effects from a new drug does not capture this information; it is constant across all economic contexts. This is analogous to the effect of the new drug P being constant, if it were derived from a comparison to placebo, regardless of the changes in the best available therapy.

If we change the set of alternative strategies from which the best alternative strategy is selected, we change β_c . This is demonstrated with the introduction of the opportunities for investment. This is analogous to the change in ΔE and ΔC if the comparator is the best alternative pharmacotherapy vs. a comparator of the best alternative non-pharmacotherapy (e.g. surgery or physiotherapy). The change in alternative strategy could also be consistent with an alternative maximand or set of maximands, an issue explored further in the Conclusion to this thesis.

2) Why can PEA and not HTA/CEA accommodate the economic context?

The key mechanism of PEA is its definition of the strategy of reimbursement (as adoption and displacement) which in turn accommodates: i) payoff to the population rather than target patients; and ii) the inefficiency in the health budget and in displacement.

The first way that PEA accommodates the economic context is by defining the nominated strategy as reimbursement, which comprises the two actions of: adoption and displacement. In this way the payoff of the strategy of reimbursement in a fixed budget is the net effect of the health effects to the population of adoption and displacement. This is in contrast to conventional HTA/CEA decision analytic structures, which define the nominated strategy as adoption; typically substitution of the best available drug with the new drug. In such a model, the payoff to the strategy of adoption is the additional cost and effect of the new drug compared to the best existing therapy. The payoff in HTA/CEA is to the target patients and not the population. In PEA the payoff of the additional effect for the target patient is accommodated as the health payoff to adoption but this payoff is netted by the loss to the population as a consequence of displacement.

The second way that PEA accommodates the economic context is by defining the best alternative strategy as comprising the best alternative actions to displacement and adoption in the Reimbursement strategy. This method allows for issues such as inefficiency in displacement (suboptimal displacement) and inefficiency in the health budget to be accommodated in the net economic benefit of reimbursement.

8 Conclusion

In summary, β_c is the *IPER* at which the Reimbursing Party is indifferent between reimbursing the new drug (adoption to place drug in a clinical context plus displacement to finance its additional costs) and

the best alternative strategy, given the economic conditions and sub-optimality of displacement. This is the *IPER* of the new drug at which the net economic benefit to the population of the strategy of reimbursement is zero. β_c is endogenous to the reimbursement decision and is defined by: i) the incremental cost and effect of the new drug; ii) the economic context (health sector inefficiency and type of budget constraint); and iii) the optimality of displacement. It is the choice of decision threshold that will ensure that the net economic benefit is never negative.

The assumption that the Reimbursers must reimburse the new drug regardless of the price is clearly unrealistic. Primarily, it is a device to identify the net effect of the strategy of reimbursement (adoption and displacement) at a given price and decision threshold. If the strategy of reimbursing the new drug has a positive net economic benefit (health), then reimbursement is population health maximising compared to the best alternative strategy, where these alternative strategies include strategies to reduce existing inefficiency, both allocative and technical.

A second advantage of using the device (forced reimbursement) is that by assuming that the Reimbursers must reimburse the new drug, regardless of the price, we do not need to consider the way that the firm chooses a price. In particular, we do not need to consider whether the *IPER* is exogenous or endogenous to the decision process. In Chapter 8, I show why it is more realistic to assume that the price of the new drug is endogenous, rather than exogenous, to the reimbursement process. The choice by the firm as to the price of the new drug is a function of the choice of decision threshold; the higher the decision threshold, the higher the firm's offer price. Price is a strategic decision by the firm, which considers the likely response by the institution when in prices the new drug.

The strategic element of reimbursement was suggested in Chapter 5. It is the behaviour of the monopolist bike shop owner who does not put price tags on her bikes. It is the action of the dung beetle patent holder who waits until the shadow price is revealed by the Council to present the price of the dung beetle. It is the reason why it is not sufficient to simply find a shadow price of the new drug, use it as an input in a HTA/CEA and make the reimbursement decision on the basis of a shadow price adjusted ICER. The economic value of the new drug is signalled via the decision threshold to the firms who will consider this information when they select their offer price. The opportunity for firms to act strategically when they price new drugs is one of the reasons why the problem set up in Drummond et al. (2005) needed to be reframed for PEA in Chapter 6. The firm is a player – it chooses the offer price.

Chapter 8, which is about the high stakes game of drug reimbursement, introduces three additional features of PEA that further distinguish it from HTA/CEA:

- 1) the Reimbursers considers net economic benefit (health) when she makes the reimbursement decision, hence taking into account the economic context;
- 2) a firm uses its market power to select the price of the new drug; and
- 3) game theoretic rather than decision theoretic models are used to accommodate this strategic rather than price taking behaviour by firms.

Chapter 8: The “New Drug Reimbursement” Game

At Incremental Price Effectiveness Ratios (*IPERs*) above β_c , the best alternative strategy to reimbursement will result in more health benefits to the population compared to the strategy of reimbursement, for the same financial cost. It is very likely that most OECD countries have fixed or constrained budgets and/or significant opportunity costs and suboptimal displacement. In these cases β_c is significantly lower than thresholds such as k (the maxWTP) and d . In such countries, if β_c is enforced as the max*IPER*, firms will now need to reduce the offer price of their new drugs compared to what they would otherwise have charged. In this case, firms might make the following threat:

At IPERs below k , it will not be financially viable to supply most new drugs to this country.

The weight of this Threat could be significant, particularly when the new drugs have substantial clinical benefit for some patient groups. How should a rational Institution respond to this threat?

In Chapter 8, the question of how an Institution should respond to this threat is first analysed in a decision theoretic model that: i) compares strategies in terms of their benefit to the **target patient groups**; ii) assumes no strategic behaviour by the firms; and iii) assumes that the new drug price is exogenous to the reimbursement process.

Then the question of optimal response by the Institution to the Threat is analysed within a PEA framework. PEA uses an applied game theoretic model that assumes firms act strategically and that the health of the **population** is the maximand.

I show that the decision analytic model cannot test whether the population will be worse off or better off at a threshold below k . The applied game theoretic model suggests that responding to this Threat by increasing the threshold will result in a net economic loss, regardless of whether there will be more or less drugs at the new lower maximum price of β_c .

When an offer *IPER* for a new drug is **endogenous** to the reimbursement process it will increase as the threshold increases. In contrast, when it is **exogenous**, it will not respond to changes in the threshold. Experience, evidence, theory and lobbying tell us that new drug price responds to changes in regulation and thresholds. Most significantly, Pharma itself argues that the price of a new drug is “controlled” by regulation including decision thresholds, that is, it is endogenous to the reimbursement process. The game theoretic model accommodates the endogeneity of price whereas the conventional decision theoretic model does not.

This chapter's first conclusion is that the decision to reimburse a new drug is best analysed as a game with multiple players who act strategically and where the objective of the Institution is to maximise population's health rather than test whether the conventional net benefit is greater than zero. The second conclusion is that the population health maximising response to the Threat is to maintain a threshold price of β_c .

1 The Reimburser's problem

The Reimburser announces that she will pay no more for the additional health effects from new drugs than β_c . She estimates β_c to be in the order of \$5,042 per additional QALY at this time;¹¹⁷ only 6.7% of the maxWTP for an additional QALY of \$75,000, which is the currently used maximum acceptable *IPER*. A group of clinicians approach the Reimburser with evidence that the majority of the new innovative drugs over the last ten years were priced at the historic threshold of k (Devlin and Parkin 2004). These clinicians also refer to an excerpt from The New York Times that suggests that society can expect to continue to pay high *IPERs* for new effective drugs into the future.

Until now, drug makers have typically defended high prices by noting the cost of developing new medicines. But executives at Genentech and its majority owner, Roche, are now using a separate argument — citing the inherent value of life-sustaining therapies. If society wants the benefits, they say, it must be ready to spend more for treatments like Avastin and another of the company's cancer drugs, Herceptin, which sells for \$40,000 a year. "As we look at Avastin and Herceptin pricing, right now the health economics hold up, and therefore I don't see any reason to be touching them," said William M. Burns, the chief executive of Roche's pharmaceutical division and a member of Genentech's board. "The pressure on society to use strong and good products is there." (Berenson 2006)

The clinicians argue that these historic and future prices are solid evidence that if the maximum acceptable *IPER* were lowered, many of the future drugs with significant clinical value of innovation and very high costs would not be available to prescribe to patients, because they will not be reimbursed. Patients will be worse off as a result. The evidence that new drugs tend to be priced at the decision threshold is consistent with the Reimburser's experience; most new drugs reimbursed in the last ten years had an *IPER* substantially above β_c and close to the maxWTP. Given this evidence of historic *IPER* of new drugs, the Reimburser is unsure whether she should enforce β_c as the threshold *IPER* of new drugs.

The Reimburser asks her Health Economist two questions:

- 1) *Will this lower maximum IPER mean that drugs that would otherwise have been reimbursed at prices above \$5,042 per QALY will no longer be available to the population at a subsidised price?*
- 2) *If less new drugs are available as a consequence of a lowered maximum IPER, will this make the population worse off than it would have been under the existing maximum IPER of \$75,000?*

The Health Economist suggests one more question:

- 3) *How should the rational Institution respond to the following Threat:*

If the threshold is reduced to β , less than 15% of the new drugs that would otherwise be approved will be made available to patients. The population will be worse off as a consequence of a lower threshold price.

¹¹⁷ This hypothetical value was derived as follows. The most cost effective of existing programs (n) is a dental program with a aICER in expansion of \$7,500 per QALY. The least cost effective of current programs in contraction is a screening program with an ICER of \$110,000 per QALY. The program most likely to be replaced is a respite care program with a aICER of \$13,500. The value of $\beta_c = \left(\frac{1}{7500} + \frac{1}{13,500} - \frac{1}{110,000} \right)^{-1} = \5042

2 A decision theoretic model of the clinicians' case

The problem posed by the clinicians can be represented as a decision theoretical model (DTM) with the following structure: the assumptions, strategies and payoffs that will lead to prediction that the number of New Molecular Entities (NMEs) that are reimbursed will reduce if the threshold *IPER* reduces.

Such a view of the world is represented in Figure 6 for the (hypothetical) case of the evidence from the previous year of 24 new drug reimbursements, where these new drugs had a proven clinical innovation compared to the best alternative therapy. The (hypothetical) evidence shows that of the 24 NMEs reimbursed in the previous year, only two had an *IPER* at or below $\beta_c = \$5,042$ per QALY. The clinicians argue that this evidence suggests that only two of the NMEs reimbursed in the previous year would have been subsidised at the maximum acceptable *IPER* of β_c . This situation would represent a loss of 22 NMEs at an average effect of $\widehat{\Delta E^P}$ per NME and hence a loss in population health effects of $22\widehat{\Delta E^P}$. The clinicians produce further evidence that suggests that the average value of $\widehat{\Delta E^P}$ was 850 QALYs per year, in the year drugs were reimbursed.¹¹⁸ Therefore, if these drugs had not been available, around 18,700 QALYs each year in benefits to the population would not have been experienced.

The world within which this DTM resides is supported, implicitly, by three key assumptions:

- 1) The budget is assumed to expand to accommodate any purchase at or below the threshold acceptable *IPER*; it is not fixed and there is no requirement to displace any services to finance the new drug. This is an unconstrained budget in PEA terminology. (See Chapter 3, page 48)
- 2) The payoff to reimbursement is the increase in the health of the target patient group $\widehat{\Delta E^P}$. Therefore, given that there is no displacement and no unfunded “value for money” option (the budget is unconstrained), we can conclude that the population will be worse off by an amount $22\widehat{\Delta E^P}$ if less future clinically innovative drugs are funded than would otherwise be the case.
- 3) There is no other price below the offer price at which these firms could produce and sell the drug, that is, there is no lower price where $\pi \geq 0$, (where π is the firm's economic rent)

¹¹⁸ This estimate would be difficult to derive in practice. It could be derived by multiplying the average incremental QALY gain per patient (derived when the ICER is calculated) by the number of patients who **commence** a course of treatment each year and calculated for the expected duration of their treatment and benefits. In following years, it would be necessary to ensure that the continuing patients whose benefits were included as a future benefit for patients commencing in previous years are not double (triple, quadruple...) counted.

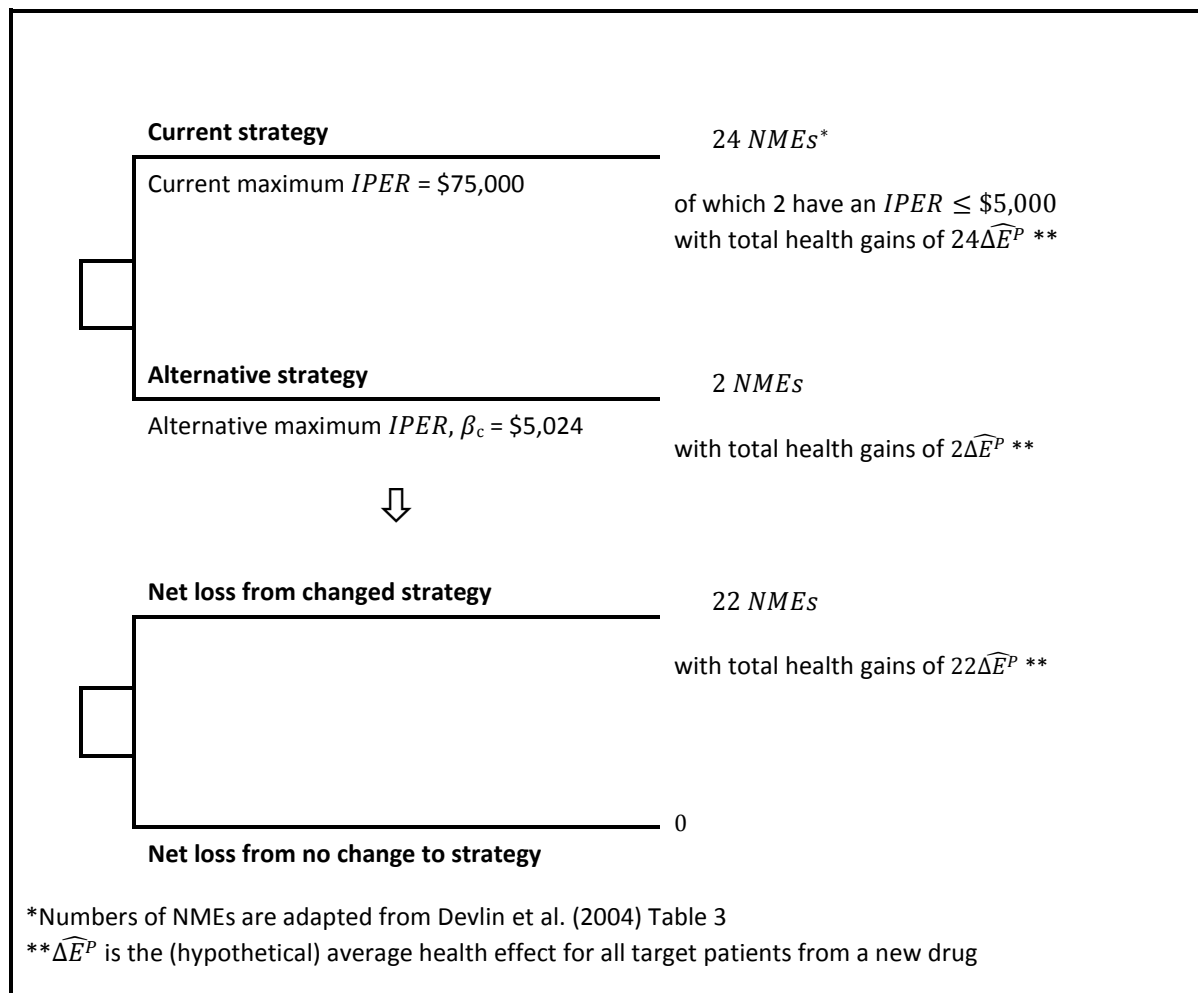


Figure 6 Decision theoretic model of lowered threshold (clinicians' case)

These three assumptions lead to a position that can be summarised as follows:

- 1) no firms will change their offer price as a response to a change in the threshold $IPER$ signalled by the Reimbursers;
- 2) a reduced threshold $IPER$ will lead to a reduction in the number of NMEs approved by the Reimbursers; and
- 3) as a consequence, the population will be worse off than would otherwise be the case.

The three assumptions that premise the above position are not necessarily applicable to the economic context of reimbursement. First, not all health budgets can be expanded to accommodate all purchases that are below an exogenously determined threshold $IPER$. This assumption could be appropriate in some jurisdictions but not in the country of interest. Second, the payoff of an additional NME to target patients is $\widehat{\Delta E}^P$, but the net impact on the population's health as a consequence of the strategy of R in a fixed budget is $\widehat{\Delta E}^P - \widehat{\Delta E}^D$, where $\widehat{\Delta E}^D$ is the average health effects displaced to finance the additional costs of a new drug. There could be a loss in potential health gains $\widehat{\Delta E}^P$ to target patients if a drug that would otherwise be reimbursed is not subsidised. However, the services that would otherwise have been displaced to finance the new drug are no longer displaced. Therefore the reduction in health gains to the target patients would need to be offset by the gain $\widehat{\Delta E}^D$ to patients whose services are not displaced. Third, if firms have market power, their current offer price is **not necessarily** the lowest price that they would be prepared to produce and sell the drug at. Firms with

market power can price above the marginal cost of production because there is a lack of competition from other firms willing to increase market share by offering a lower price.¹¹⁹

The applied economic model developed in the following section accommodates the three characteristics described in the previous paragraph. The first two characteristics are incorporated into the model using a result from the previous two chapters: that the population health payoff to the strategy of reimbursement is the net effect of adoption and displacement. More specifically, the model uses the economic payoff to the reimbursement decision, $NEBh^R$: the net population effect of adoption and displacement net the effect of the best alternative strategy. This ensures that the payoff to Reimbursement will identify whether it is the population health maximising strategy, not simply one with a net population health effect greater than zero. This payoff is analogous to the use of economic rent as the payoff to firms in economic models, rather than accounting profit, and is consistent with the objective of maximising population health. (See Chapter 7, Section 6, p.104 for a discussion of the net economic benefit.) The third characteristic, strategic behaviour, is incorporated by using a Game Theoretic Model (GTM) rather than a Decision Theoretic Model (DTM). The use of a GTM allows the reimbursement problem to be analysed as a high stakes game, where small changes in the decision threshold can result in a significant change in profits for firms and health for the population.

3 The high stakes game of new drug reimbursement

Firms hold patents for their new drugs. Patents are a policy (legislation) intended to correct for the failure of the market to provide an incentive to invest in R&D. Patents achieve this objective by providing market exclusivity; no other firms can produce the patented item, unless they are licensed by the patent holder. However, patents also create market power and therefore the patent holding firm is not necessarily a price taker, unlike a firm in a perfectly competitive market. So economic theory suggests we ask: Why would we assume that a firm with market power will offer the new drug at an *IPER* substantially below the Reimburser's threshold when: i) it knows that the Reimburser will make the same decision (reimburse for the target group) at a higher price; and ii) no other firm will compete and offer the drug at a lower price?¹²⁰

Unlike the situation in a perfectly competitive market, where at any point in time there is only one price, a profit maximising firm can charge for a given item (the market price), market power means that firms can (and must) select a price strategically. In this case, strategically means the monopolist firm makes reference to the expected response by a monopsonist purchaser in the domestic market to possible offer prices. Given the presence of strategic behaviour, the economic model used to

¹¹⁹ Whether or not above marginal cost pricing is justified by the need to cover the fixed costs of R&D (historic and/or future) is a separate issue addressed in Chapters 9 and 10. The point here is simply that, once the drug has been developed, it will only be unprofitable to produce it if the price is below marginal cost of production. In the absence of perfect competition there is no pressure from other Firms to lower the price if the price is above the marginal cost of production. Therefore, provided that the maximum price is not lowered below the marginal cost of production, it will remain profitable for the Firm to produce the drug at the lower price.

¹²⁰ We could also ask why the monopsonist purchaser does not bargain with the producer to identify the price at which the producer will no longer sell. One reason is strategy; bargaining games tend to have outcomes which result in a share of the surplus being appropriated by each player, unless there is a rule or threat that results in a corner solution (see Watson 2004 pp. 170 - 203) The second reason is that information on the threshold is in the public domain (or can be inferred from historic decisions) whereas the cost of production is in the private domain and varies across drugs. The third reason is the particular rules of reimbursement processes such as those in Australia. In Australia, the firm is required to provide evidence of the incremental cost and effect, and to demonstrate it is cost effective (at or below the threshold). If the drug is not cost effective, the Reimburser could signal that the firm should lower the price until it becomes cost effective. There is no lever beyond this threshold that can be invoked by the Reimburser. This, as I argue later in this Chapter, is what the CEO of Roche is referring to in the quotation at the start of this chapter: "the health economics holds up", that is, if the only criterion for a new drug to be reimbursed is to be cost effective, then why would it lower the price below this threshold.

characterise the reimbursement process in this section is game theoretic rather than a DTM. How does a GTM differ from a DTM? And why aren't GTMs used in pharmaco-economics?

3.1 Game theoretic vs. decision theoretic models

Games grow in the spaces where perfect competition does not exist. In perfect competition, the consumers and sellers are price takers and there is no reward for investment in strategic behaviour. In contrast, where the firm and/or the institution have market power, there is a potential for rewards from strategic behaviour. In the case of a new drug, the outcome of the Game is the allocation of the economic surplus (value) from clinical innovation between the firm and the institution as agent of consumers. The *IPEP* of the new drug is the mechanism by which this allocation of surplus occurs and a share of this surplus is the possible reward for strategic behaviour. The decision threshold signalled by the institution is a key piece of information (and decision) which, if varied can change the outcome of the game, the allocation of the surplus and the equilibrium price.

There are two elements common to DTMs and GTMs: i) decision and chance nodes; and ii) the outcomes of these nodes. However, there is a fundamental difference in the structure of, and solutions to, DTMs compared to GTMs: the latter predicts the equilibrium set of actions and strategies, given the interactions between the players with their own preferences whereas the former predict which strategy will be preferred by a single decision maker, given his or preferences. Decision analysis can be characterised as the use of a model to select the optimal action of a single decision maker faced with choices with or without uncertainty (chance nodes). In contrast, game theory can be characterised as concerned with the equilibrium outcomes of strategic interactions of two or more decision makers, with or without uncertainty. Significantly, the equilibrium outcome of a game is not necessarily the optimal outcome for either or both players. In contrast, the lone decision maker in a DTM is selecting the optimal strategy from a number of strategies in order to maximise (or minimise) expected outcomes. There are no other players influencing choice, therefore, the preferred strategy is always implemented. Hence, the result of a DTM is always the selection of the strategy with the best expected outcome for that decision maker.

This fundamental difference is expressed in the structure of the respective models. Both GTMs and DTMs typically have more than one outcome for each decision (for example, cost and effect). The task of decision analysis is for one decision maker to accommodate multiple outcomes, which might need to be traded against each other (for example, additional costs and additional effect). The additional task of game theoretic analysis to accommodate multiple objective functions (for example, the firm vs. the consumer).

3.2 Examples of published pharma-economic games

There are very few published GTMs of the drug pricing process in either the pharma-economic or the pharmaco-economic literature. Two examples in recent years analyse aspects of the drug reimbursement process (Wright 2004; Antonanzas, Juarez-Castello et al. 2011). A third game analyses the decision by firms to conduct head-to-head comparative trials of their drugs and the role of incentives in changing the predicted no-trial equilibrium outcomes (Mansley, Elbasha et al. 2007). This game is not discussed further in this thesis but it provides a powerful example of the relationship between expected profit and strategic choices in the design of clinical trials. It is a rigorous game

theoretic approach to analysing the question of “why don’t we have more head to head clinical trials”.¹²¹

Wright (2004) presented the process of drug bargaining in Australia as a five stage game of complete information. Wright was particularly interested in the welfare implications of: regulating the price below the Firm’s¹²² offer price; bargaining when Firms can be differentiated in terms of their Quality (high for innovative or low for generic); and a single drug that has differential impacts in two patient groups. Wright’s game identified conditions under which certain Firms (High Quality Firms) could benefit from price regulation. It also identified situations under which leakage¹²³ would not reduce a Regulator’s surplus. Wright structured his model such that the initial options for a Firm are: i) to have its price regulated (below what would otherwise be charged) but subsidised; or ii) unregulated and unsubsidised. There is a trade-off then to the decision to approach the Reimburer; unit price or sales. This option does not seem to be relevant to the Australian setting where almost all firms request reimbursement for drugs that are prescribed outside the hospital setting. However it is possible that Wright is referring to a situation where, for a few drugs, the Pharmaceutical Benefits Advisory Committee (PBAC) will not reimburse the drug at the offer price due to lack of evidence of effect or unacceptable cost effectiveness. In this case the Firm is effectively choosing to not lower the price it sells the drug at and have the price to consumers subsidised. Instead it is choosing to maintain the higher price and sell to a market where the financial barrier to access for a consumer could be high.¹²⁴ Wright does not refer to the presence of a decision threshold nor does the model have a concept of expressing a drug price as ICER. He refers to prices per course being equivalent across drugs within the same therapeutic group regardless of their “quality”.

Wright’s model is a reminder that drug price is endogenous not exogenous to the decision process. He also points out that there is an opportunity for firms to use lobbying to extract more of the surplus associated with the reimbursement of the drug, once the firm has agreed to a regulated price. This lobbying for higher prices occurs even though the “High Quality Firm” in Wright’s model is better off by accepting the regulated price in order to gain market share through subsidised drug prices for consumers, compared to a higher price but no consumer subsidy. Wright concludes that:

In this light, the hostility of the pharmaceutical industry to regulation and the claim that it reduces profit can be viewed as an attempt to extract more of the total additional surplus, generated by regulation, in the bargaining process. (p. 810)

¹²¹ This game about optimal trial design from a strategic perspective is probably the most intuitively accessible of these three games, from the perspective of a pharmaco-economist. The Risk Sharing game is also accessible. Both illustrate the idea of characterising players and their actions.

¹²² The Firm is a player in a game and a capital letter is used to signify this particular use of the term. Players have particular characteristics, defined mathematically, and firms with a small “P” do not necessarily have these characteristics.

¹²³ Leakage is a term used to describe the practice by prescribers of prescribing to all patients for whom there is a possible therapeutic benefit not just the patients for whom a subsidy has been approved on the grounds that it is cost effective. The effect of leakage is to increase the budget for that drug beyond the expected expenditure and increase the aICER in actual practice above what was expected due to decreasing marginal benefits and increasing marginal costs.

¹²⁴ It’s complicated. If we assume that all drugs with acceptable cost effectiveness are reimbursed at the offer price, then the benefits of a firm choosing not to have a drug reimbursed and instead sell it unsubsidised to consumers would appear limited, particularly if the new drug is very high cost. Furthermore, to sell a drug that is not subsidised when it is demonstrated to not be “value for money” would appear to be a strategy with little value. However, what is acceptable to a firm might not be acceptable to the regulator. Firms and regulators would dispute whether there are any new drugs that are not reimbursed that have acceptable evidence to support their evidence of incremental cost and effect, and have an acceptable ICER. Hence it is difficult if not impossible to count the number of drugs that meet these criteria of evidence quality and ICER acceptability and are not listed (subsidised) because the firm is unwilling to sell at that cost effective price.

However, a second conclusion is less useful in a context of a reimbursement process that uses economic evaluation, decision thresholds and ICERs. Wright observes that the use of regulation has the objective of improving equity however it has efficiency implications also. He argues that because regulation results in a single price across drugs with varying quality but in the same therapeutic group, these efficiency implications are not desirable.

These efficiency considerations suggest the policy of having a single identical price for all drug classes needs to be re-examined. If the regulated price is the same for all drug classes, then having a different regulated price for different groups of consumers using a drug of a particular class, can increase the regulator's payoff. (p. 809)

In fact, groups of drugs with a single price per course and in the same drug class are typically all generics (or all on patent). If a drug is of higher quality (which is assumed to mean more effective than a comparator) and is on patent, then it will have a higher price per course if it prices at an ICER above zero.¹²⁵ Furthermore, improving equity (in access by consumers through a co-payment scheme) is a different decision from the maximum price an institution should pay for the incremental health effects of a new drug. Wright's paper provides some insights but does not assist in the choice of a single threshold for new drugs based on their incremental cost and effect.

For their research on the conditions under which a Regulator and a Firm would both have an incentive for a Risk Sharing Agreement¹²⁶ (RSA) for a new drug of uncertain benefit, Antonanzas et al. (2011) characterised two possible contracts between Firms and Regulators: RSAs and non-RSAs. In their GTM of complete information, the stylised RSAs required Regulators to pay Firms only if a patient is cured whereas non-RSAs require payment to the Firm per patient treated, regardless of the observable response by patients. The paper established the conditions under which the preferences of the Firm and the Regulators would be aligned and a contract (either RSA or non-RSA) would be mutually preferable. They found that if drugs have a relatively low cost impact, health funders will prefer not to risk share and with high cost impact drugs and low costs of monitoring they would prefer a RSA.

3.3 Why aren't games used in pharmaco-economic models?

The pharmaco-economic literature has a rich tradition of DTMs but not GTMs. A possible explanation is that pharmaco-economics occupies the only space in the reimbursement process within which there is no strategic behaviour. This space is the (non-strategic) behaviour of the new molecule given patient characteristics, dose and duration of therapy. All other aspects of the new drug involve strategic behaviour including: the generation of evidence from clinical trials; the construction of pharmaco-economic models to maximise the possible additional benefit and minimise the additional cost; the offer price selected by the firms; and the recruitment of key clinicians in post marketing studies.

The dominance of DTMs in HTA/CEA can be characterised as a consequence of pharmaco-economic research addressing the market's failure to summarise the complex information about the health and cost consequences of adopting a new drug at a given drug offer price. DTMs can accommodate and analyse: i) uncertainty in parameters; and ii) the impact of uncertainty on optimal decision making. Therefore, DTMs are the model of choice to solve for the *IPER* of a new drug,

¹²⁵ A cursory review of the PBS schedule in a class with both generics and on-patent drugs indicates that the price per course is not identical.

¹²⁶ The highest profile RSA is that between the UK regulators and the firms that owned the patent for a range of drugs for Multiple Sclerosis. (Boggild, Palace et al. 2009)

which can then be used in the Reimbursement process. But information about the *IPER* of a new drug at a given price is not the only information the market fails to provide. DTMs cannot correct for the failure of the market to reveal an *IPER* generated by the firm that reflects competition in the market for health inputs. This market failure is a consequence of the market power of the seller that arises from patents and the market power of monopsonist purchaser. For an economic model to be used to analyse this aspect of the real world, it needs to incorporate strategic behaviour.

In summary, molecules do not act strategically, therefore it is appropriate to use DTMs to analyse the consequences (costs and effects) of new drug adoption. They can be used to estimate the *IPER* of a new drug at a given price and accommodate the associated uncertainty. However, DTMs cannot be used to analyse situations when people, firms and institutions act strategically when they buy, sell, prescribe and consume these molecules. Therefore DTMs can be used to inform, but not analyse, the decision to reimburse the drug. The Game described in the following section illustrates how strategic behaviour by players with market power can be accommodated in an economic model.

4 The new drug reimbursement game

The drug reimbursement game presented in this chapter is less ambitious than the three published games described above; its aim is to demonstrate new drug price as an equilibrium outcome of reimbursement rather than an exogenous choice by the Firm. It was developed using Grüne-Yanoff and Schweinzer's (GY-S) Architecture of Game Theory (Grüne-Yanoff and Schweinzer 2008). The GY-S framework is reproduced in Figure 7, in reverse, starting with World, which is the inspiration for applied economic models, rather than with Theory Proper, which is the inspiration for theoretical economics.

“World” characterises the economic situation which, in an applied economic model, is the justification for the analysis. “Model” comprises a Narrative and a Game Structure. The Narrative is the story that sets out the players, the ordering of events and the justifications for their payoffs. It also clarifies the opportunities for the players to act strategically. The Game Structure is analogous to the decision tree in a decision theory model. (For example compare the decision tree in Figure 6 with the extensive form game in Figure 10) The Game Structure also includes the formal expression of all the payoffs, conditions, assumptions and parameters. Theory Proper is the theoretical foundation of the problem. Solution Concepts can be thought of as theory expressed as a rule that is used to predict how a player or game will be played. Most commonly this is an equilibrium concept, the most well-known of which is the Nash Equilibrium. (See Watson 2003)

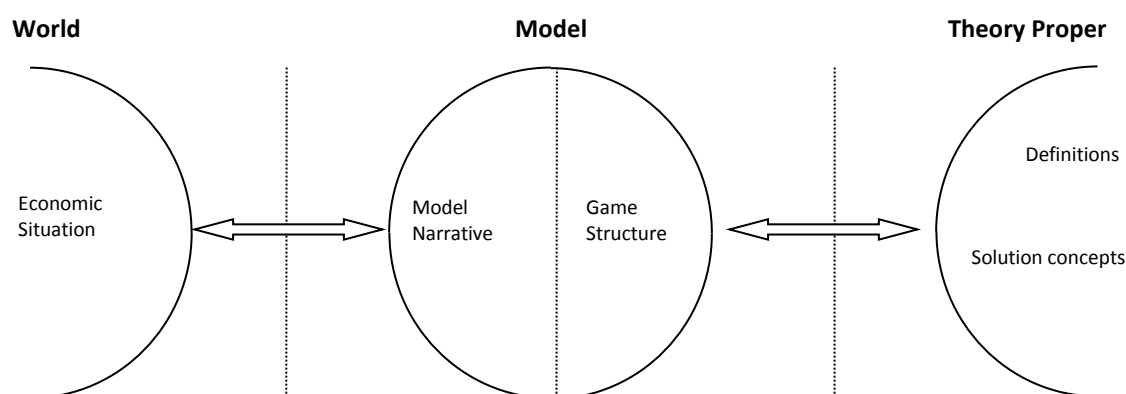


Figure 7 Grüne-Yanoff and Schweinzer's Architecture of Game Theory (Applied economic version adapted from theoretical version)

The Game's Narrative, which precedes the Game Structure in a formal expression of the overall problem, is a detail qualitative description of the Game. The Narrative's role in the GTM can be thought of as analogous to the body of empirical evidence and associated narratives that support the pharmaco-economic model, as distinct from the technical assumptions in the model.

Grüne-Yanoff and Schweinzer describe a given economic situation as having multiple interpretations and hence solutions.¹²⁷ The authors describe the role of the Narrative in supporting a game's solution as:

.... providing information about the rationality and epistemic state of the players in a specific situation, they legitimize the application of a solution concept to the game structures representing that situation. Without the narrative, model users lack justification for which solution concept to choose from the menu offered by the theory proper. (p. 144)

Accordingly, the Game presented in this chapter is designed to have sufficient detail in the Narrative to support the Solution Concepts used in the Game.

4.1 World (The economic problem)

The Reimburser is about to apply β_c as the threshold *IPER*.

$$\beta_c = \left(\frac{1}{n} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

The use of a health shadow price that accommodates the characteristics of the health care sector appeals to the Reimburser. She recognises that allocative inefficiency is a significant feature of health care budgets throughout the OECD (Garber and Skinner 2008). The Reimburser also recognises that there is no Institution analogous to reimbursing Institutions that make systematic improvements to allocative efficiency by reallocating funds across existing programmes and technologies (Culyer, McCabe et al. 2007; Elshaug, Hiller et al. 2007; Pearson and Littlejohns 2007). She also recognises that displacement could be suboptimal ($d < m$) and suboptimality of displacement is not a parameter she can control.

Then the Reimburser thinks about this threshold *IPER* from the perspective of the Firm. At \$5,042, β_c is significantly lower than the threshold of \$75,000 she used historically. She wonders whether the clinicians are correct: will this lower maximum price mean that drugs that would otherwise have been reimbursed at prices above \$5,042 will no longer be reimbursed? The Reimburser considers the idea of the opportunity cost of these additional high cost drugs. She wonders: if less new drugs are available as a consequence, will the population necessarily be worse off than it would have been under the existing maximum *IPER* of \$75,000?

The Reimburser asks her Health Economic Adviser how the Institution should respond to the following threat:

*If the threshold is reduced from \$75,000 to $\beta_c = \$5,024$ per QALY, less than 15% of the new drugs that would otherwise be approved will be made available to patients. The population will be worse off at the lower threshold *IPER*.*

¹²⁷ This particular idea of multiple solutions is distinct from the idea of a non-unique solution to a given problem. The authors describe this idea as each solution concept capturing a specific notion of rationality and that game theory tools offer to "model specific situations at varying degrees and kinds of rationality". Narratives have a role in supporting the particular rationality being used to solve a given game. Hence, the multiple solutions are a consequence of multiple rationalities, whereas non-unique solutions refer to the consequences of a single rationality.

4.2 Model

The model comprises the Narrative and the Game Structure.

4.2.1 Narrative

The Narrative comprises: the Firm's decision; the Institution's decision; and the rules of new drug reimbursement.

4.2.1.1 *The Firm's decision*

A pharmaceutical firm (the Firm) completes the R&D cycle for a new drug for Rheumatoid Arthritis called Arthmax and now two regulatory hurdles need to be cleared. The first hurdle is regulatory approval for clinicians to prescribe the Arthmax for certain groups of patients. The evidence required for this hurdle is that of the comparative clinical effectiveness of the drug. Specifically, the new drug needs to be demonstrated in a clinical trial as being no worse than the best existing drug for that condition. We assume that Arthmax has demonstrated superiority (an additional health gain for target patients) against the existing drug (Rathmab) in an appropriate clinical trial; it is clinically innovative. Furthermore, the group of patients for whom Arthmax represents a clinical benefit (the target patients) all have the same incremental benefit compared to the best existing therapy and no patients outside this group experience a benefit from this drug.

The second hurdle is approval for government reimbursement of the costs of Arthmax for a patient for whom it is prescribed. This approval is for reimbursing the entire cost of Arthmax for all patients for whom prescribing is approved (the target group). The evidence required to clear the reimbursement hurdle is that of the price of the new drug expressed as the additional financial cost to the health sector per additional unit of health effect, or, in PEA terminology the *IPER*. The estimate of this *IPER* (the evidence) is produced by the Firm and is public information in the context of the Game; it is known to both the Institution and the Firm.

Arthmax is patented and as a monopolist, the Firm needs to select rather than accept the price at which it offers the new drug to the reimbursement authority. We assume it selects price so as to maximise economic profit.

There are two factors that the Firm needs to take into consideration when selecting an offer price: the marginal cost of production (which defines the minimum price at which the Firm will be willing to produce) and the Institution's signal of the threshold *IPER*; the maximum price the Institution is willing to pay for a new health effect.

4.2.1.1.1 The marginal cost of production of Arthmax.

Figure 8 and Figure 9 sets out a "worked example" of the relationships between costs of manufacturing and economic rents. (These numbers are presented in the text in italics, bracketed and referenced to the figures. They are not used in the model, which is solved algebraically. These numbers are simply illustrative of cost concepts.)

In this example, incremental measures are compared to their own next best alternative therapy; Rathmab to Placebo; and Arthmax to Rathmab. The *IPER* is the conventional ICER for the drugs, but referred to as an *IPER* to capture the endogeneity of price. The Incremental Manufacturing cost Effectiveness Ratio (*IMER*) is a ratio of the additional costs of manufacturing the new drug to the additional QALYs of the new drug compared to the next best alternative. A new drug could have clinical innovation, but the costs of producing the new drug are the same as the cost of producing the older drug and hence the *IMER* could be zero. The Incremental Economic Profit Effectiveness Ratio

π ER is the incremental economic rent derived by the Firm per incremental QALY, at a given *IPER* and *IMER*.

In this case we assume that Rathmab, which will be entirely replaced by Arthmax, is off-patent and priced at the marginal cost of production, which is constant ($\$250(a)$) – where (*a*) references the corresponding cell in Figure 8. As is conventional in economics, the marginal cost of production includes a cost that represents normal profits (or the opportunity cost of resources owned by the firm).¹²⁸ Furthermore, we assume that the marginal cost of producing Arthmax is constant and the same as the marginal cost of producing a course of Rathmab ($\$250(a)$). Finally, we assume that the only cost consequence to the health budget of financing Arthmax is its additional cost compared to the Rathmab; there are no other resource implications. Therefore, Arthmax's *IPER* relative to Rathmab represents the Firm's economic rent on each unit of effect purchased by the Institution. ($\$75,000$ (*b*))

			See preceding text for abbreviations
QALYs per course	Rathmab	Arthmax	Per 100 patients, the clinical innovation of: Rathmab vs. placebo is 5 QALYs; Arthmax vs. Rathmab is 7 QALYs; and Arthmax v. placebo includes both its own and Rathmab's clinical innovation (12 QALYs).
Rathmab vs. placebo	0.05	0.05	
Arthmax vs. Rathmab	n/a	0.07	
vs. placebo	0.05	0.12	
IPER per course (\$ per QALY)	Rathmab	Arthmax	The <i>IPER</i> for Rathmab vs. placebo is \$5,000 per QALY. The <i>IPER</i> for Arthmax vs. Rathmab is \$75,000 per QALY at the offer price.
Rathmab vs. placebo	5,000	5,000	
Arthmax vs. Rathmab	n/a	75,000	
Each drug vs. placebo	5,000		
Expenditure per course (\$)	Rathmab	Arthmax	The total cost of a course of drugs is derived from the product of the number of QALYs per course for one patient and the cost per QALY for each drug. The drug is the only financial cost of care.
Rathmab vs. placebo	250	250	
Arthmax vs. Rathmab	n/a	5,250	
Total	250	5,500	
Cost of manufacture per course	Rathmab	Arthmax	The cost of manufacturing a course of Rathmab is the same as the price because it is a generic; it is priced at its marginal cost of production, which includes normal profit. The cost of manufacturing a course of Arthmax and Rathmab are the same.
Per total course	250(<i>a</i>)	250(<i>a</i>)	
Per course summary measures	Rathmab	Arthmax	The key indicators for the drugs are summarised on a per course basis where the comparator is placebo. For example, the health gain per course is simply the health gains compared to placebo for a patient.
QALY	0.05	0.12	
Price	250	5,500	
Cost of manufacture	250	250	
Economic rent	0	5,250	

Figure 8 A worked example of Rathmab vs. Arthmax: Per course measures

¹²⁸ When economists refer to economic profit they are referring to profit that is over and above the opportunity cost of a firm's capital, hence the Economics 101 result of the perfectly competitive market: "All firms earn zero profits in the long run competitive equilibrium." For an explanation without the maths, see Lansberg (1988) pp. 191 - 193

Per incremental QALY measures	Rathmab	Arthmax	Rathmab v. placebo
<i>IPER</i> Incremental price per incremental QALY	5,000	75,000 (b)	The <i>IPER</i> for Rathmab is the same as the <i>IMER</i> (see left) because the drug is off-patent.
<i>IMER</i> Incremental cost of manufacture per incremental QALY	5,000	0 (b)	Arthmax v. Rathmab The <i>IMER</i> captures the additional costs of manufacturing the additional QALYs for Arthmax vs. Rathmab. In this case there is no additional cost of manufacturing Arthmax therefore the <i>IMER</i> is 0.
$\Delta ER = IPER - IMER$ in this case Incremental economic rent per incremental QALY	0	75,000 (b)	The ΔER is the incremental economic rent per incremental QALY. It is 0 for the off-patent drug and the same as the <i>IPER</i> for Arthmax.

Figure 9 A worked example of Rathmab vs. Arthmax: Per incremental QALY measures

4.2.1.1.2 Maximum acceptable price

The second factor the Firm needs to consider is the Institution's maximum acceptable *IPER* for the health gains from the new drug. Unlike conventional market situations, the Firm does not need to consider the price elasticity of demand for the new drug between the maximum acceptable price and the marginal cost of production. This situation exists because, if the Institution adopts the drug, the full cost of the drug is reimbursed for all target patients and no other patients. Therefore, the quantity of the drug that will be purchased will be the same, regardless of the price at which it was adopted, provided that price is less than or equal to the Institution's maximum acceptable price. This situation, infinite price elasticity of demand below the maximum acceptable price and perfect price elasticity above this price, leads to the potential quantity of sales (measured in health effects) as either fixed at the expected incremental health effect for the target patient group $\overline{\Delta E^P}$ or zero.

4.2.1.2 The Institution's decision

Reimbursement in a fixed budget involves both adoption and displacement. The adoption of a new clinically innovative drug has the result of increasing the health of the target patients compared to the therapy they would otherwise have had. But adopting the new drug involves an additional financial cost to the health care system compared to usual therapy. The Institution's budget is fixed, therefore this additional financial cost of the new drug must be financed by displacing existing health services. Displacing these services leads to a loss in health effects for the population.

In order to finance the additional costs of a new drug, other agents in the health system will displace unpatented services. Displacement can be suboptimal; the least cost effective in contraction of current programs are not necessarily the ones that are displaced. It is outside the control of the reimbursing Institution. The Institution wants to avoid a situation where the gains from the new drug are considered in isolation from the health effects lost by displacing services. Therefore the Institution defines the net health effect of reimbursement as the net health effect for the population: the increase in the health of the target patients who are prescribed the new drug, less the loss in health for patients whose services are displaced to finance the new drug:

$$\Delta E^R = \overline{\Delta E^P} - \Delta E^D$$

There are constraints around the displacement process. The only health services that can be displaced are those that are unpatented. These services consist mainly of infrastructure and labour inputs, for example respite care and rehabilitation. These programs are infinitely divisible; the budget for a given program can be reduced or increased by the smallest increment. Furthermore, if the budget

is reduced, both the inputs, for example labour, and the output (effect measured in QALYs) are also reduced. This means the outcome of displacement is continuous; any amount can be displaced and any change in this amount will change the health effects for this group of patients. The aICER of a given program is assumed to be constant, regardless of program size, but varies across programs. We assume the estimate of the aICER of these programs is certain. Furthermore, the services that are displaced are not necessarily the least cost effective of existing services. Displacement is exogenous (outside the control of the reimbursing Institution) and possibly suboptimal; it could be any mix of the least and most cost effective existing unpatented services.¹²⁹

Other pharmaceuticals cannot be displaced to finance the additional costs of new drugs because the decision to reimburse them protects them by law from displacement, however, if a new more effective drug is developed and reimbursed for the target patients then the existing drug will be completely replaced. The loss in health gains due to replacement of the previous drug is incorporated in the clinical payoff to the new drug because the clinical innovation of the new drug is compared to the best available therapy for these patients.

The Institution is also concerned about the foregone benefit of alternative ways of accessing and allocating health budget funds. The Institution is aware that the budget is currently allocatively inefficient and that in such a situation: i) the best alternative strategy could be reallocation across programs; and ii) the foregone benefit of funds allocated to new drug purchases could be significant. An amount of funds can be reallocated from Program M, the least cost effective (in contraction) of currently financed programs, to Program N, the most cost effective (in expansion). The foregone benefits of this alternative strategy can be internalised in the reimbursement decision as a forgone benefit in the payoff to reimbursement. Hence the Institution chooses an economic net benefit (the net health gains from reimbursement less the health gains from optimal reallocation) as the payoff to reimbursement. This choice is analogous to economists' preference for using economic rent rather than accounting profit as a firm's payoff. Accounting profit is revenue less costs of manufacturing. Economic rent is revenue less cost of manufacturing and normal profit. A firm can have an accounting profit but an economic loss if the profit from the best alternative strategy is more than that from the strategy of manufacturing drugs. A profit maximising firm will not manufacture if it expects an economic loss, even if it has an accounting profit, because it would be better off taking the alternative more profitable strategy.

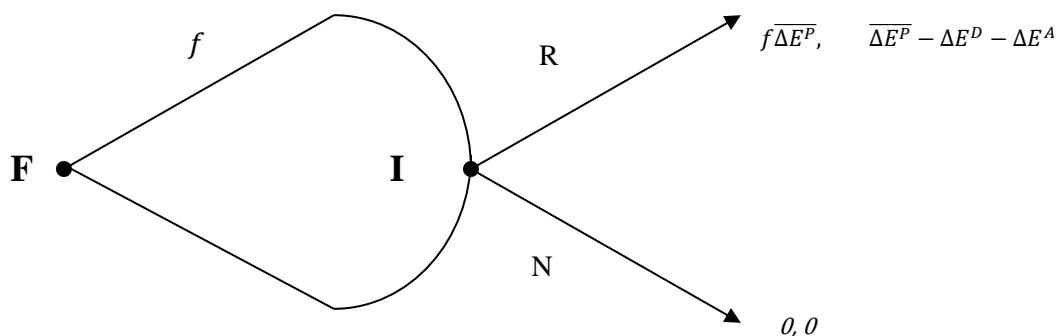
If the Institution is indifferent between reimbursement and doing nothing, we assume it is required to reimburse the new drug. This requirement is a consequence of legislation.

4.2.1.3 The rules of reimbursement

The narrative describing the Firm's and Institution's decisions contains a number of references to the Institution's rules.

- 1) The Game starts when the Firm offers the new drug at a price expressed as an *IPER*; the Institution never approaches the Firm with an offer price.
- 2) The reimbursement process comprises adoption (of new drug) and displacement (of existing non-patented services).

¹²⁹ The somewhat stochastic process of displacing existing service to finance new drugs tends to be a less directed largely politically determined process than reimbursement. It might be spread over many smaller programs and described as "budget cut-backs". There are no Institutions analogous to the reimbursement Institutions that systematically determine whether a given service or technology should be disinvested (planned contraction of programs), although there is an increasing interest in establishing such a process. (Pearson and Littlejohns 2007) It is proposed such processes would be driven by the evidence of a program or technology's lack of effect (e.g. some surgical procedures).



The players are F the Firm and I the Institution and the payoffs are in that order.

Figure 10 The New Drug Reimbursement Game

- 3) Only non-patented services and programs can be displaced to finance the additional cost of the new patented drug.
- 4) Displacement is exogenous to the reimbursing Institution and not necessarily optimal.
- 5) The decision to adopt the new drug has a discrete outcome, 0 or $\overline{\Delta E^P}$ (not adopt - no impact, or adopt - an increase in their health) whereas both the action and outcome of displacement are continuous (the program can be contracted or expanded by any amount).
- 6) If the Institution is indifferent between reimbursement and rejection, it must reimburse.
- 7) The Institution wants to avoid a situation where the health gains from the new drug are considered in isolation from the health effects lost by other patients as a consequence of displacement.
- 8) The Institution is aware that current allocation is inefficient and that the processes for reallocation are not institutionalised in the same way that drug reimbursement is.
- 9) There is no relationship between the new drug's price and future innovation.

4.2.1.4 The Threat

If the threshold is reduced to β_c , less than 15% of the new drugs that would otherwise be approved will be made available to patients. The population's health will be worse as a result.

4.2.2 Game Structure

4.2.2.1 Extensive form representation of the game

The extensive form representation of the game is presented in Figure 10 The New Drug Reimbursement Game.

4.2.2.2 Players, actions and payoffs

The players are the pharmaceutical firm (Firm, F) and the reimbursing institution (Institution, I), the health care budget holder. The Game is initiated when the Firm brings a new pharmaceutical to the Institution.

The Firm's action is to choose a price, $f \in [0, \infty)$. (In Figure 10, the arc representing the Firm's choice indicates that there is a set of possible prices from which it selected one.) The Institution's action is $a_i \in (R, N)$, where: R is reimburse (adopt and displace) and N is do nothing.

If the Institution chooses to reimburse the new drug the payoffs are:

- 1) (To the Firm) $\pi = f\overline{\Delta E^P}$, the economic rent to the Firm, where f is the IPER and $\overline{\Delta E^P}$ is the clinical innovation of the new drug for all target patients compared to best available care; and

- 2) (To the Institution) $NEBh^R = \Delta E^R - \Delta E^A = \overline{\Delta E^P} - \Delta E^D - \Delta E^A$, the net economic benefit (health) to the population where $\overline{\Delta E^P} - \Delta E^D$ is the net effect of displacement and adoption (the net effect on population health) and ΔE^A is the foregone benefit of improved allocative efficiency (the best alternative strategy given that the budget is allocatively inefficient).

If the Institution chooses to do Nothing, then there is no payoff to either the Firm or the Institution. The payoffs to both the Firm and the Institution are economic payoffs, therefore, we can conclude that, if these payoffs are positive, there is no better action available to the players.

4.2.2.3 Parameters and variables

- 1) ΔE^P is the health effect of the new drug and it can take two values, $\overline{\Delta E^P}$ (if the drug is adopted) and 0 (if the drug is rejected). The drug can only be adopted for all, not some, eligible patients and $\overline{\Delta E^P}$ is the additional health effect for all patients eligible for the new drug.
- 2) ΔE^D is the health effect displaced in order to finance the additional cost of the new drug.
- 3) ΔE^A is the net gain in population health from reallocation of resources from Program M to Program N.
- 4) f is the *IPER* of the new drug.

The parameters and variables that describe the payoffs of the actions available to the Institution can be specified in terms of the total cost and unit cost of achieving them.

$$5) \overline{\Delta E^P} = \frac{\Delta C^P}{f}$$

is the additional health effect if the drug is adopted, where ΔC^P is the additional financial cost to the health care budget of financing the additional effects from the new drug at *IPER* of f .

$$6) \Delta E^D = \frac{\Delta C^P}{d}$$

is the health effect displaced because services are displaced to finance ΔC^P , where d is the *aICER* of the services displaced to finance the new drug.

- 7) $\Delta E^A = \Delta E^N - \Delta E^M$ is the net gain in population health effects from reallocation of resources, ΔC^P from Program M to Program N. Where:

a. n and m are the *aICERs* of Programs N and M in expansion and contraction respectively.

$$b. \Delta E^N = \frac{\Delta C^P}{n}$$

where ΔE^N is the additional health effect available when the variable cost budget for Program N is expanded by an amount ΔC^P .

$$c. \Delta E^M = \frac{\Delta C^P}{m}$$

where ΔE^M is the health effect lost when Program M's budget is contracted by amount ΔC^P .

- 8) $\Delta E^R = \overline{\Delta E^P} - \Delta E^D$ is the net gain to the population from Strategy R (adoption and displacement).

And finally, the economic rent to the Firm at price f is determined by the Firm's production function. The Firm's additional cost of production for the additional health gains compared to the existing drug (the *IMER*) is 0. This is the situation because: i) the marginal cost of production of the new drug is the same as for the off-patent drug that the new drug will replace; and ii) the existing drug is priced at its marginal cost of production. The marginal cost of production includes the foregone benefit of the Firm's best alternative production options. Therefore, any payment the Firm receives for the additional health gains represent economic rent. This situation is illustrated in Figure 9 where the

generic drug is priced at the marginal cost of production and has a financial profit that is also a normal profit.

9) $\pi = f\overline{\Delta E^P}$ is the economic rent available to the Firm.

4.2.2.4 Conditions

- 1) $\overline{\Delta E^P} > 0$. The drug brought to the Institution is clinically innovative, that is, it has a clinical advantage compared to best available existing therapy for the target group of patients. The health gain is fixed (discrete) for the identified group of target patients, and is known with certainty.
- 2) $d > 0$. The aICER of the services displaced to finance the additional financial costs of the new drug is greater than zero.
- 3) $\Delta E^D > 0$. It follows from $d > 0$ that displacing services to finance the additional costs of the new drug will lead to a loss in health effects for patients who would otherwise have received these services.
- 4) ΔE^D is continuous. The funding to the displaced services can be reduced or increased by the smallest increment. If the funding is changed, the effect will change in the same direction.
- 5) $f \geq 0$. The price per additional effect of the new drug compared to the best available therapy is greater than or equal to 0.
- 6) $\Delta C^P \geq 0$. The additional financial cost to the health budget of the new drug is greater than or equal to zero. This condition is a consequence of the previous assumptions: $\overline{\Delta E^P}, f \geq 0$.
- 7) $\Delta E^A > 0$. The health care budget is currently allocatively inefficient therefore optimal reallocation results in a net gain in health effects.
- 8) $m > n > 0$

4.3 Theory Proper

This game draws on economic theory relating to the pricing decisions made by the profit maximising monopolistic Firm that takes into account both its own and the Institution's payoff. We recognise that the only decision that a rational Institution can make is to select an appropriate payoff (the net economic benefit), which it then needs to apply in the reimbursement decision. The Solution Concept used to solve the game is Backward Induction.¹³⁰

4.4 Solution

Using backward induction, assuming all terminal nodes can be reached, we solve the game starting from the outcomes of the last stages.

4.4.1 Stage 2: The Institution's decision

What decision rules will the Institution use to provide a response to any possible *IPER* offered by the Firm?

- 1) If $\overline{\Delta E^P} - \Delta E^D - \Delta E^A < 0$, the Institution will choose the action "do Nothing" (**N**).
- 2) If $\overline{\Delta E^P} - \Delta E^D - \Delta E^A \geq 0$, the Institution will choose "Reimburse" (**R**).

¹³⁰ Watson (2002) defines the solution concept of backward induction as: *The process of analysing a game from back to front (from information sets at the end of the tree to information sets at the beginning). At each information set, one strikes from consideration actions that are dominated, giving the terminal nodes can be reached.*

Hence, the critical price above which the Institution will reject and at or below which it will reimburse, is calculated as follows.

First, we obtain an expression for the population health effects from reallocation.

$$\Delta E^A = \Delta E^N - \Delta E^M$$

$$\text{where } \Delta E^N = \frac{\Delta C^P}{n} \text{ and } \Delta E^M = \frac{\Delta C^P}{m}$$

$$\therefore \Delta E^A = \Delta C^P \left(\frac{1}{n} - \frac{1}{m} \right)$$

Equation 9

is the gain in health to the population from the strategy of reallocation.

The point of indifference between Strategy R and the Strategy do Nothing (the decision threshold) occurs when:

$$(\overline{\Delta E^P} - \Delta E^D) - \Delta E^A = 0$$

Substituting Equation 9

$$\therefore \overline{\Delta E^P} - \Delta E^D - \Delta C^P \left(\frac{1}{n} - \frac{1}{m} \right) = 0$$

$$\text{Where } \overline{\Delta E^P} = \frac{\Delta C^P}{f} \text{ and } \Delta E^D = \frac{\Delta C^P}{d}$$

$$\Rightarrow \frac{\Delta C^P}{f} - \frac{\Delta C^P}{d} - \Delta C^P \left(\frac{1}{n} - \frac{1}{m} \right) = 0$$

And as $\Delta C^P > 0$

$$\Rightarrow \frac{1}{f} - \frac{1}{d} - \left(\frac{1}{n} - \frac{1}{m} \right) = 0$$

$$\Rightarrow \frac{1}{f} = \frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right)$$

$$\therefore f = \left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right)^{-1}$$

So the Institution's decision rule is:

1) Reimburse if:

$$f \leq \left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right)^{-1}$$

2) Do Nothing (Reject) if:

$$f > \left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right)^{-1}$$

This decision rule is consistent with the Institution choosing to reimburse only if the net economic benefit (health or monetary) is greater than or equal to zero and hence consistent with the objective of maximising the population's health. If the Institution could instead reallocate an amount from Program M to Program N and have a greater impact on the population's health compared to reimbursing the new drug, it would reject the drug.

4.4.2 Stage 1: The Firm's decision

The Firm has a particular profit function as a consequence of the nature of the reimbursement decision. If the Firm prices above the decision threshold, it will not sell any of the drug.¹³¹ If it lowers the price just to decision threshold it will sell the maximum possible quantity. If it lowers its price further, it will not increase the quantity sold, only reduce the *IPER* and hence reduce the revenue. Therefore, the profit maximising Firm chooses the corner solution¹³², which in this case is:

$$f = \left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right)^{-1}$$

4.4.3 Equilibrium price and payoff

Here are the equilibrium results of the Game.

1) The equilibrium price is:

$$f^* = \left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right)^{-1}$$

Equation 10

The equilibrium price is the *IPER* of the new drug at which the Institution is indifferent between the actions Reimbursement and do Nothing and the Firm's economic rent is maximised.

2) The net economic payoff to the Firm:

$$\pi = f^* \overline{\Delta E^P} = \overline{\Delta E^P} \left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right)^{-1}$$

This is the economic profit to the Firm from above marginal cost pricing of every unit of the new drug.

3) The net health benefit of reimbursement (population):

$$\Delta E^R = \overline{\Delta E^P} - \Delta E^D$$

¹³¹ This Game assumes that the Firm chooses not to lobby for the price to be above the economic threshold, once it has been declared. There are some situations where the Firm can offer a price above the threshold price and then provide a case for this price, for example the high cost of R&D needs to be financed (Chapter 9), that new drugs need a premium over the standard maximum price because Firms invest in future innovative drugs (Chapter 10), or that new drugs have additional qualities beyond health (Appendix 10).

¹³² In Consumer Theory, an example of the corner solution is when the utility maximising solution occurs when the entire income is allocated to one good rather than across two goods. In this situation, the drug reimbursement game, it is describing an outcome when there is no negotiation between a price at the threshold and a lower price, which could be also be tolerated by the Firm (it still makes an economic rent). There is no negotiation because the necessary and sufficient condition of being at or below the threshold it met at the *IPER*=threshold. It is a situation where the outcome is "extreme", given the threshold selected by the Institution.

$$\begin{aligned}
&= \Delta C^P \left(\frac{1}{f^*} - \frac{1}{d} \right) \\
&= \Delta C^P \left(\left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right) - \frac{1}{d} \right) \\
&= \Delta C^P \left(\frac{1}{n} - \frac{1}{m} \right)
\end{aligned}$$

Now: $m > n$, therefore $\Delta E^R > 0$

Hence there is a net increase in the health of the population as a consequence of reimbursement. The gain to target patients due to clinical innovation less the health effects displaced to finance the new drug is greater than zero.

4) The economic payoff to the Institution at equilibrium:

The net economic benefit (health) is:

$$NEBh^R = \overline{\Delta E^P} - \Delta E^D - \Delta E^A$$

$$\text{Where } \overline{\Delta E^P} = \frac{\Delta C^P}{f^*}, \Delta E^D = \frac{\Delta C^P}{d} \text{ and } \Delta E^A = \Delta C^P \left(\frac{1}{n} - \frac{1}{m} \right)$$

$$\begin{aligned}
NEBh^R &= \frac{\Delta C^P}{f^*} - \frac{\Delta C^P}{d} - \Delta C^P \left(\frac{1}{n} - \frac{1}{m} \right) \\
&= \Delta C^P \left(\frac{1}{f^*} - \frac{1}{d} - \left(\frac{1}{n} - \frac{1}{m} \right) \right)
\end{aligned}$$

And from Equation 10

$$f^* = \left(\frac{1}{d} + \left(\frac{1}{n} - \frac{1}{m} \right) \right)^{-1}$$

$$\therefore \frac{1}{f^*} - \frac{1}{d} - \left(\frac{1}{n} - \frac{1}{m} \right) = 0$$

If both sides are multiplied by ΔC^P .

$$\overline{\Delta E^P} - \Delta E^D - \Delta E^A = 0$$

That is, the economic payoff to the Institution is zero at the equilibrium price. This is the corner solution. The entire economic value of the clinical surplus of the new drug is appropriated by the Firm. The increase in the health of the target patients is no greater than that which could have been achieved for other patients through reallocation and hence the net economic benefit (health) of Reimbursement at equilibrium is zero.

5 Discussion and conclusion

At the equilibrium price, the Firm is maximising its economic profit by responding to:

- 1) the public information about the Institution's maximum acceptable *IPER*; and
- 2) the Institution's lack of bargaining power to negotiate a price below this maximum (despite legislation that allows it to regulate the price to one at or below the decision threshold).

Regardless of the Institution's choice of threshold *IPER*, if it is above the marginal cost of production and there is no other constraint operating on the Firm, the Firm is predicted to price at the threshold *IPER*. The equilibrium price is endogenous, not exogenous, to the reimbursement process.

5.1 The Reimburser's questions

The Reimburser revisits her questions.

- 1) *Will this lower threshold IPER mean that drugs that would otherwise have been reimbursed at prices above \$5,042 will no longer be reimbursed?*

The GTM predicts that reducing the maximum acceptable *IPER* will **not necessarily** result in drugs that would otherwise have been priced at the previous maximum acceptable *IPER* becoming unavailable to the population. The critical metric for the Firm's decision to produce and supply the new drug is whether the *IπER* on the additional units of health effects is greater than or equal to zero, (not whether the *IPER* has increased or decreased relative to previous years). While the revenue to firms will be lower under this lower threshold *IPER* (assuming the target group of patients and hence total units sold remains constant), firms have market power and can price above their marginal cost of production. Therefore some firms will still be able to produce and supply their drug at the lower threshold *IPER*, with an economic profit. If firms did not have market power (as in the case of the producers of Rathmab) lowering the price per course of the new drug would result in an economic loss for the firm (and possibly also an accounting loss) on each unit sold and the firm would no longer produce that drug. However, patent holders of new drugs have market power, which means that they could have economic rent and hence the capacity to lower their price and remain profitable.

A second issue is that even if the threshold *IPER* were 0, some firms would still produce and make an economic profit. If the example in Figure 9 were changed such that the cost of manufacturing a course of Arthmax were \$100 instead of \$250 (including normal profit), then the manufacturer of Arthmax would have an economic profit at an *IPER* of 0. The economic profit would be \$150 per course. This occurs because at an *IPER* of 0 for Arthmax (Arthmax compared to Rathmab) the price per course of Arthmax would be the same as the price per course of Rathmab (\$250); the incremental health benefits are obtained at no additional cost. However, the cost of manufacturing a course of Arthmax is lower (at \$100) due to manufacturing innovation. (See Chapter 4, Section 3.2, p. 65). Hence, the economic rent on a course of Arthmax is \$150 (\$250-\$100). Therefore a firm can have economic rent even if the *IPER* is 0.

There is a second situation where Arthmax can have an economic rent above zero and the *IPER* is 0. In the case explored in this game, the drug that is being substituted, Rathmab, has an economic rent of zero because it is off patent. However, if Rathmab were still on patent, then economic rent could be payable on the incremental QALYs for Rathmab vs. placebo. In this case, it is possible that the economic rent on the production of Arthmax could be even higher than the economic rent from the additional QALYs for Arthmax, even if the *IMER* for Arthmax is zero or less than zero. (See Figure 9) If the *IPER* for Rathmab were \$7,000 then the firm producing Arthmax would appropriate this economic rent. It could therefore tolerate an economic loss up to \$2,000 per incremental QALY for Arthmax vs. Rathmab. Critically, this economic rent would continue to be paid regardless of the patent

expiry of Rathmab. That is, the firm producing Arthmax is able to appropriate the economic rent from Rathmab long after the patent on Rathmab would have expired, provided it can be priced relative to Rathmab before that patent expires, and the regulator does not attempt to change the price post Rathmab going off patent. (This issue is discussed in more detail and with reference to the statins market in Appendix 6.)

2) *Will this result make the population worse off than it would have been under the existing threshold IPER of \$75,000?*

Less new drugs reimbursed is a possible, not inevitable, outcome of a lowered maximum acceptable *IPER*. **Patients** who would otherwise have had subsidised access to these drugs will be worse off than would otherwise be the case, assuming the drugs that would otherwise have been listed all have clinically innovative value. However, the **population** could be better off under the lower threshold *IPER* of β_c even if some target patients are worse off. In other words, while some patients will be worse off, this loss of potential health effects will be outweighed by the health gain to patients who will be better off at the lower threshold *IPER*.¹³³ There are two reasons for this.

First, the possibility of a net reduction in the population's health is excluded under β_c but not under the historic maxWTP threshold *IPER*, which does not accommodate the effect of displacement. Second, as a consequence of using β_c rather than the maxWTP, the Institution has more information about the opportunities to correct the failure of the market to provide evidence of the aICER of unpatented programs. This additional information might be developed by allocating resources to developing this evidence rather than additional evidence of the maxWTP developed using population surveys. This additional information effectively expands the set of alternative strategies from which the best alternative strategy is selected. It makes it possible for the Institution to reallocate and improve the allocative efficiency of the health care budget. If there is no drug that has an *IMER* below β_c , then this does not mean that the rational Institution has no option available to improve the population's health within given resources – reallocation is that option.¹³⁴

3) *How should the rational Institution respond to this Threat?*

The rational Institution should not respond to this threat by increasing the threshold *IPER*. The Institution should maintain β_c as the threshold *IPER*. It should also be prepared to accept that if the minimum acceptable *IPER* (to the Firms) of all new drugs is greater than β_c , then this is a signal to firms to improve their drug production processes and make clinical innovation more cost effective. It is also a signal to the Institution to improve overall efficiency by reallocating across programs rather than adopting new drugs.

5.2 Assumptions revisited

The Game presented in this chapter made three important assumptions that influence both its results and their interpretation, however, these assumptions were not justified in the Game. These assumptions are addressed in more detail in subsequent chapters, and summarised below.

¹³³ Who are these target patients who will be worse off? Until the drugs become available, there is no information about who these patients will be. This leads to the following situation. If we focus on the health benefit to the patients who will benefit from the new drug and not patients whose health is reduced because services are withdrawn to finance the drug, then we are saying that our value of the health gain for a patient is a function of the method by which it is produced, namely patented drugs, rather than say, unpatented respite care. One of the assumptions in the introduction to this thesis is that a universal access health care system will not have a preference for the method of producing a health gain. This assumption is revisited in Chapter 11.

¹³⁴ For a discussion of the possibility that the Institution will reject the drug but not reallocate, refer to the Conclusion to his thesis (Chapter 11).

The first assumption was that the marginal cost of production of the new drug was public information. In fact this information is typically private (known only to the firm). The resultant asymmetry in information can lead to the opportunity for additional strategies available to the firm which increase the chance that it can obtain a price at the previous higher threshold, despite the Reimburser lowering the threshold *IPER*. This issue is explored in more detail in Chapters 9 and 10.

The second assumption made in this game was that the *IPER* of the new drug does not influence the Firm's R&D decisions and hence has no implications for the population's future health. The relationship between the *IPER* of the new drug and pharmaceutical R&D and its implications for the decision to apply β_c as the threshold *IPER* are explored in detail in Chapters 9 and 10.

The third assumption is that there is no uncertainty in the value of any parameters. Clearly, there is uncertainty in all the parameters used in the model. The methods of characterising and analysing the uncertainty in the estimates of ΔC^P and $\overline{\Delta E^P}$ are well documented.¹³⁵ It is unlikely that any reasonable estimates of n , m and d exist. The implications of i) uncertainty and absence of evidence of these parameters for PEA and ii) the use of β_c as the decision threshold, are discussed in more detail in the Conclusion to this thesis. However, at this stage it is useful to recognise the distinction between parameter uncertainty and absence of an incentive to develop evidence under the following two scenarios:

- 1) An institution that uses economic evaluation and a maxWTP as a threshold provides an incentive for the market to develop estimates of ΔC^P and $\overline{\Delta E^P}$ and the associated uncertainty. It might also generate an incentive for academics to develop evidence of maxWTP. However this situation provides no incentive to develop evidence of n , m and d . In particular, it does not address the market's failure to provide evidence of these parameters as they pertain to unpatented programs. Nor are there any mechanisms analogous to new drug reimbursement within which this evidence has value in making a decision.
- 2) An institution that places economic (decision) value on evidence of ΔC^P , $\overline{\Delta E^P}$, n , m and d by using β_c as a decision threshold and also addresses the failure of the market to provide this evidence, will, in time, have estimates of these parameters with the associated uncertainty.

In summary, a critical difference between the application of β_c as a threshold *IPER* and other options is that it represents the first step in addressing the market's failure to develop evidence of unpatented or unpatentable programs and inputs. Hence is a first step towards providing the pharmaceutical industry with the price signal that the market would otherwise provide; the pharmaceutical industry's competition in the market for health effects from other ways of achieving these gains.

5.3 Economic implications

From an economic perspective, there are three additional implications of the results of this Game: i) price is endogenous; ii) economic loss is underestimated by the conventional net benefit; and iii) thresholds above β_c introduce a potential economic loss and the existence of strategic behaviour leads us to predict that this economic loss will be maximised for any threshold above β_c .

5.3.1 Endogeneity of the offer *IPER*

The new drug's offer *IPER* is endogenous to the reimbursement process, not exogenous as (necessarily) assumed in DTMs. Equilibrium price and offer price are both a function of the Reimburser's revealed threshold *IPER*. Therefore, while using a DTM is appropriate for estimating the

¹³⁵ For example Willan and Briggs (2006)

ICER of a new drug and the associated uncertainty, it is not appropriate for the analysis of the decision to reimburse, which is a strategic situation. This endogeneity of price is entirely consistent with the US pharma-economic characterisation of CEA_i as price control: if the threshold price goes up, so does the price of new drugs. (This issue is discussed in detail in Section 3.1, starting at p. 240, Appendix 7) Health economists have also been aware of this issue since at least 1992 when the Australian Government started using economic evaluation for new drug.¹³⁶ However, health economists do not appear to have considered the full impact of the endogeneity of input price where the manufacturer is a monopolist.

The impact on health economic thinking of recognising endogeneity of price can be illustrated with the simple but instructive example of the idealised solution to the problem of revealing the shadow price of the budget constraint. The earliest example in health economics appears to be from Weinstein and Stason's 1977 paper on the foundations of CEA (Weinstein and Stason 1977) and the most recent from Weinstein's 2008 editorial on the imperative for the US to identify how much its citizens should be willing to pay for a QALY (Weinstein 2008). Essentially the story involves the decision rule (threshold) being revealed by the actions of the social decision maker. He ranks all programs by their ICER in ascending order and then continues allocating from this list until the budget is exhausted. The ICER of the last service is the decision rule; any new programs with ICERs above this should be rejected and below this, funded. Typically, the idealism of this particular solution to the problem of the shadow price of the budget constraint is attributed to the problems of interdependence between programs, increasing and decreasing economies of scale, the vastness of the associated computational tasks and the disregard for equity by valuing all QALYs equally (Sendi, Al et al. 2004; Weinstein 2008). Now introduce the possibility that firms price at exactly the revealed threshold, and that inputs that have prices below this and have market power increase their price. The budget that is initially exhausted will continue to grow and this growth is the effect of the endogeneity of price and the public information about the revealed threshold.

5.3.2 The conventionally defined net benefit underestimates the economic loss

If the historic threshold (i) is greater than β_c ($i > \beta_c$) then the economic loss associated with adoption at a given offer price, $IPER = f$, will be underestimated by the conventionally defined net benefit (defined in Appendix 4).

The proof follows:

Using the conventional method, the net benefit of reimbursement is:

$$NBm_i = i\Delta E^P - \Delta C^P$$

$$= i \frac{\Delta C^P}{f_i} - \Delta C^P$$

where f_i is the $IPER$ of the new drug at the threshold i .

$$= \Delta C^P \left(\frac{i}{f_i} - 1 \right)$$

¹³⁶ Consider Drummond's commentary on this scheme (1992). "The link between cost-effectiveness data and pricing decisions requires additional thought and discussion. This is compounded by the fact that companies need to assume a price in calculating the incremental cost effectiveness ratio for a new medicine compared with an existing one. Therefore does the economic evaluation become an instrument for open price negotiation? At what stage does better value for money justify a higher price?" (Drummond 1992 p. 195)

and dividing through by i we obtain the NBh_i which is the conventional net benefit measured in health units and where the units are valued by i (See Appendix 4)

$$NBh_i = \Delta C^P \left(\frac{1}{f_i} - \frac{1}{i} \right)$$

However, as argued in Chapters 4 through 7, in order to assess the net economic benefit of the decision, we need to use β_c because this captures the competition in the health budget, including competition from strategies to improve reallocation. We use the net economic benefit (health) of reimbursement to illustrate this issue, although the same result is obtained by using the conventional net benefit with $i = \beta_c$. We assess the net economic benefit of the new drug using the price that would occur had the threshold been i .

$$\begin{aligned} NEBh^R &= \Delta E^P - \Delta E^D - (\Delta E^N - \Delta E^M) \\ &= \Delta C^P \left(\frac{1}{f_i} - \frac{1}{d} + \frac{1}{m} - \frac{1}{n} \right) \end{aligned}$$

The underestimate of the economic loss of a threshold i is given by the difference in the two alternative measures of the net economic benefit:

$$\begin{aligned} NBh_i - NEBh^R &= \Delta C^P \left(\frac{1}{f_i} - \frac{1}{i} \right) - \Delta C^P \left(\frac{1}{f_i} - \frac{1}{d} + \frac{1}{m} - \frac{1}{n} \right) \\ &= \Delta C^P \left(\left(\frac{1}{n} - \frac{1}{m} \right) + \left(\frac{1}{d} - \frac{1}{i} \right) \right) \end{aligned}$$

The underestimate of the net economic benefit that is a result of using the NBh_i as a proxy for net economic benefit:

- 1) increases as the allocative inefficiency ($m - n$) increases;
- 2) as the net population loss per additional health effect reimbursed ($i - d$) increases; and
- 3) as the total additional expenditure, ΔC^P increases.

The underestimate of the economic loss as a consequence of using NBh_i as a proxy for economic loss rather than $NEBh^R$ can also be expressed as:

$$\Delta C^P \left(\frac{1}{\beta_c} - \frac{1}{i} \right) \tag{Equation 11}$$

5.3.3 The potential maximum economic loss is the economic loss

The non-strategic analyses in Chapters 6 and 7 provide the metrics that allow us to calculate the potential economic loss in the case where a threshold is set too high and a new drug is approved at this threshold. There are three reasons why the actual loss is the maximum potential loss possible from the strategy of reimbursement. First, for a given value of m , n and d , the maximum possible economic loss will be experienced on every drug sold at the higher than optimal threshold, i . The reason is that, under these givens, the size of the loss is determined by the additional cost of the new drug. The additional cost of the drug is a function of the price of each unit sold.

$$\Delta C^P = f_i \Delta E$$

The Game predicts that for each unit sold, the Firm will select the profit maximising price, which is the threshold. Therefore, the maximum possible loss of using a threshold above β_c , which occurs when $f=i$, will be the economic loss that results from pricing above β_c at i .

Furthermore under the rules of the reimbursement game, which focus on the evidence of the incremental cost and effect as the rationale for an offer price, the Institution has no capacity to bargain below a revealed threshold $IPER$; only to regulate price down to that $IPER$. This situation further enforces the loss maximising effect of an error in choosing a threshold. Finally this loss is experienced on more drugs than would have been sold had the lower threshold price been enforced. These additional drugs will include drugs that are themselves more costly to manufacture, in terms of their $IMER$, than it costs for the health budget to produce health benefits from existing technologies, that is, the $IMER > \beta_c$.

5.4 Conclusion

This chapter's main conclusion is that the reimbursement process is more appropriately represented as a Game Theoretic rather than Decision Theoretic Model because the reimbursement process is strategic and new drug price is endogenous.

The main prediction from this game theoretic model is that a rational profit maximising firm will price at the reimbursing institution's threshold $IPER$, whatever that price is. This prediction appears to be supported by the results of studies such as Devlin and Parkin (2004) that suggest that the majority of new drugs recommended by the National Institute of Clinical Excellence (NICE) are priced close to or at the "inferred" or "implicit" threshold price.

Further evidence that firms price strategically is the quotation attributed to the CEO of Roche's pharmaceutical division and presented at the start of this chapter. Burns is quoted as saying of the higher price of the new drugs: "*the health economics holds up*". This position could be interpreted as follows: meeting the requirement of pricing at or below the institution's threshold $IPER$ is the necessary and sufficient justification for its offer price.

The result of the game also leads to predictions about the consequence of a lowered threshold $IPER$.

First, we cannot assume that drugs that would otherwise be priced at the threshold $IPER$ will no longer be made available at the lower threshold $IPER$. This result occurs because firms pricing at the higher price could be pricing above the marginal cost of production hence they could still have an economic rent greater than or equal to zero at a lower price. However, the game theoretic structure of this model also introduces the possibility that firms can use information asymmetry (private information about the marginal costs of production) to lobby for above threshold price for a new drug. This possibility is explored in more detail in Chapters 9 and 10.

Second, the population will always be better off with a threshold $IPER$ of β_c , because the following two situations are avoided:

- 1) the net effect of reimbursement on the population's health is negative ($d < f$); and
- 2) the best alternative strategy to reimbursement at the offer $IPER$ is not implemented.

The use of d as the decision threshold rather than k ($> d$) avoids the first but not the second situation.

And finally we can conclude that GTMs characterise and accommodate the endogeneity of price, whereas the DTMs do not. For example, if the optimality of disinvestment increases and d is used as the threshold, then DTMs would lead us to predict that the loss associated with reimbursement

decisions is decreasing because the net effect of adoption and displacement is more likely to be positive. However, as $d \rightarrow m > d$ then if $i=d$, then i is increasing and hence $i-\beta_c$ increases. From Equation 11 we see that this will in turn increase the economic loss associated with adoption decisions, because firms are predicted to price at the increasing i . Hence only Games correctly predict that the economic loss will increase as the suboptimality of displacement is reduced and hence i increases.

The Reimbursers is satisfied that the population's health will not be worse off as a consequence of selecting β_c rather than k . This is the case even though some patients might be worse off at the lower threshold price. However, the Reimbursers remains uncomfortable with the following three explicit assumptions made in the model:

- 1) evidence of the *IMER* is in the public domain;
- 2) there is no relationship between the *IPER* and future innovation; and
- 3) there is no uncertainty in the value of β_c .

She is particularly concerned with the second of these assumptions. This assumption is consistent with claims made by pharma-economists Jena and Philipson (2008) in their support for the case for the Firm's Preferred Price (the *FPP*). These authors argue that a decision threshold that is based on maximising health from existing technologies does not capture the dynamic welfare implications of this relationship between price and future health.

The previous chapters described the derivation of β_c and it is true that it explicitly excludes any consideration of the relationship between the *IPER* and the future health of the population that is the result of innovation. It is clear that the evidence base developed so far, while it identifies a threshold *IPER* suitable for the economic context of her budget, does not inform the Reimbursers on her critical question identified from the reframed political economy presented in Chapter 1:

How should the Institution respond to the Threat from Pharma that reducing the price below the FPP will result in the population's health being worse than otherwise would be the case?

The next step in developing the evidence to inform the Reimbursers's response to the main Pharma threat would appear to be to compare the payoff to the population's health of selecting β_c as the decision threshold compared to the payoff of choosing the Firm's Preferred Price (*FPP*). But what is the *FPP*? What are its theoretical underpinnings? How does the *FPP* capture information about the relationship between price and innovation? Does it capture information about the economic context in the same way that β_c does?

The Reimbursers requests that her Health Economic Adviser prepare a report on this issue which is provided in Appendix 7. The findings about the *FPP* are summarised at the start of Part 3.

Part 3 The new drug decision threshold and the relationship between price and innovation

Part Two of this thesis developed the case for the health shadow price β_c as the threshold *IPER* for a new drug; the decision threshold. This threshold accommodates characteristics of the health budget (fixed or constrained budget, suboptimal displacement and economic inefficiency) and the competition in the market for health inputs and health innovation. However, the models from which this threshold *IPER* is derived explicitly assume that there is no relationship between price and innovation. This restrictive assumption limits the capacity for a Reimbursing Institution to engage within the conventional political economy on the question of whether it is a preferable price at the *FPP* rather than β_c .

Part Three of this thesis explores the relationship between β_c and the npvPH, given the relationship between price, innovation and new drugs. It develops and applies a rigorous approach to assessing the conditions under which β_c should be adapted to accommodate this relationship, and determines how it should be adapted if this is necessary.

There are two options available to address this question. The first is to assess this question within the conventional PENDING; what is the loss, if any, in the net present value of the population's health (npvPH) if β_c rather than the *FPP* is used as the decision threshold. The second is to work within the alternative political economy developed in this thesis and analyse this question within a game theoretic framework.

Appendix 7 presents a "Report" exploring the first option and a summary of this Report follows. Chapters 9 and 10 explore the second option.

Summary:

The full "Report" (Appendix 7) presents a review of two adaptations of the prevailing political economy of new drugs that accommodate CEA_i (the use of a CEA with a threshold of i). The first adaptation is to characterise CEA_i as price control and then conclude that because price control results in a deadweight loss, so does CEA_i . The second adaptation is to accept the use of CEA_i but argue that in order to optimise the incentive for innovation, it is necessary to use $i=k$. This adaptation is referred to as Full Value Pricing.

Conclusion:

Neither of these adaptations can be supported by their posited theoretical foundations. Neither framework allows for a formal comparison of the health shadow price and the FPP (or the full value price). In simple terms both frameworks are constructed so as to define the solution (do not price below the FPP or k), not to find the solution. Three examples of the practical problems of applying these frameworks to the question of choice of i follow:

- 1) Under the price control adaptation, the papers that support the position that firms, if not regulated, would price at the price that is preferable from a social welfare perspective do not provide a formulae that shows how this price is estimated.
- 2) If all new drugs were purchased at k then the additional cost of new drugs would be exactly offset by the (lay) monetary value of their additional benefit, where this monetary value is k . The argument that new drugs represent good value because the cost (expenditure and R&D) is outweighed by their benefit would no longer apply; there is no gain in consumer welfare using full value pricing.
- 3) Consider a case where a budget holder has two options for innovation. Both have:
 - a. the same financial cost in the first year;
 - b. the same additional health effects in the future; but
 - c. one innovation will provide these effects at a lower future ICER.

Then a rational Institution should choose the investment with the lower future price of health effects. If a framework cannot identify this result then it is not consistent with simple economic principles of choice under scarcity – minimising opportunity cost. Neither adaptation above can identify this option as welfare maximising, unless it is the future drug that has the lower ICER.

The two adaptations can be rejected as rigorous frameworks for comparing two alternative thresholds. However, this does not mean that the health shadow price can be accepted as a preferable price. Instead, it means that β_c needs to be compared to alternative thresholds that are claimed to incorporate the price innovation relationship within an appropriate framework. PEA provides such a framework.

Chapter 9: The “Pharmaceutical R&D Financing” Game

Chapter 9 presents the first application of PEA to a specific Firm Threat in a Game called: "The pharmaceutical R&D financing game". The Threat is of the following or related, form:

The capital market fails to provide funds for pharmaceutical R&D; it is a risky investment and returns are long term. Therefore firms rely on internal funds (profits) to finance R&D. These internal funds are supplied through above marginal cost pricing of drugs. If institutions use monopsonist power to bargain down the offer prices, there will be insufficient R&D to finance the drugs that society requires. The population will be worse off.

The motivation for assessing this analysis is the following paradox:

Why should the health budget finance pharmaceutical R&D without a formal contractual arrangement, if firms and pharma-economists are claiming that the capital markets are unwilling to take on this risk, even with the protection of legally enforceable contracts?

The Game is set up as a choice by firms between the two strategies: Lobby (approach the Institution to request a higher price) or Borrow (go to the Capital Market and borrow funds).

The Game concludes that there is no incentive for the rational risk averse or risk neutral Institution to finance pharmaceutical R&D through higher prices financed by displacing existing services, unless a contract is negotiated. However, in this case, the risk averse nature of Institutions will make this strategy (Lobby with Contract) more expensive for firms than approaching the Capital Market.

The Game also leads us to conclude that the practice by firms of financing most of their investment in R&D from internal funds is more likely to be the result of these internal funds being imperfectly priced, not failure in the Capital market. The Game suggests that the reason internal funds are imperfectly priced is because there is no requirement for firms to repay the initial investment by consumers and no interest payments by the firm; the failure that causes the preference for internal funds is in the Institution not the Capital Market. This failure is that the Institution fails to accommodate the full risks of the investment, unlike the Capital market, which successfully accommodates the risks of a loan to Pharma.

1 The Reimburser's problem

A Firm approaches the Reimburser with a new drug and evidence of its additional cost, ΔC^P , and effect, $\overline{\Delta E^P}$. This new drug is substantially more effective compared to the best available existing therapy ($\overline{\Delta E^P} \gg 0$). The Firm's offer Incremental Price Effectiveness Ratio *IPER*, f , is much higher than the health shadow price ($f \gg \beta_c$). These two conditions mean that the drug's reimbursement will have a significant budgetary impact, in this case:

$$f\overline{\Delta E^P} \sim 5\%B^P$$

where B^P is the drug budget. Existing non-drug programs with an aICER of d will need to be displaced to provide the funds from a fixed budget to finance the new drug. These programs are unpatented, non-pharmaceutical programs such as respite care and free dental programs. The budget is currently economically efficient ($n=m$) and displacement is optimal ($d=m$) therefore:

$$\beta_c = m$$

The Firm argues that an *IPER* of f , where $f > \beta_c$, will ensure that there are sufficient internal funds to finance the development of a future drug. The Firm argues that it will invest the entire premium over β_c into new drug R&D. This investment is an amount $\bar{\mathcal{R}}$ where:

$$\bar{\mathcal{R}} = \overline{\Delta E^P}(f - \beta_c)$$

The Firm argues that it needs to fund R&D from internal funds because the capital market fails to finance pharmaceutical R&D; even with formal contracts, the investment is too risky and the returns, if they occur, are too long term. The Firm supports this argument with peer reviewed papers and US government reports that state that capital market imperfection limits pharmaceutical firms' access to external funds hence firms rely on internal funds generated from additional profit from higher prices (Vernon 2003; International Trade Administration 2004; Santerre and Vernon 2006). These authors conclude that without funds from economic rent there will not be enough funds available to finance the R&D that society requires. Therefore, lower prices, which will reduce the amount of economic rent and hence internal funds, are not in the long term interest of consumers. The Firm's case for financing pharmaceutical R&D using funds sourced from higher prices appears strong.

The Firm also provides the Reimburser with a US Congressional Budget Office Report (2006) that refers to Reinhardt (2001)¹³⁷ where the Report's authors write that:

A relatively close relationship exists between drug firms' current R&D spending and current sales revenue for two reasons. First, successful new drugs generate large cash flows that can be invested in R&D (their manufacturing costs are usually very low relative to their price). Second, alternative sources of investment capital—from the bond and stock markets—are not perfect substitutes for cash flow financing. Those alternative sources of capital are more expensive because lenders and prospective new shareholders require compensation (in the form of higher returns) for the additional risk they bear compared with the firm, which has more information about the drug under development, its current status, and its ultimate chance of success. (p.9)

The Firm uses this statement to lend support to their argument that if the Firm is required to go to the Capital Market to finance R&D, it will be more costly and the price of new drugs will need to be increased to compensate for this.

¹³⁷ Whether the authors convey Reinhardt's intent is unclear to me.

The Reimburser is confused. What does it mean to say that the firm “*has more information about the drug under development, its current status, and its ultimate chance of success*”? What sort of information do companies have prior to an RCT? What information do they have that is not understood by the Capital Market? Can this information be provided to and understood by Institutions? The Reimburser is reminded of a paper she read recently on the benefits of risk sharing arrangements for pharmaceuticals and the economics of warranties.

Warranties are useful things. They are a means of signalling high quality when product quality is not fully observable. The cost of measuring the attributes of a drug relevant to its quality can be high, especially as a product relates to a particular subset of its potential market (as in the case of pharmaceuticals), and warranties are a means of avoiding those costs of quality assessment. (Cook, Vernon et al. 2008 p. 555)

What are these unobservable aspects of quality? What is this information firms have and why would they not put it in the public domain? And how are they going to find this information out without costly RCTs?

The US literature does provide additional explanations for why large pharmaceutical firms use internal funds. Hall (2002) identified a number of possible reasons including information asymmetry, moral hazard on the part of firms and a preference by the capital market for collateral in the form of physical assets. She concludes that there is a possible case for government subsidies for smaller (start-up) firms. Hall also concludes that:

The evidence for a financing gap for large and established R&D firms is harder to establish. It is certainly the case that these firms prefer to use internally generated funds for financing investment, but less clear that there is an important role for policy beyond the favourable tax treatment that currently exists in many countries. (Hall 2002 p. 49)

The Reimburser recognises that there could be an alternative explanation for the observation that firms finance R&D from internal funds. She hypothesises that firms prefer to finance through internal funds (financed by economic rent) because this method is cheaper than raising funds through the capital market. It is cheaper because, unlike the capital market, the Reimburser does not require firms to present a case for financing the New Molecular Entity’s (NME) R&D nor does it require the firm to agree to a contract that sets out the capital repayments and interest payments.¹³⁸

Financing pharmaceutical R&D from the health budget comes at a tangible and significant cost today to the population's health. The Reimburser reviews the proposed budget cuts for programs over the next three financial years as the whole of government responds to the increasing pressure of government debt. In this climate, services that are no less cost effective than the new drug will be displaced to finance the pharmaceutical R&D premium. This displacement occurs in addition to the displacement to finance the health effects from the new drug. Furthermore, there is no contractual arrangement with the Firm to guarantee a return to consumers on their risky investment; their own health today foregone to increase the population’s health tomorrow.

The Reimburser wonders how risky it is to use the health budget to finance pharmaceutical R&D and whether her population can bear this risk. After all, firms claim that the capital market finds it too risky to lend to firms, and unlike the Reimburser, the capital market is protected by a contract.

¹³⁸ For example, the previous quotation from the Congressional Budget Office Report notes that internal funds are a cheaper source of funds than the capital market because this market requires compensation for the additional risk they bear in relation to the firm because the firm has more information about the drug being developed. However, the authors do not clarify why the providers of these internal funds, purchasers and public research funding organisations, do not require this compensation. This is the case even though the authors identify higher drug prices as a source of these funds.

The Reimbursers asks:

How should the rational and risk averse or risk neutral Institution respond to the Threat?:

2 The pharmaceutical R&D financing game

We use a game theoretic model to identify the underlying strategies and payoffs in the Pharmaceutical R&D Financing Game. Then the Game is used to make a number of predictions that are tested against real world observations. Then identify the conditions required for the risk averse Institution to respond to this Threat by increasing the threshold price above β_c . Then we consider whether, if these conditions are met the Firm will continue to have a preference for funding R&D from internal funds rather than the capital market.

An adaption of Grüne-Yanoff and Schweinzer's Architecture of Game Theory is used to develop the story as an applied game. This framework comprises the following elements i) World (the economic problem; ii) Game, which comprises the narrative and the game structure; and iii) Theory Proper (Grüne-Yanoff and Schweinzer 2008). This framework is detailed in Chapters 2, 6 and Appendix 1.

2.1 World (the economic problem)

Firms use internal funds rather than the capital market to finance R&D. This is because internal funds are less costly than capital market funds due to imperfections in the capital market, identified by authors such as Santerre and Vernon (2006). These imperfections are a consequence of the capital market being unable to incorporate the full long term benefits to society of investments in pharmaceutical R&D. They are also a consequence of information asymmetry; according to a US Congressional Report (2006), firms have information about the future benefits of a drug that is not available to capital markets or is costly to make available. Firms use the evidence of funding preferences and the associated economic rationale sourced from the peer reviewed literature to provide an evidence base for the following Threat:

The FPP is the price that is necessary in order to ensure that sufficient R&D is available for the future. If prices are lower, then funds will need to be sourced from the Capital Market rather than internal funds. This will increase the costs of capital and combined with the lower prices, firms will reduce investments in R&D and hence there will be less new drugs in the future and the population will be worse off.

How should the rational Institution respond to this Threat?

2.2 Model

The Model comprises the Narrative and the Game Structure.

2.2.1 Narrative

The Game starts when the Firm decides whether to raise the funds for R&D from either the health budget (Lobby) or capital market (Borrow). The Firm also has the option to do Nothing.

2.2.1.1 Lobby

The Firm's first option is Lobby (L): lobby purchasers to pay higher prices for the existing drug. This lobbying process uses various submissions, reports and delegations to influence decisions that impact the price of a new drug and hence the profit for a given quantity of the new drug sold. The Lobbyists' key claim is that purchasers must not use their monopsony powers to negotiate prices below

the offer price because, if this occurs, there will be insufficient funds available to finance the R&D required for future drugs. The Lobbyists' position can be summarised as: *only economic rent can finance R&D efficiently and reduced economic rent means proportionally less R&D and less R&D means less new drugs and hence health in the future.*

The Institution can either reject or accept the Firm's lobbying. If it rejects the lobbying, the game ends. If the lobbying is successful, a higher price for the existing drug is agreed upon and the additional economic profit that results from this lobbying provides additional internal funds that are invested in NME R&D. These additional funds are sourced by the higher prices on existing drugs which are in turn financed from the fixed health budget by displacing existing services that have an aICER of d . These services are the least cost effective of existing services (displacement is optimal). The budget is currently economically efficient; there are no alternative ways of producing health within existing technologies that will improve health for the population.¹³⁹ Therefore, because the conditions of optimality of displacement, $d=m$, and economic efficiency, $m=n$, are met and the budget is fixed, we conclude that $\beta_c=m$.

The Firm's investment in pharmaceutical R&D might or might not result in an NME; there is a risk. This risk is characterised inconsistently in the literature.¹⁴⁰ However the claim by the Lobbyists is that this risk is so high and the return, if it occurs, is so far into the future that the capital market will not finance this R&D, or alternatively, finance this R&D at prohibitively high rates. In the context of this model, this risk is simply expressed as a probability, q that an NME of a given value of clinical innovation will be brought to the market and a probability $(1-q)$ that there will be no NME brought to the market as a consequence of the Firm's decision to investment in new drug R&D.

If the R&D is not successful, the Game ends and there are no mechanisms in place for the Institution's investment to be returned, so there is a loss to the Institution equivalent to its original investment. If the R&D is successful then the Firm selects an offer price for the future drug and the Institution can choose to reimburse the future drug at the offer price or do nothing. (The details of this part of this Game are addressed in Game 1 from p.121 onwards.)

2.2.1.2 Borrow

The second R&D financing option available to the Firm is Borrow (B): go to the Capital Market and attempt to borrow all the funds required for the development of an NME. The process of borrowing to finance the costs of a specific project requires the Firm to present a Bank with evidence of: its financial status; the funds it requires; and the likely success of its investment in terms of future revenue and profit. This estimate of future profit would need to include an assumption about the future revenue from the future drug which would in turn require assumptions about: the potential clinical innovation of the future drug, $\overline{\Delta EP}$; the estimated costs of producing the additional health effects (the Incremental Price Effectiveness Ratio (*IMER*), in this case c per QALY); the market share of the future drug; the future threshold price; and the *IPER* of the future drug.

We assume that if the R&D is unsuccessful then there is no repayment of the loan. This assumption is a simplification but it is consistent with the observation that there is limited physical collateral held by the pharmaceutical Firm and that this is a factor influencing the decision by the Capital Market to

¹³⁹ There are ways to improve the health of groups of patient groups using technologies not currently financed. However, the additional cost of financing these technologies will require services to be displaced and health effects lost. The net effect of the loss from displacement and gain for the patient group will be to reduce the population's health because the new technologies are less cost effective than the least cost effective of existing technologies.

¹⁴⁰ A discussion of two ways that the pharma-economic literature and Pharma characterise and quantify risk and additional sources of variation in firm profits is presented in Appendix 8.

lend to Firms. It also allows the riskiness of the loan to be characterised as part of the payoff to the Capital Market.¹⁴¹

The Bank (a lender in the Capital Market) will review the case presented by the Firm and solve for the Bank's minimum acceptable interest rate. The Bank's choice of offer price (interest rate), θ will also be influenced by its assessment of the Firm's maximum acceptable price. We assume the Bank selects an offer price of θ . The Firm can either reject or accept the Bank's proposal to lend at a rate θ , or it may enter into a negotiation if its maximum acceptable interest rate is higher than the Bank's minimum acceptable rate. If the Firm and the Bank agree on an interest rate, the Firm will Borrow an amount \mathcal{R} with a requirement that it pays an interest of θ as well as repaying the loan from the revenue from the future drug, should the R&D be successful. A contractual arrangement ensures repayment if there is success and sets out the shared understanding of the risks associated with the loan. If there is no success, there will be no repayment. This condition, which is set out in the contract, makes the loan "high risk". It characterises the claimed failure of the Capital Market to finance this R&D due to high risk.

The Bank has a second option; lend to a risk free borrower at a rate of τ therefore its payoff from lending to the Firm is net of the opportunity cost of this foregone activity. This use of an economic payoff for the Bank is consistent with the use of an economic payoff for both the Firm and the Institution.

If the R&D is successful, the Firm will offer the NME to the Institution at a $IPER = f$. The Institution will either reimburse the future drug at this price or do nothing. If it rejects the drug at this price, then the Game ends. There will be no repayment to the Bank because there is no revenue stream associated with the future drug, despite the success of the R&D in bringing a drug to market.

2.2.1.3 Some other parts to the story

We assume that the expected incremental effect of the drug, $\overline{\Delta EP}$, is independent of the method used to finance the future drug. The probability of success (q) or failure ($1-q$) of the R&D process is also assumed to be independent of the method used to finance the R&D for the future drug. While the Firm would need to present a business case to the Bank to support its application for a loan, it is assumed that no such documentation is required if the Firm chooses to Lobby the Institution to obtain these funds. And while the Firm is required to repay the loan and pay interest to the Bank, if there is success, it is not required to make such payments to an Institution, if the R&D is successful.

The relationships between the additional cost, additional effect and $IPER$ compared to the best existing drug are detailed in Game 1, Section 4.2.1 p. 121. For example, the $IPER$ of the new drug is assumed to be the result of a higher price for the new drug and no additional savings elsewhere in the health budget are expected.

2.2.1.4 The rules of engagement

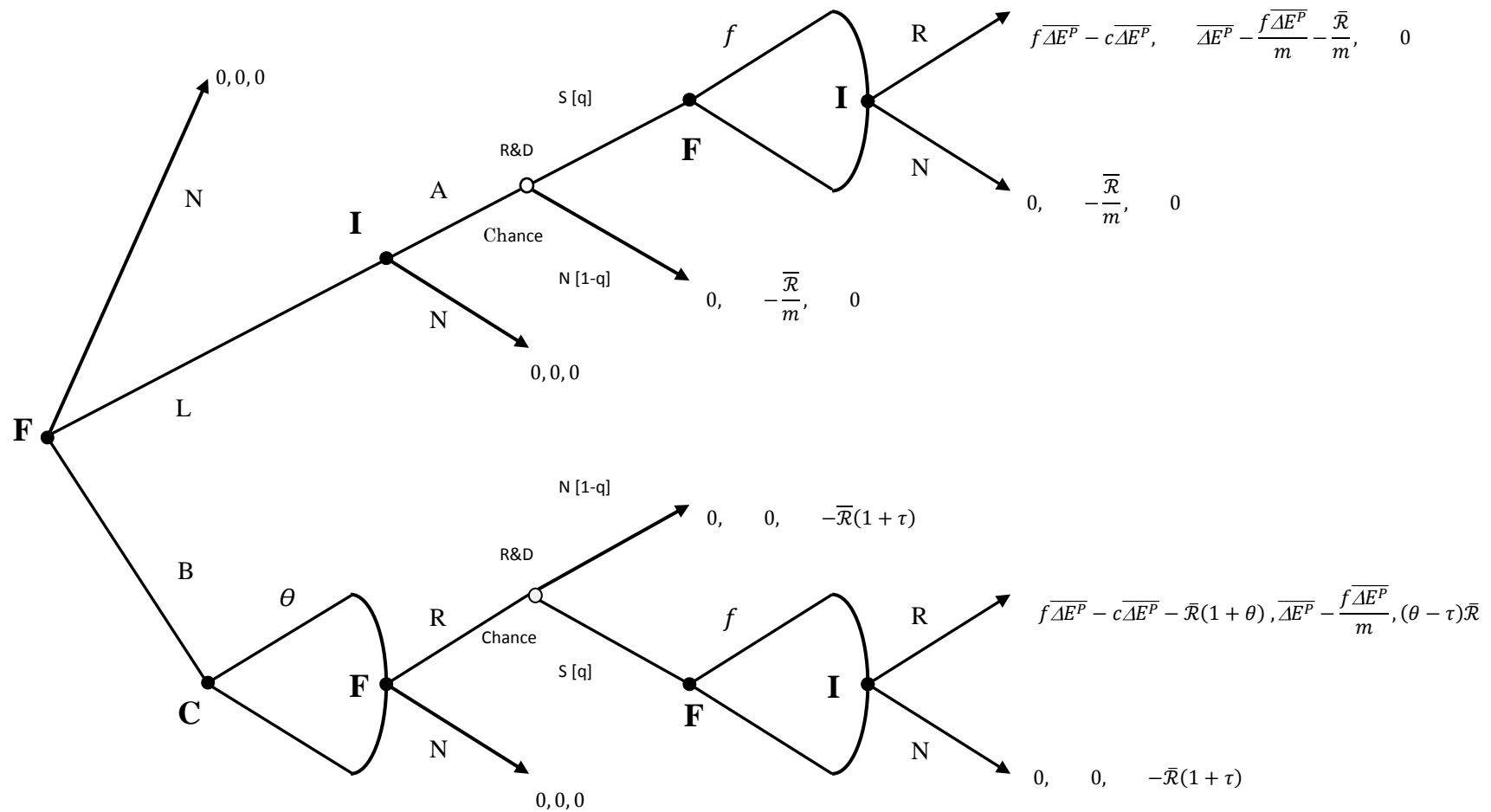
- 1) If the Institution is indifferent between reimbursing that drug at the offer price and the best alternative action then the Institution must accept the Firm's offer price for the future drug.

¹⁴¹ This problem uses the terms "investment" for the Institution and "loan" for the funding from the Capital Market. The use of the term "investment" highlights that there is an expected dividend if the R&D is successful. The use of the term "loan" suggests a schedule of repayments of the capital with an agreed interest payment. It is unrealistic to assume that the Capital Market will have no capital returned from its loan in the event of a failed R&D; this would mean the Firm becomes bankrupt. However, this device, assuming that there is no return to the Capital Market on its loan if R&D is unsuccessful, allows the claimed riskiness of this loan to be characterized and also simplifies the math. The critical issue is that the Firm enters a formal agreement with the Capital Market that ensures an agreed payment if it is successful and there is no such agreement with the Institution and the dividend is instead a future drug, which the Institution needs to pay for.

- 2) The Institution cannot negotiate below the offer price, if the offer price is at or below the decision threshold.

2.2.1.5 The Threat

The FPP is the price that is necessary in order to ensure that sufficient R&D is available for the future. If prices are lower, then capital funds will need to be sourced from the Capital Market rather than internal funds. This situation will increase the costs of capital and combined with the lower prices, firms will reduce investments in R&D and hence there will be less new drugs in the future and the population will be worse off.



The notation is detailed in the following text. Key labels are F Firm, I Institution and C Capital Market and payoffs are in the order of F, I, C

Figure 11 The pharmaceutical R&D financing game

2.2.2 The game structure

Game 2 is presented in extensive form as a dynamic game (there is a sequence of decisions) of incomplete information (there is uncertainty in the payoff to R&D) and no private information (all information that is certain is in the public domain). Even though the process of raising R&D funds, developing new drugs and obtaining reimbursement occurs over a period of several years, the Game is represented as occurring in one period. This simpler specification allows the key strategic incentives to be identified. In Chapter 8, the findings from Games 1 and 2 inform a three period game of the drug R&D process; Game 3.

2.2.2.1 Extensive form representation of the game

The extensive form representation of the Game is presented in Figure 11.

2.2.2.2 Players, actions and payoff

There are three players: the Firm (F), the Institution (I) and the Capital Market (C). The payoffs in the Game are listed in that order in Figure 11.

The Game starts when the Firm approaches either the Capital Market or the Institution to raise the funds required to develop a New Molecular Entity (NME). The Game (Figure 11) sets out three actions available to the Firm in the first stage: Do Nothing (N), Lobby (L) or Borrow (B).

2.2.2.2.1 Firm chooses to do Nothing (N)

If the Firm chooses to do Nothing, the Game ends and the payoff to each player is zero. The players will all continue to make profits (F and C) or health gains for the population (I) from existing activities, the outcomes of which are assumed not to be impacted by this particular Game.

2.2.2.2.2 Firm chooses to Lobby (L)

Lobbying (L) involves the Firm making a case to the Institution that it should provide the research funds $\bar{\mathcal{R}}$ via higher prices on the existing drug. If the Firm chooses to Lobby (L) the Institution, the Institution can choose to either Accept (A) or do Nothing (N) in response to the proposal by the Firm to raise additional funds through internal revenue (economic rent) on the existing drug. If the Institution chooses to do Nothing (N) in response to the Lobbying (L), the Game ends and the payoff to each of the Firm, the Institution and the Capital Market is 0.

If the Institution chooses to Accept (A) the Lobbying (L) and pay the Firm the additional economic rent, $\bar{\mathcal{R}}$ per unit sold, the Firm will invest the entire funds¹⁴² into the R&D and the result will be either Success (S) (an NME) or No success (N), no new drug. The probability of these two outcomes is q and $1-q$ respectively. If there is No success (N) the game stops and the payoffs to the Firm and the Capital Market are both 0, whereas the financial payoff to the Institution is the net financial cost for the population's health budget: $-\bar{\mathcal{R}}$

The payoff to the Institution is the loss of the Institution's investment of health budget funds into the R&D process raised via the increased price of existing drugs paid to the Firm as a consequence of Lobbying. The health payoff to the Institution if there is No success is the net change in the population's health:

¹⁴² In fact the evidence suggests that the Firm will invest < 33% into R&D for new drugs (see Vernon's Equation (International Trade Administration 2004 p. 29). Reinhardt also makes this point, although indicates the percentage of revenue rather than economic rent that goes to R&D. (Reinhardt 2007 pp. 41-43) The implications of relaxing this assumption are considered in the discussion.

$$\Delta E = -\frac{\overline{\mathcal{R}}}{m}$$

The payoff is the loss in health effects as a consequence of financing the pharmaceutical R&D by displacing services with an aICER of m . The health budget is currently economically efficient and displacement is optimal ($d=m$) therefore the NEB_h (which is negative) is the same as the net health loss for the population.

If the R&D is successful, then the Firm will offer the future NME at an $IPER$ of f . The Institution will either Reimburse (R) or do Nothing (N) when the Firm presents the future drug at the offer price f . If the Institution Reimburses (R) the drug at the offer price, the payoff to the Firm, π_F is:

$$\begin{aligned}\pi_F &= f\overline{\Delta E^P} - c\overline{\Delta E^P} + \overline{\mathcal{R}} - \overline{\mathcal{R}} \\ &= \overline{\Delta E^P}(f - c)\end{aligned}$$

This payoff comprises:

- 1) the revenue from the new drug that has an $IPER$ f where the total additional health effects for the target patients are $\overline{\Delta E^P}$ and hence revenue is $f\overline{\Delta E^P}$;
- 2) less the costs of production of the future drug, an $IMER$ of c per unit additional health effect produced ($\overline{\Delta E^P}$) and hence a total manufacturing cost of $c\overline{\Delta E^P}$;
- 3) plus the amount raised by lobbying, $\overline{\mathcal{R}}$; and
- 4) less the investment into NME R&D, $\overline{\mathcal{R}}$.

The Lobbying is assumed to be costless; an assumption that will be relaxed in the discussion.

The payoff to the Capital Market will be zero and the payoff to the Institution, the net health benefit to the population, ΔE will be:

$$\Delta E = \overline{\Delta E^P} - \frac{f\overline{\Delta E^P}}{m} - \frac{\overline{\mathcal{R}}}{m}$$

This payoff comprises:

- 1) the additional health effects for target patients of the future new drug compared to the best existing therapy in the future, $\overline{\Delta E^P}$;
- 2) $\frac{f\overline{\Delta E^P}}{m}$ the health effects lost due to the requirement to displace an amount $f\overline{\Delta E^P}$ of services with aICER= m to finance the future drug; and
- 3) less $\frac{\overline{\mathcal{R}}}{m}$, the health effects displaced to finance the additional amount $\overline{\mathcal{R}}$.

If the Institution chooses to Not reimburse (N) the NME at the offer price, the payoff to the Firm and the Bank is 0 and the payoff to the Institution is the incremental change in the population's health:

$$\Delta E = -\frac{\overline{\mathcal{R}}}{m}$$

This payoff is the loss to the Institution from displacing services at an aICER of m to finance the amount lobbied for by the Firm, $\overline{\mathcal{R}}$.

2.2.2.2.3 Firm chooses to Borrow (B)

If the Firm chooses to Borrow and accepts the Capital Market's offer price of θ , it borrows the funds, and if the R&D is successful and the Institution agrees to the offer price, then the Firm's payoff to Borrow (B) is:

$$\begin{aligned}\pi_F &= f\overline{\Delta E^P} - c\overline{\Delta E^P} - \overline{\mathcal{R}}(1 + \theta) \\ &= \overline{\Delta E^P}(f - c) - \overline{\mathcal{R}}(1 + \theta)\end{aligned}$$

This payoff (π_F) differs from the payoff of the strategy Lobby followed by Successful R&D and Reimbursement of the future drug, by the amount that the Firm is required to repay for the loan from the capital market, an amount of:

$$\overline{\mathcal{R}}(1 + \theta)$$

The Institution's expected payoff to this series of eventualities is the change in the population's health:

$$\Delta E = \overline{\Delta E^P} - \frac{f\overline{\Delta E^P}}{m}$$

This payoff comprises:

- 1) the additional health effects of the future new drug compared to the best existing therapy in the future, $\overline{\Delta E^P}$; and
- 2) $\frac{f\overline{\Delta E^P}}{m}$

the health effects lost due to the requirement to displace an amount $f\overline{\Delta E^P}$ of services with aICER m to finance the future drug; and

And the Capital Market's payoff is:

$$\pi_C = \theta\overline{\mathcal{R}} - \tau\overline{\mathcal{R}} = \overline{\mathcal{R}}(\theta - \tau)$$

where $\theta\overline{\mathcal{R}}$ is the interest from the loan to the Firm and $\tau\overline{\mathcal{R}}$ is the foregone interest from a loan that the Capital Market could make to a zero risk borrower.

If the Firm does not accept the Capital Market's offer of funds at price θ then the Game ends and there is a payoff of 0 for each player. If the Firm agrees to the Capital Market's offer of i and the R&D is unsuccessful then the Game ends and the payoff to the Capital Market is a loss of:

$$\overline{\mathcal{R}}(1 + \tau)$$

The loss of $\overline{\mathcal{R}}(1 + \tau)$ includes the economic loss, the foregone interest, as well as the loss of the capital loaned to the Firm. In simple terms, if the Bank had lent to the risk free borrower, it would have retained the capital and received the interest.

The payoff to the Firm is 0.

If the Capital Market lends to the Firm and the R&D is successful and the Institution does not accept the offer price, f , then the payoffs are a loss of $\overline{\mathcal{R}}(1 + \tau)$ and 0 for the Capital Market and Firm respectively.¹⁴³

2.2.2.3 Parameters and variables

- 1) $\overline{\mathcal{R}}$ is the Firm's fixed cost for developing and trialling a future drug.
- 2) q is the probability that the R&D will be successful and result in a future drug.
- 3) $\overline{\Delta E^P}$ is the additional health effect of the future drug (should R&D be successful) compared to the best alternative therapy at the time.
- 4) m is the aICER of services displaced in order to finance the additional cost of existing drug that is necessary to raise the funds for pharmaceutical R&D. It is also the aICER of the services displaced to finance additional cost of the future drug.
- 5) c is the *IMER* - the additional cost per unit of additional health effect of manufacturing the future drug, compared to current drug.
- 6) f is the *IPER* of the future drug.
- 7) θ is the interest rate charged by the Capital Market to the Firm, over the period of the loan.
- 8) τ is the interest rate charged by the Capital Market to a zero risk borrower.

The parameters and variables that describe the payoffs of the actions available to the Institution can be specified in terms of the total cost and unit cost of achieving them.

9) $\frac{f \overline{\Delta E^P}}{m}$

is the health effects displaced if the additional cost of the additional health gains from the future drug ($f \overline{\Delta E^P}$) are financed by displacing services of an aICER m .

10) $\frac{\overline{\mathcal{R}}}{m}$

is the health effects displaced if the additional cost of financing firm R&D ($\overline{\mathcal{R}}$) are financed by displacing services of an aICER m .

2.2.2.4 Conditions

- 1) The value of q , the probability of success of R&D, is known, even though the *ex-ante* outcome of R&D is uncertain. There is no uncertainty in the value of any other parameters or variables in the Game at any stage in the Game for either player.
- 2) There is no private information, for example, the costs of manufacturing are known by all players.
- 3) The Institution is risk averse or risk neutral. The Capital Market is risk neutral.
- 4) The Firm is efficient in its R&D process; there is no way of trialling and developing a future drug that would reduce the fixed costs of R&D.

¹⁴³ The Institution and Firm can of course enter a bargaining process. However, the key issue is that the public domain decision threshold combined with the requirement for the Institution to agree to reimburse the new drug if its price per effect is less than or equal to the threshold means that the profit maximizing offer price. If it cannot offer the drug at this price then it will be able to assess the impact of this constraint via the backward induction process. This situation is illustrated in Game 1, Chapter 8.

- 5) There is no option for the Institution or other Firm to invest in the development of a non-pharmaceutical innovation, such as a new medical device. The implications of relaxing this assumption are considered in the discussion.
- 6) $\overline{\Delta E^P} > 0$. The future drug brought to the Institution is clinically innovative, that is, it has a clinical advantage compared to best available existing therapy for the target group of patients. It is constant for the identified group of target patients, and is known with certainty.
- 7) $m > 0$. The aICER of services displaced to finance the additional financial costs of the future drug is greater than zero. It is also the least cost effective of all existing options to contract programs (efficient displacement). Using PEA terminology: $d = m = \beta_c$.
- 8) $\frac{\overline{\Delta E^P}}{m}, \frac{\overline{R}}{m} > 0$. It follows from $\overline{\Delta E^P}, \overline{R}, m > 0$ that displacing services to finance the additional costs of the pharmaceutical R&D and the future drug will lead to a loss in health effects for patients who would otherwise have received these services.
- 9) $f \geq 0$ The *IPEP* of the future drug compared to the best available therapy is greater than or equal to 0.
- 10) $c > 0$ The *IMER* is greater than zero.
- 11) $0 > \theta, \tau, q > 1$ The interest rates and the probability of success of R&D both lie between 0 and 1.

2.2.2.5 And other assumptions

- 1) It is assumed that both lobbying and preparation of a business case for a Capital Market are costless. This assumption is not consistent with the real world experience and the implications of relaxing this are considered in the discussion.
- 2) The costs of R&D, the incremental effect of the NME and cost of its production is independent of the method used to finance the R&D.
- 3) The health budget is fixed.
- 4) The health budget is initially economically efficient ($m = n$) and the displacement process is optimal ($m = d$). Therefore the quantitative value of the health shadow price β_c is m .
- 5) Because the health budget is economically efficient and displacement is optimal, the net economic benefit or loss of reimbursement is the same as the net health benefit or loss for the population.
- 6) If the Institution is indifferent between reimbursing a drug at the offer price and doing nothing it must reimburse the drug.
- 7) Both the Firm and Capital Market seek to maximise economic rent.
- 8) The Institution seeks to maximise npvPH from allocations and purchases made from this and future budgets.
- 9) The Firm allocates the entire economic rent raised through lobbying into the R&D process for new drugs. The implications of relaxing this assumption are explored in the discussion.

2.3 Theory proper

The Game draws upon the following theory: a player will select from options so as to maximise the expected economic profit or the expected economic value of the health effect. The latter is the same as maximising the population health effect because the budget is economically efficient (see Chapter 7). The solution concept used for the Game is backward induction.

2.4 Solution

The key strategic choice is whether the Firm chooses to Lobby, Borrow or do Nothing at the start of the Game. We compare the expected payoff to the Firm to these three actions by considering the consequences of each initial decision. These eventualities are in turn influenced by both the results of the chance nodes (the chance result of R&D) and the strategic response by the other players. We solve the Game by backward induction, starting with the outcome had the Firm chosen to Lobby in Stage 1.

2.4.1 Lobby

2.4.1.1 Stage 5 (Lobby): the decision by the Institution to Reimburse the future drug at the offer price or do Nothing

The process of displacement is optimal and the budget is allocatively and technically efficient, hence:

$$\beta_c = m$$

Therefore the Institution will accept the future drug at the offer price if the payoff from doing Nothing (the health loss from investment in R&D) is greater than the payoff to Reimbursement:

$$\overline{\Delta E^P} - \frac{f \overline{\Delta E^P}}{m} - \frac{\bar{\mathcal{R}}}{m} \geq -\frac{\bar{\mathcal{R}}}{m}$$

$$\Rightarrow \overline{\Delta E^P} - \frac{f \overline{\Delta E^P}}{m} \geq 0$$

$$\Rightarrow 1 - \frac{f}{m} \geq 0$$

$$\Rightarrow m \geq f$$

The Institution will accept the future drug at the offer price f if there is a net increase or no net change in the population's health as a consequence of its reimbursement. Hence, at an offer price at or below m , the Institution will accept the future drug with an *IPER* of f .

At Stage 5 (Lobby), the Institution has a sunk cost, which can be expressed in terms of health effects:

$$\frac{\bar{\mathcal{R}}}{m}$$

Regardless of whether the Institution chooses to Reimburse the future drug or do Nothing, it will make a loss. The Institution's objective at this stage is to minimise the loss.¹⁴⁴ How do we know the Institution will have a "sunk cost" in Stage 5 of the "Lobby" arm? In simple terms, it is the only way that the Game could have reached this point. If the Institution had not lent the funds it would not have reached this stage.¹⁴⁵

¹⁴⁴ This situation analogous to impact of sunk R&D costs on the firm's decision to manufacture a new drug. "By the time a pharmaceutical product reaches the market, the R&D costs incurred to bring the product to market are known as sunk costs, and are thus irrelevant from a firm's decision-making perspective." (Vernon JA, Golec JH et al. 2006)

¹⁴⁵ This is a critical issue in the understanding of backward induction as a solution method. See Watson 2003.

2.4.1.2 Stage 4 (Lobby): the decision to price the new drug

When

$$f = m$$

the Firm maximises its profit. At this price the units of additional health effect sold are:

$$\overline{\Delta E^P}$$

Above this price there will be no sales and below this price there will be no increase in sales and hence revenue and economic profit will fall.

2.4.1.3 Stage 3 (Lobby): the chance node – success or failure of R&D

The chance node influences the expected payoff of the R&D process. For the Institution, the expected (E) payoff the Firm's decision to invest in R&D is:

$$E[\Delta E] = q \left(\overline{\Delta E^P} - \frac{f \overline{\Delta E^P}}{m} - \frac{\bar{R}}{m} \right) + (1 - q) \left(-\frac{\bar{R}}{m} \right) \quad \text{Equation 12}$$

where q is the chance outcome of R&D.

The expected effect on the population's health includes the sunk costs of responding to Lobbying, regardless of whether R&D is successful, however if it is successful the Institution will also have the net benefit or the health gains for target patients less the health effects foregone from displacing programs to finance the future drug.

From Stage 4 we have the result that

$$f = m$$

Substituting this result into Equation 12, it follows that:

$$E[\Delta E] = q \left(\overline{\Delta E^P} - \overline{\Delta E^P} - \frac{\bar{R}}{m} \right) + (1 - q) \left(-\frac{\bar{R}}{m} \right)$$

$$= -q \left(\frac{\bar{R}}{m} \right) - \frac{\bar{R}}{m} + q \left(\frac{\bar{R}}{m} \right)$$

$$E[\Delta E] = -\frac{\bar{R}}{m} \quad \text{Equation 13}$$

That is, the Institution's expected payoff to the Firm's R&D is the loss of the sunk costs of R&D financed by the Institution.

For the Firm, the expected payoff of R&D, at an $IPER=f=m$ is:

$$\begin{aligned} E[\pi_F] &= q \left(m \overline{\Delta E^P} - c \overline{\Delta E^P} \right) + (1 - q)(0) \\ &= q \overline{\Delta E^P} (m - c) + 0 \end{aligned}$$

$$E[\pi_F] = q \overline{\Delta E^P} (m - c)$$

The Firm's expected economic rent (payoff) from R&D is the expected economic rent ($m-c$) on each unit sold adjusted by the probability of successful R&D (q).

2.4.1.4 Stage 2 (Lobby): The Institution decides whether to accept or reject the Firm's lobbying

The Institution will Accept the Lobbying if expected payoff to this action is greater or equal to the payoff of the action N – do Nothing (reject). From Equation 13, we have the expected payoff to accepting Lobby, therefore the relevant decision rule is to accept Lobbying if:

$$-\frac{\bar{\mathcal{R}}}{m} > 0$$

However:

$$m, \bar{\mathcal{R}} > 0$$

$$\Rightarrow -\frac{\bar{\mathcal{R}}}{m} < 0 \forall \bar{\mathcal{R}}, m$$

Therefore there is no situation where the Institution will accept the Lobbying.

2.4.1.5 Stage 1 (Lobby): the Firm's payoff to Lobby

The Firm's payoff to Lobby is 0 because from Stage 2 (Lobby), we see that there is no incentive for the Institution to respond to Lobbying by increasing prices.

2.4.2 Borrow

Now we consider the payoffs to the action Borrow.

2.4.2.1 Stage 6 (Borrow): the Institution's decision to accept the offer price

The situation is as for Stage 5 (Lobby) and the condition that needs to be met for the Institution to accept the future drug at the offer price is:

$$f \leq m$$

Where m is the least cost effective in contraction of existing programs, which, because the budget is fixed and efficient, and displacement is optimal, is the quantitative value of the health shadow price.

2.4.2.2 Stage 4 (Borrow): the Firm's decision to price the new drug

The situation is as for Stage 5 (Lobby) and the offer price selected by the Firm is:

$$f = m$$

2.4.2.3 Stage 4 (Borrow): the chance node – success or failure of R&D

The expected pay off to R&D depends upon whether the Institution will reimburse the new drug. For simplification, we assume that it is profitable for the Firm to produce the drug at an *IPER* of m , that is, $m \geq c$. This simplification will not change the result of the Game. It is a reasonable assumption because all information is in the public domain and therefore all players know m and c . Therefore, because firms will consider the price of the future drug when they make the decision to invest in R&D,

they will only make this decision to invest if they expect the new drug to be profitable to manufacture.¹⁴⁶

The expected payoff to each player is as follows:

For the Firm, the expected payoff of R&D is:

$$E[\pi_F] = q \left(f \overline{\Delta E^P} - c \overline{\Delta E^P} - \bar{\mathcal{R}}(1 + \theta) \right) + (1 - q)(0)$$

$$E[\pi_F] = q \left(f \overline{\Delta E^P} - c \overline{\Delta E^P} - \bar{\mathcal{R}}(1 + \theta) \right)$$

where $f=m$, therefore the expected payoff to the Firm is:

$$E[\pi_F] = q \left(\overline{\Delta E^P}(m - c) - \bar{\mathcal{R}}(1 + \theta) \right) \quad \text{Equation 15}$$

This result is saying that the expected profit to the Firm is economic rent on each unit sold, less the interest and capital payment to the Capital Market and adjusted by the probability of the R&D being successful.

For the Institution, the expected payoff of R&D is:

$$E[\Delta E] = q \left(\overline{\Delta E^P} - \frac{f \overline{\Delta E^P}}{m} \right) + (1 - q)(0)$$

where $f = m$, therefore the expected payoff is

$$E[\Delta E] = q \left(\overline{\Delta E^P} - \overline{\Delta E^P} \right)$$

$$E[\Delta E] = 0 \quad \text{Equation 16}$$

The payoff to the Institution is zero, regardless of the outcome of R&D, because of the profit maximising *IPER* of the future drug, m , which exactly offsets the health gains foregone by displacing the least cost effective of existing programs.

For the Capital Market, from Figure 11 we see that the expected payoff of Firm R&D is:

$$\begin{aligned} E[\pi_c] &= q(\theta - \tau)\bar{\mathcal{R}} - (1 - q)\bar{\mathcal{R}}(1 + \tau) \\ &= \bar{\mathcal{R}}(q\theta - q\tau - (1 - q)(1 + \tau)) \\ &= \bar{\mathcal{R}}(q\theta - 1 + q - \tau) \end{aligned}$$

which can be simplified to:

$$E[\pi_c] = \bar{\mathcal{R}}(q(\theta + 1) - (1 + \tau)) \quad \text{Equation 17}$$

The expected payoff to the Capital Market is a function of the probability of success of R&D. It is the return on the loan $\bar{\mathcal{R}}$ to the Firm, at a rate θ , weighted by the probability of the success of R&D, q ,

¹⁴⁶ For example Vernon et al. (2006) See Footnote 143

less the foregone benefit of the Capital Market's zero risk alternative, which would have guaranteed a return on capital plus interest at a rate of τ . In Equation 17, the expected profit is expressed as an economic rent quantum (the amount required for R&D) loaned to the Firm.

2.4.2.4 Stage 3(Borrow): the Firm accepts or rejects the Capital Market's offer of i

The Firm will accept the Capital Market's offer of θ if the Firm's expected payoff to R&D (Equation 15) is greater than or equal to zero.

$$q \left(\overline{\Delta E^P}(f - c) - \bar{\mathcal{R}}(1 + \theta) \right) \geq 0$$

where $q > 0$, therefore:

$$\overline{\Delta E^P}(f - c) - \bar{\mathcal{R}}(1 + \theta) \geq 0$$

$$\overline{\Delta E^P}(f - c) \geq \bar{\mathcal{R}}(1 + \theta)$$

$$\frac{\overline{\Delta E^P}(f - c)}{\bar{\mathcal{R}}} - 1 \geq \theta$$

Equation 18

2.4.2.5 Stage 2(Borrow): Capital Market selects its offer of θ

The risk neutral Bank will select a minimum θ such that the expected return on the decision to lend (Equation 17) is equal to zero.¹⁴⁷

$$E[\pi_c] = \bar{\mathcal{R}}(q(\theta + 1) - (1 + \tau)) = 0$$

where $\bar{\mathcal{R}} > 0$, therefore

$$q(\theta + 1) - (1 + \tau) = 0$$

$$q\theta + q - 1 - \tau = 0$$

$$q\theta = 1 - q + \tau$$

$$\theta_{min\ bank} = \frac{1 + \tau}{q} - 1$$

Equation 19

The maximum acceptable θ to the Firm will occur when the Firm's expected payoff to accepting the Capital Market's price is greater than or equal to zero.

From Equation 18 we have the condition:

$$\frac{\overline{\Delta E^P}(f - c)}{\bar{\mathcal{R}}} - 1 \geq \theta$$

This condition provides the following maximum price:

¹⁴⁷ This is an equality because the Bank is risk neutral. See the consumer equivalent in Jehle and Reny (2001) p. 105.

$$\frac{\overline{\Delta E^P}(f - c)}{\bar{\mathcal{R}}} - 1 = \theta_{max\ firm} \quad \text{Equation 20}$$

There are two possible situations for the price θ . First, if the minimum price acceptable to the Bank is more than the maximum price acceptable to the firm, the Bank could still offer its minimum acceptable price, but the loan would be refused by the Firm.

$$\theta_{min\ bank} > \theta_{max\ firm}$$

We substitute in the above with Equation 19 and Equation 20:

$$\Rightarrow \frac{1 + \tau}{q} - 1 > \frac{\overline{\Delta E^P}(f - c)}{\bar{\mathcal{R}}} - 1$$

$$\Rightarrow \frac{1 + \tau}{q} > \frac{\overline{\Delta E^P}(f - c)}{\bar{\mathcal{R}}}$$

$$\bar{\mathcal{R}}(1 + \tau) > q \left(\overline{\Delta E^P}(f - c) \right) \quad \text{Equation 21}$$

This condition is saying that the return that the Bank could receive on a no risk loan of $\bar{\mathcal{R}}$:

$$\bar{\mathcal{R}}(1 + \tau)$$

is more than the expected additional rent

$$q \left(\overline{\Delta E^P}(f - c) \right)$$

that the Firm can make on its investment of $\bar{\mathcal{R}}$. In this case we assume that the Capital Market makes an offer to the Firm of:

$$\theta_{min\ bank} = \frac{1 + \tau}{q} - 1$$

which the Firm will not accept.

The second possible situation is if the minimum price acceptable by the Bank is less than the maximum price acceptable to the Firm, in which case the resultant equilibrium price θ^* will be between these two and will depend upon the relative bargaining powers of the Firm and the Bank.

That is:

$$\theta_{min\ bank} \leq \theta^* \leq \theta_{max\ firm}$$

2.4.3 Should the Firm Borrow, Lobby or do Nothing?

The key strategic decision is whether the Firm should Lobby, Borrow or do Nothing. To establish the conditions under which the Firm will select from these three options, the payoffs to each are calculated. What will determine this choice?

Note: The pharma-economic literature recognises the influence of future price on a firm's decision to invest in R&D. For example: *Of course, if firms had not expected to obtain prices that would have covered their R&D investments, they would not have undertaken the R&D in the first place (Vernon, Golec et al. 2006 p. 182).*

This dynamic GTM also recognises this issue. This Game also recognises that the Institution will take into consideration future prices in their payoff to accepting lobbying today. The latter analogous fact is not widely, if at all, recognised in the pharma-economic literature.

2.4.3.1 Payoff to do Nothing

The payoff from the Game for all players from the Firm choosing to do Nothing is 0.

2.4.3.2 Payoff to Lobby

The expected payoff to the Firm of Lobby is 0. There is no incentive for the Institution to invest in R&D via a higher price today. The reason is that there is no mechanism whereby the Institution can recoup its initial investment in R&D via higher prices for the existing drug.

2.4.3.3 Payoff to Borrow

If the minimum acceptable interest rate for the Bank is higher than the maximum acceptable rate for the Firm, then there will be no payoff to Borrow. These conditions are presented in Equation 21. In this case the Firm will chose to do Nothing. However, if this condition is not met, then the Firm will choose to Borrow and from the expected payoff will be:

$$\mathbf{E}[\pi_F] = q \left(\overline{\Delta E^P}(f - c) - \bar{\mathcal{R}}(1 + \theta^*) \right) \quad \text{Equation 22}$$

where we assume:

$$\theta_{min\ bank} \leq \theta^* \leq \theta_{max\ firm}$$

Substituting Equation 19 and Equation 20 we have:

$$\frac{1 + \tau}{q} \leq \theta^* \leq \frac{\overline{\Delta E^P}(f - c)}{\bar{\mathcal{R}}} - 1$$

Therefore the expected payoff per unit sold to the Firm from Borrow (given that it is greater than 0) is between the profit at the maximum interest and the profit at the minimum interest rate, where the profit for the Firm as a function of θ is sourced from Equation 15.

$$q \left(\overline{\Delta E^P}(f - c) - \bar{\mathcal{R}} \left(1 + \frac{\overline{\Delta E^P}(f - c)}{\bar{\mathcal{R}}} - 1 \right) \right) \leq \mathbf{E}[\pi_F] \leq q \left(\overline{\Delta E^P}(f - c) - \bar{\mathcal{R}} \left(1 + \frac{1 + \tau}{q} \right) \right)$$

$$\Rightarrow 0 \leq \mathbf{E}[\pi_F] \leq q \left(\overline{\Delta E^P}(f - c) - \bar{\mathcal{R}} \left(1 + \frac{1 + \tau}{q} \right) \right)$$

$$\Rightarrow 0 \leq \mathbf{E}[\pi_F] \leq q \overline{\Delta E^P}(f - c) - \bar{\mathcal{R}}(q + 1 + \tau)$$

That is, the expected payoff to the Firm is between:

- 1) 0 (if the Bank appropriates the entire surplus and charges at the Firm's $\max\theta$); and
- 2) the additional profit $(f-c)$ from each unit of health effects sold $\overline{\Delta E^P}$, adjusted by the probability of Success of R&D (q) less the costs of borrowing R&D funding at the Bank's $\min\theta$.

2.4.4 Equilibrium

What are the conditions at equilibrium? The equilibrium result will depend upon whether there is an interest rate that provides an incentive for the Firm to Borrow and the Bank to lend. If there is no such rate, then the equilibrium result is no action and the payoff is 0 for all players. However if there is an incentive for the Firm to Borrow and the Bank to lend, then there will be a payoff greater than zero to the Firm and/or Capital Market.

The expected payoff to the Firm will be a function of θ :

$$0 \leq E[\pi_F] \leq q\overline{\Delta E^P}(f-c) - \bar{\mathcal{R}}(q+1+\tau)$$

The expected payoff to the Capital Market, also a function of θ :

$$E[\pi_C] = \theta\bar{\mathcal{R}}$$

$$E[\pi_C] = \bar{\mathcal{R}}\left(\frac{1}{q} - 1\right)$$

And the expected payoff to the Institution will be:

$$E[\Delta E] = \overline{\Delta E^P} - \frac{f\overline{\Delta E^P}}{m}$$

Where:

$$f = m$$

$$\therefore E[\Delta E] = \overline{\Delta E^P} - \overline{\Delta E^P} = 0$$

So at equilibrium, regardless of whether the Firm chooses Borrow or No Action, there is no net increase in the health of the population. This outcome is a consequence of the Firm's incentive to price at the threshold *IPEP* and the lack of the Institution's capacity to bargain below this price. In conclusion, the economic value of clinical innovation (*EVCI*) from the development of the new drug, if it exists, it will be shared between the Capital Market and the Firm.

3 Discussion

Firms claim the reason that they rely on economic rent to source their R&D funds is because banks are unwilling to lend at a rate that allows firms to be profitable. This state of the world is consistent with the situation described in the Game where the minimum interest rate required by the Bank is higher than the maximum interest rate that the Firm can pay and still be profitable. This Game shows that if this situation exists, there is no incentive for the Institution to increase prices to finance this R&D because there are no mechanisms whereby this investment can be recouped.

But there is one more option suggested by this Game; the Firm could offer to contract with the Institution, which can recoup its initial investment \mathcal{R} . This contract could be in the form of a discount on the *IPEP* of the future drug, which would otherwise be β_c , which in this case has a quantitative value of m . The Game can be used to predict whether the Institution will be willing to enter such a

contract by taking into account the risk preferences of the Institution relative to those of the Capital Market. If Institutions appropriately accommodated the risks (as the Capital Market does) and had the same attitude to risk as the Capital Market, then it is unclear why we would expect the payoff to the Firm to contracting with Institutions to be higher than the payoff to the strategy Borrow. That is, the Institution would require the same minimum share of surplus should the R&D be successful as the Capital Market does, in addition to recouping its initial investment and the cost advantages to the Firm of the strategy “Lobby” relative to the strategy “Borrow” would be removed.

This conclusion could appear counter intuitive; the Institution can benefit from the additional future health effects whereas the Capital Market does not. If the Institution were provided with the additional health effects at no financial cost then there would be an additional incentive for the Institution. However, the Institution is required to pay for these additional health gains (possibly at or above β_c) as well as finance the R&D. At β_c the Institution is indifferent between health effects from the new drug and health effects purchased through other strategies. Therefore, there is only one way the Institution can be made better off by contracting compared to relying on the Firm to Borrow from the Capital Market. This incentive is if there is a return on their investment \mathcal{R} (via a lower future price) and an additional incentive of a further discount on the price to account for the risk.

If institutions, the agent of consumers, are more risk averse than the Capital Market, then we would expect that institutions would require a higher value of θ to accommodate the risks of R&D, compared to that required by the Capital Market. Hence, the Firm's return on Borrow could be higher than the return on Lobby and Contract with the Institution.

In conclusion, if $EVCI > 0$, then by entering into a contract to be paid a share of this surplus in addition to being repaid the capital, an incentive for the Institution to provide the funds to the Firm is generated. However, it is likely that in order for the relatively risk averse Institution¹⁴⁸ to be willing to enter such a contract, it will need to be compensated for undertaking the loan and this compensation would need to be more than that required by the risk neutral Capital Market. Hence, if risks are appropriately accommodated the Firm is predicted to prefer the strategy Borrow to that of Lobby and Contract.

In the real world, we observe that a Firm sources its R&D from internal funds raised by economic rent which in turn results from Lobbying. Does this mean the Game has poor predictive value? In the polite language of Game Theory, the Institution has made a “mistake” rather than acted “irrationally”.¹⁴⁹ The observation that it is cheaper to source funds internally is a consequence of a mistake by the Institution in providing these funds and not requiring a return; the failure is by the Institution not the Capital Market.

The Game reveals that if the Firm knows that there is a possibility that the Institution will make a mistake in its response to lobbying, then there is an incentive for the Firm to Lobby in order to gain the funds for R&D at a cheaper rate (no interest) plus no requirement to repay the capital. Furthermore, the evidence suggests that only a share of the funds raised by lobbying are invested in NME R&D, between 20% and 30% (Reinhardt 2007). There is a cost to lobbying. However, the

¹⁴⁸ More risk averse than the Bank and not a risk taker.

¹⁴⁹ A mistake is an error made by a player, possibly a result of the complexities of a strategy. For example see Watson (2002) page 27. The idea of irrationality could suggest that the player is acting in a way that is not consistent with their objectives. The idea of players acting rationally is significant in game theory because it is the assumption that allows players to select their own strategy based on the expected response by the other player. There could still be strategic uncertainty in the other player's response, even if all players act rationally. It is unusual in Game Theory to assume that there is only one definition of rationality, but some concepts of rationality dominate. (See Watson 2002 and Grüne-Yanoff and Schweinzer 2008) Games however can incorporate the idea of mistakes and in Evolutionary Game Theory mistakes can play a significant role in achieving an evolutionary stable equilibrium. See Samuelson (2002).

returns to the Firm in excess of the funds invested in lobbying and the savings compared to the strategy of Borrow makes Lobby a very effective strategy. The ostensibly evidence based Threat, that the population will be worse off if it does not finance R&D through higher prices, is an effective tactic within this strategy of Lobbying. Investing in the evidence to support this Threat is also an important part of this strategy of Lobbying.

And finally, if the Institution provides the funds to the Firm in a situation where there is no interest rate that was acceptable to both the Firm and the Capital market, then there is a dead weight social loss if the Institution responds to Lobbying. Society would have been better off if these funds were instead invested by the Institution into other strategies, for example, the development of unpatentable but very cost effective innovation ($aICER < \beta_c$). This issue is addressed in more detail in the following chapter.

4 Conclusion

Drug companies and pharma-economists use a range of arguments to defend the position that institutions should not use their monopsony power to negotiate a price below the *FPP*. Some of these arguments are contradictory. For example, firms and pharma-economists argue that firms need to be compensated for the risky investments that they make into pharmaceutical R&D. However, at the same time firms argue that they need to finance R&D for future drugs from internal funds because the capital markets will not bear this risk. These internal funds are sourced from above marginal cost pricing of drugs. There are no contracts or agreements for firms to repay this investment by, for example, lowering the price of the future drug, therefore the purchasers not only bear the risks of this investment, they bear the entire costs and the risks.

The Reimburser is convinced by Game 2 that the observation that firms finance their R&D from internal funds does not mean that unless firms access these internal funds through higher prices, there will be either no R&D, or less R&D and the health of the future population will be worse off. She also recognises that only 20% to 30% of these additional funds finance NME R&D and therefore the benefits to the Firm of the strategy of Lobby are underestimated by focusing on the return of future profit alone.

However, the Reimburser is still reluctant to accept that there is no benefit to the population's health from adjusting β_c to take into account the relationship between price and innovation. But how should it be taken into account?

Jena and Philipson (2008) proposed that there should be a premium paid for health effects purchased from new drug manufacturers because the purchaser is buying both current technology health effects and future technologies, whereas for other services, the purchaser is only buying health effects from current technologies. This strategy would effectively be a premium over β_c . In the following chapter this proposition for a decision threshold plus premium for new drugs is explored in a dynamic three stage game that explores the incentive for an Institution to move away from β_c as the decision threshold.

The following chapter also explores the possibility that overall social welfare (economic rent plus consumer welfare) will be higher if the Institution pays a premium, even if the population's health is worse. This methodological issue was one of the findings of the review of the pharma-economic literature presented in Appendix 2.

Chapter 10: The “Pharmacotherapy Needs a Premium” Game

Chapter 10 presents the second application of PEA to a specific Firm Threat in a Game called: “The pharmacotherapy needs a premium” Game. The specific threat is of the following or related form:

CEA applied with a threshold of β_c (CEA_{β_c}) captures information about the budget constraint and can improve static efficiency in a fixed budget. However, it does not capture information about the loss in future health as a consequence of lower prices today. New drugs should have a premium above the threshold for other programs because when a fund holder buys new drugs they are also buying future innovation. If this premium is not paid then there will be a suboptimal incentive to invest in pharmaceutical R&D and the health of future populations will be worse than it would otherwise be.

The Game is set up as a Firm’s choice between the strategies: i) invest in R&D; or ii) do nothing. The Game extends over three periods and up to two drugs (a new drug and a future drug) can be developed in the Game. The key decision by the Institution is whether or not to pay a premium over β_c for the new drug (the first drug) in order to facilitate development of the future drug.

The result of the Game is that there is no incentive for an Institution to price above β_c for the new drug in order to generate an incentive for the Firm to develop the future (second) drug. Furthermore, pricing above β_c is found to be neither a necessary nor sufficient condition for the development of the future drug.

The following situation is analysed. There is a social welfare loss over the three periods compared to the situation where both drugs are produced. The population health maximising Institution chooses not to price above β_c for the first drug and hence, only the first drug is produced. The population’s health is maximised at the cost of social welfare.

Again, clinical innovation of a future drug is found to be neither a necessary nor sufficient condition for this outcome, which could result from manufacturing innovation alone. In this situation, the Firm needs to provide an incentive to the Institution to pay a premium in Period 2. This incentive is generated by contracting with the Institution to allow it to appropriate a share of the surplus associated with the future drug, which in turn requires that it prices below β_c . This arrangement will allow the Institution to recoup its initial investment plus an amount to compensate the Institution for undertaking this investment.

However, even if these conditions are met, as in the previous game, if institutions are more risk averse than capital markets, this will make this strategy of contracting with institutions more expensive for firms than simply approaching the capital market and borrowing the required funds.

We conclude that the Institution should respond to the Threat by suggesting that the Firm approach the Capital Market and that this is the social welfare maximising solution. If the Firm claims it “has more information about the drug under development, its current status, and its ultimate chance of success” compared to the Capital Market (US Congressional Budget Office 2006 p. 9), then the Institution should advise the Firm to provide that information to the Capital Market.

1 The Reimburser's problem

The Reimburser is presented with a new drug by a pharmaceutical Firm. The new drug is more effective compared to the best existing drug, $\Delta E^P > 0$, however it also comes at an additional financial cost, $\Delta C^P > 0$. In order to finance the new drug within the fixed economically efficient health budget, an existing program needs to be displaced; the least cost effective of existing programs. However, this existing program has an aICER less than the *IPER* of the new drug ($m < f$), therefore, the health effects displaced to finance the new drug will be more than the health effects gained from reimbursing the new drug. Furthermore, the budget is currently economically efficient, therefore, using PEA, the threshold is $\beta_c = d = m$, where, d is the aICER of an optimally displaced services and m is the aICER of the least cost effective in contraction of an existing program.

The Reimburser is reluctant to choose to reimburse the new drug in this situation, however the Firm presents the Reimburser with a paper by pharma-economists Jena and Philipson (2008) who propose that new pharmaceuticals should have a higher threshold applied to them than the threshold applied to non-pharmaceutical inputs. The authors' reasoning is that purchasing the former is simply buying health effects from current technologies. Purchasing the latter has the benefits of both current health effects and future innovation.

Indeed, static efficiency, dynamic efficiency, and improved patient health may all be induced by the cost-effectiveness of the technology being at its worst level. The choice should not be seen as one between cheap or expensive technologies once marketed – as CE adoption suggests – but one between an initially expensive technology and no technology, the latter which would entail higher real prices for producing a healthy life. (Jena and Philipson 2008, p. 1235)

The Reimburser recognises that the program that will be displaced does not have an R&D component, so there appears little potential to change the efficiency of future health budgets through improved technology via this program. Jena and Philipson's conclusion has intuitive appeal: why not pay that bit extra for a new drug given that we are getting more than just the health effects of that drug? The Reimburser asks her Health Economist how the Institution should respond to the following Threat:

When the Institution buys this new drug, it buys the health effects from this drug and the health benefits from future innovation. This is not the case with other health programs. Therefore, unless the Institution pays a premium for the health effects from the new drug, the population will be worse off because innovation will be suboptimal and the future drug will not be produced.

2 The new drug needs a premium

Chapter 8 presented a one period GTM of the reimbursement process. The following Game extends that one period model to a three period model where the decisions linking successive time periods are: the Firm's decision to invest today in the R&D required for future drugs; and the Reimburser's decision to change the threshold price in order to change the availability of future NMEs.

2.1 The World

In 2008 a Firm developed a new drug, Arthmax for rheumatoid arthritis (RA). The evidence from double blinded randomised control trials showed a statistically and clinically significant gain to a subgroup of patients with RA compared to the existing best therapy, Rathmab. Purchasing Arthmax will come at a significant additional cost to the health care sector, ΔC^P , which will be financed by displacing an existing program. The aICER of the displaced program is less than the *IPER* of the new

drug and hence, there will be a net loss in the population's health. However, the Firm claims that because the new drug has dynamic as well as static welfare implications, whereas the existing program only has static welfare implications, the new drug should be purchased at the offer price despite the short term reduction in the health effects for the population.¹⁵⁰

The Firm makes the following Threat:

When the Institution buys this new drug, it buys the health effects from this drug and the health benefits from future innovation. This is not the case with other health programs. Therefore, unless the Institution pays a premium for the health effects from the new drug, the population will be worse off because innovation will be suboptimal and the future drug will not be produced.

How should the Institution respond to this Threat?

2.2 The Model

2.2.1 The Narrative

The Game takes place over three periods. Currently RA patients use a drug called Rathmab which is off-patent and hence its *IPER*, compared to placebo, is the same as its *IMER*; there is no economic rent. It is produced by a different Firm to the one in this Game.

Note: The relationship between the *IMER*, *IPER* and *IπER* of each of the three drugs is illustrated using numeric values for variables in Table 10 and Table 11. The Game is solved algebraically and hence these values are illustrative only. These numbers are referenced in brackets and italics throughout the narrative.

2.2.1.1 Period 1

The Game starts in Period 1 when the Firm makes a decision about whether to invest a fixed research budget financed by internal funds into pharmaceutical R&D or do nothing. The Firm's objective is to maximise economic rent. If the Firm invests in R&D, at the end of Period 1 they will have a new drug (Arthmax) for RA. This new drug will have an additional clinical benefit compared to the best existing pharmaco-therapy (Rathmab). This additional effect is for a sub-group of RA patients and is a reduction in pain and stiffness to a threshold that allows normal daily living. The additional effect is experienced by: i) all RA patients in the sub-group who have the drug (intervention); ii) no RA patients in the subgroup who do not have the drug (the control group); and iii) no RA patients who have this drug and are outside this subgroup (control and intervention).

2.2.1.2 Period 2

If the Firm does invest in R&D in Period 1, then at the start of the Period 2, the Firm offers the Institution the new RA drug, Arthmax, which has an *IPER* calculated relative to the best existing drug, Rathmab. ($\$75,000_{(a)}$) (All references in italics are to Table 10 and Table 11.) Rathmab is currently priced at its *IMER*; calculated compared to placebo. ($\$5,000_{(b)}$) The cost of producing a vial of Arthmax is more than the cost of producing a vial of Rathmab. ($\$500 > \$250_{(c)}$) Each vial of Arthmax "contains" more health effects compared to placebo than a vial of Rathmab compared to placebo. ($0.1 > 0.05_{(d)}$) This is the clinical innovation of Arthmax. ($0.1 - 0.05 = 0.05_{(e)}$) Therefore the *IMER* of Arthmax (compared to Rathmab)¹⁵¹ is greater than zero ($250/0.05 = \$5,000 > 0_{(f)}$) and assumed to be the

¹⁵⁰ By static efficiency the authors are referring to the aICER of the current budget and current technologies. The capacity for innovation to change dynamic efficiency refers to its influence on the aICER of a future budget.

¹⁵¹ The *IMER* of Arthmax relative to Rathmab the additional cost of manufacturing the additional health effects in each vial.

same as the *IMER* for Rathmab (compared to placebo) ($\$5,000_{(b)}$). This means there is clinical innovation (more health effects per vial) but no manufacturing innovation (the incremental costs of manufacturing each incremental health gain is the same for Arthmax and Rathmab).

The Firm makes no economic rent on the non-clinically innovative units of Arthmax because these are priced at their *IMER*. However, on every unit of additional health effect (Arthmax compared to Rathmab) sold, the difference in the *IPER* and the *IMER* of these additional health effects represents economic rent to the Firm on the innovative health effects, the *I π ER* ($\$75,000 - \$5,000 = \$70,000_{(g)}$).

The Institution can choose to reimburse Arthmax or do nothing. The Institution seeks to maximise the health of the population given the existing budget. If the Institution is indifferent to the payoff of reimbursement compared to that for doing nothing, it must choose to reimburse. If the Institution chooses to reimburse Arthmax, it will reimburse it for all patients who are in the sub-group for whom there is an effect. None of the patients who currently have their access to Rathmab subsidised will continue to be prescribed Rathmab. Instead they will all be prescribed Arthmax, which is clinically superior. If Arthmax is not reimbursed, no patients will have the new drug due to its very high annual cost (around 75% of the average salary of a person with severe RA).¹⁵² In this way the health effect of the policy to reimburse Arthmax is discrete rather than continuous.

The Institution, which has a fixed budget, must displace existing services to finance the additional cost of the new drug for every year that Arthmax continues to be the best available pharmaco-therapy for these patients. Furthermore, once Arthmax is reimbursed, it cannot be displaced until a new drug that is clinically superior for this group of patients is reimbursed; Arthmax cannot be displaced to finance a different program or a new drug for which it is not a clinical substitute. The health budget is allocatively efficient at the start of Period 2; there is no alternative allocation of resources across existing inputs and technologies that can improve health outcomes for the population. There is also no investment in improved practice that can be made today that will have returns of lower aICER for a program in the future that offsets the health effects foregone today due to the initial investment. And finally, if Arthmax is reimbursed, it is financed by optimal displacement ($d=m$). The contracted program is unpatented and continuous, that is, it can be contracted or expanded by any unit and there will be a corresponding decrease or increase in health effects.

If Arthmax is reimbursed at the start of Period 2 then the Firm will produce it at an *IMER* of c_1 ($\$5000_{(f)}$). At the start of Period 2 the Firm has to decide whether it will use some of the economic rent from the production and sale of Arthmax to develop a new RA drug, or whether it will no longer innovate and simply continue to produce Arthmax. The Firm's payoff to continuing to manufacture Arthmax will be the economic rent from the sale of the drug in Periods 2 and 3. If the Firm decides to invest in the development of a new RA drug, it will incur a cost of R&D in Period 2 in addition to the cost of manufacturing Arthmax. It will also be in receipt of the revenue from the sales of Arthmax.

2.2.1.3 Period 3

If the Firm chose not to invest in R&D in Period 2 then in Period 3 the Firm continues to manufacture Arthmax and the Institution continues to displace services to finance its additional cost and reimburse Arthmax for eligible patients.

¹⁵² In 2005, The cost of etanercept (a disease modifying agent -DMARD) was estimated at £178.75 per dose, 52 doses of 50 mg per year, which is £9295 per year. (Chen, Jobanputra et al. 2006) At that time the average disposal salary in the UK was £16,761. <http://www.worldsalaries.org/uk.shtml> Accessed: 21-02-12. A person with Severe RA is likely to earn less than the average salary, therefore it is conceivable that a new RA drug could be more than 75% of the salary of a person with severe RA.

If the Firm chose to invest in R&D in Period 2 then at the end of Period 2 the Firm has a new drug, Arthmaxplus, a more effective drug than Arthmax. The gain compared to Arthmax is significant both clinically and statistically. It works for the same patient group as for Arthmax and if Arthmaxplus is approved for reimbursement then all patients who currently have Arthmax will now instead be prescribed Arthmaxplus. If the Institution chooses to reimburse Arthmaxplus it must displace additional services to finance the additional cost of these additional health effects.

2.2.1.4 Political Economy

This narrative contains two aspects of the political economy of the reimbursement process:

- 1) If the Institution is indifferent between reimbursing the new drug and continuing funding the existing drug, it must select the new drug.
- 2) The Institution cannot displace a drug that it has reimbursed to finance care for the same or different group of patients; it can only replace it with a superior drug for the same patient group.

2.2.1.5 The relationship between *IMERs*, *IPERs* expenditure and costs of manufacturing

This Game introduces the possibility that a future drug can have both clinical and manufacturing innovation; a reduction in the average cost of manufacturing each incremental QALY compared to either placebo or the previous drug. It also demonstrates how successive drugs capture the economic rent of previous drugs as a consequence of the combined effect of new drugs being introduced before comparators are off-patent and the application of CEA_i .

Table 10 and Table 11 set out a hypothetical example of the drugs that this Game characterises. These tables illustrate some of the characteristics of *IMER*, *IPERs* and *IπERS* in the case of drugs reimbursed successively. Arthmaxplus has clinical innovation. If Arthmax is still on patent and the $IPER > IMER$ ¹⁵³ then the economic rent appropriated by the Firm in relation to the clinically innovative health effects of Arthmax relative to Rathmab ($\$70,000_{(g)}$ where (g) refers to a cell in Tables 10 and/or 11), are also available on the sale of Arthmaxplus. This is in addition to the *IπER* available on the clinically innovative health effects of Arthmaxplus compared to Arthmax. (See also Appendix 6 for a discussion of the Appropriation of Surplus by subsequent drugs.)

Now consider the consequences for the *IπER* of Arthmaxplus (compared to Arthmax) if there is manufacturing innovation. The additional cost of manufacturing a course of Arthmax relative to Rathmab ($\$500_{(c)} - \$250_{(c)} = \$250$) is more than the additional cost of manufacturing a course of Arthmaxplus relative to Arthmax ($\$620_{(h)} - \$500_{(c)} = \$120$). Also, Arthmaxplus has an *IMER* on the innovative units relative to Arthmax ($\$1,000_{(i)}$) that is less than the *IMER* of the clinically innovative units of Arthmax relative to Rathmab ($\$5,000_{(f)}$). Therefore there is manufacturing innovation relative to both Rathmab ($\$2818_{(k)} < \$5000_{(b)}$) and Arthmax ($\$2176_{(m)} < \$5000_{(f)}$). This innovation reduces the average cost of producing additional health effects. The *IPER* is the same for the innovative units of Arthmax and Arthmaxplus, Arthmaxplus appropriates Arthmax's economic rent and the average cost of manufacture of all of these health effects is reduced. Hence, the economic rent on all clinically innovative health effects relative to placebo is increased for Arthmaxplus compared to Arthmax ($\$35,000_{(l)} < \$56,273_{(m)}$). This means that with the same conventionally calculated *IPER* for Arthmaxplus and Arthmax, the economic rent for the new drug is higher due to the effect of the manufacturing innovation.

¹⁵³ The $IMER = IPER$ if there is perfect competition in the generic drug market and the drug is off-patent. If the drug is on patent, the *IPER* could still be equal to the *IMER*. This situation is a consequence of the choice of threshold *IPER* and the cost function for the drug, which can be assumed to be independent. However, provided that the Firm only produces and sells the drug if it makes a normal profit, then the *IMER* cannot be greater than the *IPER*.

Table 10 Per Course summary measures for three drugs: a hypothetical example

Per course	R	A	A+	Description
Clinical innovation per course (QALYs)				Each successive drug is clinically innovative compared to placebo and the previous best available drug and also contains the clinical innovation of the previous drug(s).
Compared to placebo	0.05 _(d)	0.1 _(d)	0.22	
Compared to Rathmab	n/a	0.05 _(e)	0.17	
Compared to Arthmax	n/a	n/a	0.12	
Price per course (\$)	250	4,000	13,000	The price per course is derived from the <i>IPER</i> . In this case the price of A and A+ is based on an <i>IPER</i> of \$75,000 per QALY.
Cost of manufacture per course (\$)	250 _(c)	500 _(c)	620 _(h)	The cost of manufacturing a course of the drug increases for each successive drug due to changes in the methods of manufacturing. It includes a normal profit.
Economic rent per course(\$)	0	3,500	12,380	The economic rent on each course sold is simply the revenue from sales less the cost of manufacturing course of the drug.
Legend: This table is discussed in the text in sections 2.2.1.2 and 2.2.1.5. The notes such as _(a) allow the text to be cross-referenced to this table.				

Table 11 Per QALY summary measures for three drugs: a hypothetical example

Per incremental QALY	R	A	A+	Description
<i>IPER</i>				The <i>IPER</i> for R is the same as the cost of manufacturing because the drug is off patent. The <i>IPER</i> for clinical innovation of both A and A+ is \$75,000. A+ is paid an <i>IPER</i> of \$75,000 for both its own innovative QALYs and those of A.
Compared to placebo	5,000	40,000	59,091	
Compared to Rathmab	n/a	75,000 _(a)	75,000	
Compared to Arthmax	n/a	n/a	75,000	
<i>IMER</i>				The <i>IMER</i> of R is the cost of manufacturing per QALY compared to placebo. Both A and A+ are clinically innovative, however, in this example, only A+ has innovation in manufacturing also; the <i>IMER</i> of A+ vs. A is only \$1,000 compared to the <i>IMER</i> of \$5,000 of the previous two drugs.
Compared to placebo	5,000 _(b)	5,000 _(f)	2,818 _(k)	
Compared to Rathmab	n/a	5,000 _(j)	2,176 _(n)	
Compared to Arthmax	n/a	n/a	1,000 _(i)	
<i>IπER</i>				The <i>IπER</i> of R is zero because the drug is off patent. Significantly, because A is on patent when it A+ is reimbursed, A is able to capture the economic rent on the clinical innovation of both A and A+.
Compared to placebo	-	35,000 _(l)	56,273 _(m)	
Compared to Rathmab	n/a	70,000 _(g)	72,824	
Compared to Arthmax	n/a	n/a	74,000	
Legend: This table is discussed in the text in sections 2.2.1.2 and 2.2.1.5. The notes such as _(a) allow the text to be cross-referenced to this table.				

2.2.2 Game structure

There are two payers (the Firm and the Institution). It is a dynamic (consecutive decisions) three period game of complete (public) and perfect (no uncertainty) information hence both players know the value of all parameters and variables, with certainty, at the start of the game. (We will relax these assumptions in the discussion).

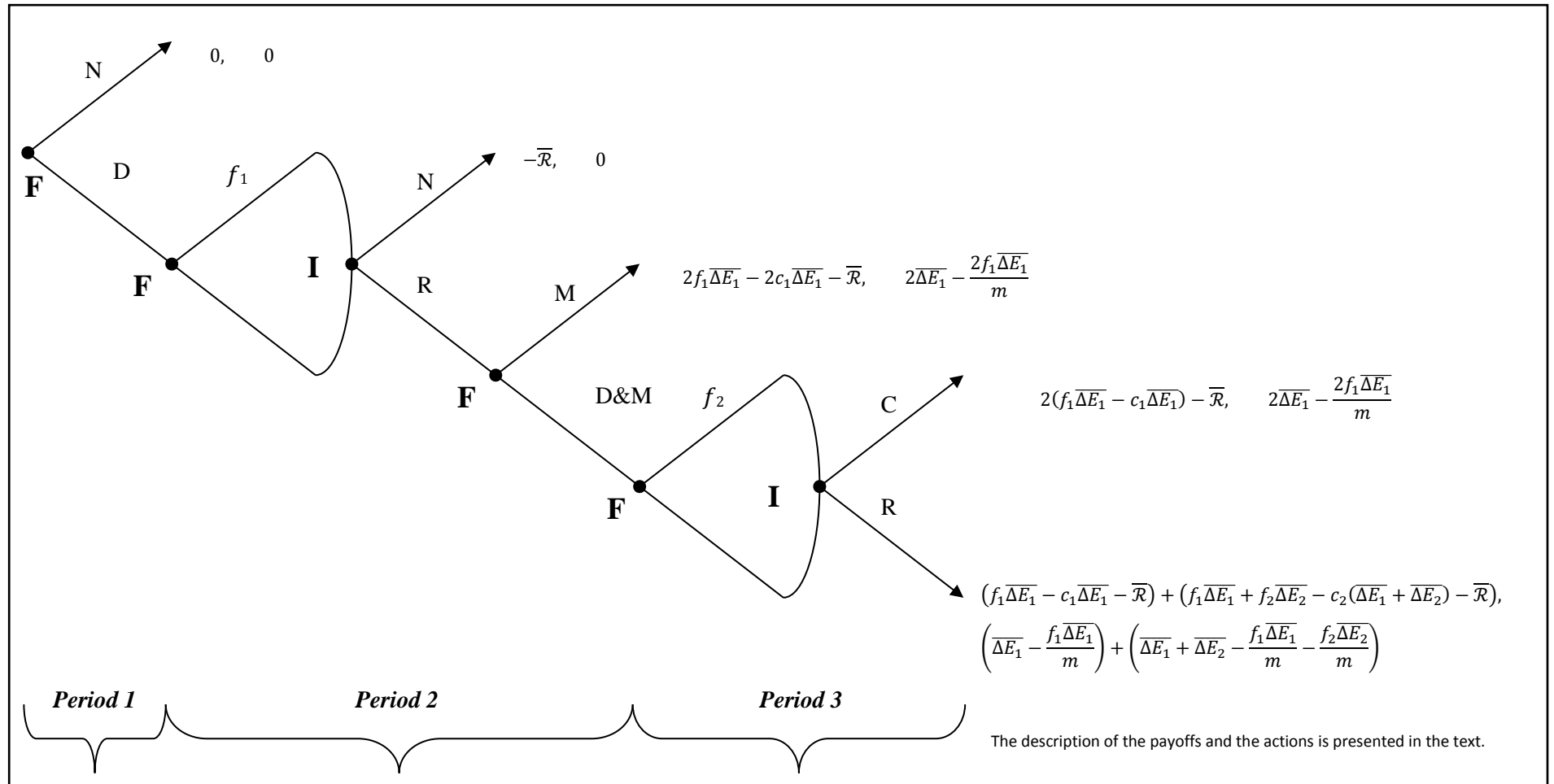


Figure 12 The pharmacotherapy needs a premium game

2.2.2.1 Strategies and payoffs

The Game starts with the Firm.

2.2.2.1.1 Firm

The Firm has five possible actions: Develop a new drug (D); Develop a new drug and manufacture the current drug (D&M); price the new or future drug f ; manufacture the new drug only (M); or do nothing (N).

At the start of Period 1, the Firm can choose to Develop or do Nothing. If it chooses to Develop, at the end of Period 1 it can then choose a price f_1 for the first new drug, Arthmax. If the Institution chooses to Reimburse the new drug at the offer price, at the start of Period 2 the Firm can then choose to either develop a second drug, Arthmaxplus, while continuing to manufacture and sell Arthmax (D&M) or manufacture only (M). If it develops Arthmaxplus (the future drug), it must choose a price f_2 for Arthmaxplus when it goes to the market at the end of Period 2.

The pay-off to the Firm from N is 0. If the Firm chooses to develop Arthmax but it is not reimbursed by the Institution, its payoff is a loss of $\bar{\mathcal{R}}$, the fixed cost of developing a new drug. The Firm's payoff if it manufactures and sells Arthmax for two periods and does not develop a second drug is the sum of the economic rent over Periods 2 to 3:

$$\pi_2 + \pi_3 = 2f_1\bar{\Delta E}_1 - 2c_1\bar{\Delta E}_1 - \bar{\mathcal{R}} \quad \text{Equation 23}$$

where the revenue $2f_1\bar{\Delta E}_1$ comprises the sales of health gains $\bar{\Delta E}_1$ at price f_1 over these two periods less the fixed cost of R&D $\bar{\mathcal{R}}$ and the variable cost of manufacturing $c_1\bar{\Delta E}_1$.

And finally, the economic rent in Periods 1 to 3 if Arthmaxplus is developed in Period 2 and is reimbursed by the Institution is:

$$\pi_2 + \pi_3 = (f_1\bar{\Delta E}_1 - c_1\bar{\Delta E}_1 - \bar{\mathcal{R}}) + (f_1\bar{\Delta E}_1 + f_2\bar{\Delta E}_2 - c_2(\bar{\Delta E}_1 + \bar{\Delta E}_2) - \bar{\mathcal{R}}) \quad \text{Equation 24}$$

where:

- 1) Arthmaxplus has gains of $\bar{\Delta E}_1 + \bar{\Delta E}_2$ compared to the original drug Rathmab, and $\bar{\Delta E}_2$ compared to Arthmax.
- 2) The health effects $\bar{\Delta E}_1$ in Arthmaxplus (which are appropriated from Arthmax) are sold at the *IPER* that was used for Arthmax (f_1) whereas the *IPER* of $\bar{\Delta E}_2$ (the health gain of Arthmaxplus compared to Arthmax) is f_2 . This situation is a consequence of the sequential reimbursement decisions that are always based on the *IPER* of the new drug vs. the existing drug. (See Table 10, Table 11 and Appendix 6). Therefore the revenue in Period 3 from the sales of Arthmaxplus is:

$$f_1\bar{\Delta E}_1 + f_2\bar{\Delta E}_2$$

- 3) Producing the additional health effects compared to Rathmab ($\bar{\Delta E}_1 + \bar{\Delta E}_2$) has a cost of c_2 per unit health effect. Therefore c_2 is the *IMER* of Arthmaxplus compared to Rathmab.
- 4) Therefore the economic rent on the sales of Arthmaxplus is the revenue per unit (the *IPER*) less the variable cost of manufacture of each additional unit (the *IMER*) multiplied by the number of units of effect less the fixed cost of R&D ($\bar{\mathcal{R}}$).

2.2.2.2 Institution

The Institution has three possible actions: Do Nothing (N) in relation to the offer price for Arthmax or Arthmaxplus, Reimburse (R) the new drug being offered by the Firm at the offer price or Continue (C), continue to reimburse Arthmax in Period 3 rather than Reimburse Arthmaxplus.

The Institution's payoff to Do Nothing when offered Arthmax at the end of Period 1 is 0.

The Institution's payoff to R only (Reimbursing Arthmax at the offer price and continuing to purchase it over the next two periods with no offer of a second drug) is the net increase in the population's health:

$$\Delta E = 2\overline{\Delta E_1} - \frac{2f_1\overline{\Delta E_1}}{m}$$

Where $2\overline{\Delta E_1}$ is the health effects of Arthmax compared to Rathmab over two periods, for the target patients and:

$$\frac{2f_1\overline{\Delta E_1}}{m}$$

is the health gains displaced to finance the additional costs of financing Arthmax over each of the two periods ($2f_1\overline{\Delta E_1}$) by displacing services with an aICER of m .

The Institution's payoff to reimbursing Arthmax in Year 2, then Arthmaxplus in Period 3 is:

$$\Delta E = \left(\overline{\Delta E_1} - \frac{f_1\overline{\Delta E_1}}{m} \right) + \left(\overline{\Delta E_1} + \overline{\Delta E_2} - \frac{f_1\overline{\Delta E_1}}{m} - \frac{f_2\overline{\Delta E_2}}{m} \right)$$

where:

$$\overline{\Delta E_1} - \frac{f_1\overline{\Delta E_1}}{m}$$

is the net health effect for the population from reimbursing Arthmax in Period 2, compared to continuing to reimburse Rathmab and:

$$\overline{\Delta E_1} + \overline{\Delta E_2} - \frac{f_1\overline{\Delta E_1}}{m} - \frac{f_2\overline{\Delta E_2}}{m}$$

is the net health effect for the population from financing Arthmaxplus in Period 3 compared to the health that would have occurred if the Institution continued to finance Rathmab.

2.2.2.3 Parameters, variables and conditions

- 1) $\overline{\mathcal{R}}$ is the Firm's fixed cost for developing and trialling a new drug. It is the same for both drugs.
- 2) $\overline{\Delta E_1}$ is the additional health effect of Arthmax compared to Rathmab.
- 3) $\overline{\Delta E_2}$ is the additional health effect of Arthmaxplus compared to Arthmax.
- 4) m is the aICER of the services of the least cost effective existing program in contraction, which is optimally displaced in order to finance the additional cost of the new drug Arthmaxplus in Years 2 and 3.

- 5) c_1 is the *IMER* (compared to Rathmab) of producing Arthmax.
- 6) c_2 is the *IMER* (compared to Rathmab) of producing Arthmaxplus.
- 7) f_1 is the *IPER* of Arthmax compared to Rathmab.
- 8) f_2 is the *IPER* of Arthmaxplus compared to Arthmax.

The parameters and variables that describe the payoffs of the actions available to the Institution can be specified in terms of the total cost and unit cost of achieving them.

9) $\frac{f_j \overline{\Delta E_j}}{m}$

is the health effects displaced if the additional cost of the additional health gains ($f_j \overline{\Delta E_j}$) are financed by displacing services of an aICER of m , where $j=1$ or 2 and refers to the *IPERs* of the two drugs.

2.2.2.4 Conditions

- 1) There is no uncertainty in the value of any parameters and variables at any stage in the Game for either player.
- 2) The discount rate is zero.
- 3) The Firm is efficient in its R&D process; there is no way of trialling and developing a new drug that would reduce the fixed costs of R&D.
- 4) $\overline{\Delta E_1}, \overline{\Delta E_2} > 0$. The drugs brought to the Institution are clinically innovative. This is, they have a clinical advantage compared to best available existing therapy for the target group of patients. The clinical innovation is constant for the identified group of target patients, and is known with certainty.
- 5) $d = m > 0$. The aICER of the services displaced to finance the additional financial costs of the new drug is greater than zero. It is also the least cost effective of all existing options to contract programs (efficient displacement), therefore $\beta_c = m$
- 6) $\Delta E^D > 0$. It follows from $m > 0$ that displacing services to finance the additional costs of the new drug will lead to a loss in health effects for patients who would otherwise have received these services.
- 7) ΔE^D is continuous. The funding to the displaced services can be reduced or increased by the smallest increment. If the funding is changed, the effect will change in the same direction.
- 8) $f_1, f_2 > 0$ The price per additional effect of the new drug compared to the best available therapy is greater than 0.
- 9) $c_1 > c_2 > 0$ The *IMER* (compared to Rathmab) of Arthmax is c_1 . ($\$5,000_{(j)}$) The *IMER* (compared to Rathmab) of Arthmaxplus is c_2 . ($\$2,176_{(n)}$) The total cost of producing a vial of Arthmaxplus is higher than for Arthmax which is in turn higher than a vial of Rathmab. ($\$250_{(c)} < \$500_{(c)} < \$650_{(h)}$) The technique of producing Arthmax was fundamentally different to that of producing a vial of Rathmab, which accounts for the significantly higher cost of production per vial.

However, the slightly more complex technique required to produce the more clinically effective version of the drug Arthmax only increases the overall cost slightly, hence the *IMER* of Arthmax (for the incremental health compared to Rathmab) is higher than that for Arthmaxplus (for the incremental health gains compared to Rathmab). Arthmaxplus contains innovation in manufacturing as well as clinical innovation.

2.3 Theory proper

We assume that the Firm will select its strategy by maximising its economic rent and the Institution will select its strategies so as to maximise the npvPH from the current and future budgets.

2.4 Solution

We use backward induction to solve the game.

2.4.1 Stage 6

In Stage 6, the Institution can choose to reimburse Arthmaxplus at the offer price or continue to purchase Arthmax at the prevailing price. Its decision rule is to select the action Reimburse if the payoff is greater or equal to the payoff to continuing purchasing Arthmax. These payoffs are presented in Figure 12.

$$\left(\overline{\Delta E_1} - \frac{f_1 \overline{\Delta E_1}}{m} \right) + \left(\overline{\Delta E_1} + \overline{\Delta E_2} - \frac{f_2 \overline{\Delta E_1}}{m} - \frac{f_1 \overline{\Delta E_2}}{m} \right) \geq 2 \overline{\Delta E_1} - \frac{2f_1 \overline{\Delta E_1}}{m}$$

$$\Rightarrow \overline{\Delta E_2} - \frac{f_2 \overline{\Delta E_2}}{m} \geq 0$$

$$\Rightarrow (m - f_2) \geq 0$$

$$\Rightarrow m \geq f_2$$

This decision rule can be expressed in words as: if the *IPER* of the future drug Arthmaxplus (calculated relative to Arthmax) is less than or equal to the aICER of displaced services, the Institution will reimburse the future drug.

2.4.2 Stage 5

In Stage 5, the Firm chooses to price the future drug at $f_2 = m$ because if it reduces the price below this *IPER* it will not sell any more of the drug and if it prices higher it will not sell any of the drug. This characteristic is a consequence of: i) the decision rule that the Reimburser is required to follow at indifference between Reimbursement and the best alternative strategy; and ii) the discrete nature of the policy to reimburse a new drug in a universal health care system.

Therefore:

$$f_2 = m$$

Equation 25

2.4.3 Stage 4

In Stage 4, the Firm makes the decision to either: i) manufacture and sell Arthmax and also develop the second drug, Arthmaxplus; or ii) only manufacture and sell Arthmax. The Firm will choose to invest a second fixed budget into R&D if the payoff from investing in the second drug's development is greater than the payoff from manufacture of Arthmax only. These payoffs are presented in Figure 12.

$$(f_1 \overline{\Delta E_1} - c_1 \overline{\Delta E_1} - \overline{\mathcal{R}}) + (f_1 \overline{\Delta E_1} + f_2 \overline{\Delta E_2} - c_2 (\overline{\Delta E_1} + \overline{\Delta E_2}) - \overline{\mathcal{R}}) \geq 2f_1 \overline{\Delta E_1} - 2c_1 \overline{\Delta E_1} - \overline{\mathcal{R}}$$

$$\Rightarrow f_2 \overline{\Delta E_2} - c_2 (\overline{\Delta E_1} + \Delta E_2) + c_1 \overline{\Delta E_1} - \overline{\mathcal{R}} \geq 0$$

$$\Rightarrow \overline{\Delta E_2} (f_2 - c_2) + \overline{\Delta E_1} (c_1 - c_2) - \overline{\mathcal{R}} \geq 0$$

Equation 26

The economic profit from the sale of the additional health effects of Arthmaxplus compared to Arthmax:

$$\overline{\Delta E_2} (f_2 - c_2)$$

and the savings that come from selling the health gains of Arthmax relative to Rathmax at the same price but at a lower *aIMER*:

$$\overline{\Delta E_1} (c_1 - c_2)$$

must outweigh the additional costs of R&D. However, from Equation 25 we know that:

$$f_2 = m$$

So we can substitute this result into Equation 27. Therefore if the following condition applies:

$$\overline{\Delta E_2} (m - c_2) + \overline{\Delta E_1} (c_1 - c_2) \geq \overline{\mathcal{R}}$$

Equation 27

then the Firm will choose to develop the second drug. (We assume that the Firm will invest in R&D for Arthmaxplus if it is indifferent between this action and the action of manufacture only.)

If the following condition applies,

$$\overline{\Delta E_2} (m - c_2) + \overline{\Delta E_1} (c_1 - c_2) < \overline{\mathcal{R}}$$

Equation 28

then the Firm will choose not to develop Arthmaxplus because the additional costs of R&D ($\overline{\mathcal{R}}$) are greater than the two sources of gains to the Firm from development:

- 1) the additional economic rent ($m - c_2$) from the additional units of health effects that can be sold ($\overline{\Delta E_2}$); and
- 2) the reduction in the cost per effect of producing the units $\overline{\Delta E_1}$ which occurs because $c_1 > c_2$

And finally, the following exogenous parameters drive this decision: $\overline{\Delta E_1}$, $\overline{\Delta E_2}$, m , c_1 , c_2 and \mathcal{R} .

Stage 4 highlights that the opportunity for the Firm to generate innovation in the manufacturing process is a driver of investment in R&D, in addition to the opportunity to generate clinical innovation.

2.4.4 Stage 3

The Institution chooses to Reimburse the new drug Arthmax or do Nothing in Stage 3. The payoff to this decision depends upon the Firm's decision in Stage 4.¹⁵⁴

¹⁵⁴ The reason that the Institution can anticipate the outcome of Stage 4 when the Game is at Stage 3 is because all information is in the public domain, the motivations for players are in the public domain and each player makes decisions that take into account the other Player's responses. This is effectively the rationale for solving this game using backward induction.

2.4.4.1 *Arthmaxplus is not produced in Stage 4*

From Equation 28, if:

$$\overline{\Delta E_2}(m - c_2) + \overline{\Delta E_1}(c_1 - c_2) < \overline{\mathcal{R}}$$

then the Firm will not produce the second drug, Arthmaxplus, hence the payoff to the Institution's decision to reimburse Arthmax if the second drug is not produced is:

$$\Delta E = 2\overline{\Delta E_1} - \frac{2f_1\overline{\Delta E_1}}{m}$$

Therefore the decision rule is that the Institution will Reimburse if:

$$2\overline{\Delta E_1} - \frac{2f_1\overline{\Delta E_1}}{m} \geq 0$$

$$\Rightarrow m - f_1 \geq 0$$

$$\Rightarrow m \geq f_1$$

Hence, if the Institution anticipates that the Firm will choose not to develop the second drug Arthmaxplus, then the Institution will choose to reimburse Arthmax if the *IPER* of Arthmax compared to Rathmab is less than or equal to the aICER of displaced services.

2.4.4.2 *Arthmaxplus is produced in Stage 4*

However, from Equation 28 if:

$$\overline{\Delta E_2}(m - c_2) + \overline{\Delta E_1}(c_1 - c_2) \geq \overline{\mathcal{R}}$$

then the Firm will produce the second drug and the Institution's payoff to Reimbursing Arthmax is:

$$\Delta E = \left(\overline{\Delta E_1} - \frac{f_1\overline{\Delta E_1}}{m} \right) + \left(\overline{\Delta E_1} + \overline{\Delta E_2} - \frac{f_1\overline{\Delta E_1}}{m} - \frac{f_2\overline{\Delta E_2}}{m} \right)$$

Therefore the decision rule is to reimburse the drug at the offer price if:

$$\left(\overline{\Delta E_1} - \frac{f_1\overline{\Delta E_1}}{m} \right) + \left(\overline{\Delta E_1} + \overline{\Delta E_2} - \frac{f_1\overline{\Delta E_1}}{m} - \frac{f_2\overline{\Delta E_2}}{m} \right) \geq 0$$

$$\Rightarrow 2\overline{\Delta E_1} + \overline{\Delta E_2} - \frac{2f_1\overline{\Delta E_1}}{m} - \frac{f_2\overline{\Delta E_2}}{m} \geq 0$$

but from Stage 5 we have the result that $m = f_2$

$$\therefore 2\overline{\Delta E_1} + \overline{\Delta E_2} - \frac{2f_1\overline{\Delta E_1}}{m} - \overline{\Delta E_2} \geq 0$$

$$\Rightarrow 2\overline{\Delta E_1} - \frac{2f_1\overline{\Delta E_1}}{m} \geq 0$$

$$\Rightarrow 2d - 2f_1 \geq 0$$

$$\Rightarrow m \geq f_1$$

Therefore, if the Firm will not produce Arthmaxplus, then the Institution anticipates this action (best response and complete and perfect information) and provided that $m \geq f_1$ it will reimburse Arthmax.

2.4.4.3 Result of Stage 3

Regardless of whether the Firm will choose to develop the second drug in Stage 4, the Institution will only reimburse Arthmax if the *IPER* is less than or equal to the aICER of the displaced services.

2.4.5 Stage 2

In Stage 2 the Firm will choose to price the new drug and it will choose price so as to maximise economic rent. This will occur when $f_1 = m$. Above this price there will be no sales and at a lower price there will be no increase in sales.

2.4.6 Stage 1

In Stage 1, the Firm chooses to invest in the R&D for Arthmax or do nothing. If the Firm does nothing, the game ends.

The payoff to R&D for Arthmax depends upon whether or not the exogenous parameters: $\overline{\Delta E_1}$, $\overline{\Delta E_2}$, m , c_1 , c_2 and $\overline{\mathcal{R}}$ are such that the Firm has an incentive to invest in the development of Arthmaxplus, the second new drug.

2.4.6.1 Firm has incentive to develop Arthmaxplus in Stage 4

If the Firm has an incentive to develop the second drug rather than manufacture and develop only the first drug, then the Firm's payoff to Development in Stage 1 is:

$$\pi = m\overline{\Delta E_1} - c_1\overline{\Delta E_1} - \overline{\mathcal{R}}$$

Therefore, the Firm's decision rule is to invest in R&D if the payoff to Develop is greater than the payoff to do nothing:

$$(f_1\overline{\Delta E_1} - c_1\overline{\Delta E_1} - \overline{\mathcal{R}}) + (f_1\overline{\Delta E_1} + f_2\overline{\Delta E_2} - c_2(\overline{\Delta E_1} + \overline{\Delta E_2}) - \overline{\mathcal{R}}) \geq 0$$

where

$$f_2 = f_1 = m$$

$$\therefore (m\overline{\Delta E_1} - c_1\overline{\Delta E_1} - \overline{\mathcal{R}}) + (m\overline{\Delta E_1} + d\overline{\Delta E_2} - c_2(\overline{\Delta E_1} + \overline{\Delta E_2}) - \overline{\mathcal{R}}) \geq 0$$

$$\Rightarrow 2m\overline{\Delta E_1} + m\overline{\Delta E_2} \geq c_2(\overline{\Delta E_1} + \overline{\Delta E_2}) + c_1\overline{\Delta E_1} + 2\overline{\mathcal{R}}$$

$$m(2\overline{\Delta E_1} + \overline{\Delta E_2}) \geq c_2(\overline{\Delta E_1} + \overline{\Delta E_2}) + c_1\overline{\Delta E_1} + 2\overline{\mathcal{R}}$$

Equation 29

That is, the Firm will invest in the Development of Arthmax in Period 1 if the revenue from the clinical innovation over the two periods:

$$m(2\overline{\Delta E_1} + \overline{\Delta E_2})$$

is greater than the cost of developing and manufacturing the two drugs:

$$c_2(\overline{\Delta E_1} + \overline{\Delta E_2}) + c_1\overline{\Delta E_1} + 2\overline{\mathcal{R}}$$

Otherwise the Firm will choose to do Nothing.

2.4.6.2 Firm has no incentive to invest in the second drug

If the Firm will not invest in the second drug, then the payoff to the Firm from developing the first drug rather than do nothing is:

$$2f_1\overline{\Delta E_1} - 2c_1\overline{\Delta E_1} - \overline{\mathcal{R}} > 0$$

Hence, if the following condition is met

$$2\overline{\Delta E_1}(m - c_1) - \overline{\mathcal{R}} > 0$$

Equation 30

then the Firm will develop the first drug, Arthmax, but not Arthmaxplus. That is, the Firm will Develop and Manufacture Arthmax if the additional economic rent on the total units sold at an *IPER* of f_1 and produced at an *IMER* of c_1 is greater than the cost of R&D. Otherwise, the Firm will do nothing.

2.5 Results

2.5.1 At equilibrium

There are three possible equilibrium outcomes: i) no drugs are produced; ii) Arthmax only is produced; and iii) Arthmax and Arthmaxplus are produced.

The equilibrium price under scenarios ii) and iii) is m , the threshold *IPER*. There is no increase in the health of the population relative to scenario i) under either ii) or iii). The Firm's profit will depend upon the scenario. If there had been existing inefficiency in the health care budget, then there would have been a gain in health effects for the population, under scenarios ii) and iii). However, this would have been as a consequence of the budget being inefficient initially and the allocative inefficiency reduced. The same health gain for the population could have been achieved by a process such as PBMA.

The gain in social welfare is given by the combined payoffs of the Firm and the Institution. The entire economic value of the surplus is appropriated by the Firm as a consequence of the profit maximising choice of offer price by the Firm and the rule that requires the Institution to Reimburse the new drug if $f \leq \beta_c$.

3 Discussion

The equilibrium *IPER* of the two drugs (Arthmax and Arthmaxplus) is the same; it is the Institution's reimbursement threshold price, which for this Institution is β_c with a quantitative value of m . It is the same as the equilibrium price in Games 1 and 2.

3.1 Is a premium a necessary or sufficient condition for investment in a future drug?

- A premium is neither a necessary nor a sufficient condition for the Firm to invest in a future drug.

The **premium** on the current drug is **not a sufficient condition** because the decision for the Firm to invest in R&D for the both drugs is a function of a number of parameters, only one of which is the *IPER* of the future drug and even with a premium there may be no incentive to invest, for example if $c_2 \gg c_1$. The other parameters that this decision is a function of, and that are specified in the Game are:

- 1) \bar{R} , the fixed cost of R&D;
- 2) c_2 and c_1 the costs of manufacturing the drugs expressed as *IMERs*, relative to the *IPER*;
- 3) The difference in the *IMERs* of the two drugs (innovation in manufacturing, $c_2 - c_1 > 0$); and
- 4) The clinical innovation of the drugs relative to the best available therapy ΔE_1 and ΔE_2

Note: We have assumed that the information about the future costs of manufacture and all other parameters are known with certainty and are public information. This is unrealistic and the implications of relaxing this assumption are set out in the discussion.

The **premium is not a necessary condition** because the Firm has an incentive to invest in R&D for the second drug even without the premium in Period 2 for Arthmax, provided that the above parameters meet the requirements set out in Stage 4 and Stage 1. Other factors that influence the decision to invest in R&D are not included in the Game: competition from me-too drugs and development of alternative non-pharmaco-therapies are examples.

The Institution is indifferent between the three outcomes of the game (no drugs, one drug or two drugs), because there is no increase in the population's health as a consequence of any outcome. Had allocative inefficiency been an initial condition, the health of the population would have increased, but there would be no net economic benefit from reimbursement; the health benefit was a consequence of improving overall efficiency and this could have been achieved by reallocation.

In conclusion, there is no price above β_c whereby the npvPH is increased hence there is no incentive for the Institution to pay a premium for Arthmax in Period 2. Any premium will represent a loss to the Institution because the Firm prices the future drug at β_c and hence there is no mechanism whereby the Institution can recoup the health gains foregone in Period 2.

However this result does not necessarily mean that there is no economic justification for pricing above β_c in Period 2. Some economists could argue that maximising social welfare (economic rent plus consumer welfare) is society's objective whereas maximising consumer welfare (increase in population health) is the Institution's objective. The two are not necessarily consistent.

3.2 Is there a situation whereby a premium for Arthmax in Period 2 will increase social welfare?

Is it possible that the Institution's decision to not price above β_c in Period 2, in order to maximise the npvPH from this and future budgets, is at the cost of a social welfare? The possibility of this outcome can be inferred from Santerre and Vernon (2006). These authors found that every dollar invested by consumers in pharmaceutical R&D via higher prices for drugs over the period 1960 to 2000 led to an additional \$28 in social welfare (consumer welfare plus economic rent).¹⁵⁵ Assume that

¹⁵⁵ The reasons why this return is likely to be a significant overestimate of the ratio intended by the authors are discussed in Appendix 1. The reasons why the ratio intended by the authors could result in an overestimate of the ratio of interest to a

Santerre and Vernon's result is an accurate estimate of the ratio intended by the authors. The result cannot tell us whether consumers have recouped their initial investment or whether the entire social welfare was appropriated by the firm and the consumers have a net loss in consumer welfare. But Santerre and Vernon do not comment on this issue. This lack of comment could signal a difference in the US approach to health economics compared to the rest of the OECD. Maybe in the US, economists would argue that the allocation of this gain in social welfare across producers and consumers is irrelevant; what matters is that the social welfare is maximised.

In terms of the Game presented in this chapter, this position would mean that an outcome that results in maximising the net present value of social welfare (npvSW) is preferable to the outcome that maximises the net present value of population's health (npvPH), but at a lower npvSW.

The possibility that the equilibrium outcome of the Game presented in this chapter could be maximising npvPH at the cost of maximising npvSW cannot be excluded. Hence the following question:

Is it possible that in seeking to maximise npvPH, the Reimbursing makes a decision in Period 2 that maximises npvPH over the three periods but does not maximise npvSW over these periods?

First we establish the necessary and/or sufficient conditions under which this situation would occur. Then we establish the changes in the Game that would have to occur in order for the production of the second drug to occur and the npvSW to be maximised.

3.2.1 Conditions

Two equations are used to define the conditions that correspond to the problem of nonproduction of Arthmaxplus at an $IPER=m$ for Arthmax in Period 2 but production of Arthmaxplus if there were a premium for Arthmax over β_c in Period 2.

- 1) The Firm cannot finance the production of the second drug from the economic rent available from the first drug in Period 2.

$$\overline{\Delta E_1}(m - c_1) < \overline{\mathcal{R}} \quad \text{Equation 31}$$

Where $m - c_1$ is the economic rent received on each incremental health effect sold in Period 2.

- 2) There is a price above β_c , which is $\beta_c + \gamma$, at which the Firm can finance the R&D.

$$\overline{\Delta E_1}(m + \gamma - c_1) = \overline{\mathcal{R}}$$

which can be rearranged as:

$$\gamma = \frac{\overline{\mathcal{R}}}{\overline{\Delta E_1}} + c_1 - m \quad \text{Equation 32}$$

Now we determine the conditions under which the following scenario occurs:

The social welfare is maximised if both drugs are produced, and the above two conditions (Equation 31 and Equation 32) apply.

country with a fixed or constrained budget are discussed in Chapters 1 and 3 and also Appendix 2. In short, it does not consider the allocation of surplus between the firm and consumers.

The approach we take is to apply the strong and weak compensation tests.¹⁵⁶ The formal definitions of the terms strong and weak compensation tests are set out in Mas-Colell et al. (1995 pp. 829-831) and discussed in Appendix 9.

3.2.2 Applying the hypothetical compensation test

Our starting point is the observation that there is a loss to the Institution if they choose to reimburse the new drug at an *IPER* above m in Period 1. This loss is given in terms of units of health and is:

$$loss = \frac{\gamma \overline{\Delta E_1}}{m} \quad \text{Equation 33}$$

This is the health gains forgone due to the additional expenditure (the premium) on the sale of each unit of clinical innovation from Arthmax.

The hypothetical compensation test is passed if under the scenario defined by 1) and 2) above, the gain in producer's surplus as a consequence of producing two rather than one drug is greater than the amount that would be required to be paid by the Firm to the Institution to compensate for the loss in Period 2. If this test can be passed for all values of relevant parameters then the strong compensation test is passed. If the hypothetical compensation is conditional on values of the relevant parameters, then the weak compensation test only applies.

From Equation 33 we see that the amount that the Firm would need to pay the Institution to compensate them for the loss is:

$$\gamma \overline{\Delta E_1}$$

The additional producer's surplus in Period 3 from two rather than one drugs is given by the difference in the Firm's payoff in Period 3 under the two scenarios. The difference in the economic rent in Period 3 can be derived from Equation 23 and Equation 24

$$\begin{aligned} \Delta \pi_3 &= (f_1 \overline{\Delta E_1} + f_2 \overline{\Delta E_2} - c_2 (\overline{\Delta E_1} + \overline{\Delta E_2})) - (f_1 \overline{\Delta E_1} - c_1 \overline{\Delta E_1}) \\ &= f_2 \overline{\Delta E_2} - c_2 \overline{\Delta E_1} - c_2 \overline{\Delta E_2} + c_1 \overline{\Delta E_1} \\ &= \overline{\Delta E_2} (f_2 - c_2) + \overline{\Delta E_1} (c_1 - c_2) \end{aligned}$$

This is the additional economic rent ($f_2 - c_2$) on the sales of the clinically innovative units of Arthmaxplus plus the additional economic rent due to the reduced cost of producing ($c_1 - c_2$) the clinically innovative units first developed with Arthmax $\overline{\Delta E_1}$.

Now we need to find the conditions under which:

$$\overline{\Delta E_2} (f_2 - c_2) + \overline{\Delta E_1} (c_1 - c_2) > \gamma \overline{\Delta E_1} \quad \text{Equation 34}$$

Now $f_2 = m$, that is, the *IPER* in Period 3 for the future drug Arthmaxplus is β_c which has a quantitative value of m . That is, we are assuming the compensation is separate to any payment related to the purchase of the new drug.

¹⁵⁶ In simple terms the strong compensation test means that the policy of a premium in the situation specified by Equation 31 and Equation 32 will always result in a gain in npvSW – the gain in economic rent in Period 3 to the Firm is greater than the loss to consumers in Period 2. In this case, policy of a premium always passes the hypothetical compensation test. If only the weak compensation test is met, then the hypothetical compensation test can be passed by the policy conditionally only. (For a more extensive discussion see Appendix 9)

And furthermore,

$$\overline{\Delta E_2} = \kappa \overline{\Delta E_1} > 0$$

where $\overline{\Delta E_1}, \kappa > 0$.

That is, the clinical innovation of Arthmaxplus relative to Arthmax can be expressed as a linear function of clinical innovation of Arthmax relative to Rathmab. $\overline{\Delta E_2}$ can be less than or greater than $\overline{\Delta E_1}$ but must be greater than zero.

Therefore we substitute this relationship into Equation 34:

$$\kappa \overline{\Delta E_1} (m - c_2) + \overline{\Delta E_1} (c_1 - c_2) > \gamma \overline{\Delta E_1}$$

Now $\overline{\Delta E_1} > 0$, therefore we can divide through to obtain the conditions under which the hypothetical compensation test can be met:

$$\kappa(m - c_2) + (c_1 - c_2) > \gamma$$

Equation 35

Where the first term is the economic rent on clinically innovative units and the second term is the economic rent due to manufacturing innovation. This condition says that in order to compensate the Institution for their loss in Period 2, the Firm requires sufficient additional economic rent from Period 3, where this rent is sourced from economic rent on clinically innovative units of Arthmaxplus and manufacturing innovation on clinically innovative units of Arthmax.

We can derive a second alternative expression for this condition. From Equation 32:

$$\gamma = \frac{\overline{\mathcal{R}}}{\overline{\Delta E_1}} + c_1 - m$$

Which we can substitute into Equation 35:

$$\kappa(m - c_2) + (c_1 - c_2) > \frac{\overline{\mathcal{R}}}{\overline{\Delta E_1}} + c_1 - m$$

$$\Rightarrow \kappa(m - c_2) - c_2 + m > \frac{\overline{\mathcal{R}}}{\overline{\Delta E_1}}$$

$$\Rightarrow (\kappa + 1)(m - c_2) > \frac{\overline{\mathcal{R}}}{\overline{\Delta E_1}}$$

Equation 36

The second (alternative) expression of the condition for the compensation test is saying that the additional economic rent on every additional innovative health effect of Arthmaxplus compared to Rathmab (the existing drug), must be greater than the cost of R&D per incremental health effect of Arthmax compared to Rathmab.

3.2.3 Results of the hypothetical compensation test

The first result is that the hypothetical compensation test can be passed conditionally, but not unconditionally. The strong (unconditional) compensation test cannot be passed because there are values of κ , c_1 , c_2 , $\overline{\Delta E_1}$, $\overline{\mathcal{R}}$, and m such that the additional premium, even though it will result in an

additional drug, will result in a net reduction in social welfare. Similarly, the weak compensation test can be passed because these parameters can take values that result in a net social welfare gain as a consequence of the premium compared to the situation of no premium. What this means is that if the conditions in Equation 31 and Equation 32 are met, then using a premium will result in Arthmaxplus being produced but this will only result in an increase in npvSW under certain conditions as outlined in Equation 36.

The second result is that regardless of whether the compensation test is passed, the Firm will be better off if a premium is paid, for two reasons. First it maintains a share of the additional premium paid in Period 2 as economic rent. This is because less than 30% is allocated to NME R&D, under current conditions (Reinhardt 2007). This amount could change if those conditions were changed. Second, it is in receipt of any additional economic rent from the future drug, which it would not have been in receipt of otherwise. And if there is no actual compensation, it will maintain this rent.

3.2.4 Necessary and sufficient conditions for the premium policy to pass the compensation test

Now we can determine the necessary and sufficient conditions for there to be a gain in the npvSW and hence to pass the weak compensation test. Of particular interest in the PEND is the role of clinical innovation of the future drug in these conditions. Is clinical innovation either a necessary or sufficient condition or is it neither?

First, Equation 35 and its alternative expression, Equation 36, set out the necessary conditions for the policy of paying a premium when there is no incentive for the Firm to invest in R&D in Period 2, because the funds are not available from internal funds (economic rent) in Period 2.

Second, from Equation 35 and Equation 36 we can see that even if there is no clinical innovation in the second drug, ($\kappa=0$), there is still an opportunity for there to be a gain in social welfare that could pass the hypothetical compensation test. That is, there exist values of the parameters c_1 , c_2 , ΔE_1 , \mathcal{R} , and m such that the Institution can be compensated even if there is no clinical innovation. One example is significant manufacturing innovation, characterised by $c_1 - c_2 > 0$. Therefore, the existence of clinical innovation for Arthmaxplus is not a necessary condition for there to be a net gain in Social Welfare as a consequence of the premium and second drug.

Third, also from Equation 35 and Equation 36 we can see even if there is clinical innovation ($\theta > 0$), there are values of c_1 , c_2 , ΔE_1 , \mathcal{R} , and m such that there is a net loss in social welfare by producing the second drug. For example, in Equation 36, even if $\kappa \gg 0$, if the cost of manufacturing these incremental gains is more than the cost of purchasing them within existing technologies, there is a net social welfare loss. Even if $m > c_2$, if the cost of R&D (\mathcal{R}) are too high, then the situation fails the hypothetical compensation test. Therefore, the existence of clinical innovation in Arthmaxplus is not a sufficient condition for the post premium world to pass either the strong or weak compensation test.

In conclusion, even if there were a premium that can be paid above β_c that results in innovation that would otherwise not occur, then this result, an additional future drug, is neither necessary nor sufficient for there to be a net increase in social welfare; the strong compensation test is not passed by the policy of a premium over β_c . Furthermore, clinical innovation of the future drug (Arthmaxplus) relative to the new drug (Arthmax) is neither a necessary nor sufficient condition for this to occur, regardless of the extent of this innovation. Manufacturing innovation and more efficient R&D are also drivers of the net social welfare benefit. Furthermore, the analysis above assumes that all internal funds generated by the premium are allocated to R&D for the future drug. If we were to take into account the evidence that only a proportion of internal funds are invested in NME R&D, possibly less than 30% (Reinhardt 2007), then this would make it less likely that there is sufficient future rent to

compensate the Institution, whose foregone benefit, per additional future drug, will be higher as a result.

But the analysis did identify situations where the payment of this premium does result in a net gain in social welfare; cases where the conditions in Equation 36 are met and the weak compensation test is passed. It is possible that pursuing a strategy to maximise the npvPH can be at the cost of npvSW? What should the Institution do in this case?

3.2.5 What incentives are required for the Institution to agree to price above the equilibrium price in Period 1?

As the Game is specified currently, there is no incentive for the Institution to price above $\beta_c = m$ in Period 2. This is because even if this results in a net social welfare gain (the conditions in Equation 35 are met), if no compensation occurs, there is a net reduction in the population's health. There is no incentive for the Institution to pay a premium.

At this point there are two options for taking the analysis forward: i) to adopt the premium policy, conditionally and accept the final division of social surplus across the consumers and the producers (no actual compensation) or ii) to generate a situation in which there is actual compensation.

Under the first option we could argue that this result (that if the premium is not paid the npvSW is reduced) is proof that there are conditions under which there is a deadweight social loss to price control. (See Appendix 7). Therefore, the Institution should accept that maximising social welfare is the relevant test and accept an outcome of lower npvPH but higher npvSW (economic rent plus health). However, given that the scenario above passed only the weak not the strong compensation test, it would be necessary for the Firm to demonstrate that the conditions in Equation 35 are met for the particular future drug. If these conditions are not met then the premium will result in an additional drug and increased economic rent but less npvPH and less npvSW. Whether or not the Firm is able to demonstrate that these conditions are met is unclear, given the uncertainty associated with future drugs characteristics. What is even less likely is that consumers and policy makers will accept this result of reduced npvPH and higher npvSW, even if this outcome is apparently acceptable to US pharmaceutical economists such as Santerre and Vernon.

Significantly, even if the Firm is able to demonstrate that these conditions are met, then the outcome of worse health and more social welfare is particularly difficult to defend. The political reason is that even though some economists might argue it is an acceptable outcome, the entire political economy of new drugs is premised on the position that higher prices are a win-win situation – more for the firm and more for the population's health. The economic reason is: when there is an opportunity for any surplus to be shared between the producer and consumers via a lower price for the future drug, then what is stopping the compensation from actually occurring and making all parties better off. This is particularly the case when it is the Institution not the Firm that has taken on the costs (and risks) of financing R&D. Hence the first option, to adopt the policy of a premium conditionally and accept the final allocation of surplus without actual compensation, is unlikely to be acceptable.

The second option is that, if the conditions in Equation 35 are met, we could generate an incentive for the Institution to pay this premium despite the short term reduction in health. This incentive is achieved by the Firm offering a contract to the Institution for it to be able to recoup its up front additional costs in Period 2. This in turn leads to the result from Chapter 9: the Firm would prefer to contract with a Bank, if the Institution is risk averse relative to the Bank and requires appropriate compensation for the risky investment in Firm R&D. The question of whether the Firm can demonstrate that these conditions can be met, prior to the final clinical trials of the drug remains a significant barrier to such a contract.

In summary, even though there are conditions under which paying a premium for a current drug will lead to an additional future drug and net gain in social welfare, Institutions need an incentive to provide this premium. It is unlikely that a Firm can demonstrate that the conditions under which this premium can result in a net increase in social welfare are met with sufficient certainty. Even less likely is the acceptance of a policy such as that proposed by Jena and Philipson whereby all new drugs are provided with a premium, regardless of whether the conditions in Equation 35 are met. In this case, the only certain result is the increased economic rent in that period from the additional premium.

4 Conclusion

The Reimburser revisits her question.

How the Institution should respond to the following Threat:

When the Institution buys this new drug, it buys the health effects from this drug and the health benefits from future innovation. This is not the case with other health programs. Therefore, unless the Institution pays a premium for the health effects from the new drug, the population will be worse off because innovation will be suboptimal and the future drug will not be produced.

- 1) The existence of a premium for the current drug is neither a necessary nor sufficient condition for there to be an incentive for the Firm to produce a future drug.
- 2) If there exists a situation in which a premium is necessary to produce a second drug and the premium is paid, then the development of this future drug is not a sufficient condition for this to action to result in a net increase in npvSW (the increase in economic rent plus the increase in future consumer welfare net the loss from reduced health today).
- 3) The existence of clinical innovation in the future drug, regardless of the size of this innovation, is neither a necessary nor sufficient condition for the hypothetical compensation test to be passed. However, for a given *IMER* and *IPER*, the greater the clinical innovation the greater the surplus, all of which is appropriated by the Firm if the $IPER = \beta_c$.
- 4) If the conditions are met such that the weak hypothetical compensation test can be passed by the policy of a premium, then the Firm should generate an incentive for the Institution to provide the premium. This incentive would be achieved by the Firm contracting to provide the Institution with a share of the future drug's surplus, including the value of manufacturing as well as clinical surplus. However, the information required to demonstrate that the conditions for passing the compensation test are passed is unlikely to be available prior to the drug's development.

The Reimburser asks the Firm for proof that the conditions for passing the compensation test are met by the premium payment for Arthmax. The Firm provides her with the following evidence: i) they cannot fund Arthmax's development without the premium; ii) they can fund it with the premium; and iii) that Arthmax will be highly clinically innovative. The Reimburser points out that this is not sufficient for the Firm to guarantee that the hypothetical compensation test is passed.

The Reimburser explains to the Firm that she would prefer that they approach the Capital Market for the additional funds that they require in order to develop Arthmaxplus. The Institution cannot bear the risks that arise from being uncertain about the value of parameters such as the level of manufacturing innovation of the future drug and the costs of R&D, both of which are private information for the Firm (not in the public domain). The Firm responds by providing an excerpt from the Congressional Budget Office Report on Research and Development in the Pharmaceutical industry (US Congressional Budget Office 2006).

A relatively close relationship exists between drug firms' current R&D spending and current sales revenue for two reasons. First, successful new drugs generate large cash flows that can be invested in R&D (their manufacturing costs are usually very low relative to their price). Second, alternative sources of investment capital—from the bond and stock markets—are not perfect substitutes for cash flow financing. Those alternative sources of capital are more expensive because lenders and prospective new shareholders require compensation (in the form of higher returns) for the additional risk they bear compared with the firm, which has more information about the drug under development, its current status, and its ultimate chance of success. (p.9)

The Reimburser asks the Firm whether it believes that the Institution does not need to be compensated for its investment of “large cash flows” (foregone health). After all the Institution has not been provided with this information either. The Firm responds that patients benefit from the new drugs, but the Capital Market does not. The Reimburser points out that the price that she pays for the health effect of new drugs is the same price as what she could purchase health gains from existing technologies ($IPER = \beta_c$). There is no economic benefit to the population from purchasing at the health shadow price.

Then the Reimburser asks: What is this information? How can the Firm have this information about future costs and effect before they start the clinical trials? The Firm assures the Reimburser that they have this information. The Reimburser offers to act as a knowledge broker and explain this information to the Capital Market; provided that the Institution can see this information first.

Chapter 11: Conclusion

In an age obsessed with quantification, in which the technology of the computer has begun to spread like an all-devouring fungus insatiable in its craving for fresh data, it is not surprising that economic calculation in particular the methods of cost-benefit analysis should grow in popularity. (Mishan 1982 p. 29)

1 The first problem

The Reimburser looks at her original brief.

“The Minister for Health and the Minister for International Trade ask the Reimburser her opinion on whether applying a decision threshold price per effect for new drugs that is lower than the FPP will lead the population's health to be worse off in the longer run.”

Her answer is that if the decision threshold is enforced at an *IPER* below the *FPP*, it is likely to lead to improved health for the population in both the short and long run, compared to *FPP*, provided that the threshold is β_c . Also, lowering the price below the *FPP* is certain to reduce the profits to Pharma, and there is a significant incentive for Pharma to protect these rents.

Then she presents the Ministers with her reframed critical research question.

How should a rational Institution respond to the following threat by Pharma?

If a purchase price for a new drug is below a Firm's preferred price (FPP), this will lead to:

- 1) suboptimal incentives for R&D;*
- 2) less new drugs in the future; and*
- 3) a future population whose health will be worse than it would otherwise be.*

The Reimburser is confident that, if we assume there is no relationship between price and future innovation, β_c is the reimbursement decision threshold that will maximise the health of the population from current and future budgets. β_c achieves this because it:

- 1) characterises reimbursement as comprising both adoption and displacement and can therefore accommodate inefficiency arising from either or both of these actions, not just resulting from adoption as is the case with conventional CEA and
- 2) accommodates :
 - a. competition in the market for both R&D and current health inputs (as n decreases so does β_c);
 - b. inefficiency in displacement ($d < m$);
 - c. the fixed or constrained budget (there is foregone benefit); and
 - d. allocative inefficiency ($m - n > 0$) and technical inefficiency ($m - \mu > 0$).

Furthermore, the use of β_c addresses the market's failure to develop evidence of: i) unpatented or unpatentable services; or ii) services that will be displaced if evidence of their ICER or *IPER* is developed (because they are cost ineffective). The use of β_c achieves this by placing an economic (decision) value on the following:

- 1) the least cost effective of current services (in contraction), m ;

- 2) the most cost effective of current services (in expansion), n ;
- 3) the most cost effective investment strategy μ ; and
- 4) the ICER or *IPER* of services that are displaced, d .

The Reimburser is also confident to state that the evidence of a positive relationship between price and future innovation is not sufficient to establish a case for pricing at the *FPP*. Furthermore, she has learnt to ask for the derivation of an *FPP* when Firms claim it is the price that will maximise the population's health.

The Reimburser is not willing to say: "There is no situation in which a drug should be reimbursed at a price higher than β_c , in order to account for the relationship between price and innovation." Only two specific reasons why the Reimburser should pay the *FPP* or a premium were assessed by the Health Economic Adviser (Games 2 and 3). There is no doubt that Pharma will continue to generate more win-win reasons for the *FPP*. Pharma is behaving exactly as we would expect a large industry protecting its economic rent to behave. However, the Reimburser now has two tools to help her assess any argument put forward by Pharma. The first tool is to analyse the problem as game theoretic model not a decision theoretic model. The second tool is a range of parameters that are relevant to assessing the question of pricing higher than β_c including: the *IMER* of current and future drugs; ΔE^P of the future drug; and the uncertainty surrounding these estimates. She is however quietly confident that there is no case that Pharma can present that would result in a premium above β_c . Her confidence has two sources. First, there is significant uncertainty in the characteristics of a future drug; even if its development is already in Phase 3. Second, the fact that the Institution is more risk averse than the Capital Market means that Pharma will always prefer the Capital Market option, if the Institution seeks a return on its investment in R&D via higher prices that compensates for the associated risk.

And finally, the Reimburser is keen to apply β_c as the new drug decision threshold as soon as possible so that she can redress:

- 1) the long term failure of the Institution to correct for the failure of the market to provide incentives for the development on unpatented or unpatentable technologies; and
- 2) the additional distortions introduced by generating incentives for Firms to price over the economic value of the clinical innovation at the maxWTP.

She is reminded of Arrow (1963):

The social adjustment towards optimality thus puts obstacles in its own path. (p. 947)

2 It's about the journey

The Reimburser notes the other original concepts introduced during her "Adventures in Pharmaland" and realises that to arrive at the simple result of β_c as the maximum acceptable *IPER* regardless of the relationship between price today and innovation, many smaller simple problems needed to be solved.

With hindsight, she and the Health Economic Adviser realise that seven references were critical to the development of PEA and the health shadow price:

- 1) Danzig (1963) identifies the competitive nature of an input market, even though a producer of a specific input is a monopolist. The idea that the firm must be paid the maxWTP (appropriate the entire consumer surplus without reference to competition) in order to generate appropriate incentives for R&D neglects this aspect of the economics of the competitive market.

- 2) McKean (1972) explains, in words, a number of options for calculating a shadow price, and what these options mean.
- 3) Comanor (1986) clarifies that the political economy of new drugs is dynamic and defines the research agenda, in terms of both inclusion and exclusion criteria.
- 4) Mishan (1982) critiques Williams “social decision making approach” as an alternative to welfare economic criteria and is a reminder that health economic evaluation could have developed along different paths (the counterfactual).¹⁵⁷
- 5) Birch and Gafni (1993) reminds the health economics profession of the centrality of the concept of opportunity cost in the application of economic evaluation to decision making. Ignore it at patients’ peril.
- 6) Mishan and Quah (2007) explains the difference between the shadow price of the budget constraint and the shadow price in CBA.
- 7) Buchanan (2008) reminds economists of the difference between the operational definition of the counterfactual (alternative strategies available to the decision maker) and the economic concept (the best alternative end state, even if the strategy to achieve this is not directly available to the decision maker).¹⁵⁸

The smaller problems solved on this journey relate to both pharma-economics and pharmaco-economics.

1) Pharma-economics:

- a. The recognition that the claim by Pharma that the population will be worse off if prices are lowered is a Threat, with a significant payoff to Pharma if successful. This Threat may or not be supported by the evidence.
- b. The conventional political economy of new drugs, and the associated rate of return on investment in higher prices excludes the possibility that more drugs in the future will lead to worse health than would otherwise be possible.
- c. It is possible to have a very high and positive estimate of the conventional rate of rate of return on consumer investment but for this to result in lower health for the population in the future.
- d. Reframing the political economy of new drugs to include the possibility that more additional drugs will reduce the population’s health compared to what would otherwise be the case.

2) Pharmaco-economics:

- a. The strategy of reimbursement has two actions: adoption and displacement.
- b. The endogeneity of the price of new drug; it is the result of negotiation, regulation and bargaining power, not the result of an RCT, a systematic review of the literature nor the adjustment of a charge to become a cost. Prices are not constants.

¹⁵⁷ “Analyst A” (misrepresenting Mishan) would have been calculating the shadow price of inputs rather than the maxWTP. “Analyst B” could benefit from reading Appendix 10. “Analyst C” (representing Williams) should not have been excused for ignoring the market’s failure to provide evidence of the cost and consequences of unpatented and unpatentable programs. (See Drummond et al (2005) p. 18 for details of these Analysts)

¹⁵⁸ Some health economists might argue that this is “first best economics gone mad”. However, the ongoing neglect of the failure of the market to generate incentives for evidence relating to unpatented or unpatentable programs while generating (inflated) incentives to firms to provide evidence of patented technologies is a consequence of the neglect of the first best world.

- c. The *IPER*, *IMER*, and *IπER*, which were developed to facilitate the math, highlight different sources of innovation (including manufacturing innovation) and the appropriation of economic rent from previous innovative NMEs by subsequent NMEs.
- d. The distinction between types of budgets: fixed, constrained, unconstrained and no budget.
- e. The use of game theory to engage with Pharma's rent seeking (lobbying).
- f. The idea of a health shadow price that accommodates allocative or technical inefficiency as competition in the institution's market for health inputs.
- g. Price effectiveness analysis, which compares the effect of the strategy of reimbursement on the population with the best alternative strategy, giving a value to the evidence of the counterfactual.

The Reimburser also acknowledges that there are many opportunities for further research. For example, expected value of information methods such as those described in Drummond et al. (2005) and by Eckermann and Willan (2007) could be used to identify and quantify the value of reducing the uncertainty around β_c . Conventional expected value of information methods could be adapted to accommodate endogeneity of the new drug price, which is assumed to be exogenous in current models. But is all this enough to ensure that β_c will be adopted as the threshold price?

3 The next problem

The Reimburser is surprised when a chorus of criticism of β_c as the decision threshold of choice emanates from, not Pharma and pharma-economists, but the health economic community. She identifies nine arguments against using β_c and for using either k or d . She is also provided with a book chapter by a US health economist that suggests a theoretical approach to incorporating the cost of R&D in a CEA (Pauly 2007).

3.1 Benefits beyond QALYs

The first criticism is that β_c assumes that there is no benefit from a new drug other than the incremental QALYs. There are many cases when a new drug has additional benefits beyond health, for example, it could also improve productivity. Alternatively, the new drug could address "equity" in situations where patients with end stage cancer have no other treatment options. And finally, characteristics of patients such as severity could also be seen to have a value independent of capacity to benefit in terms of health effects. The Reimburser is so confident in the answer to this question that she does not even ask her Health Economist Adviser. She refers to Chapter 6 and shows that if the objective of the reimbursement process is changed to, for example, "QALY plus other thing", so should the set of alternative strategies from which the best alternative strategy is selected. If the impact of the drug on factors such as productivity and equity are measurable and valued, then any means of achieving the same outcomes should be assessed. In fact, if the additional non-health benefits of the new drug are also valued, then it is possible that the most cost effective alternative strategy results in a shadow price lower than β_c , a "health+" shadow price; a counterintuitive but plausible result. (See Appendix 10 for an example of this situation.)

3.2 But no one will implement the best alternative strategy ...

The second criticism is: what if β_c is applied, the new drug is rejected because $f > \beta_c$, but then the best alternative strategy is not adopted? The Reimburser is confused. What does this mean? Is this concern simply a justification for the decision to reimburse the new drug at a higher threshold? This justification is underpinned by the following or similar logic:

If we reject the drug at the offer IPER because $f > \beta_c$ even though $d > f$ no one will actually perform the reallocation (the best alternative strategy). Therefore, we might as well just reimburse at f because at least the population's health will increase.

Then the appropriate response is to explicate and solve the following paradox:

Why would an Institution not adopt an alternative more effective strategy, but be willing to reimburse the new drug instead, even if this action foregoes the more cost effective opportunity.

Perhaps the costs of reducing allocative efficiency are too high? If there are costs to improving allocative efficiency, then these should be incorporated into the estimate of the β_c by redefining the set of alternative strategies. However, in this case, the costs of uptake of new significant drugs should also be included in the IPER, for example, the ongoing costs of prescriber education programs.¹⁵⁹ Any reason that an Institution can give to not adopt the more effective strategy should be analysed, and where appropriate, accommodated in the estimate of β_c . What if all of the possible explanations are exhausted and a reluctance to implement the best alternative strategy remains? Then it is a question of “finding the market or institutional failure”; working out why the Institution will not implement the better strategy.

3.3 Decision makers need to understand the health shadow price

The third criticism is: What if the Social Decision Maker¹⁶⁰ cannot understand why he should use β_c rather than the maxWTP? This criticism is slightly harder to address. An intuitive explanation for using β_c is quite simple: this is the lowest ICER at which the health budget holder could use the funds required to finance the incremental cost of the new drug to purchase QALYs from some other source. So why might the Social Decision Maker not understand this definition?

It could be because the Social Decision Maker does not understand the idea or consequence of a budget constraint. It could be because he has conflated the idea of displacement and opportunity cost. It could be that he is convinced of the price-innovation relationship as evidence of the need to price at high thresholds. Any of these issues could be resolved by a bit of education. However, the preference for the maxWTP as the threshold could be a consequence of a social decision maker being **unwilling to accept** rather than **unable to understand** the difference between a shadow price and a maxWTP. (Chapter 5) This scenario introduces another possibility:

- 1) The Social Decision Maker seeks to maximise the number of new technologies funded;
- 2) he works within the constraint of the lay concept of economic accountability (value for money); and hence
- 3) the preference for the maxWTP rather than the shadow price is a preference for the maximum possible threshold that is also accountable.

That is, the maxWTP threshold maximises the number of new drugs funded, with the minimum of delay, while meeting the constraint of “value for money”, as understood in the lay sense.

One possible response to this situation is to provide the Social Decision Maker with evidence of the health effects lost for patients whose services are displaced (d) or forgone yet to be expanded (n). Then the net economic loss of reimbursement at above β_c can be expressed as a trade-off between health gains for the target patients and forgone benefit to other patients and, if necessary, the Social

¹⁵⁹ Such programs are run by organisations such as the National Prescriber Service (www.nps.org.au)

¹⁶⁰ For a discussion of this character, see the Glossary of Characters Table 1 p. 10. This is the Social Decision maker that Analyst C provides information to. (See Drummond et al (2005) p. 18)

Decision Maker's preference for "new technology" can be derived. The forgone benefit to these patients could be documented in as rich detail as the benefits of reimbursement to target patients for the new drug. The Social Decision Maker might not understand the economics behind this comparison. However, improving the comparability of the depth and breadth of evidence of the potential and forgone benefits of the decision of reimbursement should go some way in personalising the foregone benefit.¹⁶¹

If the Social Decision Maker chooses to reimburse the new drug, even if there is an economic loss, then at least the decision can be framed as one that reveals a preference for the method of production (new things) rather than a preference for health benefits to patients.

3.4 Social decision makers do not understand opportunity cost

Clinicians appear to find the concept of opportunity cost difficult to understand and hence this lack of understanding seems to become a justification for not using it to guide decisions. Alternatively social decision makers could argue that opportunity cost is "not a concrete concept".

As discussed in Chapter 4, opportunity cost in the economic sense is analogous to the decision by health technology assessment groups to use the most effective current treatment for the specified clinical context as the comparator against which a new drug is compared in order to determine its clinically innovative value. The benefit of the new drug is determined by comparing it to the best alternative strategy – the benefit that must be foregone to the patient in order for it to obtain the benefits of the new drug; the opportunity cost of using the drug for that patient.

Appendix 11 includes a presentation that the Health Economist used to explain to the Reimburer (and other pharmaco-economists and health economists) the relationship between opportunity cost in a clinical and economic context and why the economic value of a new drug can only be calculated with reference to the loss from the best alternative strategy.

3.5 Reimbursement of the new drug and reallocation are not mutually exclusive strategies

"The funder could both reimburse the new drug and reallocate resources; they are not mutually exclusive strategies in the same way that choosing to build a new road through a city using either route A or Route B are," said the Operations Research expert.

This is true; the budget holder could fund reimbursement and perform reallocation. However, this does not mean that the strategy of improving efficiency (reallocation or investing in improved practice) is not the strategy against which reimbursement should be compared to determine whether the strategy of reimbursement has a net economic cost or benefit. Without a reference strategy, the question of whether there is an economic benefit to the strategy of reimbursement cannot be answered.

But is choosing a reference strategy a complex problem? It is not complex when we are choosing between Routes A and B for a motorway that will maximise the number of people who can be transported in peak hour, given a budget. Nor is it complex when we are choosing between Drugs A and B in order to maximise the health benefit for the patient given that the patient can only have one course of medications. The complexity occurs when we consider that there may be other actions outside those nominated previously that could be more effective at achieving the goals of improved

¹⁶¹ Towse (2010) describes this problem as comparing the benefits to a "known" group of patients with the potential loss to an unknown group of patients whose health benefits are foregone. He describes the choice of decision threshold as follows: "If NICE exaggerates the cost-effectiveness of the treatment then it favours the known group of patients against the unknown. If it chooses to take a pessimistic view then it ends up favouring the 'unknown' patients at the expense of the known." p. 361.

transport at peak hours and improved population health respectively. These strategies include reducing the number of cars or improving respite care, both of which could be currently unfunded. It becomes even more complex when the endogeneity of price and hence strategy cost is considered. If improved efficiency is not considered as a reference strategy, the possibility that a population will benefit if a firm lowers the price of the new drug to be more competitive with other strategies available to the Reimburser.

PEA provides a framework that corrects for the reasons why an Institution will continue to adopt a new drug based on evidence of its incremental cost and effect, even though strategies that are preferable to it continue to go unfunded. If instead we say both strategies could both be implemented and hence we should just continue to reimburse, the question of “what is the threshold price” remains unanswered and the probability that the more cost effective strategies are never funded also remains high. The consequence is that at any point in time in the future the population’s health will be less than what it could have been had the reference strategy been recognised and firms either forced to change their price or the reference strategy adopted.

Another way of considering this issue is to invert the well-known story of how to find the shadow price of the budget constraint by starting with an unallocated budget and allocating funds to each project, ranked by decreasing cost effectiveness (page 133) until the budget is exhausted. This problem defines the optimum set of rules by which an unallocated budget can be allocated so as to maximise the health benefits possible. In this case we start with a fully allocated budget that is allocatively inefficient. We recognise that an institution could potentially implement both the strategy of reimbursement of the new drug and the strategy of improving allocative inefficiency; these strategies are not functionally mutually exclusive in the way that choosing between the Routes A and B to build a motorway are. The problem is to select from two mutually exclusive sets of rules that can be used to address each successive reimbursement decision.

The first set of rules is to adopt the health shadow price and apply this as a threshold price for the health effects from a new drug; adopt PEA. The second set of rules is to continue to implement both of these strategies (reimbursement and improved efficiency), and to repeat this each time a new drug is considered for reimbursement. Which of these two rules will be certain to have the higher health benefits at each point in time? Which of these two rules provides a clear signal to the firm as to the value ion exchange of a health effect? How is the threshold price selected in the second set of rules? Now take into account the complexities such as, under reimbursement institution rules, the new drug cannot be displaced to finance a future new unrelated drug, only unpatented programs can be displaced.

It is true that the two strategies of reimbursement and improving efficiency are not functionally mutually exclusive, however, in order to maximise the health of a population from a given budget over successive reimbursement decisions, it is necessary to minimise the economic cost of each decision. In order to use the first set of rules, a reference strategy is necessary in order to estimate economic loss and to send a price signal to the firm. The only reference strategy that is grounded in economic theory is the strategy with the largest net effect on the population, the strategy to improve efficiency.

3.6 The decision threshold should not be revealed to the industry

The next criticism is that the decision threshold should not be revealed to the firm and that instead the institution should keep it as private information and use this private information to bargain a price below the threshold. At first glance this appears to address the problem of firms pricing at the maximum price (their best response to a revealed maximum) and seems to introduce the possibility that the price will be lower that would otherwise be the case. There are two reasons why the simple bilateral bargaining model such as wage bargaining model will not lead to the result of maximising

population's health by increasing the proportion of decisions that have their price below the shadow price.

First, the objective of this exercise of using the health shadow price is to provide a signal to manufacturers and other advocates, agents and owners of inputs of the cheapest way that an incremental health effect can be obtained. It is about addressing the markets' failure to supply such a price and to develop evidence of the effectiveness of unpatentable and unpatented technologies.

Furthermore, the critical problem faced by reimbursing authorities is not how far they bargain below the decision threshold, but how to counteract the pressure to price above any price that they nominate as a maximum price. This characteristic of the PEND is why the decision to impose a decision threshold is characterised as price control: the argument from Pharma is to not go below the firms' preferred price, which is higher than the institutions preferred price, whatever that institution's price is. This is why the US pharma-economists characterise a free market in pharmaceuticals as a unilateral rather than a bilateral monopoly where only firms have market power. (See Appendix 7, Section 3 Price Control p. 239)

Therefore, the decision threshold that is the health shadow price should not only be in the public domain, empirical evidence to support its value should be valued at least as much as the evidence of the ICER of a new drug and the social value of investing in this evidence should be recognised.

3.7 The games only apply to the Australian setting

"This story is a thinly disguised narrative of the Australian experience over the 20 years since 1991 since economic evaluation first started to be used for new drug. It has limited relevance to the rest of the OECD" said the European health economist.

Some characteristics of the games and stories are strongly reflective of the Australian experience; this is true. However characteristics of the PEND, the structure of the games and the narrative are common to all countries that use economic evaluation to inform the decisions about new drugs. Games can be uniquely specified using the different reimbursement rules in each country and then solved for the different strategies adopted by Pharma. Furthermore, the novel aspects of the solution (the use of game theory, the *IMER*, *I_PER* and *I_πER* to specify a firm production function and the health shadow price) provide the economic tools with which a country specific game constructed. These tools represent a new way to engage in the political economy of new drug price. These games and the methods are in the public domain; they have value if they are adapted and used by institutions.

3.8 What about the political cost of reallocation?

"But there is a political cost to reallocating, otherwise we would already adopted this strategy" said the employee of a major European public health authority. This is partly true; political costs of actions do mean that the strategy that maximises the health of the population will not necessarily be implemented.

First, political cost is only one reason that this reallocation, while population health improving, has not yet occurred. A second reason is the market's and institution's failure to generate the necessary evidence and to provide an institution path by which strategies that are cost effective can be implemented and the resultant decision protected from displacement. Hence, the use of the health shadow price corrects for this failure of market and institutions to provide evidence.

Second, even if this alternative strategy is identified and it is considered too politically costly to implement it and the drug is reimbursed instead, there is an opportunity to translate this political cost to a health cost. Under PEA and the health shadow price, institutions are presented with as much

information about the health gain to the patients who could benefit from reallocation (and those who will lose) as they are of the information about the services that will be displaced and the health benefits of the new drug. Hence, the market's and institutions failure to reveal the health cost of not undertaking a reallocation can be addressed at least partly and this cost put into the public domain and compared to the benefits of reimbursement of the new drug.

Third, it would be useful for the political cost to be converted to units such as health gains foregone in order to compare it to the economic cost of not implementing the strategy of improved efficiency. The economic cost of reimbursing but not improving efficiency is clear – it is a loss in population health gains compared to what would otherwise occur. It is unclear how the politicians compare the political cost to the economic cost or improving efficiency. Do politicians have a sense of the economic cost or does it have no value in their decision making?

And finally, if this alternative strategy is identified and it is politically costly to implement, that does not necessarily mean that the new drug should be reimbursed. Are there other strategies that are preferable to reimbursement that are less politically costly? Alternatively is the problem that Institutions are so convinced by the conventional political economy of new drugs that they are unwilling to challenge this conventional wisdom lest they make significant losses in areas such as increased barriers to agricultural exports.

3.9 The costs of R&D can be incorporated into a CEA

The next criticism is that the costs of R&D should be incorporated into the cost effectiveness analysis to determine the price that optimises the incentives for innovation (Pauly 2007). Pauly's method incorporates factors that determine extent and distribution of R&D that are not considered in this thesis, such as countries with different regulatory structures and the incentive to invest in one country rather than another. However, it is important to note that his discussion does not refer to the competition from other sources of inputs or innovation. Nor does Pauly refer to the potential for firms to make strategic use of private information about the costs of R&D and the marginal costs of production of drugs. He assumes this information will be supplied – placed in the public domain - , even though this could be to the firm's disadvantage. He also assumes firms will not be strategic in exactly which information they put in the public domain, that is, they will be honest and fully reveal the true costs of R&D.

3.10 There is no evidence of n , d , m , and μ

Most significantly, it could be argued that there are no estimates of the parameters: n , d , m , and μ .

The Reimburser notes that some pharma-economists have accepted the argument that the *FPP* is the price that will optimise future innovation, without requiring evidence of the value of that future innovation (ΔE of the future drug) or the maths used to derive this *FPP*.

She offers five starting points for health economists who wish to make headway into an otherwise intractable problem: we can't apply the health shadow price because we do not know its value but we do not know its value unless we provide a value for this evidence.

- 1) There are two aspects to reducing uncertainty in the estimate of β_c . Uncertainty as to which programs and technologies correspond to n , d , m , and μ and uncertainty as to the value of the ICER or *IPER* of each of these programs.
- 2) The expected cost of reducing uncertainty in the estimate of these parameters depends upon a number of factors, including the currently preferred threshold. If the currently preferred threshold is k then estimates of all three parameters need to be obtained. If the current preferred estimate is

d and this is accompanied by a strategy to reduce the inefficiency of displacement, (identification of m) then the only additional parameter that needs to be estimated is n .

- 3) The value of reducing uncertainty also depends upon the current choice of threshold; the greater the economic loss associated with the prevailing threshold, the greater the value of evidence of β_c , the greater the incentive to generate evidence. The economic loss (health) of each decision to reimburse a new drug of additional cost ΔC^P , using the current threshold CEA_i where $i > \beta_c$ and the Firm prices at i , is given by:

$$\Delta C^P(i - \beta_c)$$

- 4) In the case of CEA_d accompanied by a strategy of disinvestment¹⁶² the value of reducing uncertainty in the value of β_c increases and the cost of reducing this uncertainty decreases over time.
- assume that k provides an upper limit to the choice of threshold;
 - as the efficiency of displacement increases, d approaches m ;
 - hence the economic loss of using the preferred threshold, approaches the economic loss associated with k ;
 - however, as more reliable estimates of d and m become available, then the incremental cost of evidence of β_c reduces; the only additional parameter that needs to be estimated is n .
- 5) There is no requirement to identify the shadow price of the budget constraint (in expansion) λ_e^B in order to make an estimate of β_c . The analogous parameter in PEA is n , the most cost effective program in expansion or most cost effective unfunded program or technology; it is a concrete rather than abstract concept.
- 6) A first cut set of parameter estimates could be obtained relatively easily. Vernon et al. (2010) required an estimate of the least cost effective of existing programs to estimate the full value threshold. The authors' choice of the ICER of dialysis is probably a reasonable starting point in most health systems for the estimate of m . The weighted average ICER of programs that were contracted or not implemented in the last round of health budget cuts is d . And then the value of n could be the first program that could be expanded or implemented and that has an ICER above $d - m$. This will ensure that the first approximation of β_c is above zero.¹⁶³

4 Postscript

The Reimburser presents a new brief to her Health Economic Adviser.

She asks him to **reframe the political economy of the choice of new drug decision threshold**. The starting point to this reframed political economy is the question: Why don't we know n , d , m , and μ ? This replaces the conventional starting point: we don't know λ_e^B , (the shadow price of the budget constraint in expansion) therefore we should apply k or d as the threshold. Then, he is to follow any avenues this opens up and find the key empirical questions to inform the policy of choice of decision

¹⁶² There is now a sizeable body of literature looking at the practicalities and merits of disinvestment strategies. A number of the studies associated with NICE also raise the relationship with the choice of threshold. (Culyer, McCabe et al. 2007; Elshaug, Hiller et al. 2007; Pearson and Littlejohns 2007; Walker, Palmer et al. 2007)

¹⁶³ The Reimburser has grown to be quite tolerant of hard-core economics. However, if $\beta < 0$ because the existing budget has significant allocative inefficiency well, she can see the headlines now – “Companies asked to pay the government if drugs are innovative”. She understands that this will not necessarily be the effect of a threshold below zero, and firms could still make an economic profit on these drug sales (see Chapters 8, 9 and 10). But why let economic sense stand in the way of a good headline? Such is the political economy of new drugs.

threshold for new drugs. As he leaves the room, the Health Economic Adviser mutters something about “ β_c is just one flower in a big bouquet of trouble”¹⁶⁴.

¹⁶⁴ Appropriated from: the line “You’re just one flower in my big bouquet of trouble” from the song “Bouquet of Troubles” by Spencer. P. Jones 2010.

Appendices

Appendix 1: An architecture of evidence based policy

1 Introduction

This Appendix informs the development of the alternative political economy of new drug price and is referred to in Chapters 1, 2, and 3 and also Appendix 3. The discussion about of Grüne-Yanoff and Schweinzer's (GY-S) Architecture of Game Theory (Grüne-Yanoff and Schweinzer 2008) also informs the structure of each of the games in Chapters 8, 9 and 10. This appendix provides a background to why this architecture was developed, and a discussion of this Architecture.

2 Background

When this research was in its early stages, I performed a review of the US pharma-economic literature with the objective of finding the evidence supporting the following claim: if a country such as Australia increased the price of new drugs, for example by increasing the decision threshold, this would lead to a return, in terms of additional health for the population, that would significantly outweigh the initial consumer investment in higher prices. The results of this review are summarised in Appendix 2. When I performed the review, I found I was not able to accommodate the results in a conventional evidence based medicine framework, for example, summarised under: research question, results and caveats. Reasons for this situation included the following.

- 1) There were gaps between the claimed interpretation of a given result and the most generous interpretation of this result: for example, evidence that price control leads to a reduction in number of NMEs does not support the conclusion that there is a net loss in social welfare as a consequence of price control.
- 2) There were significant omissions in the stated assumptions underlying models. The most common unstated but inherent assumptions were: i) no sources of innovation other than pharmaceuticals and; ii) no budget constraint (hence all new drugs could be funded without any foregone benefits).
- 3) There were studies that were probably funded by pharmaceutical companies but this information was not disclosed in all cases. The mainstream academic economic literature does not require authors to reveal potential conflict of interest. The relationship between authors and pharmaceutical companies was traced by: i) examining the website of drug companies; ii) the website for some academic centres; and iii) studies published by these authors in the medical literature which required potential conflict of interest to be revealed.
- 4) Many papers had extensive policy narratives replete with evidence (e.g. the link between price and R&D, the link between R&D and NMEs) and a clear definition of the key empirical question (the requirement for evidence of the ratio of costs to benefits of R&D), but no empirical evidence of this relationship.

As the literature review continued, a number of other issues became apparent. For example, the possibility that the health of the population could be worse off if there were more compared to less NMEs was excluded from both the research agenda and the analytical models. This exclusion occurred even though the possibility of such an outcome, even with returns of 28 to 1 such as those estimated by Santerre and Vernon (2005) is straight forward to demonstrate. (See Chapter 3.) It became clear that the political economy was framing the research agenda; an observation previously made by Comanor (1986).

Then, for a separate part of this thesis, I read a paper about the role of the narrative in constructing and solving a game theoretic model (Grüne-Yanoff and Schweinzer 2008). This paper highlighted the

role of the narrative in defining which of many possibly “rationalities” would prevail in a particular game where all of these “rationalities” could be potentially supported by theory. For a separate project I read a paper by Roe on the role of the policy narrative in development economics (Roe 1991) . Roe argued that policy narratives tended to focus on one key cause and effect mechanism and could often completely ignore the evidence.

The model I developed to understand and analyse this body of literature drew on these three papers: Comanor (1986); Grüne-Yanoff and Schweinzer (2008); and Roe (1991). The model allowed me to characterise and understand this literature in the context of the political economy of new drugs and the role of this political economy in shaping, the research questions, the policy narrative and the policy questions.

3 An architecture of evidence based policy

The Architecture of Evidence Based Policy (AEBP) is an adaptation of Grüne-Yanoff and Schweinzer's (GY-S) Architecture of Game Theory (Grüne-Yanoff and Schweinzer 2008). It also incorporates the issues raised by Comanor (1986) about the relationship between the economic research agenda and the political economy of the US pharmaceutical industry and by Roe (1991) about the role of the simple cause and effect model in the policy narrative.

The GY-S framework explores the relationship between both the narrative and theory proper in defining the game structure, its solution set and the selection of the solution concept from this set. It emphasises the non-unique rationality of a game and its solution. The analyses performed by the authors using this framework lead them to conclude that "game theory is not a universal theory of rationality, but only offers tools to model specific situations at varying degrees and kinds of rationality". Similarly the AEBP highlights the relationship between the evidence based narrative, the choice of empirical questions and policy options and finally the solution. It illustrates how evidence based policy making does not necessarily identify a universally preferable policy but instead identifies a case to support a strategy from a given policy choice set, where this policy choice set might be suboptimal, that is, not include the best alternative strategy to the nominated strategies.

Three adaptations were made to the GY-S framework to arrive at the AEBP framework.

First the AEBP framework starts with World, which is the inspiration for applied economic models, rather than with Theory Proper, which is the inspiration for theoretical economics and the starting point of the GY-S framework. This adaptation also allowed the following analogy between: i) the solution concept (the preferred solution concept from the set of possible solution concepts) in game theory as a determinant of non-unique rationality and; ii) the policy concept (the preferred policy question from the choice of possible policy questions) as a determinant of non-unique rationality.

Second, the model of interest in this case is a non-strategic model of policy making rather than a game theoretic model. (A separate framework examines the implications of placing the Pharma's lobbying into a game theoretic model. See Chapter 8) And finally, in the AEBP framework the model comprises policy options, the evidence based narrative and the empirical question. In the GY-S framework, the model comprises the narrative and the game structure.

The main methodological advantage of this framework in the context of this research was that it allowed me to explore the outcomes of an alternative way of framing the political economy of the question of new drug price and the relationship between the policy question, the policy narrative, the theoretical framework and the structure of the key piece of empirical evidence.

Without this framework, the only approach to critiquing this set of pharma-economic evidence would have meant reviewing each of the published studies in detail and critiquing their analyses on

technical and theoretical grounds. This approach would not have identified the omissions in the research agenda.

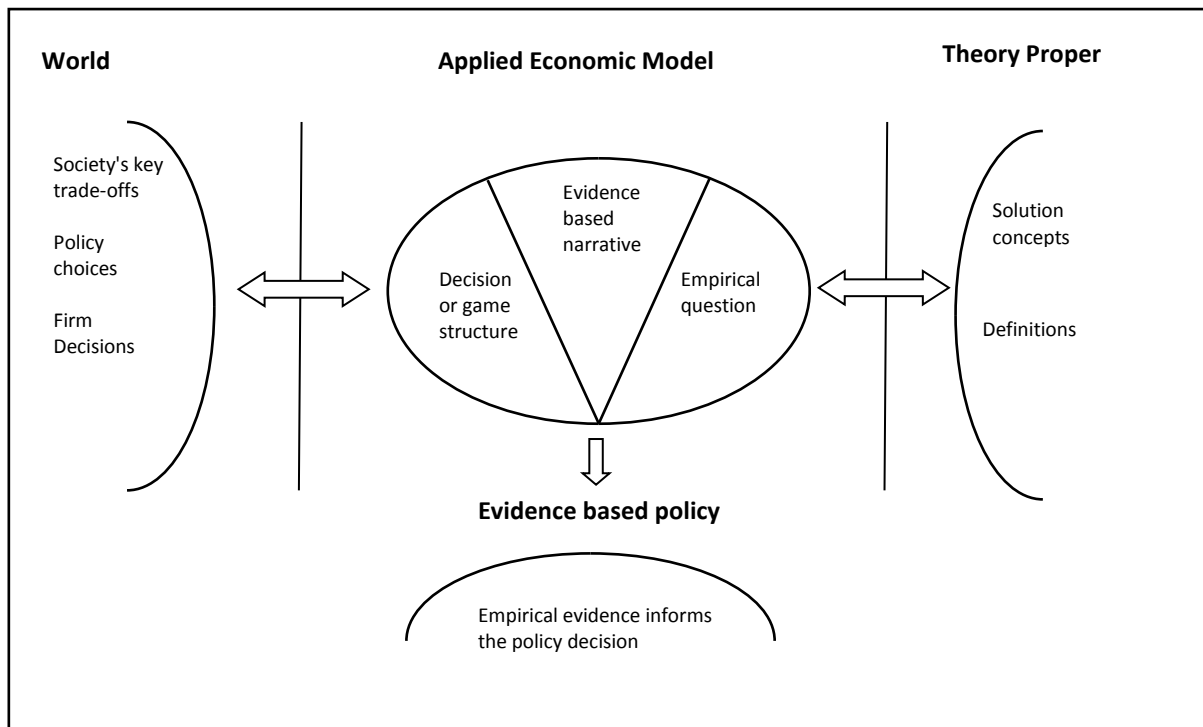


Figure 13 Architecture of political economy of evidence based policy (Adapted from Grüne-Yanoff and Schweinzer's Architecture of Game Theory)

Appendix 2: An overview of the US pharma-economic social rate of return literature

"Hands up who wants to die!" from Sonny's Burning, The Birthday Party 1983

1 Introduction

This Appendix is referenced in Chapters 1, 2, 3, 9 and 10, and in Appendix 7. It serves two purposes: i) it establishes and critiques the published evidence of the social rate of return on pharmaceutical R&D; and ii) it provides examples of the methodological issues in the US pharma-economic literature. Both of these issues are referred to throughout the thesis.

2 Background

This review was performed at the start of this research with the expectation that the evidence of return on consumer investment in pharmaceutical R&D via higher prices could be accommodated in an estimate of a health shadow price. The review was premised on the existence of this evidence, which had been referred to in numerous discussions I have had with industry economists. One of these "leads" was provided by an economist who heads a European industry lobby group. He assured me that the evidence was clear; investment in pharmaceutical R&D was *"the most cost effective way to improve the health of future populations, far more cost effective than other investments that could be made by the health sector."* (This economist did not provide me with the evidence supporting his claim and despite extensive searches I have not found such a study.)

As it turns out, the conventionally measured rate of return is not useful in the context of a constrained or fixed budget (Chapter 3). And in Chapters 9 and 10 I showed that regardless of the size of the return, unless the Institution as the agent of consumers can appropriate an adequate share of the resultant gain in social surplus via a prospective contract, there is no incentive for the consumers' agent to make this investment in pharmaceutical R&D via higher prices today. The surprise result of the review was that only two estimates of the return on consumer investment in R&D were published since Comanor's 1986 observation that this ratio, while critical in analysis of drug pricing policy, had not been estimated. The almost 80 other papers that were reviewed provided a range of estimates that could be used to paint an empirical story about new drugs, but did not provide an estimate of this critical ratio.

The process of reviewing this literature provided a number of insights into the differences between pharmaco-economists and pharma-economists in how they see the world of new drugs. It also developed my understanding of the policy narrative that surrounds the US and international political economy of new drugs.

3 Objective of review

The objective of this review of the pharma-economic literature is to identify the empirical evidence that could inform the following policy question.

- Should the Reimburser purchase new drugs at the firm's preferred price (FPP), which is above her preferred price?

This policy question is a response to the following claim.

- If a Reimburser purchases a new drug at the FPP, where this represents a premium above her preferred price, then this additional expenditure will result in a return that would justify this investment.

Hence the critical piece of empirical evidence is:

- an estimate of the return on additional consumer investment in pharmaceutical R&D through higher prices and/or additional publically funded R&D, where this return is the increase in the population's future health compared to what otherwise would have occurred.

4 Methods

A review of the US pharma-economic literature on pharmaceutical innovation and the return to R&D published over the period 2000 to 2010 was conducted.

- 1) The databases searched were: ECONLIT and PUBMED.
 - a. The search term used in these databases was: “pharmaceutical” AND (innovation OR R&D OR “research and development” OR “investment”) AND “return”.
- 2) The websites for WHO, OECD, the US government websites for Health, the FDA, the NIH and Commerce, and the website for the PhRMA were searched.¹⁶⁵
- 3) Excluded from the review were:
 - a. Papers that did not have an author with a US affiliation or were not pertaining to US industry.
 - b. Studies that examined the rate of return on pharmaceutical firms' investment in R&D, where this return was defined as economic rent to the investing firm.¹⁶⁶
- 4) Included in this review were:
 - a. Peer reviewed papers sourced from medical and economic citation databases, with either at least one US author (regardless of whether they were using US data) or on the topic of the US industry.
 - b. Books on the topic of pharmaceutical innovation that had at least one US pharma-economic author or editor. The studies included in the one relevant text (Sloan and Hsieh 2007) included studies from outside the US, however, the commentary on these drew a number of conclusions relevant to the US.
 - c. US Government reports such as that justifying the funding of medical research through the NIH (Joint Economic Committee 2000).
 - d. Any other publications that were presented by pharmaceutical firms and pharmaceutical manufacturers associations in support of this claim.
 - e. Studies that were published before 2000 were included in the review if:

¹⁶⁵ www.FDA.gov – The US Food and Drug Administration; www.PhRMA.org – The Pharmaceutical Research and Manufacturers of America; www.oecd.org The Organisation for Economic Cooperation and Development; www.NIH.gov – The National Institutes of Health; www.commerce.gov – The US Department of Commerce.

¹⁶⁶ These studies provide indications of the profitability of firms' decisions to invest in R&D. They also provide evidence that as price increases, two mechanisms work to increase investment in R&D: i) more internal funds (economic rent) are available for investment in R&D; and ii) the incentive to invest in R&D increases (expected return on this investment increases as expected future price increases). However, rate of return on consumers' investment in R&D via higher prices cannot be inferred from these studies.

- i. they were referenced in studies published between 2000 and 2010; and
- ii. the citing studies suggested that these previous studies provided evidence of this return.

More than 80 articles were retrieved and reviewed for this project. Only two provided estimates of the return on consumer investment in R&D. A detailed discussion of this literature, in particular the inconsistency between stated and actual interpretation of results and methodological limitations, is outside the scope of the current research; it is a significant research project in itself. Instead: the references were classified into four groups; the characteristics of each group were summarised; issues relevant to the thesis were identified; and the two estimates of returns on investment in R&D were critically analysed.

5 Four main types of studies and their capacity to inform the policy question

The four main types of studies that were identified in this review and their capacity to address the key question are summarised below.

Group 1: The evidence based narrative

The majority of the literature is in this group; it supports the policy narrative and defines the key policy question of interest (the return on consumer investment in pharmaceutical R&D) but does not provide evidence that informs this question. Many of these studies provided estimates that contribute to the policy narrative (for example evidence of the relationship between price and R&D investment or the value of gains in life expectancy) but not the costs and benefits of such investment.

Group 2: The cost and benefits of additional expenditure on new drugs

The second group comprised ten studies, most of which were specific to conditions.¹⁶⁷ These studies look at the return on incremental pharmaceutical expenditure (increased expenditure on drugs). Cost-benefit studies of historic incremental changes in aggregate drug expenditure compared to incremental changes in longevity provide an estimate of the return on pharmaceutical expenditure. They do not provide the evidence to inform the policy question; the return on consumer financed R&D. They raise a significant methodological issue: what is the bias inherent in a historic analysis of such a relationship, where increases in longevity are attributed to one factor of production (new drugs) at the exclusion of other inputs (for example, the health workforce and other forms of health technology).

Group 3: Ostensibly, but not in fact, evidence of a return on R &D

The third group comprised two studies that appeared to provide evidence of a return on consumer funded pharmaceutical R&D but on closer review are addressing questions that are related to but distinct from the critical question (Murphy and Topel 1999; Lakdawalla, Goldman et al. 2009).

Group 4: Evidence of social return on investment in R&D

Two studies did provide an estimate of the return (measured in health effects) to consumer investment in R&D (Lichtenberg 2004; Santerre and Vernon 2006). These studies raised a significant methodological issue, namely, should the return on increased R&D financed by higher prices to consumers be measured as combined social welfare or increased consumer welfare and economic rent

¹⁶⁷ For example Lichtenberg (2009) estimated that the cost per life year gained from new cancer drugs was in the order of UED6K

separately. In other words, does distribution of this return across consumers (who financed the R&D) and producers (who own the patent) matter?

The results for each of these groups are discussed in more detail in the following sections.

6 Group 1: Supports the policy narrative, not the empirical question

The majority of the literature that appeared to be providing evidence supporting the claim that investments in R&D by consumers through higher prices represented value for money was not in fact presenting this evidence. Instead, it was informing the “evidence based policy narrative” (See Appendix 1 and Chapter 2) and defining, but not estimating, the key empirical question; evidence of the return to consumers from higher prices today or the trade off in financial savings today and additional health tomorrow. This issue is summarised by Vernon (2005) in the conclusion to his study, which predicted a decline in R&D investment if prices were reduced in the US.

In sum, it is critical to put the results presented in this paper into proper perspective, both because of the caveats associated with the results themselves and because of the uncertainty surrounding their implications for social welfare. The predictions that pharmaceutical price regulation in the US will lead to a decline in industry R&D investment from between 23.4 to 32.7% is insufficient for determining what the net effect of this policy will be on social welfare. (Vernon 2005 p. 14)

In other words, Vernon’s results supported the policy narrative (reduced prices will reduce R&D) but not the policy questions (what is the loss in consumer welfare as a consequence of this reduction in R&D and how does it compare to the loss due to higher prices). Two features of this group of papers are discussed in the following section. First, I discuss the practice of framing the study as if it were supporting the policy choice, but then only estimating the cost side of price control (for example). Then, I discuss one of the numerous methodological issues in these studies; underestimating the investment by consumers into pharmaceutical R&D via higher prices.

6.1 Consistency between the actual and claimed significance of the studies

In a number of cases, studies were framed in the abstract, introduction and conclusion as providing this evidence, but on closer review, no such evidence was provided. Some US pharma-economists’ have a practice of framing the motivation for their research as estimating the risk of attempts to control drug prices, namely the potential loss of significant benefits of new drugs, in order to compare these to the benefits. However, these papers only estimate the reduction in benefits from price control and not the additional benefit in terms of additional health effects possible by allocating savings from price control to other uses. This is the case, even though in order to calculate the loss in future innovation due to less investment in R&D, they must first calculate the financial savings that occur today. An example from Giaccotto et al. (2005) follows. First the authors start with a reference to the inevitability of new drugs leading to improved health.¹⁶⁸

Benjamin Franklin once remarked, “In this world nothing can be said to be certain, except death and taxes.” Spokespersons for the pharmaceutical industry might be inclined to argue that the benefit-generating capability of prescription drugs also belongs in this exclusive category. They could make a compelling case: recent studies suggest that pharmaceutical products increase

¹⁶⁸ This quotation also points to one of the advantages held by countries that use economic evaluation, compared to the US; these countries have not had to wait until 2005 and use econometric studies without counterfactuals to assess whether or not new drugs improve longevity and have an impact on quality of life. Instead these countries use cost effectiveness analyses to predict the likely costs and effect of adoption at a given price.

longevity, improve quality of life, and often result in medical cost savings. (Giaccotto, Santerre et al. 2005 p. 195)

Then the authors make a statement about the very significant size of these benefits and how the potential loss of these is an important consideration in policy and hence there is an imperative for their research, which is about the relationship between price and R&D.

Because of the important benefits promised by new-drug innovations and the sizeable costs associated with the innovation process, a number of researchers have explored the determinants of pharmaceutical R&D. Not surprisingly, a major aspect of these studies concerns how various types of public policies, such as drug price regulations, might affect pharmaceutical R&D. The notion is that public policies should foster, or at least not inhibit, R&D investment, particularly investments that offer societal benefits in excess of costs. (p. 196)

The authors are suggesting that R&D should be fostered, particularly when the social benefits are greater than the costs. We can infer that they are supporting public policy to foster R&D even if the social benefits are less than the costs. It is unclear which criterion of policy assessment the authors are using in this case. And finally the authors conclude that they have been able to demonstrate that the costs of lower prices and less R&D are significant, in this case less NMEs, and hence there is reason to be cautious. They then clarify that they have not compared these costs against the benefits of lower prices hence this finding of high costs is not sufficient to determine policy.

Our findings suggest that the trade-off between improved access to pharmaceuticals today and innovation tomorrow may be much greater than previously thought. Furthermore, since our analysis focuses strictly on the costs associated with pharmaceutical price controls, both in terms of forgone R&D investment and new drugs, it is important to keep in mind that this is just one side of the economic issue. Meaningful social policy will need to weigh such potential costs against the economic benefits that would be achieved through greater access to prescription medications under a drug price control policy in the United States. (p. 212)

In summary, their research, like most papers in this group, examined the costs of lower prices only, and did not make any attempt to assess the benefits. However, in most papers, it is inferred that if these costs are significant, they are likely to outweigh the benefits.

6.2 A common methodological problem – underestimating the investment by consumers

A problem common to a number of studies across all groups is that the investment in R&D by the firm is conflated with the investment by consumers in higher prices. The latter represents the investment by consumers and former the investment by the firm. The former is estimated at around 20% to 30% of the latter. The consequence of using the former as the denominator of a social return to R&D is an overestimate of this return. This result occurs for three reasons. Common to all of these reasons is the evidence of the cost of bringing one new drug to market, which for the purpose of illustration, I will assume is \$1B.

First, some analyses assume that 100% of increased pharmaceutical R&D is allocated to new drugs. Hence, if a firm invests an additional \$1B into R&D this type of model will lead to one additional new drug in the future. However, only around two thirds of R&D is allocated to new drug R&D.¹⁶⁹ Therefore, a model that makes this assumption will overestimate by 50% the number of additional new

¹⁶⁹ ITA (2004) p. 30

drugs that will result from every dollar increase in R&D. Hence the return (additional new drugs) to an additional dollar invested in R&D calculated using this method will overestimate the return by 50%.

Second, only a share of the additional funds raised through higher prices (consumers' investment) are invested in R&D of any kind. Some is taxed, some is maintained as economic rent and some is allocated to other costs. One study used an estimate of 30% as the share of additional expenditure by consumers will be invested in R&D of any kind.¹⁷⁰ Therefore, if a model assumes that 100% of an additional \$1B in additional funds raised by increased prices will be invested in R&D and that all of these R&D funds will be invested in new drug research, then they would estimate that one additional NME would be generated from each additional \$1B raised from higher prices. However, a more reasonable estimate is that for each \$1B in revenue, there is an additional 0.3 (=30% × 67%) NME. Hence, there is a threefold overestimate of the return on higher prices using the assumption that 100% of increased revenue goes to new drug R&D.

Third, the investment into the development of new drugs includes funding from sources outside the firm, specifically private-not-for-profit and public medical research institutes.¹⁷¹ The value of continued investment by the public sector is an important part of the policy narrative. However, the estimates of the costs of bringing one drug to market calculated by DiMasi et al are the cost to the firm and exclude the cost incurred by other organisations. Assume, for the purposes of illustration that for every \$1B of R&D invested by a firm into R&D, an additional \$0.1B is invested by other sectors. Then, an increase in firm investment funded by higher prices, by \$1B, with no other increase in investment, will lead to an additional 0.9 not 1 NME. Alternatively, assume there was an additional \$0.1B in public sector investment, in addition to the investment financed via higher prices. Then, having the latter alone as the denominator, will result in an underestimate of the cost to the public sector and consumers of achieving an additional NME. Either way, not recognising the investment by the organisations outside the firm will result in an overestimate of the return on higher prices by either underestimating the investment required to obtain an additional NME, or by overestimating the number of additional NMEs possible from a given increase in prices.

It is beyond the scope of this project to identify every way that studies have estimated the investment by the non-capital market sector into new drug development. Not all studies have significantly overestimated the number of new drugs that are possible from increased prices (or the loss from lower prices). One study of the effect of increased prices on additional new drugs in the future that assumes correctly that only a share of the additional funds raised by higher prices will be allocated to R&D and only a share of these R&D funds is allocated to new drug R&D; the ITA study on the implications of price controls throughout the OECD (ITA 2004).

7 Group 2: Cost-benefit studies of incremental changes in aggregate drug expenditure

Studies on the themes of the cost-benefit of increased drug expenditure were identified as a distinct group within this review because they identify a net benefit of new drugs in aggregate: the additional value of health gains less the expenditure to achieve these gains. These results could potentially be combined with an estimate of the investment in new drug R&D to provide an estimate of the social

¹⁷⁰ The estimate of 30% was derived from the information stated in ITA (2006 pp. 28-29). The ITA stated that if between \$17.6B and \$26.7B additional revenue is raised from reducing controls on prices throughout the OECD (excluding the US) then an additional amount of \$5.7B and \$8B will be invested into R&D of any kind. This implied that 30% of this additional revenue would be allocated to R&D.

¹⁷¹ Jena and Philipson (2008 p. 1229) and Lichtenberg (2004 p. 376)

return. This net benefit of new drugs is perceived as significant. The editors of a review of the theoretical and empirical issues around pharmaceutical innovation from an international perspective concluded that:

With the rates of return of 10 to 1 based on measures of increased life expectancy alone, not even considering improvements in the quality of life, pharmaceutical research has successfully provided developed countries with better health at a cost that has been far exceeded by the value of improved longevity. (Sloan and Hsieh 2007 p. 273)

The two studies the editors referred to analysed historic evidence of the relationship between additional expenditure on new drugs and the gains in health that could be associated with this increased spending. In addition to the two studies contained in Sloan and Hsieh (Cremieux, Jarninen et al. 2007; Hsieh, Lo et al. 2007) a study by Lichtenberg was included in this group (Lichtenberg and Duflos 2008). Other studies in this group referred to specific conditions, for example Lichtenberg (2009). Only the whole of health studies are considered in this section.

These studies do provide some insight into the methods that are used by pharma-economists to attribute a gain in average life expectancy at birth to new drugs and to value this increase. They can be thought of as retrospective CEAs (without the HTA component) that aggregate the additional costs of all drugs and compare these costs to the attributed health gains of all new drugs. In the following section, an unusual aspect of the interpretation of these results by Lichtenberg and Duflos is discussed. Then the interpretation by Sloan and Hsieh of the results of the two studies presented in the text they edited are reviewed. Section 7 concludes with some questions about how the results of such studies can be used to inform the question of new drug price, in the context of the need for consumers to have a return on their investment through higher prices.

7.1 Lichtenberg and Duflos 2008

In this study, Lichtenberg does not claim to provide evidence of the return on additional R&D. Instead, in all three versions of this study (Lichtenberg 2006; Lichtenberg and Duflos 2008; Lichtenberg and Duflos 2008) the authors claim to provide evidence that increased expenditure on new drugs leads to increases in life expectancy worth around seven times the additional expenditure on these drugs. Putting aside the less than conservative assumptions made in his study,¹⁷² one of the more puzzling aspects of his research is his interpretation of his result that 65% of increase in life expectancy can be attributed to pharmaceutical innovation. This claim is that:

During the period 1995-2003, mean age at death increased by about 2.0 years, from 74.4 to 76.4. The estimates imply that, in the absence of any increase in drug vintage, mean age at death would have increased by only 0.7 years.

This claim is made in his original working paper prepared while located at an Australian university (Lichtenberg 2006 pp. 2, 11, 12), the later National Bureau of Economic Research Working Paper (Lichtenberg and Duflos 2008 pp. 2, 13, 14) and the final peer reviewed paper (Lichtenberg and Duflos 2008pp. 95, 107,109).

It is difficult to dismiss as a small technical error, a mainstream economist's failure to identify the opportunity cost of that additional expenditure on new drugs. If the additional expenditure on new drugs had not occurred, consumers and the public health budget holders could have allocated these funds to other activities, which might even have been more cost effective than new drugs. The

¹⁷² There were a number of significant methodological limitations to this study. For example, the only type of innovation Lichtenberg used as an explanatory variable was pharmaceutical innovation as measured by "drug vintage".

evidence Lichtenberg produced tells us nothing about what would happen in the absence of that additional expenditure on new drugs (the counterfactual). These three versions of Lichtenberg's paper do not disclose any potential conflict of interest due to his financial relationships with pharmaceutical companies; relationships that he willingly discloses in the private domain.¹⁷³

7.2 What can Sloan and Hsieh's conclusions tell us about pharma-economists' understanding of the benefits of pharmaceutical innovation?

Two aspects of pharma-economists' understanding of this type of evidence and its role in informing decisions contrast with how health economists and pharmaco-economists observe the world. First, Sloan and Hsieh seem have a different understanding of the potential of evidence to inform policy. From a health economist's perspective, it is unclear how studies on the retrospective value of drug expenditure should inform policy about purchasing and adopting new drugs. Is it intended to be used by decision makers such as those in the US who until recently have resisted routine use of HTA/CEA or comparative effectiveness studies to inform decisions about purchasing and adopting drugs? (Chandra, Jena et al. 2011) Is it intended to inform general policies on drug adoption? For example, "positive association between the adoption of pharmaceutical innovation and health suggests that excluding new drugs to save money is unlikely to be wise" (Sloan and Hsieh 2007 p. 273). Alternatively, it is framed as evidence to support caution against public policy that could "inadvertently harm an innovative industry" (Sloan and Hsieh 2007 p. 275). Or ultimately, as evidence to inform a policy of less, or no, price control:

"Conversely, those countries with stringent controls on prices will reduce the rate of productive innovation worldwide below what it would be in the absence of such controls and, in terms of the more narrow self-interest, deny access of their populations to recent and important innovations." (Sloan and Hsieh 2007 p. 275)

Second, discussions about the results of these studies of the value of improved longevity from new drugs reveal a misunderstanding in the pharma-economic literature about the additive value of quality of life gains and life expectancy gains. In such studies, the estimate of life years gained due to additional expenditure is typically assigned a monetary value. It is reasonable to assume that the monetary value that is used is not adjusted by the quality of life of these years. This assumption can be made because this point is not discussed in these studies. Researchers and authors frequently infer or claim that such estimates of value of life years gained underestimate the full benefit of these new drugs because they do not include the increase in quality of life that occurs without a gain in duration of life. For example, in reference to the result quoted above of the ten to one ratio of benefits of extended quantity of life to costs of drug expenditure, the Sloan and Hsieh conclude that:

Not considering the value of improvements in quality of life, such as from reductions in pain, emotional health, and symptoms from short term illnesses, should lead to a substantial underestimate of the value of health. (Sloan and Hsieh 2007 p. 273)

¹⁷³ **The "Catch 22" of research that uses studies by US pharma-economists who publish in the mainstream economic literature or as working papers.** The authors are not required to reveal potential conflict of interest in the academic economic literature, nor in their working papers. However, when questioned in private, they are happy to reveal this relationship but deny that it causes any conflict of interest. However, because this revelation occurs in the private domain, I cannot refer to it in a published paper or a thesis. The possibility that there is a conflict of interest cannot be discussed in the public domain, without the private revelation of association with a pharmaceutical company being placed in the public domain.

Is it reasonable to claim that additionally counting the benefits of improvements in **quality of life** would necessary increase this initial estimate of the monetary value of health gains from new drugs? There are two reasons why this inference, which seems to be uncontroversial to pharma-economists, is unlikely to be accepted by health economists.

First, some of the main sources of extended quantity of life are not years of perfect quality of life, therefore, if we are additionally considering quality of life gains (with no increase in quantity), the previously fully valued additional years of life would need to be devalued to account for their less than perfect quality. Consider the examples of HIV drugs and dialysis. The additional life years from pharmaco-therapy for both of these conditions is not in doubt, however, the quality of life for people with HIV and undergoing dialysis is far from perfect (Campsmith, Nakashima et al. 2003; Lin-sun, Sathick et al. 2008). Assume for the purpose of this argument that improvements in quality of life gains can be attributed to pharmaco-therapy as distinct from other inputs and innovation using retrospective uncontrolled studies. Why would we expect that additionally considering improvements in quality of life for years that remained constant in length would mean that the quantity of life years already valued should not be adjusted down?

Second, prescription drugs do not only have health benefits, they have associated health costs. These studies do not adjust the quantity of life gains from new drugs by the loss in quality and quantity of life due to hospital admission from adverse drug events. The loss in quality of life from addiction to prescription drugs should be included in the estimate of the value of the net health gains of increased drug expenditure, if the additional positive benefits are included.

The practice of assuming that a monetary value of quantity of life gains from new drug underestimates the full benefit of the additional benefit of new drugs is difficult to support. This is particularly the case when, by applying a full monetary valuation of a year of life to these life year extensions, it is implicitly assumed that the quantity of life gains are at full quality.

7.3 Group 2 evidence

Are the results from this group of studies sufficiently rigorous to combine with an estimate of the costs of R&D to estimate a social return on investment? From a health economic perspective, the validity of both this type of analysis and the conclusions drawn by Lichtenberg and by Sloan and Hsieh are questionable. How accurately can either the health gain attributable to new drugs or the incremental cost of additional drugs be assessed at this aggregate level? And what about the additional costs of all the other resources required for the delivery of drugs?

There is one possible application of this result to reimbursement decisions. This evidence can be used to argue **against** threshold pricing of new drugs at the maxWTP (See Appendix 7). The main theme of these studies is that the additional expenditure on these new drugs is more than adequately justified by the additional health gains because the additional life years gained have a dollar value much greater than the additional expenditure on the drugs. Following this line of reasoning, if all new drug provided to an institution had an incremental price effectiveness ratio (*IPER*) of k , the maxWTP, then the historic evidence of a 10 to 1 ratio of the additional costs of drugs suggests new higher price drugs are not going to result in this historic return; the additional expenditure on new drugs is no less than the maxWTP for the incremental health effects associated with that new drug. The additional costs to consumers of R&D now has no net benefit to consumers, where the net benefit to consumers is defined as the additional value of health gains less the additional costs of purchasing these drugs.

In conclusion, these studies might have some role to play in developing the case for lobbying for higher prices for new drugs or supporting existing high prices for new drugs, however, it is not clear whether they have any role to play in decisions made by regulators and purchasers who use

prospective HTA/CEA or make decisions about drug price regulation. The exception is the provision of an argument against full value pricing.

8 Group 3: Two studies that were reviewed closely but rejected

Three studies were cited in numerous other studies as providing analysis of the social return on pharmaceutical R&D but when reviewed, were found to have not provided this evidence: Murphy and Topel (1999; 2006) and Lakdawalla et al. (2009).

8.1 Murphy and Topel

Two of Murphy and Topel's studies (Murphy and Topel 1999; Murphy and Topel 2006) were reviewed. These studies have a significant overlap in methods and messages. The authors developed methods to provide an economic value to observed gains in life expectancy in the US. This economic value is based on a particular derivation of the maxWTP for an additional year of life.¹⁷⁴ In their 1999 study, they concluded that:

The historical gains from increased longevity have been enormous, on the order of \$2.8 trillion annually from 1970 to 1990. The reduction in mortality from heart disease alone has increased the value of life by about \$1.5 trillion per year over the 1970 to 1990 period.

To put these gains into the perspective of the benefits of past medical research, the authors take this additional value and reduce it by the health expenditure over this period. They then demonstrate that the total public and private medical research over that period was substantially lower than the difference between the economic value of gains in life expectancy and the expenditure on health. They use this result to conclude that past investment in medical innovation was clearly worthwhile. In their 1999 paper they infer from their results that the future gains from medical research are high, using the following argument:

The potential gains from future innovations in health care are also extremely large. Eliminating deaths from heart disease would generate approximately \$48 trillion in economic value while a cure for cancer would be worth \$47 trillion. Even a modest 1 percent reduction in cancer mortality would be worth about \$500 billion. Unless costs of treatment rise dramatically with the application of new medical knowledge, these estimates indicate that the social returns to investment in new medical knowledge are enormous.

The authors do not explicate their reasons for inferring the \$47T in economic value for curing cancer and the \$48T for eliminating deaths from heart disease are additive. Nor do they question whether other conditions such as dementia could offset these gains.

In their 2006 paper, the authors provide an upper limit to their estimate of how much should be invested in medical R&D and the associated treatment, for a given objective, expressed as a percentage reduction in mortality:

For example, take our estimate that a 1 percent reduction in cancer mortality would be worth about \$500 billion. Then a "war on cancer" that would spend an additional \$100 billion on cancer research and treatment would be worthwhile if it has a one in five chance of reducing mortality by 1 percent and a four in five chance of doing nothing at all

¹⁷⁴ The reader is referred to their paper for the details of this method.

That is, the authors' view is, because the maxWTP of a 1% reduction in death from cancer is \$500B, society should be willing to spend an additional \$100B with only a one in five chance of the \$500B outcome. This is a "no expected return to consumer on consumer investment in R&D" outcome, involving significant risks which are not accommodated in this analysis via the opportunity cost of this additional investment. It is also a non-marginal approach to analysing optimal expenditure - spend until the total costs are equivalent to the total benefits, without regard to whether an additional dollar of expenditure will lead to an increasing or decreasing marginal gain in average life expectancy at birth. Furthermore, there is no evidence presented in their research linking additional medical innovation directly to additional health gains. The health budgets (private and public) appear to be unconstrained; the opportunity cost to their expansion is not explicated. There is also no discussion about the impact on the health workforce such increased numbers of new technologies would require; not only in terms of the increased employment, but also the increased training and infrastructure. And finally, the sheer size of this additional expenditure on treatment and medical research relative to the GDP suggests that the simplistic approach of letting value of health gains drive R&D pays little regard to the economics of economic growth and public finance. At the time of their published study, total US expenditure on health in 2005 was 15.7% of GDP, which in 2005 was USD12.5T (where T is 10^{12}).¹⁷⁵ If the expenditure on medical research and treatment increased two or three fold, how fast would the US GDP have to grow to accommodate this increase in expenditure without reducing expenditure on other areas?

However, from the perspective of many other participants in the political economy of new drugs, the authors' results provide a compelling case for increased investment in pharmaceutical R&D. The contribution of medical innovation to longevity is typically expressed in the business press as evidence of the value of medical innovation.

The return on past medical innovations has been nothing short of astonishing. For example, at the onset of the baby boom generation, heart disease and stroke were near death sentences. The chances of surviving each today are 60% and 70% greater, respectively, thanks to cutting-edge medicines and surgical techniques. (Pipes 2011)

The following citation of Murphy and Topel's demonstrates how the results of their first study influenced the NIH's attitude to ongoing investment in medical research.

In May 2000, the U.S. Congressional Joint Economic Committee (JEC) issued The Benefits of Medical Research and the Role of NIH, which examined the role of federal funding for medical research and the benefits that derive from that research. The Committee report states that, although the rate of return on publicly funded research is difficult to quantify, the benefit of increased life expectancy in the U.S. as a result of advances in health care creates annual net gains of about \$2.4 trillion (using 1992 dollars). The Committee concluded, "if only 10 percent of these increases in value (\$240 billion) are the result of NIH-funded medical research, it indicates a payoff of about 15 times the taxpayers' annual NIH investment of \$16 billion".¹⁷⁶

Murphy and Topel research is cited as having demonstrated that there is likely to be under investment in R&D; in the US at least. Consider for example:

¹⁷⁵ Source: OED statistics, www.oecd.org Accessed: 21-02-12

¹⁷⁶ This 2001 policy statement from the NIH office of Technology Transfer is available from their website :http://www.ott.nih.gov/policy/policy_protect_text.html#a Accessed: 21-02-12

Although recent research has documented the significant benefits associated with medical and pharmaceutical research, and even suggested that the United States might be currently under investing in R&D, (Santerre and Vernon 2006 p. 243)

Also:

For example, econometric estimates reported in Lichtenberg (Lichtenberg 2002) suggest that for every \$US1345 invested in pharmaceutical R&D, the US gains approximately 1 human life-year. Given that recent estimates for the 'value' of a US life-year range between \$US100 000 and \$US160 000 (Murphy and Topel 1999; Cutler and McClellan 2001) the social returns to increased future levels of industry R&D will almost certainly generate benefits in excess of costs. This is consistent with research that suggests the US is currently 'under investing' in medical and pharmaceutical R&D (Murphy and Topel 1999). (Cook, Hunter et al. 2009 p. 361)

But can this evidence inform policy about price increases for drugs in order to finance more R&D by increasing prices? From a health economic perspective, there are concerns about accepting a monetary valuation of longevity that is not adjusted by quality of life. (See Section 7.2, p.208.) It is also difficult to accept the method of attributing life gains to technological innovation rather than other drivers that also require investment, for example, the medical workforce. Taking a non-marginal approach to the analysis is also difficult to accept, as is the failure to consider the full costs of implementing any gains from medical innovation. And finally, it is unclear how historic information, even if it were accurate, could inform decisions about prices of individual drugs. The question of whether this type of analysis has any value other than as further support for the lobbying process is left to the reader.

8.2 Lakdawalla, Goldman, Michaud, Sood, Lempert, Cong, de Vries, and Gutierrez

The study compared two policies, both of which aimed to improve use of medications by patients in the US for whom costs represented a barrier. The simulation models used to test these policies are premised on evidence that improved compliance, as a consequence of reduced financial barriers improves health. The first policy was pharmaceutical price control which would reduce prices to both firms and consumers. The second was increased prices (or no decrease) to firms plus patient subsidy to reduce the cost to the patient. The authors describe the first policy as representing the trade-off between: i) lower prices, improved access and ii) less future drugs and hence less future increases in health. The authors characterise the second policy as having no trade-off¹⁷⁷; improved access today through lower prices is achieved at no cost to future number of new drugs because the prices to firms are not lowered.

The models included only two drivers of health benefits to the population: the health benefits of improved access to drugs today due to lower cost to patient; and the health benefits of additional future drugs financed by economic rent from higher prices. Given that both policies included the driver of more health today (lower prices to consumers) but only one included a loss due to less future health benefits, it is no surprise that the authors found that a policy of subsidy to consumers but no change in price to firms was preferable to one of reduced price to firms and consumers. But were these models fully, or at least equivalently, specified? No. The first model includes a foregone benefit of the lower prices to consumers as a result of price control, (less rent to producers), whereas in the second

¹⁷⁷ It is difficult to understand why an economist would state that a policy that required an additional expenditure (the subsidy) had no trade-off.

model, the forgone benefit of allocating resources as a subsidy to consumers (less expenditure on other forms of health) is not included. The authors claim that the second policy does not have a trade-off, however it is more accurate to say that the model does not specify the trade-off, which does exist.

Specifically, the following drivers of health benefits for the current and future populations were excluded from the model: alternative ways to spend both the additional costs of the drug subsidy and the additional cost of future drugs. That is, this study did not include an estimate of the foregone benefits of the subsidy. Nor did it include the foregone benefits of the additional financial costs to consumers of the additional future drugs. Therefore, the model did not fully specify the consequences of either policy. Given that these effects could be expected to be different across each policy,¹⁷⁸ the failure to express the full consequences of these policies results in a bias; towards to the policy of a subsidy on price.

And finally, Lakdawalla et al. (2009) was reviewed because it was cited in the PhRMA website as presenting evidence that.

“Price controls depress innovation and shorten life expectancy, according to research by RAND that was published in Health Affairs.”^{179,180}

The claim made on the PhRMA website that price controls “shorten life expectancy”, is not consistent with the claims made in the cited evidence. The authors did claim that they had estimated that additional cost of the policy of price control as \$50K per person whereas the net savings from the alternative policy were \$30K per person. It is not clear how these results could be inferred as saying that life expectancy would shorten as a consequence of price control policies. The authors did not provide an estimate of the return on pharmaceutical R&D funded via higher drug prices and it cannot be inferred from their estimates.

8.3 Conclusion

In conclusion, these three studies do not provide the evidence of the return on investment by consumers in pharmaceutical R&D via higher prices. Whether these studies have any practical value in pharmaceutical policy, other than to assist the lobbying process, is unclear.

9 Group 4: The empirical evidence of the return to consumers from higher prices

Two peer reviewed studies (Lichtenberg 2004; Santerre and Vernon 2006) estimated the social value of investment in pharmaceutical R&D. Lichtenberg estimated that every USD926 of investment in pharmaceutical resulted in an additional year of life, giving a benefit/cost ratio of USD162 worth of additional life years for USD1 spent on pharmaceutical R&D. Santerre and Vernon estimated that for every USD1 consumers invest in higher prices, there is at least an extra USD28 worth of additional life years for US consumers. This evidence seems to suggest that the current pattern of pricing above a

¹⁷⁸ The additional financial costs to the health budget of the subsidy plus maintained price is higher than the alternative state of the world where there are less drugs (less future innovation) and the price of the drugs is controlled. Hence, if the health benefits foregone due to this additional expenditure are included in the model, this will increase the health benefits associated with the price control subsidy.

¹⁷⁹ Source: <http://www.phrma.org/media/releases/phrma-statement-regarding-benefits-us-innovation> Accessed 28-12-2011. The actual citation was not provided on this webpage but this was then traced back to the Rand Website and identified as Lakdawalla et al. (2009). It was then included as part of the review.

¹⁸⁰ The study was criticised as most likely overestimating the long run costs of price control (Scherer 2009).

threshold price has short term costs but these are outweighed by long term benefits of more health for the population.

How robust are these estimates to their underlying assumptions? Are the results generalisable to settings outside the US? Are these results suitable for informing the decision to invest in pharmaceutical R&D via higher prices?

Both of these studies had two empirical components: an econometric analysis and a simulation that combined the results of the econometric analysis with other variables to reach an estimate of the net benefit of higher prices. These studies are reviewed and summarised in this section using the following structure: i) the study's stated conclusion; ii) clarification of the results and assumptions of the econometric analysis that underpins the study; iii) clarification of the results and assumptions of the simulation that uses the results of the econometric study; iv) using these clarifications, re-estimate and qualify the study's stated conclusion; and v) discussing the implications for the Reimburser's decision to pay an above threshold price.

9.1 Result 1: USD162 worth of additional life years for USD1 spent on pharmaceutical R&D

Lichtenberg's study of the relationship between pharmaceutical innovation and longevity used 41 years of data (1960 to 2001) to develop an estimate of the cost effectiveness of additional expenditure on pharmaceutical R&D and publically financed expenditure on health and an estimate of the cost benefit ratio of additional expenditure on R&D.

9.1.1 Lichtenberg's conclusion

In the abstract for his paper, Lichtenberg describes his main conclusion as follows:

The empirical analysis provides support for the hypothesis that both medical innovation (in the form of new drug approvals) and public health expenditure contributed to longevity increase during the period 1960–2001. The estimates imply that the public health expenditure needed to gain one life-year is about US\$ 9640, and that the pharmaceutical R&D expenditure needed to gain one life-year is about US\$ 926.

To clarify Lichtenberg's conclusion, it is represented as a choice between two strategies

- 1) Invest \$1M in pharmaceutical R&D
- 2) Invest \$1M in increased publically funded health expenditure

He concludes that investment in pharmaceutical R&D is ten times more cost effective than increased public expenditure on health in increasing longevity by comparing the value of an increase in expenditure.

He estimates the return to pharmaceutical R&D as follows:

$$k\Delta LY^R (\Delta C)^{-1} = k(ICER^R)^{-1} = 150,000(926)^{-1} = 162$$

He estimates the return to increased publically funded health expenditure as follows:

$$k\Delta LY^P (\Delta C)^{-1} = k(ICER^P)^{-1} = 150,000(9640)^{-1} = 16$$

Where:

- 1) k = USD150,000 is the average value of a human life
- 2) ΔLY^R is the change in life years for the US population for a given change in expenditure on pharmaceutical R&D

- 3) ΔLY^P is the change in life years for the US population for a given change in publically financed expenditure on health
- 4) $\Delta C = \text{USD } 1\text{M}$ is the expenditure on the strategy
- 5) $ICER^R = \text{USD } 926$ per LY is the cost per additional life year of additional R&D expenditure (derivation reviewed in text)
- 6) $ICER^P = \text{USD } 9,640$ per LY is the cost per additional life year of additional publically financed health expenditure (derivation reviewed in text)

The decision analysed is the choice between additional expenditure on Pharmaceutical R&D and additional publically financed expenditure on health. Lichtenberg concludes the former is 10 times more cost effective than the latter ($162/16=10$). He reaches this conclusion using an estimate of the longevity increase from additional expenditure on these two strategies derived from his econometric model. When he combines this result with an estimate of the average value of a human life, he achieves a cost benefit ratio of 162 to 1 for increased expenditure on pharmaceutical R&D. In the words and punctuation of the author:

This figure implies that the benefit-cost ratio of general medical expenditure is 16, and that the ratio for pharmaceutical R&D is 162! (p. 385)

So how did Lichtenberg arrive at this conclusion? Essentially he performed two analyses: i) an econometric analysis that investigates the relationship between four independent variables and life expectancy at birth and ii) a simulation that combined six assumptions, one of which was the result from the economic analysis. Each of these analyses are reviewed in turn and then I revisit this conclusion.

9.1.2 Lichtenberg's econometric analysis

The four independent variables, the dependant variable and the coefficients from his econometric analysis are summarised in Table 12. He tested five models, and the model that was used to estimate the cost effectiveness of pharmaceutical R&D was linear and included four variables :

- 1) NME_t Number of NMEs in year t
- 2) NME_{t-1} Number of NMEs in year t-1
- 3) EXP_PUB_{t-1} Public sector expenditure on health
- 4) LE_{t-1} Life expectancy at birth in year t-1

Although Lichtenberg describes his study as exploring the relationship between medical innovation and longevity, the only medical innovation he specifies in his model is NMEs.

Lichtenberg summarises the result of this econometric analysis as: "the empirical analysis provides support for the hypothesis that both medical innovation (in the form of new drug approvals) and public health expenditure contributed to longevity increase during the period 1960–2001". His interpretation of the coefficient for NME approvals is: "Evaluating the elasticity at the sample mean implies that, if one additional drug were approved every year, life expectancy at birth would increase by 0.135 years (1.62 months).

This interpretation (attribution of the elasticity in longevity to additional drugs) requires that we assume there is no correlation between NMEs and other forms of medical innovation, that is, that the entire impact of medical innovation over the period 1960 to 2001 can be attributed to pharmaceutical innovation. Lichtenberg justifies the specification of his model (and hence his implicit assumption) as follows:

We estimated the longevity model using annual U.S. time-series data on life expectancy, health expenditure, and medical innovation for the period 1960–2001. Reliable annual data are available for only one type of innovation: new drugs. Although new drugs represent only one type of medical innovation, pharmaceutical R&D accounts for a significant fraction of total biomedical research. In 1993, pharmaceutical industry R&D accounted for 61.3% of industry-funded health R&D, and for 31.0% of total health R&D. (p. 386)

The R^2 of Lichtenberg's linear regression is 0.996. This result suggests that a substantial degree of the variation in longevity is captured in the specified equation. However, this does not mean that the equation is correctly specified because there is a significant scope for unspecified independent variables to be correlated with the specified independent variables. Therefore, it is not appropriate to conclude, as Lichtenberg does, that the high explanatory power of the equation provides robust evidence that the coefficient of the NME variable can be interpreted as the NME elasticity of longevity. Specifically, regardless of Lichtenberg's argument for the significance of pharmaceutical R&D as a component of health R&D, it is not reasonable to attribute the coefficient of NMEs in his expression, entirely to the effect of NMEs, as Lichtenberg has done.¹⁸¹ Over the period of 1960 to 2001, some of non-pharmaceutical innovations include: diagnostic imaging; cardiac surgery; the digital information revolution; and the changes in hospital financing. Furthermore, innovation in health care is not necessarily only the result of investments in R&D for patented technologies. In order to account for the possibility that other forms of medical innovation are captured in the coefficient for NMEs, I will use an alternative assumption in the respecified simulation: only 50% of the estimated effect is attributed to NMEs (rather than 100% as Lichtenberg has done).

Table 12 Results from econometric analysis, Lichtenberg

<p>Data: 1960 to 2001 US data on longevity, expenditure on health and NME approval.</p> <p>Dependent variable is: Life expectancy at birth in year t</p> <p>Explanatory variables: (Co-efficient)</p> <ol style="list-style-type: none"> 1) NMEt Number of NMEs in year t (0.0047) 2) NMEt-1 Number of NMEs in year t-1 (0.0032) 3) EXP_PUBt-1 Public sector expenditure on health (0.0088) 4) LET-1 Life expectancy at birth in year t-1 (0.7975) 5) Intercept (0.5958) <p>$R^2 = 0.996$</p>
--

9.1.3 Lichtenberg's simulation

Lichtenberg states that: "The estimates (*of the coefficients from the econometric analysis*) imply that the public health expenditure needed to gain one life-year is about US\$ 9640, and that the pharmaceutical R&D expenditure needed to gain one life-year is about US\$ 926." Lichtenberg

¹⁸¹ The evidence cited by Lichtenberg that 61.3% of industry financed health R&D is by the pharmaceutical sector and 31% of total health R&D is financed by this sector would not appear to support the specification of the innovation drivers in his model as including only NMEs.

performed a simulation using six assumptions to extrapolate from the econometric analysis to these results of cost per life year gained. These six assumptions are summarised in Table 13 and alternative assumptions are also listed. These six assumptions were combined in a series of calculations, reproduced below to obtain a benefit to cost ratio of the social value of life years gained from additional expenditure on pharmaceutical R&D. Lichtenberg's result is 162:1 whereas the revised result of the same metric is 23:1.

Table 13 Lichtenberg's assumptions and alternatives

Simulation Assumptions	Lichtenberg	Alternative	Sources and issues
1) Long-run Elasticity of NMEs derived from regression coefficient	0.039	0.0195	Sourced from Lichtenberg's econometric analysis. Alternative assumes only 50% of this effect can be attributed to NMEs
2) Mean longevity in years over the period of his model	73.1		From Lichtenberg's analysis
3) Mean NMEs per year over the econometric model	21.1		From Lichtenberg's analysis
4) Average number of births a year	4.0M	3.67M	Lichtenberg states: "There are approximately 4 million Americans born each year" (no source provided) The average number of annual births over 1960 to 2001 was 3.67M. (Source: derived from Department of Health and Human Services, National Center for Health Statistics, web: www.dhhs.gov)
5) Annual cost of permanent unit increase in exogenous variable (R&D cost per NME)	\$0.5B	\$1.1B	Lichtenberg states: "The average cost of obtaining FDA approval of a new drug is generally thought to be in the neighborhood of US\$500 million" (no source provided) Alternative is an estimate at time of Lichtenberg's publication. ¹⁸²
6) Value of life year gained	\$150K	\$100K	The alternative assumption is consistent with Santerre and Vernon's assumption (Santerre and Vernon 2006)

¹⁸² The detailed reasoning behind this alternative assumption is as follows. The relationship derived statistically by Lichtenberg is between the number of NMEs and longevity in US population; not the expenditure on pharmaceutical R&D and longevity. Lichtenberg simulates the R&D cost per NME by dividing an unattributed estimate of cost of R&D (Assumption 5, Table 13) by a simulated estimate of life years gained per additional NME (Result 8, Table 14). His justification of the choice of \$0.5B is that "the average cost of obtaining FDA approval of a new drug is generally thought to be in the neighbourhood of US\$500 million." (with no attribution). At the time Lichtenberg's paper was published (2004), DiMasi et al.'s estimates of the capitalised out-of-pocket costs of R&D per molecule brought to market with a mean approval date of 1997 (USD809M) had been published (DiMasi, Hansen et al. 2003) In this paper the authors estimated that the capitalised cost for drugs brought to market in 2000 was \$1.1B. Therefore, the alternative estimate is no less plausible than USD0.5B as an assumption. For a discussion of why the capitalised costs are the more appropriate than uncapitalised costs in this context, see DiMasi, Hansen et al. (2005)

Table 14 Lichtenberg's simulation (Results)

Simulation Results (numbers results in bracket correspond to this table and previous table)	Lichtenberg	Alternative	Description
7) Marginal Long-run effect (1)x(2)/(3)	0.135	0.068	The higher this coefficient, the lower the cost per effect of pharmaceutical innovation.
8) No. Of life years gained per year from permanent unit increase in exogenous variable (4)x(7)	539,973	249,560	This is the increase in life years from one additional NME. The higher the births, the higher this estimate.
9) Cost of R&D per increase in one life year (5)/(8)	\$926	\$4407	This alternative cost of R&D per additional life year gained is higher than Lichtenberg's estimate.
10) Benefit cost ratio of social value of life years gained to R&D expenditure (6)/(9)	162:1	23:1	

Additionally, the cost per life year gained from public expenditure was estimated by Lichtenberg \$9,640 and was recalculated using the revised estimate of births to provide an estimate of \$10,489.

9.1.4 Lichtenberg's conclusion revisited

The first strength of Lichtenberg's estimate is that it is an attempt to provide an estimate of the incremental gain in life years for an additional NME, which is an improvement on models that double count the benefits of innovation of previous NMEs in following NMEs. (For example, see Comanor's discussion of Wu in Comanor (1986)). A second strength is that it compares the costs of R&D with the benefits. However, Lichtenberg's results are not robust to his models' assumptions. A set of assumptions that are more plausible than those used by Lichtenberg were used to develop an alternative estimate of the cost per life year gained per dollar of R&D. At \$4407, this estimate is 4.8 times higher than that provided by Lichtenberg. But even at this higher cost per LYG, the strategy of investing in Pharmaceutical R&D still appears more cost effective compared to the cost per LYG from publically financed health expenditure. (\$10,489)

But does it make sense to compare the cost per LYG of pharmaceutical R&D with that of publically financed health expenditure and assume that this is the evidence required for a choice between these two strategies? In simple terms, Lichtenberg compares:

- 1) the health effect of publically financed health care with the financial costs of achieving this effect; and
- 2) the health effect of additional drugs with some of the financial costs of achieving them.

The health gains from new drugs are the result of the consumption of the drug, not the listing of an NME. Therefore, while the investment in R&D represents the financial costs of achieving an additional NME, they do not represent the entire financial costs of achieving these health gains. In the

US, these costs are currently included in private health expenditure (not included in this analysis) and public health expenditure (included in this analysis).

We can assume that the expenditure on pharmaceutical R&D would substantially underestimate the public and private health expenditure associated with achieving the LYG associated with new drugs.¹⁸³ Therefore, even if we accept the analysis that led to Lichtenberg's estimates of cost per LYG, his inference of the relative cost effectiveness of publically financed health care and investment in pharmaceutical R&D is without foundation. For example, on the basis of this evidence, it would not be rational to stop public sector subsidy of drug costs in the US and instead spending these funds on R&D.

9.1.5 The Reimburser's decision and Lichtenberg's conclusion

Can Lichtenberg's result (original and revised) be used to inform the Reimburser?

The Reimburser's decision is whether or not to accept the firm's offer price, which is above the economic threshold. The critical evidence to inform the decision is whether the return to consumers (in the form of additional health benefits from the same budget) as a consequence of this higher price outweighs the loss to consumers (reduced health gains today). Furthermore, she has the opportunity to compare the increase in expenditure on a new drug to the increase in expenditure on other publically financed health services.

First, she needs to clarify exactly how much of the health budget is being invested today to achieve the additional years of life. Lichtenberg's result is the life years from an additional dollar of R&D expenditure: specifically, the R&D cost per additional life year is \$926 (\$4407, revised). In order to be extrapolated to the additional cost to the health budget, this amount needs to be increased to account for the evidence that around 20% of economic rent from increased prices is allocated to research on NMEs.¹⁸⁴ This suggests that five times this amount would need to be invested via higher prices into pharmaceutical R&D to achieve a given increase in R&D expenditure. Therefore the financial cost today per life year gained from an increase in drug prices is \$4,630 (original) or \$22,035 (revised). This revision does not apply to the public expenditure on health which in turn makes this expenditure at \$9640 more cost effective compared to expenditure on additional R&D via higher drug prices.

But even at this higher financial cost per life year gained, higher prices seem like a reasonable “bang for the buck”. However, as discussed in the previous section, this metric does not consider the entire financial cost to the health budget holder; it excludes the incremental financial cost of adopting the new drug. The surplus generated by the clinical innovation is allocated between consumers and producers via the price per health effect of the new drug (a conventional CEA). If the equilibrium price of the reimbursement process is the maximum price that the Reimburser is willing to pay (Chapter 8), then we would predict that the value of the health gains to consumers is entirely offset by the price that is paid per unit effect by the Reimburser; the entire value of the additional health gains is allocated to the producer therefore none of the Reimburser's investment into R&D via the higher price is returned to the consumer. And finally, this analysis does not consider other forms of investment today for improved efficiency in the future as an alternative strategy. Therefore, Lichtenberg's result,

¹⁸³ While the proportion of total revenue that is allocated to R&D across the industry is difficult to establish from available data, the financial reports for Pfizer show that in 2009 around 15.7% of total revenue was invested in R&D. (Firm revenue represents purchaser expenditure.)

¹⁸⁴ The application of Vernon's equation in the OECD report found that 30% of an increase in revenue would be used for R&D and the remainder used for profit and cash flow. The same report used an estimate of 67% of the total R&D budget being allocated to NMEs and the remainder allocated to other research related activities. (International Trade Administration 2004)

even adjusted for more plausible assumptions, is not sufficient to justify accepting the higher offer price of a new drug.

9.2 Result 2: For every dollar of higher prices today there is a return of USD28 worth of additional years of life

Santerre and Vernon provided this conclusion to their study:

This simple first approximation places the cost of our hypothetical price control policy at between \$19.7 and \$21.8 trillion in terms of value of lives lost or at \$23 billion worth of lives lost per new drug. This range of figures is over 28 times larger than our estimated range for the consumer surplus gains produced by this drug price control policy (\$176-\$767 billion). This leads to the conclusion that a price control regime of the type described here would have done much more harm than good from a social welfare perspective. (Santerre and Vernon 2006 p.243)

Their conclusion was based on a comparison of the number of life years possible if the firm's offer price was accepted ($\Delta LY^P(1+n)$) valued at the average value of a life year k compared to the number of life years possible from fewer new drugs that would have been developed at a lower price.

9.2.1 Santerre and Vernon's econometric analysis

The authors made statistical estimates of the expenditure on drugs that would have occurred had the growth in US drug prices been controlled at the same rate as the prices in the rest of the medical sector.

Their first objective was to estimate a demand curve for pharmaceuticals. They used 40 years of data to estimate the demand for pharmaceuticals in terms of a number of variables, the log of: i) out-of-pocket real price of drugs; ii) out-of-pocket fraction; iii) real price of drugs; iv) out-of-pocket real price of medical care; v) real GDP per capita less premiums per capita; and vi) one-year lagged measure of real pharmaceutical expenditures per capita. Items ii) and iii) were substituted for item i) in the unrestricted equations. The authors found a negative coefficient and statistically significant result for the three drug price variables. They also found a positive and statistically significant result for medical care, which they interpret as evidence that pharmaceuticals and medical care are substitutes. And finally, they found a positive and statistically significant coefficient for income.

The second objective of the empirical analysis was to develop an estimate of the gain in consumer welfare had a hypothetical price control policy been operating. Their estimate took into account the income and substitution effects of changed price. They describe their estimate as representing:

... the range of savings that would have accrued to consumers at the end of the 20-year period if government had held the rate of growth of drug prices to the same rate of growth as the overall CPI. It also reflects the future value of annual improvements in health because of better financial access to existing drugs as a result of the price control. (Santerre and Vernon 2006 p. 242)

9.2.2 Santerre and Vernon's simulation

The authors constructed a simulation populated by estimates from a range of studies, including one result from their empirical analysis. They estimated the value of the additional NMEs that were developed as a result of the higher prices that actually occurred; the payoff to not regulating price. The derivation of this estimate is presented in Table 15, but framed as the benefits of maintaining higher prices rather than the cost of not paying them. The key result of this simulation is that there is a return of at least USD28 in social surplus for every additional USD1 of consumer surplus foregone in higher prices.

Like Lichtenberg's simulation, two of the assumptions specified in Santerre and Vernon's simulation have alternatives that are more plausible and the results of their simulation are sensitive to these assumptions. First, the authors use a related but not matched analysis that provided an estimate of the reduction in R&D that corresponds to the reduction in firm revenue due to price control (Assumption 2 in Table 15) (Giaccotto, Santerre et al. 2005). This estimate of the reduction in R&D is 38% to 150% of Santerre and Vernon's estimate of reduced revenue available to the firm. That means that if the expenditure on new drugs is decreased by \$1B, then there would be a reduction in R&D in the order of \$0.4B and \$1.5B. Another option available to Santerre and Vernon would have been to use the equation developed by Vernon in a separate piece of work, namely that around 20% of total economic rent is invested in NME R&D.¹⁸⁵ In this case a reduction in expenditure of \$1B would lead to a reduction in new drug R&D of \$0.2B. Given that this is translated directly to a reduction in the number of NMEs using the estimates of the costs of bring one drug to market, the use of Giaccotto et al's result would result in a loss in future NMEs that is between 2 and 7 times higher than that estimated using Vernon's equation. Second, the authors used a cost of R&D per additional life year from an earlier non-peer reviewed version of the published analysis by Lichtenberg, reviewed above.¹⁸⁶ In the alternative Santerre and Vernon simulation, I used the alternative estimate of USD4,407, the derivation of which is shown in Table 15 and Table 16. There are other assumptions that are open to debate.¹⁸⁷

The alternative estimate of USD4.5 worth of life years gained for every USD in increased prices is lower than that obtained by Santerre and Vernon of USD28. As with the alternative estimates from Lichtenberg's simulation, the alternative specification is not intended to represent a better estimate of the social surplus return on US consumer's investment in R&D through higher prices. Instead it illustrates that if assumptions were used that are at least as plausible as those by Santerre and Vernon, a lower result is obtained.

¹⁸⁵ The application of Vernon's equation in the OECD report found that 30% of an increase in revenue would be used for R&D and the remainder used for profit and cash flow. The same report used an estimate of 67% of the total R&D budget being allocated to NMEs and the remainder allocated to other research related activities. (International Trade Administration 2004)

¹⁸⁶ The published Lichtenberg study was peer reviewed and also covered the same period as Santerre and Vernon's study.

¹⁸⁷ For example, the assumptions that the marginal NME has the same impact on the life years saved as the average NME brought to market is not necessarily valid and it is likely to be lower. (Pekarsky 2010)

Table 15 Santerre and Vernon's estimates

Original	Range		Mid	Best
	Low	High		
Simulation Assumptions (a)				
1) Increase economic rent to firm (transferred from consumer surplus)	\$176.0B	\$767.0B	\$471.5B	\$217.8B
2) Decrease in R&D as a consequence of decreased economic rent (b)	\$264.5B	\$293.5B	\$279.0B	\$267.0B
3) Pharma R&D expenditure per additional life year (Lichtenberg)	\$1,345	\$1,345	\$1,345	\$1,345
4) Value of an additional Life year	\$100,000	\$100,000	\$100,000	\$100,000
Simulation Results				
5) Value of lives lost (sic) (c, d) (2)/(3)	\$19.7T	\$21.8T	\$20.7T	\$19.9T
6) Ratio of Value of additional lives lost (sic) to Consumer surplus transferred to Firms (1)/(11)	112	28	44	91
<p>Notes</p> <p>a. Santerre and Vernon's analysis is framed as the consequences of decreasing prices from what they would otherwise have been. In this table they are reframed as the consequence of increasing price by this amount.</p> <p>b. The final estimate in this row was not provided by Santerre and Vernon. Derived as follows: from row 1 $(217.8)/(767-176)=6.9\%$ Therefore a corresponding estimate of R&D for the last column row 2 is from row 2 $264.5B + (293.5B - 264.5B) \times 6\% = 267.0$. Results in this column are derived from this estimate of R&D.</p> <p>c. The value in Lichtenberg's study was \$926 of R&D expenditure per life year gained. Santerre and Vernon used a figure of \$1,345</p> <p>d. This is an estimate of the value of life years lost, not of lives lost as described by Santerre and Vernon.</p>				

Despite deriving an estimate of a return on consumer investment in terms of social welfare, this study did not attempt to estimate the return to consumers. This is inconsistent with the result inferred by the title of their paper: “Assessing consumer gains from a drug price control policy in the United States”. Specifically, if the entire surplus had been allocated to the producers (pricing at the maxWTP) then the return to consumers in terms of increased consumer welfare would have been zero; there would be a loss to consumers, equivalent to their initial investment, despite the increase in social welfare. The analysis also made a series of assumptions that systematically biased the estimate of the benefits of higher prices towards a larger future health benefit. For example, the authors assumed that the entire additional expenditure on drugs that was possible as a consequence of not regulating the price is allocated to NME R&D; an assumption which is not consistent with the evidence that was available at the time. Furthermore, the analysis implicitly assumed that had the price of new drugs been lowered, that consumers or health budget holders would not have invested in any other health related programs. In short, if the assumptions underlying their estimates were made more realistic, then the possibility that this return on the consumers’ initial investment is one to one is plausible. Furthermore, if we accept that at least a portion of this additional surplus was allocated as economical rent, the possibility of a loss to consumers (return is less than 1) is plausible.

Table 16 Santerre and Vernon's Simulation (alternative assumptions, no budget constraint)

Alternative	Range		Mid	Best
	Low	High		
Simulation assumptions				
1) Increased economic rent to firm (transferred from consumer surplus)	\$176.0B	\$767.0B	\$471.5B	\$217.8B
2) % of economic rent that would otherwise have been NME R&D	20%	20%	20%	20%
3) Pharma R&D expenditure per additional life year (from alternative Lichtenberg table)	\$4,407	\$4,407	\$4,407	\$4,407
4) Value of an additional Life year	\$100,000	\$100,000	\$100,000	\$100,000
Simulation Results				
5) Increase in R&D as a consequence of increased economic rent (1)X(2)	\$35.2B	\$153.4B	\$94.3B	\$43.6B
6) Value of additional life years (5)/(3)	\$0.8T	\$3.5T	\$2.1T	\$1.0T
7) Ratio of additional social surplus to consumer surplus foregone (6)/(1)	4.5	4.5	4.5	4.5

10 Conclusion

Many US pharma-economic studies claim to provide support for the claim that investment in pharmaceutical R&D has a significant return. In most cases these studies support the policy narrative rather than provide specific evidence of the benefit to cost ratio of pharmaceutical R&D. These studies reveal a number of differences in the way that pharma-economists view the idea of benefits and costs of pharmaceutical innovation and pharmacotherapy.

The estimates of the return on pharmaceutical R&D from Lichtenberg and Santerre and Vernon are likely to be significant overestimates of the social return on increased investment via higher prices to consumers. These two studies raise an important methodological issue: Is the distribution of the increase in social welfare across consumers and producers relevant to the reimbursement decision? This issue is addressed in Chapter 10.

Appendix 3: Beyond the backyard- US gains in life expectancy in an international context

"I see the world, in my backyard. I see the world, from my kitchen window. I see the world, and it looks good to me." "Backyard Blues", Tav Falco's Panther Burns

1 Introduction

Appendix 3 presents some data that places the evidence of the longevity gain to the US in the context of gains to three other countries. This Appendix is referenced in Chapter 2 as support for the development of an alternative political economy of new drug price.

2 Background

The US policy narrative rests on the evidence of the substantial contribution of new drugs to improved life expectancy. A notable omission in this narrative is that the gains in the US since the 1960's are smaller compared to the rest of the OECD; significantly smaller. Furthermore, the US has one of the lowest life expectancies within the OECD and the highest level of pharmaceutical expenditure as a percentage of GDP.

The decision by US pharma-economists to not look beyond their own backyard when constructing their policy narrative removes the requirement for these authors to identify reasons why US life expectancy has not improved as much as other less wealthy OECD countries. Instead the focus of this pharma-economic narrative is on estimating the contribution made by pharmaceutical innovation to this growth in longevity and to use this estimate to justify the continued investment in pharmaceutical R&D. How significant is this difference between the US and the rest of the OECD? If this difference is included in the policy narrative, how does this change the narrative and the research agenda?

3 The evidence beyond the backyard

Consider the following three graphics (All sourced from the OECD statistical data). The four countries that are being compared are: Australia, Canada, the UK and the USA Figure 14 shows how the US population has a significantly lower life expectancy compared to the other countries. And at an increase of only 2.7 years over these 18 years, it is significantly lower than the increase in Australia, for example, of 4.5 years. Figure 15 shows that this lower rate of growth in life expectancy occurred despite the US having a significantly higher proportion of its GDP expended on pharmaceuticals compared to the other three countries. And finally, Figure 16 shows the significantly higher proportion of US GDP that is expended on health. In summary, these three graphics place the US policy narrative into the international context. The US policy narrative does recognise the differences in expenditure on pharmaceuticals as a proportion of GDP, but this is frequently attributed to the US bearing the greatest share of the burden of global pharmaceutical R&D. However, the narrative does not refer to the difference in life expectancy between the US and the rest of the OECD.

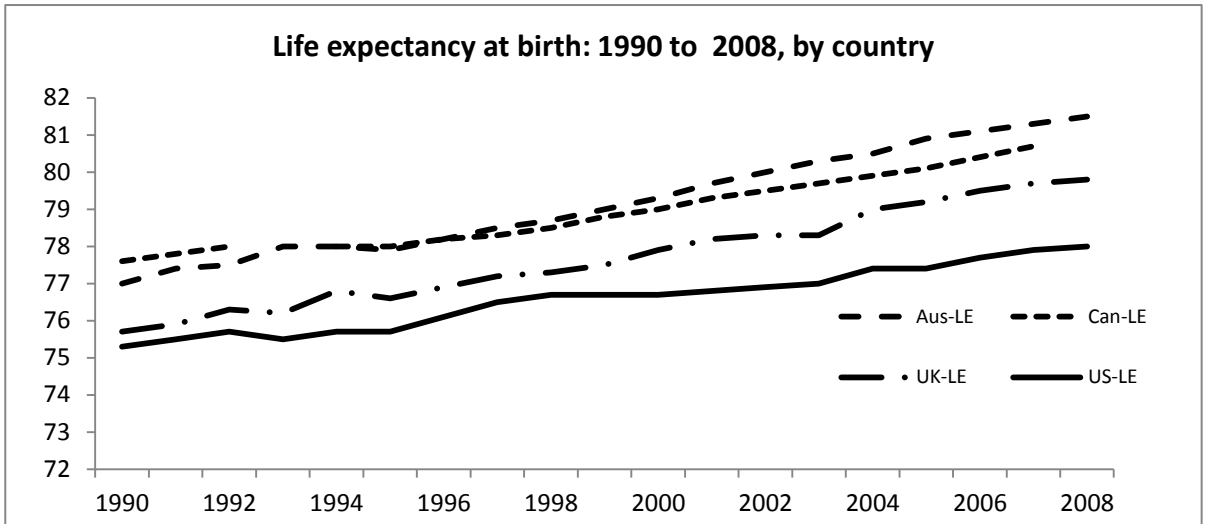


Figure 14 Life expectancy at birth 1990 to 2008, four countries: Source OECD statistics

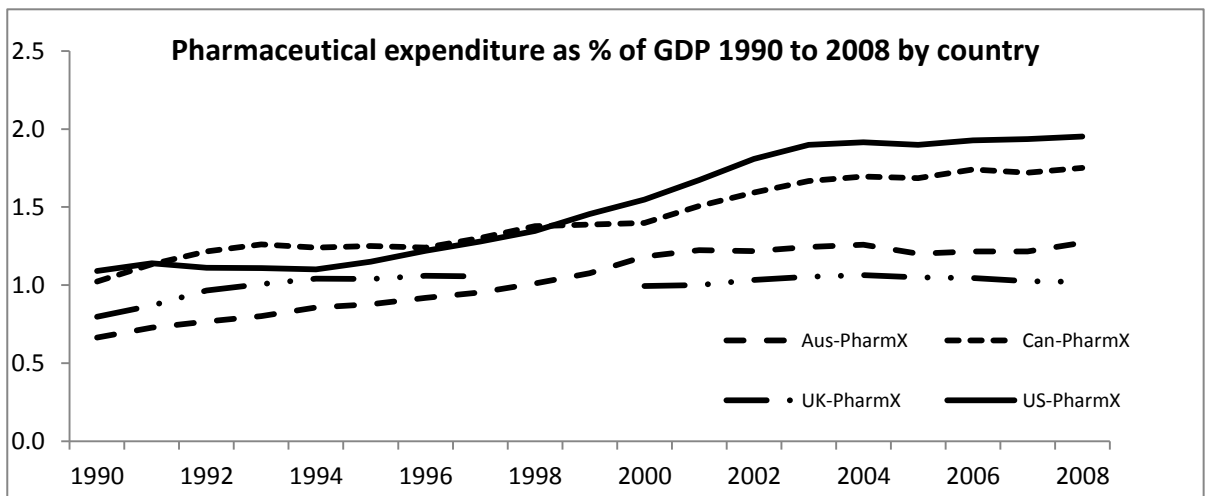


Figure 15 Pharmaceutical expenditure as a % of GDP 1990 to 2008, four countries Source: OECD statistics

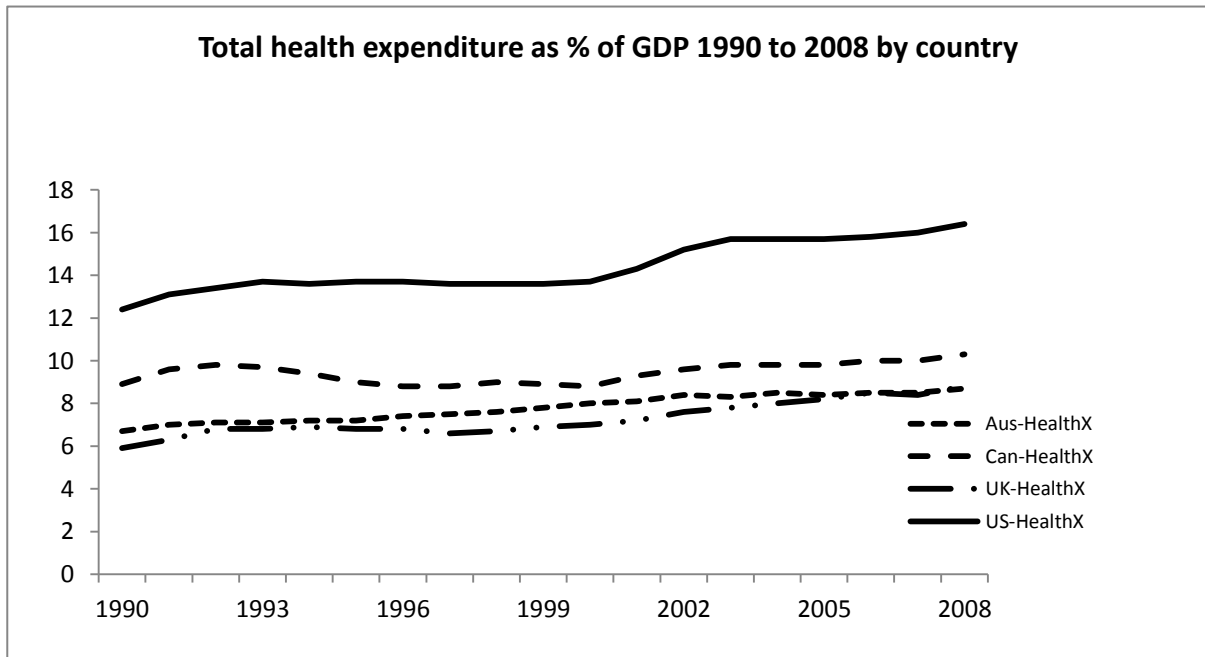


Figure 16 Total health expenditure as a % of GDP 1990 to 2008, four countries: Source OECD statistics

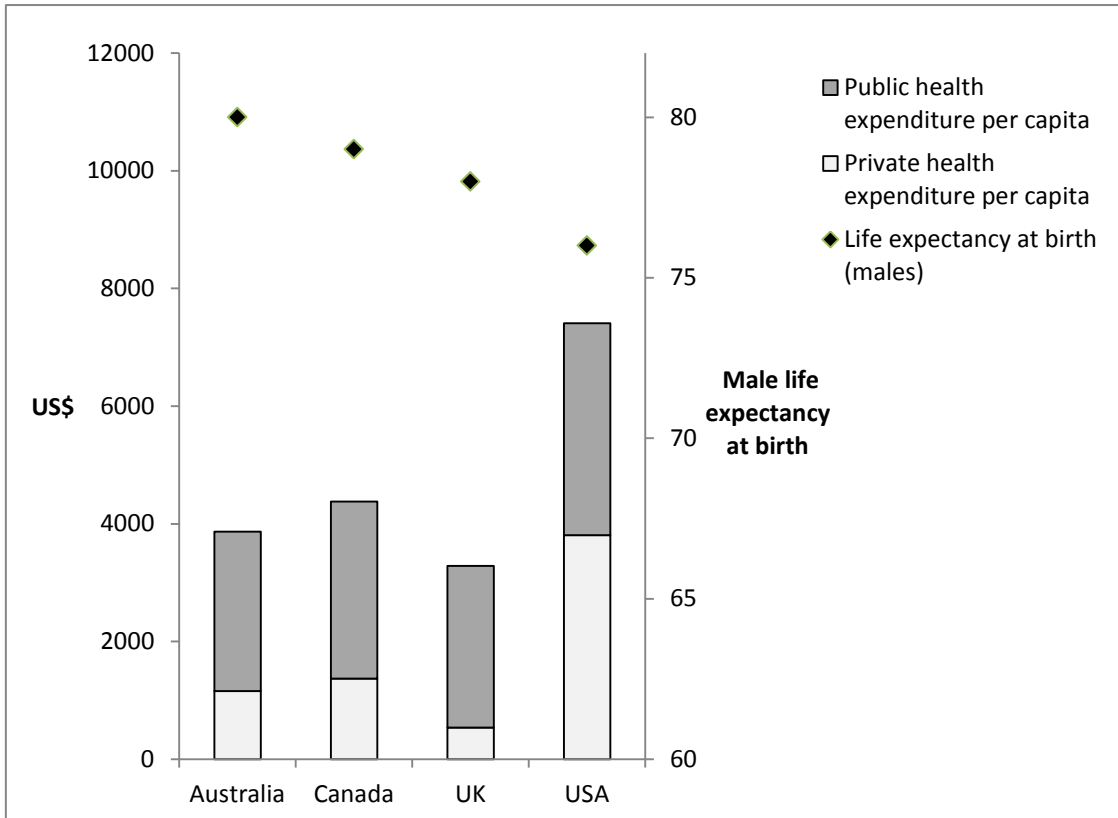


Figure 17 Per capita expenditure on health (2009 USD – international comparisons using 2009 exchange rate) and Life Expectancy at Birth 2009 (Males) Source: OECD statistics

4 How much lower are the life expectancy gains in the US compared to those in Australia, Canada and the UK?

In 2009, the life expectancy of a male at birth was estimated at 80 for an Australian male and 76 for a US male. (Figure 17) This represented an improvement of 6 and 4 years from 1990 life expectancy for an Australian and a US male, respectively. Hence the gain in average life expectancy at birth for a US citizen was two thirds of that of the gains for an Australian citizen. This result occurred even though the US is consistently ranked as a wealthier country (in terms of GDP per capita) than Australia, Canada and the UK.¹⁸⁸ Also, the per capita expenditure on health services in the US is notably higher than that in the UK, Australia and Canada, mainly as a consequence of the much higher level of private expenditure in the US.¹⁸⁹

Adult mortality, the probability of dying between the ages of 15 and 59 is another way in which a population's changes in health status can be explored. A systematic review of global adult mortality rates compared these rates for all countries for 1970, 1990 and 2010 (Rajaratnam, Marcus et al. 2010). The results for four countries are summarised in Table 17 Adult mortality - deaths per 1000 people between ages 15 and 59. The authors found that the probability of an Australian male dying between the ages of 15 and 60 decreased from 202 to 76 deaths per 1000 population from 1970 to 2010 (127 less deaths per 1000 or 63% reduction in deaths). Over the same period the gain for US males was from 228 to 130 deaths per 1000 population a reduction of 98 deaths or 48%. The deaths of US adult males per 1000 population was 13% higher than for Australian adult males in 1970 and in 2010 was

¹⁸⁸ For example, see the OECD statistics www.OECD.org

¹⁸⁹ This in turn is the result of differences in the insurance systems in the US compared to Canada, Australia and UK, which all have universal health care for the majority of primary and hospital care.

72% higher. While US adult males are now less likely to die between the ages of 15 and 59, their position relative to Australian males has worsened, substantially.

Table 17 Adult mortality - deaths per 1000 people between ages 15 and 59

Gender and country	Deaths by Year			1970 to 2010		1990 to 2010	
	1970	1990	2010	absolute decrease	% decrease	absolute decrease	% decrease
Females							
Australia	113	67	44	70	61%	23	34%
Canada	101	70	52	50	49%	18	26%
UK	107	78	58	49	46%	20	26%
US	126	89	77	48	38%	12	13%
Males							
Australia	202	124	76	127	63%	48	39%
Canada	185	127	84	101	55%	43	34%
UK	180	129	93	87	48%	36	28%
US	228	167	130	98	43%	37	22%

Source: derived from (Rajaratnam, Marcus et al. 2010)

5 Why does it matter if the evidence beyond the backyard is omitted from the policy narrative?

From the perspective of this thesis, what is the significance of the omission of the evidence of the US life expectancy gains relative to the rest of the OECD from the US policy narrative? It is significant in that it excludes consideration of the possibility the US could have achieved more with lower drug prices and more expenditure on other areas, including improved access to new drugs. The main evidence the US population is presented with currently is:

- 1) that their life expectancy has increased by ten years since 1960;
- 2) pharmaceutical innovation contributed to this gain in the order of 10% to 60%; and
- 3) that pharmaceutical innovation will reduce if prices reduce.

That the evidence about the US life expectancy in a context wider than its own backyard is omitted from the policy narrative is consistent with the way the political economy is framed in the US. The possibility that the US could have done better with less expenditure on drugs has to be excluded from the evidence based policy narrative, because it is excluded from the political economy. Had the authors that contribute to this narrative had to explain the difference between the US gains and the gains for the rest of the OECD, they might have had to explore the possibility that the US could have done better with less drugs. One different state of the world for the US to have had is universal access to health care, such as the schemes in the UK, Canada and Australia. New drugs are important, but without appropriate access to these drugs and the associated health professionals, the benefit to patients cannot be realised. For example, a study on the management of diabetes in seven countries found that: "in the three countries with available data, insurance status was a strong predictor of diagnosis and effective management, especially in the United States" (Gakidou, Mallinger et al. 2011).

The point of these comparisons is not to attribute differences between the US and the rest of the OECD to specific policy differences or differences in risk factors for mortality. Even if this difference were entirely the result of differences in for example, motor vehicle accidents and firearm deaths, then the point would remain: the US might or might not have done better had it developed strategies to

reduce the incidence of deaths from these preventable causes rather than invest in the development of new drugs via higher drug prices.

6 Conclusion

When the gains in life expectancy to the US over the period 1960 to 2010 are considered in the context of its own backyard, the impetus of research and policy is to focus on the drivers of this gain and to ensure that these drivers are maintained. The question of whether the US could have done better over this period had it instead invested in alternative policies is not high on the research agenda.

When these gains are placed in an international context, the question of why the gains to the US are less than the gains experienced by the rest of the OECD would appear to be at least as interesting as the question of the drivers of the gain. This change to the research agenda introduces another possibility: that the US could have done better had it had different policies. While it is possible that the US could have had worse health outcomes with lower drug prices over the period 1960 to 2010, the possibility that the US population could have done better under a scenario of lower prices cannot be excluded. This is the case even if the evidence of the contribution of new drugs to US population longevity is accepted.

Appendix 4: The reimbursement process, the value of new drugs and the decision threshold: current practice and PEA terminology

1 Introduction

Price effectiveness analysis (PEA) uses some specific terminology and notation to distinguish between conventional expressions of the net benefit and the net economic benefit defined using the health shadow price. It also uses notation to ensure that the parameter used to value health effects in the net benefit or to compare the incremental cost effectiveness ratio against a threshold is identified. Appendix 4 is referred to throughout the thesis.

2 Terminology

Within the reimbursement process, the Reimbursers signal the value of the health effects of the new drug in the context of its adoption using one of two methods:

- 1) the "net benefit" (which indicates whether at the offer price the adoption of the drug will represent a net benefit or a net loss to the population); or
- 2) the "threshold price per effect" (which indicates the maximum price per effect that the payer is willing to pay).

For both methods, there are multiple ways that value that be signalled. To capture this variation, the following terminology is used in Price Effectiveness Analysis (PEA): NBm_i , NBh_i , $ICER_i$, and CEA_i . These terms are defined as follows.

The NBm_i summarises the practice of expressing the results of a CEA of a new drug as a "net monetary benefit":

$$NBm_i = i\Delta E - \Delta C$$

- 1) where i is the qualitative value of the price per unit effect signalled via the Reimbursers' threshold price; the price that signals: "this is how much our institution values an additional health effect". Possible qualitative values for i include: d (the cost per effect of displaced services) (Sendi, Gafni et al. 2002); n (the cost per effect of the marginal program, assuming perfect efficiency and no price distortions) (Birch and Gafni 1992); and k (the maxWTP for additional health effects) (Drummond, Sculpher et al. 2005; Vernon, Goldberg et al. 2009);
- 2) where $\Delta E > 0$ is the additional health effects from the new drug against the best alternative care for the group of target patients; and
- 3) where $\Delta C > 0$ is the additional financial cost from the new drug against the best alternative care for the group of target patients.

The corresponding decision rule is:

Adopt if:

$$NBm_i \geq 0$$

The NBh_i summarises the practice of expressing the results of a CEA of a new drug as a "net health benefit":

$$NBh_i = \Delta E - \frac{\Delta C}{i}$$

where each of the terms is defined as for the previous metric.

The corresponding decision rule is:

Adopt if:

$$NBh_i \geq 0$$

Additionally, $ICER_i$ summarises the practice of expressing the results of a CEA of a new drug as the ICER:

$$\frac{\Delta C}{\Delta E}$$

and comparing this to a threshold of i , where the terms are all defined as above. In this case the decision rule is:

Adopt if:

$$\frac{\Delta C}{\Delta E} \leq i \text{ where } \Delta C, \Delta E > 0$$

And finally, CEA_i summarises the practice of using the results of HTA/CEA to inform a new technology adoption decision by comparing any metric generated by HTA/CEA to the threshold of value i .

Appendix 5: Scenario 4: Adoption financed by displacement in an economically inefficient budget (investment version)

This Appendix presents the full exposition of the scenario summarised in Section 5, Chapter 5.

1 Introduction

We now consider a dynamic decision analytic model. A dynamic model contains an action that links two time periods, in this situation, an investment in Year 1 has implications for the overall average ICER (aICER) of the health budget in following years.¹⁹⁰

In Scenario 4 we change our set of alternative strategies to include all investment decisions, specifically, strategies that:

- 1) involve an investment of ΔC^P in the improvement of practice in Year 1;
- 2) reduces the aICER of a program of health care in subsequent years by:
- 3) increasing health benefits in subsequent years; and
- 4) achieving these benefits with no net effect on the cost of that program in any subsequent year.

This Scenario has similar results to the Scenario 3 Chapter 5. It is included because it facilitates the analysis of a claim by pharma-economists explored in Chapter 10; new drugs should be paid a premium over other programs because new drugs, unlike say respite care programs, are assumed to include an impact on an investment for future benefits from future drugs.

2 The investment

Consider a program to reduce deaths due to drug-drug interactions where this program is run from a pharmacy with a fixed budget. The pharmacy is located in a hospital which also has a fixed budget.

The outcome of this program is the number of deaths due to drug-drug interactions in the hospital. An investment strategy could be investment in software that reviews prescribing and dispensing data sets and detects situations where drug-drug interactions might occur in a hospital. Such software might have an additional cost in the first year but the ongoing costs of running the pharmacy in future years remain the same. Furthermore, when deaths are prevented, for simplicity we assume that there are no costs associated with these deaths and hence there are no financial savings resulting from this reduction in deaths. Consequently, there is no net effect on either the pharmacy or hospital budget in following years. In this discussion, it is assumed that the effects of a future investment are known with certainty.¹⁹¹

¹⁹⁰ We could argue that many new drugs have a dynamic component that is expressed as the following result in a pharmaco-economic simulation: the present value of the ICER of the strategy to initiate therapy in Year 1 and continue for t years decreases as the time horizon of the pharmaco-economic model increases. An example of such a drug is a bisphosphonate, which has constant variable costs over a number of years but the health benefits and cost advantages resulting from fractures prevented are likely to accrue in subsequent years. For an example of a study with such a result, see (Iglesias, Torgerson et al. 2002) This dynamic component of drugs and new technologies is accommodated in the cost and effect estimates in the simulation and there is no requirement for a separate analysis of the investment decision to accompany the evidence of cost effectiveness of the program.

¹⁹¹ This assumption is clearly unrealistic but does not impact on the analysis and also has a rationale, namely, the language used by pharma-economists about the certain future return to investments in drug R&D by consumers and their agents. For example, consider the following quotation from Giaccotto et al. (Giaccotto, Santerre et al. 2005) "*Benjamin Franklin once*

In this case, the overall costs of supplying care (monitoring drug-drug interactions) using that program remains the same in subsequent years but the health benefits from that program increase relative to prior to the program (less deaths from drug-drug interactions). The aICER of that program will reduce (less deaths same dollars). Hence, the efficiency of the pharmacy, hospital and the health budget overall will increase in a future period.

However, the pharmacy’s budget is fixed and constant every year and so in the first year, the additional cost of the software needs to be funded by having one less pharmacist. As a result there are more deaths in the hospital as a consequence of a reduction in quality of dispensing. Hence the efficiency of the pharmacy budget (aICER compared to no change in the Pharmacy drug-drug interaction program) reduces in the first year.

In summary, there is a reduction in the static efficiency (the first year) of the Pharmacy and there is an improvement in the technical efficiency of the drug-drug interaction program and hence the overall Pharmacy budget in following years (dynamic efficiency).

3 The analysis

The nominated strategy is Reimbursement (R) within a fixed budget, as in Scenarios 2 and 3 in Chapter 5. The first change compared to Scenario 3 is that the set of best alternative strategies now includes only investment strategies. The second change is that the budget is technically rather than allocatively inefficient.

The best alternative strategy (T) is selected from the set of **investment** strategies that could improve clinical practice. The selected strategy (V) is investment in practice improvement (I) financed by reducing the pharmacists’ salary budget and displacing a pharmacist (M). The action of practice improvement (investing in software, I) reduces the aICER for Program G (drug-drug interaction monitoring), from g to g' . This reduction in aICER is only possible if an amount ΔC^P is invested in practice improvement in Year 1. This investment ΔC^P is financed optimally by displacing the least cost effective (in contraction) of existing programs funded by Pharmacy, area M (the employment of pharmacists to dispense drugs) at an aICER of m . This displacement only occurs in Year 1 and in the following years the Pharmacists’ budget, M, is restored and the pharmacist is re-employed. This situation is illustrated in Figure 18 Payoff to reimbursement with initial condition of technical inefficiency.

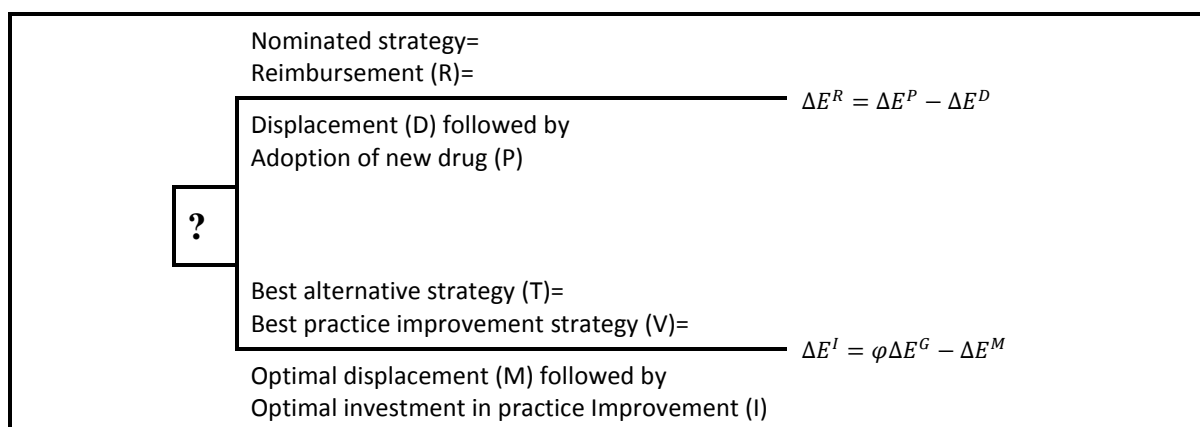


Figure 18 Payoff to reimbursement with initial condition of technical inefficiency

remarked, “In this world nothing can be said to be certain, except death and taxes.” Spokespersons for the pharmaceutical industry might be inclined to argue that the benefit-generating capability of prescription drugs also belongs in this exclusive category. “

The net health benefit of the best alternative investment strategy ΔE^V from the set of investment strategies is:

$$\Delta E^V = \varphi \Delta E^G - \Delta E^M$$

Where:

- 1) ΔE^G is the additional health effects produced by Program G each year, using current technologies.
- 2) $\varphi \Delta E^G$ is the present value of the stream of future incremental benefits of Program G with the new technology, referenced to effect of the existing program, where $\varphi > 1$; and
- 3) ΔE^M is the loss in health effects due to having one less pharmacist in Year 1 in order to finance the investment into the new system.

The initial conditions include technical inefficiency; there is an opportunity to improve the net present value of the present and future hospital patients' health by making this investment. Therefore, we assume that:

$$\Delta E^V > 0$$

Now let:

$$\varphi \Delta E^G = \frac{\Delta C^P}{\mu}$$

Where μ is a constant and the lower μ is, the more cost effective the investment strategy is compared to current care and:

$$\Delta C^P, \mu > 0$$

The net financial cost to the fixed Pharmacy budget of the best alternative strategy from the set of investment strategies is:

$$\Delta C^P - \Delta C^P = 0$$

The $NEBh^R$ is:

$$NEBh^R = (\Delta E^P - \Delta E^D) - (\varphi \Delta E^G - \Delta E^M)$$

$$= \frac{\Delta C^P}{f} - \frac{\Delta C^P}{d} - \frac{\Delta C^P}{\mu} + \frac{\Delta C^P}{m}$$

$$= \Delta C^P \left(\frac{1}{f} - \frac{1}{d} - \frac{1}{\mu} + \frac{1}{m} \right)$$

β_c is the *IPER* of the new drug at which the $NEBh^R$ is 0.

$$\therefore \Delta C^P \left(\frac{1}{f} - \frac{1}{d} - \frac{1}{\mu} + \frac{1}{m} \right) = 0$$

$$\Rightarrow \left(\frac{1}{f} - \frac{1}{d} - \frac{1}{\mu} + \frac{1}{m} \right) = 0$$

$$\Rightarrow f = \left(\frac{1}{\mu} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

Therefore:

$$\beta_c^v = \left(\frac{1}{\mu} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$$

4 Discussion

In this scenario, the set of alternative strategies was changed from, one that includes reallocation only, to one that includes only the opportunity to improve dynamic efficiency. If investment strategies are also considered, there is a potential to generate a different, lower health shadow price, if the aICER that results from investing in changed practice is lower than those possible within current technologies. The key parameters for Scenario 4 are summarised in Table 18 in this Appendix and in Table 9, page 105, Chapter 5.

Table 18 Summary of key parameters for Scenario 4: Technical inefficiency, investment strategies and fixed budgets

Clinical Value of innovation (target patients)	$CVI = \Delta E^P$
Net health effects from reimbursement (population)	$\Delta E^R = \Delta E^P - \Delta E^D$
Net economic benefit from reimbursement (health)	$NEBh^R = (\Delta E^P - \Delta E^D) - (\varphi \Delta E^G - \Delta E^M)$
Health shadow price (investment)	$\beta_c^v = \left(\frac{1}{\mu} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$
Shadow price of the budget in expansion	<i>not defined</i>
Economic value of clinical innovation	$EVCI = \Delta E^P \left(\frac{1}{\mu} - \frac{1}{m} + \frac{1}{d} \right)^{-1}$

Appendix 6: Appropriation of the surplus from a previous drug

1 Introduction

This Appendix is referred to in Chapters 8, 9 and 10. Its aim is to show the conditions under which the use of decision thresholds will allow the patent holders of a drug with clinical innovation to appropriate the economic rent from its own and a previous drug. First a theoretical and then a practical example is used to illustrate this idea.

This analysis can be performed within price effectiveness analysis (PEA) and not HTA/CEA because the former can accommodate economic rent to the firm, whereas the latter does not. In this way PEA achieves some integration between the imperative of pharma-economics (the incentive to innovative expressed as available economic rent) and pharmaco-economic (the value of innovation to the population).

2 Surplus appropriation of previous drugs: hypothetical example

Under what conditions will a constant decision threshold of \$75,000 for two successive drugs lead to the second drug to appropriate a share of the economic value of the clinical innovation of the first drug? This scenario is demonstrated in Table 19. Assume there are no costs associated with the therapy other than the costs of the drug itself. Assume Drug B is more effective than Drug A (250 vs. 100 QALYs compared to placebo for 1000 patients). Assume, initially, that Drug A is on-patent and currently priced at an incremental price effectiveness ratio *IPER* of \$75K per QALY (with the comparator of placebo).

Then, if the new drug, Drug B, were listed at the max *IPER* (\$75K), it would have a total revenue \$18.75M, whereas had Drug A been off-patent (and priced at the marginal cost of production), the total revenue for Drug B would be \$11,75M; it cannot appropriate the full clinical surplus from Drug A. If Drug B completely substitutes for Drug A (for at least one indication) then the market for Drug A (for that indication) will reduce to 0. However, Drug B will continue to be priced at the same price, appropriating the clinical innovation until it goes off patent.

Table 19 Drug B appropriates the surplus of a previously reimbursed comparator

	QALY (a)	Incremental cost to health budget		Incremental price effectiveness ratio (<i>IPER</i>)		One year of revenue	
		Drug A on patent (b) =(a x d)	Drug A off patent (c) =(a x e)	Drug A on patent (d)	Drug A off patent (e)	Drug A on patent	Drug A off patent
Drug A vs. placebo	100	\$ 7.5M	\$500K	\$ 75K	\$5K	\$ 7.5M	\$500K
Drug B vs. Drug A	150	\$11.25M	\$11.25M	\$ 75K	\$75K	\$18.75M	\$11.75M

The market for Drug A could continue if substitution is not complete. Partial substitution could occur if the new drug is only slightly more effective and patients having used the Drug A for long periods might not change. In this case, when Drug A goes off patent and the generics reduce the price of Drug A, then regulators might need to consider whether Drug B is:

- 1) referenced to the new lower price of Drug A and can only access the monetary value of clinical innovation of itself against Drug A; or
- 2) remains referenced to placebo and can access the monetary valuation of the clinical innovation of Drug A against placebo in addition to Drug B against Drug A.

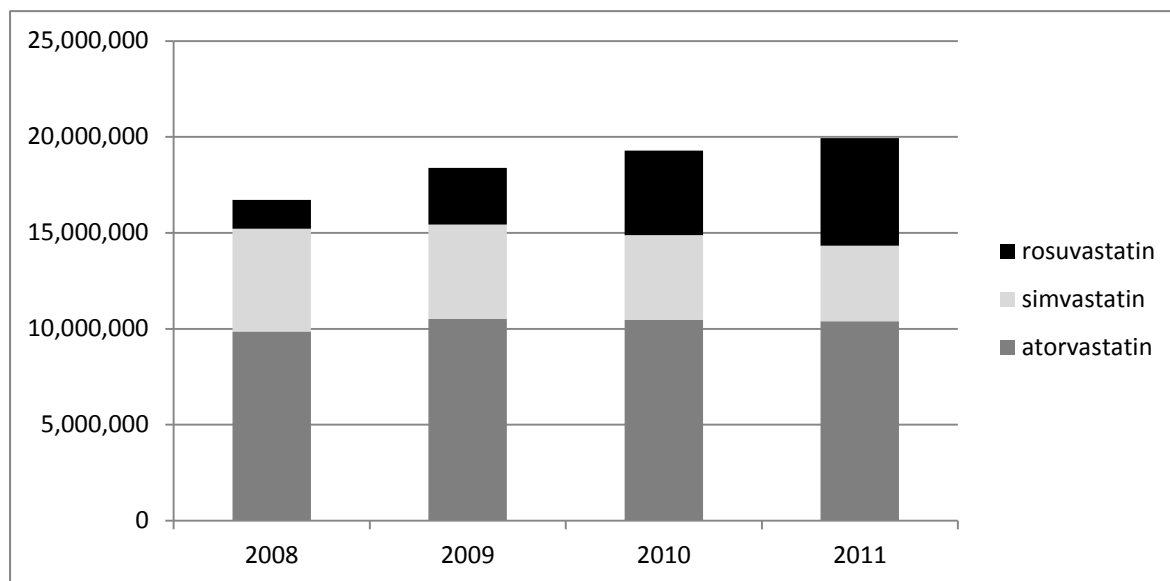


Figure 19 Volume of scripts of three statins reimbursed by the PBS over four years

3 Real world example - statins

This scenario is played out in the real world. In 2012, atorvastatin went off-patent, but a more recently listed statin, rosuvastatin, will not go off patent until 2016. The regulatory and health budget implications of these changes are discussed by Clarke and Fitzgerald (2009) and a newspaper article by Song reviews this issue from the perspective of the patient and prescriber (Song 2011). Song provides evidence that the latter could be more effective at the biochemical endpoints. The politically charged debate surrounding rosuvastatin concerns the question of whether its price should be decreased when the drug it is referenced against goes off patent and its price is reduced. Figure 19 illustrates how the sales of the three top selling statins have increased since 2008 in Australia. Rosuvastatin has an increasing share of an increasing market. If the price of rosuvastatin is not reduced with the price of the generic, it will continue to appropriate the clinical surplus from atorvastatin.

Appendix 7: Changing the problem to fit the solution – Report on the Firm’s Preferred Price

"Changing the problem to fit the solution"

Birch and Gafni (1993)

1 Introduction

A summary of this “report” is presented in the main section of the thesis, at the start of Part 3. Appendix 7 justifies the approach taken in Chapters 9 and 10 to assess the research question: how should an institution respond to the Threat that pricing below the firm’s preferred price (*FPP*) is worse for the population’s health than accepting the higher price.

At the start of Part 3, two options as to how this issue could be analysed were identified. The first was to stay within the conventional political economy and compare the social welfare gains or losses of using the *FPP* rather than the health shadow price using a nonstrategic model. The second was to change the problem to one of the conditions under which an institution should agree to price above the health shadow price, expressing the *FPP* as any price above this shadow price and working within a game theoretic model. In order to take the first approach, an analytical framework needed to be identified. In this Appendix, two possible frameworks are analysed. Both of them represent attempts by US pharma-economists to adapt the political economy of new drug price to include the rise of HTA/CEA in conjunction with a decision threshold (See Chapter 2, Table 5 5, p. 43). The critical issue is whether these frameworks can be used to compare two options for the optimal price (*FPP* and β_c) by quantifying and comparing the resultant social welfare gain or loss.

2 Reimburser's problem

The Reimburser is satisfied that β_c is the threshold Incremental Price Effectiveness Ratio (*IPER*) for the clinical innovation of a new drug that will maximise the population’s health from a given budget. At prices above the *IPER*, the net health gains for the population as a consequence of reimbursing the new drug are less than those that could have been achieved by alternative strategies. In an allocatively inefficient health budget, these alternatives include allocating funds for the least effective program (in contraction) to the most cost effective (in expansion), as practiced in Program Budgeting Marginal Analysis (Mooney, Russell et al. 1986). Alternatively these health gains could be achieved by investing in changed practice that will reduce the aICER of specific programs and hence the overall budget.

The Reimburser also understands the value of the alternative framing of the political economy of new drugs (PENDING). The conventional framing does not accommodate the possibility that fewer future drugs will improve the health of a future population. She is confident that the alternative framing allows for the possibility of the net impact of more drugs in the future to be either an increase or decrease in the population’s health; it accommodates the counterfactual to higher drug price in the context of a constrained budget.

It is reasonable to assume the net health impact of new drugs for patients who are targeted by a reimbursement policy will be greater than or equal to zero; regulatory processes around the world work to minimise the risks associated with potential adverse events and new drugs. However, without an understanding of the aICER of the services displaced to finance the additional cost of a new drug, a net positive effect on target patients cannot be assumed to lead to a net positive effect on the

population's health. Furthermore, without an understanding of the foregone benefits of this additional expenditure, even increased population health from reimbursing more new drugs does not exclude the possibility that the population's health could have been better without that innovation.

However, the Reimburser is also aware that the models used to derive the health shadow price, β_c , explicitly exclude the possibility of a relationship between price of a new drug today and the availability of new drug in the future. (See Chapters 6, 7 and 8) As far as she can see there is no simple rule to adjust β_c to accommodate the evidence of a positive relationship between price today and the number of drugs in the future.

The Reimburser asks Pharma to provide her with evidence of why it is preferable to price at the *FPP*, rather than the threshold she has nominated β_c . Firms present her with two published arguments against pricing below the *FPP*. The first is that using a decision threshold, regardless of its value, is price control and price control is well known to result in a deadweight loss (International Trade Administration 2004; Jena and Philipson 2007). The second is an argument that the socially optimal level of investment into R&D occurs when firms appropriate the full value of that innovation as rent and this occurs when $f = \text{maxWTP}$. Furthermore, the maxWTP is argued to be the aICER of the least cost effective of existing services, for example dialysis (Vernon, Golec et al. 2010). The Reimburser recognises that, in price effectiveness terminology (PEA), this is m .

Before the Reimburser applies β_c , which is only 10% of the current maxWTP threshold, she needs to be sure that the net present value of Population health (npvPH), including the impact on the number of future new drugs and the associated health consequences, is higher under β_c than the *FPP* that corresponds to either of the two arguments presented by Pharma.

β_c is calculated with reference to the best possible return on an investment in changed practice. The reason the return on this investment is so high, and hence β_c is so low, is because the aICER of the more technically efficient practice is expected to be significantly lower than the aICER of the least cost effective of current programs (See Appendix 5). This investment in practice innovation is an option available to the Reimburser, who has a fixed budget. This investment is the same in dollar terms (ΔC) as the additional expenditure (over and above the expenditure at a price of β_c) that the Firms state they require in order to have a socially optimal incentive to invest. Both types of innovation (pharmaceutical and practice) will also provide the same additional health effects for target populations (ΔE) but different groups of patients. The critical difference in these two investments is the cost to the Reimburser of purchasing the health effects from the two programs. The innovation in practice represents a better buy for the Reimburser because: i) it is priced at its marginal cost of production; and ii) after the innovative practice becomes available, the program will have a significantly lower aICER than the additional future drug, which is expected to be priced at the *FPP*, just as the current drug is currently offered at.

The Reimburser cannot understand why firms argue she should provide a sufficient incentive for the firms to invest in R&D when as far as she can tell, she is better off investing these additional funds in practice innovation. In simple terms, she would prefer if firms did not invest in pharmaceutical R&D, unless the final technology has a sufficiently low *IPER*.

The Reimburser instructs her Health Economic Adviser to:

- 1) *Critically review the FPP consistent with both the price control and the full value of surplus arguments.*
- 2) *Test each argument's capacity to compare the present value of population health under the FPP and $IPER = \beta_c$.*

- 3) *Test each argument's capacity to compare the strategy of investing in a future drug via a higher price for a current drug ($FPP > \beta_c$) with that of the strategy of investing in practice innovation, where the latter results in the same quantity of innovative health gains as those of the future drug, but are expected to be priced significantly lower at $<< \beta_c$.*

3 Price Control

The price control argument is premised on the position that price control leads to a deadweight social loss and price control in the pharmaceutical sector is not an exception to this rule. Scherer's conclusion to his review of the pharma-economic literature on the relationship between price control and health outcomes is typical of much of this literature.

"In sum, efforts by national authorities to curb pharmaceutical costs and offset the demand increasing effects of generous health care insurance by imposing drug price controls are found throughout the industrialised and less developed world. These sometimes succeed in their proximal goals, but cause bulges in other parts of the health care balloon, bias new drug research and development incentives, and distort international trade and investment patterns. Although one may share the underlying cost control goals, a review of the consequences suggest that the aversion of most economists to price controls is well founded." (Scherer 2000)¹⁹²

When expanded to the critique of CEA_i ¹⁹³ as practiced by OECD countries, an additional element is added to the conventional line of reasoning: CEA_i is price control by another name and therefore the enforcement of threshold prices below the FPP will lead to the same consequence as price control; a reduction in the population's health.

The argument that any attempt to regulate drug prices results in a deadweight loss by reducing the incentive for R&D probably has the same origins as the impetus for the Kefauver Committee.¹⁹⁴ However, the origins of this particular adaption to the conventional political economy are unclear. For example, Scherer's review of the literature in relation to price controls was published in 2000 but it did not make reference to CEA_i as price control, however, the ITA report published in 2004 made clear reference to the use of a CEA_i as price control. (See Section 3.1 of this Appendix starting p. 240)

A review of the literature conducted for this thesis identified three elements to the price control argument against decision thresholds.

- 1) CEA_i is price control.
- 2) Price control leads to a deadweight social loss.
- 3) Therefore, CEA_i leads to a loss in a population's health.

Each of these elements are critically analysed below. The exact expression (or qualitative value) of the FPP characterised in this argument is identified. Then this framework is used to compare β_c with

¹⁹² The Section in which Scherer states this conclusion (profits and price controls) includes extensive references to evidence about the unintended consequences of drug price controls which include bilateral monopoly negotiations, rate of return regulation and reference pricing. However, there is no evidence that reports on the net effect of the regulations on the benefits to consumers to lower drug prices and the costs of reduced incentives for R&D. The criticism made by Comanor in 1986 appears relevant to Scherer's chapter – the unintended consequence is proven, the result of a net loss is inferred, not proven. (See the discussion of this point in Chapter 1, Section 2.)

¹⁹³ The application of a threshold of value i in conjunction with the results of a CEA (Refer to Appendix 4)

¹⁹⁴ See the previous footnotes on the Kefauver Committee, Footnote 2 on page 20.

the *FPP* in terms of its impact on the NPV of the population's health, including consideration of the impact of the relationship between today's price and future NMEs. And finally, we test whether this argument against pricing below the *FPP* can identify that the changed practice investment strategy is preferable for the Reimbursers compared to pricing at the *FPP*.

3.1 CEA_i is price control

The first element in this argument is that CEA_i is the same action as price control.

Is this a reasonable premise?

The belief that enforcing a threshold price is the same action as price control is widespread amongst US pharma-economists. For example, the strategy of price control is defined by the authors of the ITA report on pricing practices throughout the OECD as encompassing a wide range of government actions:

While the mechanics of price-control regimes differ widely from country to country, the end result is the same. Pharmaceutical companies are prohibited from charging a market based price for the products they manufacture. Reference pricing, approval delays and procedural barriers, restrictions on dispensing and prescribing, and reimbursement controls are the principal methods employed by OECD governments to control pharmaceutical prices and costs. (International Trade Administration 2004 p. 4)

Under this definition, even the act of restricting reimbursed prescribing of a new drug only to patients for whom the drug is "cost effective" (however defined) is price control.

Even if off-formulary drugs can legally be prescribed, the fact that they are not reimbursed is a sufficient disincentive to effectively prevent or severely limit prescription, given current prohibition on manufacturers' communications to patients about the benefits of off-formulary or higher-priced brands. (International Trade Administration 2004 p. 8)

And this view is widespread:

Technology adoption through cost-effectiveness is a price-control policy in disguise and might therefore have many of the properties of such policies. (Jena and Philipson 2007 p. 697)

However, there would appear to be some significant differences between the impetus for price control (used in the conventional sense of the term) and that for enforcing a CEA_i .¹⁹⁵

In mainstream economics, price control is a term typically used to describe the response by regulators to increasing prices generally or to specific groups of prices, for example wages (Galbraith 2008). In the context of pharmaceutical regulation, price control typically refers to placing limits on the rate of growth of the price of new drugs, if this growth appears to be faster than the rest of the health sector price index (Giaccotto, Santerre et al. 2005; Santerre and Vernon 2006). It is also used to describe a regulatory response that is motivated by the perception that prices are too high in an absolute sense because firms are exploiting their monopoly power at the cost of consumers' surplus (Comanor 1986).

In contrast, enforcing a CEA_i is about constraining the *IPER* of new drugs by referencing it to some concept of the maximum value of these gains. Examples of this maximum value include: i) d , the

¹⁹⁵ CEA_i is the application of the results of a CEA study for a particular drug to a decision threshold of i , where i can take a range of qualitative or quantitative values, including k , d , n and β . See Appendix 5.

a) ICER of the displaced services; ii) k , the social decision maker's maxWTP for a health effect; and iii) β_c , the economic value of a health effect given the existing economic context.

The difference in the mechanism or action of price control (in the conventional sense) and CEA_i can be summarised as follows:

- 1) conventional pharmaceutical price control is about controlling the increase in **price per course of new drugs compared to older drugs** with reference to other price indices; whereas
- 2) CEA_i is about controlling the **additional cost to health sector per additional health effects** of a new drug with reference to some concept of the value of these health gains.

Not only do the mechanisms of price control and CEA_i differ but so do the relative price outcomes of the two approaches. Appendix 7A demonstrates this issue with four drugs: A, B, C, and D that are currently priced identically on a per course basis. Then, an innovative version of each drug is made available: A', B', C' and D'. Under price control, for example a limit of 10% higher cost per course, the new drugs remain equivalent to each other on a price per course basis, but the *IPERs* vary. Under a decision threshold, where each firm is assumed to choose to price at the threshold, the new drug prices are uniform on an *IPER* basis but vary relative to each other on a per course basis. Some are higher priced than the price that would occur under a 10% limit on increased prices, some are lower.

Given these differences in the effects of price control and CEA_i (both the actions and the results), how is it that the literature so readily supports the position that CEA_i is price control?

Significantly, in the context of the pharmaceutical price control argument (but not the mainstream use of the term), the question of whether it is control of the price per course or placing a ceiling on the price per health effects is irrelevant. A review of this literature suggests that regardless of the mechanism, if the purchase price of a new drug is lower than it would be in an unregulated unilateral monopoly (or in some cases, unregulated bilateral monopoly), then, within this argument, the action is referred to as price control. This particular use of the term price control appears unique in terms of general economics but is ubiquitous in pharma-economics.

The analysis prepared by the US International Trade Administration, (International Trade Administration 2004) articulates clearly what US pharma-economists appear to mean when they refer to price control as a situation in which the purchase price is lower than the price that would occur in an unregulated pharmaceutical market. This report presented a simulation of the effects (additional NMEs available to the US and hence additional life years) of imposing an unregulated unilateral monopoly (a free market) throughout the OECD (except in the US). The ITA Report provides an economic rationale for restricting the price regulation activities by US trading partners.

The ITA Report defines an unregulated price as:

Market forces, rather than government regulatory processes, would set pharmaceutical prices in the absence of price controls. (International Trade Administration 2004) page 15

This price is consistent with the price in an unregulated bilateral monopoly, where there is no government regulation and market forces, including those of the monopsonist purchasers, influenced price. However, the Report's analysis goes one step further and explicitly excludes monopsonist purchasing power from the factors that could influence the purchase price below the *FPP*. The prices used for the ITA study were sourced from data on the "pre-discounted price" which were acknowledged in the report as the starting price in negotiations with both the private and public health insurers, but not the final price. In the words of the Report's authors, the pre-discounted prices in the IMS health data were used because:

IMS Health data for the United States do not include off-invoice manufacturing rebates given to managed-care and government buyers, which would make U.S. prices less expensive relative to foreign prices if taken into account. (International Trade Administration 2004) p13

Hence the undiscounted price was assumed to be the US market price, the price that would occur in a “free market”. This strategy was justified because the study's aim was to:

to quantify the difference between market-based prices in the United States and drug prices in other OECD countries. (International Trade Administration 2004) p13

Therefore the free market price the authors use is the price that would occur in an **unregulated unilateral monopoly**: there is no regulation **and** no purchasers (public or private sector) have bargaining power. This definition of the market price begs the question, if we exclude the markets in which the private organisational and public sector purchasers operate, in which US market does this market price occur? The only market left is for that for uninsured people, however this market also does not have a single price; according to the PhRMA website there are significant attempts made to reduce the cost of medicines to uninsured Americans, by industry and various charity groups. Hence this market includes subsidised and unsubsidised scripts, with US pharma apparently subsidising many scripts and hence the price that firms receive for these scripts is not the nominal price.

*But biopharmaceutical companies recognize not everyone has access to the medicines they need. That is why they offer assistance to financially struggling, uninsured Americans through the Partnership for Prescription Assistance. Since its launch in April 2005, PPA has helped connect millions of people to patient assistance programs that may meet their needs. The program brings together pharmaceutical companies, healthcare providers, patient advocacy organizations and community groups to help qualifying patients get free or low-cost medicines. PPA, whose goal is to increase awareness of and boost enrollment in patient assistance, offers a single point of access to more than 475 such public and private programs.*¹⁹⁶

Within the price control argument, the definition of "market based prices" is the unregulated unilateral monopoly price. It is not the price that could occur, for example, in the unregulated transaction between firms private purchasers and Pharma (the unregulated bilateral market price). Therefore it seems reasonable to conclude that if we accept the US pharma-economic definition of price control then CEA_i (and bargaining with a private monopsonist) is price control. This is the case even if CEA_i is likely to provide very different signals and result in different relative prices than a conventional price control policy that would regulate the increase in the per course cost of a new drug. (As demonstrated in Appendix 7A)

In conclusion, under the pharmaceutical price control argument, CEA_i is price control because it leads to a price that is lower than the price that would result in an unregulated unilateral monopoly. Defining price control in this idiosyncratic way means that CEA_i is price control, even if the FPP is higher than the maxWTP for the health effects of a new drug, k .

3.2 Price control leads to a deadweight social loss

Whether or not CEA_i can be described as price control, where this term is used in the conventional sense, might be of little relevance to an economic analysis of the impact of using the FPP rather than i generally or β_c specifically; it could be a semantic issue only. However, the reason the choice of this term to describe CEA_i is significant is because of the connotations of the term "price control" in the

¹⁹⁶ Source: www.Phrma.org/issues/access-affordability Accessed on 21-01-2012

economic debate; price control is "bad economics". If economists and regulators are convinced that the action of CEA_i is price control, the inevitability of a deadweight loss does not even need to be stated; simply inferred. For example, in their conclusion to their analysis of the gains to social welfare as a consequence of increased prices in the US from 1960 to 2000, Santerre and Vernon make the following concluding statement.

Rising drug prices have captured the attention of the media, various public interest groups, and politicians. Some have pointed to price controls as a way of reining in what many perceive as "runaway" drug prices. But as economists have known for centuries, price controls simply represent "bad economics." Economic theory suggests that price controls often can create shortages, reduce quality, lead to price discrimination, and harm incentives for innovation. The only benefit to price controls is that some individuals gain, at the expense of others, through an increase in their consumer surplus as a result of the lower controlled prices. (Santerre and Vernon 2006 p. 244)¹⁹⁷

The theoretical basis for the prediction that price control leads to a deadweight loss is the well-known argument against imposing price control in a perfectly competitive market that is in equilibrium. Economists are trained to identify both the unintended consequences of well-intentioned policies and the subsequent mismatch between actual and intended consequences of policy. As part of this training, many students of economics will have been presented with the unintended consequences of rent control in New York: rationing and running down the rental housing stock.¹⁹⁸ The example of price control in the rental market is the exemplar of choice for a good reason: the unregulated rental market is assumed (apparently reasonably) to be a perfectly competitive rental market that would otherwise be at equilibrium and hence the predictions of the dire consequences of price control are confirmed by evidence.

But a first year student of economics could also readily identify the pharmaceutical market as one that does not meet the conditions of a perfectly competitive market:

- 1) both the sellers and many purchasers have market power (with the notable exception of the US uninsured);
- 2) information on the price of new drugs in a form that allows it to be compared to other sources of health gains is not cost free to obtain;
- 3) transactions are not costless; and
- 4) uncertainty is the rule rather than the exception.

There is a gap between the conditions of perfect competition and the structure of the pharmaceutical market. Given this situation, economists would be hard pressed to find a theoretical foundation for the prediction that the inevitable results of price control in a perfectly competitive market at equilibrium apply to price control in the pharmaceutical market.

This point is not new. Comanor (1986) made the following point in relation to the empirically demonstrated reduction in NMEs following a shift to more stringent FDA regulations in the 1960's

¹⁹⁷ Santerre and Vernon do test the costs and benefits of price control and estimate that the costs of price control outweigh the benefits by a factor of 28 to 1. The problems with this analysis are reported in Appendix 2. This excerpt is included because it infers that the result is not surprising because it is consistent with economic theory on the consequences of price control.

¹⁹⁸ Olsen's econometric study is an example of such a study that found that the gains to tenants for price control were outweighed by the losses to landlords. (Olsen 1972)

and 70's that required demonstration of superior effectiveness of new drugs compared to existing drugs.

Even if the FDA position is correct and only harmful or fully imitative have been precluded, some observers still doubt the social gain from these regulations. This Grabowski writes that, "the greater the number of drugs with similar properties on the market at any given time, the greater the likelihood of competition by price cuts that will convey direct benefits to consumers." (Grabowski 1976) But that conjecture does not follow in this industry. Prices depend more on the extent of patent protection than on the number of competing patented products, and even largely imitative drugs, as long as they are new chemical entities, generally command patent protection. While Grabowski's position may be applicable to a world of nonpatented products, it is less applicable to markets characterised by extensive patent protection. (Comanor 1986 p.1209)

In conclusion, even if we accept that the action of CEA_i is price control, then the inevitable results of price control in a perfectly competitive market do not apply in the pharmaceutical market and therefore we cannot conclude that CEA_i leads to a deadweight social loss. However, this situation does not rule out the possibility that imposing either price control or CEA_i will lead to a deadweight loss in social welfare and a net reduction in population's health compared to the case of no regulation.

3.3 CEA_i leads to a reduction in population health and social welfare

Even if we accept that CEA_i is price control, we cannot conclude that the inevitable results of price control in a perfectly competitive market apply to this context. But can we conclude that pricing at the FPP will increase the population's future health compared to the any other price below this? As discussed in Chapters 2 and 3, the existing political economy assumes that an increase in the population's future health is always the outcome of pricing at the FPP compared to a lower price and the empirical issue is whether the additional benefits are outweighed by the costs today of achieving this future gain. However, as shown in Chapter 3, this result only applies if there is no budget constraint or a budget constraint but no options other than pharmaceutical innovation to improve a population's health. Parameters that influence the impact of more future drugs on future health include d and the $IPER$ of the future drug. This impact could be negative; it is possible to have higher prices today and either increased or decreased future population health.

So how is it that studies construct their analyses so as to show that removing CEA_i and other forms of "price control" will improve social welfare and health?

A number of studies estimate the change in NMEs as a consequence of a change in price control regulation in the US, for example, Giaccotto et al. (2005). Two studies estimate the costs and benefits of reduced prices (Lichtenberg 2004; Santerre and Vernon 2006) (See Appendix 2). The conditions under which these studies can be interpreted as evidence that lower prices will reduce future health are set out in Chapter 3 and in Appendix 2.

The study that is used in this section to illustrate these issues is the ITA report. In contrast to the studies reviewed in Chapter 3 and Appendix 2, it includes an international element and also draws conclusions about the impact on social welfare across the OECD; that removing regulation of price throughout the OECD (excluding the US) will have the impact of increasing OECD welfare and health in all countries. Some of the devices they use are different to those used in the studies reviewed in Appendix 2. Additionally, unlike most other studies, the authors are careful to explicate their assumptions regarding the nature of budget constraints.

3.3.1 The five devices used in the ITA report to maximise the estimated benefit and minimise the estimated costs of no regulation throughout the OECD

The ITA report is significant because it is the first study to estimate the gain to the US in terms of the consumer surplus associated with more new drugs in the future as a consequence of enforcing a policy of no price regulation throughout the OECD. In many cases this would mean no longer using CEA_i . This result would be achieved by mechanisms such as a series of bi-lateral FTA (see Introduction). The ITA report also represents one of the rare occasions when the pharma-economic literature comes close to explicating the critical assumptions of no budget constraints and, in this case, perfectly price inelastic demand for pharmaceuticals.

The authors of this report use five devices to allow them to conclude that:

“The benefit to U.S. drug purchasers from the new drugs that would be developed and marketed if there were no price controls is in the range of \$5 billion to \$7 billion per year.” (ITA 2004 p. ix)

and that the OECD countries that currently regulate prices would also be better off from improved access to existing and additional drugs:

While the available information suggests that consumers in countries with stringent price controls will benefit from improved access to new medicines as a result of price deregulation, consumers everywhere will likely benefit from an increased flow of new medicines. (ITA 2004 p. 32)

Finally, the Report concludes that OECD countries (ex. US) will in fact have the additional higher costs of on-patent drugs offset by the savings due to lower prices of generics; there will be a net financial benefit of deregulating on-patent drug prices:

This range of potential savings suggests that if prices of on-patent drugs were to rise to competitive market levels, then the additional cost to OECD countries could be significantly or fully offset by a more competitive generic market. (ITA 2004 p. 24)

In summary: everyone in the OECD will be better off in terms of health with no additional financial cost if the OECD (ex. US) stopped regulating the price of new drugs.

In simple terms, the function they used to derive this result is:

$$\Delta CW = F(\sigma, \Delta N(\omega, \Delta X, \mathcal{R}))$$

where

- 1) ΔCW is the total increase in consumer welfare;
- 2) σ is the average increase in consumer welfare per additional new drug;
- 3) ΔN is the number of additional new drugs available as a consequence of investing a share of the additional funds from higher prices into additional NME research;
- 4) ω is the share of increased revenue that is allocated to NME research;
- 5) ΔX is the increase in expenditure as a consequence of higher prices, with no change in the units sold (hence this is also additional economic rent available to firms, given that the firms are currently selling at the lower price); and
- 6) \mathcal{R} is the cost of R&D for one new drug.

First, the authors maximised the number of new drugs possible in the future by maximising ΔX , the change in Pharma’s economic rent, by applying the following three assumptions:

- 1) The maximum possible increase throughout the OECD in the per unit price of a drug is achieved by assuming that the price that would apply if price controls were removed is the price that corresponds to a price in a hypothetical unregulated monopoly in the US, not the post discounted price that actually applies; (see previous section)
- 2) Increased drug prices (in other OECD countries) would not affect sales volumes in these countries (zero price elasticity of demand, regardless of the price); and
- 3) Funds (in other OECD countries) would be available to pay the higher prices, without displacing any other activities.

The last two of these assumptions are stated on page xi of the Report. They could be correct in the US but they do not apply to the rest of the OECD. The increase in expenditure on patented drugs is expected to be in the order of 25% to 38% and is therefore not inconsequential in terms of its impact on a health budget.¹⁹⁹

Second, the authors reduced the cost to the US of this increase in future drugs (ΔN) by assuming the entire costs of the additional R&D required to achieve these additional future new drugs is financed by the rest of the OECD, not the US. This is the case despite the recognition that US prices are generally below the so called “unregulated market price” that is assumed to become the prevailing price throughout the OECD. Hence the possibility that a bilateral FTA that prevents other countries from using monopsony purchasing power will have implications for the US purchasers is ignored.

Third, the authors do not appear to have taken into account the possibility that the US purchasers would need to buy less of other health inputs in order to finance the additional financial costs of the additional future drugs, hence possibly overestimating the gain in consumer welfare to US consumers.²⁰⁰

Fourth, the authors did not apply a discount rate to the future increase in consumer welfare, despite stating that this will occur several years into the future.²⁰¹

Fifth, the authors exclude the possibility that the net effect of increased consumer welfare in the US will be less than the loss in consumer welfare throughout the OECD as a consequence of increased prices. In fact they argue that there will be an increase in consumer welfare throughout the OECD as a consequence of this price rise (removal of protection) and hence this policy is consistent with the rationale for reduced trade protection (net global welfare increases) and with the political requirement that no country is worse off. (The details of this reasoning are presented in Appendix 7B)

In summary, the ITA study claims to provide evidence that removing decision thresholds and other forms of price control throughout the OECD is in the interest of consumers throughout the OECD because it has the net effect of increasing the population’s health in the US and throughout the OECD.

¹⁹⁹ “This represents a 25 to 38 percent increase in revenues over actual 2003 revenues from sales of patented drugs in the OECD countries considered.” (ITA 2004 p. x)

²⁰⁰ It is possible that the authors use of consumer welfare associated with new drugs rather than the social welfare overcomes this problem of the opportunity cost of increased expenditure on new drugs (see Santerre and Vernon (2005) who use social welfare as a return to investment in consumer welfare and Appendix 1 which reviews the problems associated with this). However, there is not sufficient discussion in the report to determine how the consumer welfare is calculated in the study the report references. Furthermore, the study, as cited in the ITA report (Berndt, Gottschalk et al. June 2004) is not available in the public domain. A report which could be similar was reviewed (Philipson, Berndt et al. 2008) but it remains unclear whether the benefits of previous innovation are excluded from the estimate of consumer welfare.

²⁰¹ “These estimated benefits, of course, would occur in the future, after prices had adjusted, and not as an immediate response to foreign deregulation of prices. The full effect of price deregulation would be observed only after drugs in the development pipeline were in the market, or abandoned.” (International Trade Administration 2004 p. 33)

However the study makes a number of assumptions, such as no budget constraint, that are unlikely to be met throughout the OECD.

3.3.2 What about economic rent?

The Report's lack of direct reference to the additional profit available to Pharma from this policy, while focusing on the additional consumer welfare, is notable. The study includes a realistic assumption that, of the estimated \$18B to \$27B increase in profit to firms each year (in 2003 dollars), only \$5B to \$8B each year will be invested in New Molecular Entity (NME) R&D. This leaves an additional \$13B to \$19B of additional profit from higher prices, which is not invested in NME R&D each year.

The study quantifies and emphasises the increase in annual consumer surplus of \$5B to \$7B each year, which will occur 6 to 8 years hence from the resultant additional drugs. The study does not explicate that there will be an increase in economic rent of at least this amount in each year prior to the consumer welfare increases, and for each year after this. In addition the firms will receive economic rent from the additional future drugs.

The additional economic rent can be inferred from the data presented in the report. Assume that half of this additional profit post investment in NME R&D is maintained as economic rent and assume a discount rate of 5%. Assume also that the additional consumer welfare from the new drugs is first gained 6 years hence. Then the present value in 2003 of additional economic rent over ten years for Pharma is between \$50B and \$73B whereas the present value of the stream on consumer welfare is between \$16B and \$23B. The present value of the additional economic rent is about three times the present value of the increase in consumer surplus to US citizens.

In excluding this indicator of additional economic rent, the possibility that advocating bilateral FTAs to prevent price regulation is about maximising economic rent, not consumer welfare, does not enter the policy narrative.

3.3.3 Is there a theoretical basis for the price control framework?

The premise of the pharmaceutical price control framework cannot be supported with reference to economic theory. The critical claim made in the line of reasoning is that if the purchase price is lower than the firm's preferred price then the health of the population will be worse off. The validity of this claim is questionable. First, the criticisms outlined in Chapter 3 apply. This simple positive relationship between price and future health is only valid under conditions of an unconstrained budget or a constrained budget where there are no options other than new drugs and pharmaceutical innovation. Second, there is no reason to believe that the firm has the knowledge that is required to provide each reimbursor throughout the world with the price that will maximise future health of their population. Significantly, the literature avoids the question of how this price is determined by firms; what information do they use? What are the formulae they use to derive this price? If firms have made these calculations, they have not placed their evidence in the public domain. If they were to place them in the public domain, then these equations could be assessed. Third, economists will readily accept that there is a deadweight social loss if prices in a perfectly competitive market are controlled however these results do not necessarily apply outside such a market. This premise can therefore be rejected.

Models such as those used in the ITA Report that attempt to apply analyses to develop results consistent with this premise – that there is a net gain in social welfare if price control is removed - require implausible assumptions. One example is positive price elasticity of demand for new drugs: as price goes up, there is no reduction in demand for the existing new drugs and when more additional drugs enter the market more rapidly as a consequence of higher prices, there is demand for them as well. Another example is the assumption that there is no opportunity cost to a significant increase in

expenditure on new drugs, where this increase is in the order of 25% to 38% and is therefore expected to have a significant impact on the health budget. A final example is no substitution between generic and patented drugs, despite the price of the former decreasing and the latter increasing. Additionally it is necessary to draw attention to the gains to consumers without highlighting the significant, immediate and certain gains to producers.

3.4 Applications of the price control argument

Despite the lack of theoretical basis for the central premise of the price control framework, it might still have a role in: i) comparing the *FPP* with β_c in terms of its impact on the net present value of the population's health (npvPH); and ii) being able to differentiate between the two possible investments available to the Reimburser with a fixed budget.

3.4.1 Is a rigorous comparison of the NPV of the population's health under *FPP* and β_c possible under the price control framework?

Can the price control framework be used to compare the net present value under the *FPP* with that for β_c ? There is no qualitative value (an equation) for the *FPP*. Therefore it is not possible to formally compare the outcome, the net present value of population health (npvPH) of the *FPP* and β_c within this framework. Furthermore, under this particular way of defining the problem, there is no advantage to the Reimburser to analyse an economically grounded shadow price, such as β_c , rather than any randomly selected price that is below the *FPP* within this argument; the solution is always the same: if the price is lower than the *FPP*, it will lead to a deadweight loss. In an adaptation of the words of Birch and Gafni (1993): the political economy is defined so as to define the solution. The solution is: i) the *FPP* is the preferred price; ii) any price below this will reduce the population's health below its value at this price; and iii) the optimal policy is to not regulate the *FPP*.

3.4.2 Can the price control framework identify which of two strategies is optimal for an institution with a fixed or constrained budget?

At the start of this project, the Reimburser had presented the Health Economist a second investment option available to her: practice improvement, which results in a higher increase in the npvPH compared to the investment in pharmaceutical innovation via higher prices for new drugs today. This is the case even though the investment in practice improvement has this advantage because the clinically innovative health effects will be purchased at a lower *ICER* compared to the *IPER* of the future drug.

The reason the price control framework cannot identify investment in practice improvement is a better option for the Reimburser and her fixed budget is primarily because the framework does not accommodate any reasons to lower the price below the *FPP*; it does not recognise options other than pharmaceutical innovation, nor does it recognise the budget constraint.

It is unclear what applying the price control framework to the choice between these two options means for the Reimburser's decision. Should she: i) make this alternative investment rather than require the firm to lower the price below the *FPP*; or ii) not make the alternative investment otherwise the firm would be required to price below the *FPP* in order to compete against this option. This ambiguity is a consequence of the framework's lack of theoretical underpinnings and unrealistic assumptions concerning competition and budget constraints.

3.4.3 Summary

In summary, it is unlikely that CEA_i , regardless of the value of i , is price control in the sense that it is used in mainstream economics, or even mainstream US pharmaceutical policy economics. The

relative prices structures that result from the application of each regulatory approach differ significantly, as do their motivations and mechanisms. Furthermore, even if CEA_i were identical to price control regulation in its relative price outcomes, there is no basis for arguing that price control in the pharmaceutical sector inevitably leads to a deadweight social loss. The price control argument simply does not provide insight into the mechanisms by the FPP has an advantage over any other price. And finally, there is no reason to believe that firms have the information and the formulae required to estimate a price per course of their new drug that takes into account the socially optimal level of R&D.

However, rejecting the price control argument as a tool for assessing the social welfare outcomes of CEA_i does not mean that the possibility that CEA_i leads to a deadweight social loss can be rejected. A second adaption of the conventional political economy to accommodate CEA_i is the argument that CEA_i is useful but the value for i should be the maxWTP for a QALY.

4 Value pricing

Some US pharma-economists appear to have accepted that HTA/CEA will be adopted as a guide to adoption decisions. (Danzon, Towse et al. 2011) Most of these authors understand the dual impact of this shift: the change in evidence (HTA/CEA) and in decision rules (CEA_i). One paper signals that the increased use of head to head RCTs (rather than new drug to placebo) will increase the costs of R&D, but, as is apparently the convention in US pharma-economics, it does not quantify the benefits of this additional information (Vernon, Golec et al. 2010).²⁰² Another signals that a threshold choice will need to consider the impact on the incentives for R&D (Vernon, Goldberg et al. 2009). Vernon and Goldberg et al set out the case for accommodating CEI_i within the conventional political economy of new drugs by setting the value of i at its maximum value in order to ensure optimal incentives for innovation. The authors go on to describe the economic value of a life year as that ICER that corresponds to the maximum willingness to pay for a health effect and suggest that a service such as dialysis provides an indicator of this price at USD129K.

The theoretical basis for this argument has its roots in Arrow (1962). Jena and Philipson (2008) refer to the origins when they describe the result of their analysis of the threshold at which incentives are optimal. (Their argument for a price premium is explored in Chapter 10.)

This expression directly highlights the well-known implication that first-best dynamic efficiency occurs when those undertaking the costs of R&D have incentives that are properly aligned with society, which is true when social surplus is entirely appropriated as profits, i.e. $a = 1$ (see e.g. Arrow, 1961; Tirole, 1988). In other words, the key factor driving dynamic inefficiency in this model is that profits are less than social surplus. (Jena and Philipson 2008 p. 1229)

Authors such as Vernon, Goldberg et al have taken this reasoning and translated it to a policy of pricing at the maximum willingness to pay. In fact the arguments presented in Arrow (1962 (not 1961)) and Tirole (1988) at no stage suggest their analyses suggest a policy of ensuring that firms are paid the full, unconstrained willingness to pay for their innovative outputs.

Arrow (1962) states that the problem of invention has "three of the classical reasons for possible failure of perfect competition to achieve optimality in resource allocation: indivisibility, inappropriability and uncertainty." Arrow's discussion of economic welfare and the allocation of resources for innovation highlights the complexity of the problem, in particular those which occur as a

²⁰² Would US pharma-economists prefer to have their own treatment based on evidence from head to head RCTs or new drug to placebo RCTs? Or even observational studies?

consequence of uncertainty and risk bearing. Arrow's primary conclusion in relation to market structure is that "the only ground for arguing that monopoly may create superior incentives to invest is that appropriability may be greater under monopoly than under competition. Whatever differences may exist in this direction must of course still be offset against the monopolist's disincentive created by his preinvention monopoly profits." He later adds that "the previous discussion leads to the conclusion that for optimal allocation to invention it would be necessary for the government or some other agency not governed by profit-and-loss criteria to finance research and invention". Arrow then goes on to argue for a stronger role for non-profit organisations, highlighting the role of universities and the innovative use of organisations other than firms.

Nor does Tirole make this claim regarding the requirement for full appropriability of social surplus by the monopolist. The model of pure innovation used by Tirole to introduce the concept of investment in R&D uses a manufacturer who is a monopolist in the output market and acquired (at zero cost) manufacturing innovation. There is no change in the price to the consumer. Tirole then goes on to expand from this simple model a series of examples of increasingly strategically complex markets. Most of these models are explored using game theory. At no stage does Tirole argue that a policy of full value pricing for the monopolist is necessary in order to ensure optimal levels of innovation.

Danzig (1963), which is reproduced in Attachment 1, is an example of how if the monopolist firm faces competition in a market, it must price accordingly.

The question of whether the full economic value that Vernon et al refer to is the maximum willingness to pay or the shadow price cannot be resolved from their paper (See Chapter 4 for details of this distinction). The authors might well accept that the health shadow price is the economic value. However, to cover the possibility that the authors are referring to the maximum willingness to pay, I use a proof by contradiction to challenge this claim.

Assume that it is true that all new drugs should be priced at the maximum willingness to pay for the health effects, where this is used in the lay sense of the term and does not consider the competition within a fixed or constrained budget. If this argument were applied to pharmaceutical pricing it would need to be applied to all medical innovation. It should also be applied to the health care workforce if they are keen to invest their time in developing their own skills in order to address the increased complexity of the rapid growth in medical technology. Investment in unpatented or unpatentable innovation would also need to increase to correct for the failure of the market to invest optimally in these areas. There could be some complexities as to how the resultant surplus would be allocated amongst all the participants who all seek to have their contribution to this growth rewarded. This strategy would increase health care spending and investment into health care technology. The total share of the US GDP allocated to health would increase, maybe to twice the current level, unless the growth in the US economy could keep up with the growth on expenditure in health. We could extend this argument to green energy technologies; governments could be required to purchase these technologies at the full social value of the reduction in carbon emissions to ensure an appropriate incentive to invest in green energy innovation. There are some downsides: pharma-economists would no longer be able to argue that expenditure on new drugs represented a good investment because the ratio of additional expenditure to the additional value would be 1:1 (for example see Appendix 2, Group 2 papers Section 7.3 starting on page 209).

There is a further inconsistency in Vernon et al's arguments for full value pricing. According to Santerre and Vernon 2006, the ultimate investor in pharmaceutical is in fact the consumer (See Appendix 2) whose investment of consumer surplus via higher prices leads to an increase in surplus due to new drugs valued, according to the authors, 28 times the original investment by consumers. So

shouldn't the ultimate investor, the consumer, be the one who has this incentive to invest? And what would their return on their investment in consumer surplus be if the entire surplus were appropriated by the firm? It would seem that they would have a loss. Where is the incentive for this investment by consumers?

5 Discussion and conclusion

Pharma's and pharma-economists' rationale for the *FPP* is clear; it will maximise the npvPH and, therefore, any price lower than this will be at the cost of a reduction in the npvPH. In recognising that a Firm responds to the signal of the threshold (endogeneity of price), both frameworks can be considered to be a more realistic representation of the reimbursement process compared to conventional health economic approaches, which assume exogeneity of new drug prices. However, like conventional health economic analyses of the decision threshold as the maxWTP, the conditions under which the results can be generalised are very limited. The most critical conditions are that budgets are unconstrained or budgets are constrained but there are no other competitive options for improving future health other than pharmaceutical innovation.

Neither of these two frameworks provides a rigorous theoretical foundation for comparing the npvPH under the *FPP* compared to any alternative price below the *FPP*. The first case rests on one pivotal premise; the pharmaceutical market is perfectly competitive and the *FPP* is the equilibrium price in this market. More significantly, the case does not provide a mathematical derivation of a given *FPP* and hence it is unclear what the *FPP* actually represents and whether it considers competition from other sources of innovation.

The advantage to the conventional political economy in framing the case for the *FPP* (defining the problem to fit the solution) is illustrated in these two cases. Specifically, the conventional political economy rules out the possibility that increasing the number of future NMEs will result in a reduction in the population's health, but does not provide a constraint in terms of an upper price. In both examples, the particular *FPPs* are effectively the rationale for an economic rent maximising constraining price on an otherwise unconstrained specification of the problem of optimal pricing. The possibility that pricing below these prices will increase the npvPH is excluded from these cases because no competition in the form of either innovation or other producers of health are recognised. The additional assumption that there is no budget constraint means that the lack of recognition of competition in the health input and innovation markets goes largely uncommented on in the pharmaceutical literature.

Appendix 7A: Relative prices, price control and CEA_i

In this Appendix, the relative price implications of CEA_i and a price control are illustrated. This is an explanation of a point raised in Appendix 7 Section 3.1, p. 240.

Four current drugs (A, B, C and D) have a price per course of \$250 and $IPER$ compared to the previous best therapy ranging from \$1,250 to \$5,000. A new drug will replace each of these four drugs, for example drug A' will replace A. Each of these new drugs has a QALY gain compared to the previous drug, except drug B' which has a resource innovation only. A resource innovation is innovation which reduces the financial costs elsewhere in the health sector compared to the current best practice. For example, it reduces the number of times a patient needs to attend a clinic for an injection from 5 times a week to once a month. There is no advantage in terms of effect. (See Chapter 4 for a discussion of three different types of innovation.)

The price per course of the new drug is assumed to be a function of either:

- 1) price control policy (assumed to be a 10% increase in the price for a course of a drug); or
- 2) a cost per QALY threshold of \$75,000.

The price per course could be higher or lower under the price control relative policy compared to a policy of CEA_i . The final relative prices depend upon characteristics of the drug, not just the policy. These characteristics are the gain in QALYs and the impact on financial savings. This result is illustrated with hypothetical data in Table 20. We can conclude that the relative price implications of these two policies vary and only CEA_i reflects clinical innovation (QALY gain) and resource innovation (the net financial costs of uptake in addition to the net financial costs of the new drug).

Table 20 The impact of price control vs. CEA_i

Current Drug	Group 1	Group 2	Group 3	Group 4
Drug	A	B	C	D
Price of a course	250	250	250	250
QALY compared to previous best	0.05	0.075	0.1	0.2
Net financial cost of course (net of other costs)	\$250	\$100	\$350	\$250
Cost per QALY	\$5,000	\$1,333	\$3,500	\$1,250
New Drug	A'	B'	C'	D'
QALY compared to existing drug	0.01	0	0.02	0.2
Net financial Cost (ex. drug)	\$770	-\$70	\$1475	\$13,250
"Controlled" price per course	A'	B'	C'	D'
CEA_i , where $i = \$75,000$				
Price per course	\$230	\$320	\$275	\$2,000
Incremental cost	\$1,000	\$250	\$1,750	\$15,250
Cost per QALY	\$75,000	n/a	\$75,000	\$75,000
10% limit increase in price per course				
Price per course	\$275	\$275	\$275	\$275
Incremental cost	\$1,045	\$205	\$1,750	\$13,525
Cost per QALY	\$79,500	n/a	\$75,000	\$66,375

Appendix 7B: How the ITA report reached the conclusion that all OECD countries will be better off if all OECD countries (excluding the US) increased drug prices.

1 Background

The ITA report explored the consequences of a change in international trade policy that in simple terms would result in all countries, except the US, increasing the price of new drugs. The way the analysis is constructed in this report means that the US has only benefits (no costs) from this policy and this source of benefit is the additional future drugs. This situation is a consequence of the additional R&D required for the future drugs being financed by the increase in prices of patented drugs in all countries in the OECD, with the exception of the US. A share of the additional US surplus from the new drugs is assumed to go to the consumers, and the remainder to producers and economic rent.

The hypothesis explored in this Appendix is that in order to make a policy of increased surplus to the US financed by the rest of the OECD acceptable, the ITA report needed to generate a net increase in social welfare to all the other OECD countries as a consequence of increased prices, or at least to minimise the costs. This Appendix explicates the assumptions the ITA report needed to make in order to achieve this result. They are discussed in the context of the analysis of the price control argument in Appendix 7. It starts with a brief summary of the relative desirability of outcomes of changes in international trade policy in the form of an introduction of a bilateral FTA.

2 Social welfare consequences of international trade policy

In simple terms, there are four possible combined efficiency (size of pie) and distribution (allocation of pie) consequences of changes in international trade policy between two countries:

- 1) a net increase in social welfare for both participating countries with:
 - a. no losses to any group within a country; or
 - b. losses to some groups with either country and gains to others, but a net gain overall for both countries.
- 2) a global net increase in social welfare where one country has a net reduction in welfare but these losses are offset by the gains to other country; or
- 3) one country has a net gain, the other has a net loss and the net global effect is a reduction in welfare.
- 4) both countries have a net reduction in social welfare.
 - a. no gains to any group in any country; or
 - b. losses to some groups within some countries and gains to others, but a net loss overall for each country.

From an economic perspective, Scenario 1 and 2 are acceptable (they increase social welfare) and also achievable (both countries are better off, even though in case 1b they may need to redistribute the gains). In relation to Scenario 2, economic theory would lead us to predict that there is no incentive for the country with a net loss from joining, to join that FTA. Therefore there would be a case for some redistribution of any net gain from the FTA to be redistributed across the two countries. Scenario 3

results in a global net loss in welfare, but because there is an incentive for the country that makes a gain to adopt such a policy, an incentive for such an outcome exists. However, because there is a net reduction in global welfare, it would be difficult to justify this outcome on economic terms. Scenario 4 is a possible unintended outcome of an FTA.

The following section presents the assumptions that needed to be made by the authors of the ITA report to reduce the probability that international trade policy of accepting the firms' offer price for new drugs would lead to a Scenario 3 result.

3 How to convert a global economic loss to an economic gain.

At first blush, a policy of increased prices in all other OECD countries except for the US would appear to result in an additional cost for the rest for the OECD and no benefits, whereas the US would have additional benefits (the additional consumer welfare from the additional future drugs). The ITA Report makes a series of assumption to allow the authors to conclude that not only will the US experience a net benefit, the rest of the OECD will also have a net benefit. In terms of the typology above, from what would appear to be a potential Scenario 3 outcome, the authors have argued that it is a Scenario 1 outcome. Four assumptions (explicit and implicit) were used to achieve this result. The reader is left to assess the plausibility of these assumptions.

- 1) **Minimise the health cost of drug price increases to the other countries:** The authors assume "that funds would be available (*in the rest of the OECD*) to pay the higher prices" (p. xii). This implicitly assumes no loss in the health outcomes from services displaced to finance these additional costs.
- 2) **Offset the additional financial costs of the drug price increases by reduced price of generics:** The authors assume all OECD countries will enact a policy to decrease the price of generics to the level that they are in the US and hence there will be financial savings. It is reasonable to assume that there would be savings should such a policy be enacted and this issue was raised in the Australian context most recently by Clarke (2012). This assumption fails to recognise that innovative firms are significant producers of generics and hence any reduction in economic rent due to lower prices in this market will impact on their profits as well as the profits for generic firms.²⁰³ Therefore this reduction in profits will reduce the R&D investment by firms.

Also, we would assume that the acceptability to the pharmaceutical industry of a policy that increased prices (in the case of patented drugs) would be high whereas a policy that would reduce prices would result in significant resistance from the industry, and, in the case of Australia, the retail pharmacists who currently appropriate a significant share of the gains from the gap between high centrally set costs to consumers for generics and high competition across generic wholesalers in the price to retail pharmacies (Beecroft 2007). A policy that would increase expenditure by the health budget would not lead to rent protection whereas a policy to reduce the price of generics would.

- 3) **Maximise the health benefits of the policy:** The authors assume that higher prices of patented drugs today will allow more new drugs, or more rapid entrance of new drugs, into the countries that currently control price and hence increase today's health.²⁰⁴ They infer that, therefore, the

²⁰³ Consider the claim made by Pfizer in their 2009 Financial Report that notes their additional profits from some sources were offset by "the impact on chargebacks of decreased sales within our generics business." Page 12, Financial Report 2009. Decreased prices in the generics market will decrease profits for innovative firms and hence as internal funds are a source of R&D investments, R&D can be expected to decrease as well.

²⁰⁴ According to the ITA report, countries' populations will be better off if they increase prices to the level of the US undiscounted prices and combine this with a strategy to reduce the price of generics to the US discounted level. They will be

health of the population will increase more rapidly than it otherwise today because the price of new drugs is increased. Second, the authors assume there will be more sales of generics as their price drops, and additional health gains will therefore be available to the population. This assumption recognises that pharmaceutical demand is price elastic, in contrast to a previous assumption; there is no reduction in demand for drugs following a 25% to 38% increase in patent drugs price. Third, the authors assume that because there will be more drugs in the future and these will be purchased by patients in these countries as well as the US, future health will be improved even further.²⁰⁵ In summary, the effect of price increases for new drugs and reduced price for generics is claimed to be an increase in the health in other OECD countries compared to what it would be under regulated prices.

- 4) **Minimise the health loss from the policy** : The assumption of the unconstrained budget in the US and in the rest of the OECD allows the analysts to achieve the following result: the gross gain in health effects from the policy as described in point 3 above is assumed to be the same as the net gain in health effects to every country, because no services are displaced to finance these additional costs.

4 Conclusion

The authors conclude that there will be health wins to both the US and the rest of the OECD from this policy and infer that the net financial cost of the policy to the rest of the OECD will be more than offset by additional value of the additional health gains to these countries. This is a shift from a Scenario 3 to a Scenario 1a. We can accept the claim that it is a policy with no trade-off, provided the assumptions discussed above are accepted.

better off health wise for three reasons. The increase in price of the innovative drugs will result in additional future drugs. The higher price will also encourage firms to make these drugs available in these countries earlier than they would otherwise. And the lower price of generic drugs will increase their use (but will not substitute for innovative drugs so the maximum number of NMEs from more R&D (more revenue) will become available). Whatever

²⁰⁵ “While the available information suggests that consumers in countries with stringent price controls will benefit from improved access to new medicines as a result of price deregulation, consumers everywhere will likely benefit from an increased flow of new medicines.” Page 32 ITA report

Appendix 8: How does Pharma and the pharma-economic literature characterise the riskiness of R&D

1 Background

Game 2 (Chapter 9) is intended to assess the claim by Pharma and pharma-economists that capital markets fail to invest optimally in risky pharmaceutical R&D. The characterisation of this risk in Game 2 is:

- the probability, q , that a given investment, \mathcal{R} , will or will not result in a NME being brought to market suggests a risk of loss of $(1-q)\mathcal{R}$.

This way of characterising the riskiness is consistent with the policy narrative: \mathcal{R} and q are so high that the Capital Market cannot bear the risk of a loan to the firm to finance this drug. In Appendix 8, I ask the question, is this characterisation consistent with the evidence presented in the academic and commercial literature? First I consider the two ways that this risk is characterised in the literature. Then I look at the determinants of variability in profits, according to firm financial reports.

2 Risk in the literature

There are at least two ways in which Pharma and the pharma-economic literature characterises and quantifies the risks of pharmaceutical R&D.

2.1 Number of molecules that need to be patented before one is brought to market

The first method is to highlight the number of molecules that are patented but not brought to market. This approach could be characterised and quantified as the proportion of patents, Phase 1, Phase 2 and Phase 3 trials that result in an NME being brought to market and argue this is an indicator of risk. For example, a search of the Australian patent data base on February 28 2011 of patents where the applicant's name contains the word Pfizer contains 2,513 results, not all of which are NMEs.²⁰⁶ In the Pfizer 28 February 2011 Pipeline Report, the company reported 93 NMEs in the pipeline of which 4 were in the Registration phase and 13, 28 and 49 of which were in Phase 3, 2, and 1 respectively. It is not possible to determine the number of NMEs with Pfizer patents on this date, but not yet in Phase 1, from this report.²⁰⁷

2.2 The investment required to bring one drug to market

The second way that risk is characterised and quantified is to estimate the present value of the R&D investment required to bring one NME to market, where this estimate includes the investment in R&D for drugs that go no further than, for example, Phase 1 trials.²⁰⁸

The business press often characterises this as the link between: i) the high costs of R&D, due to the uncertainty about which of many potential molecules will become a drug that can be brought to

²⁰⁶ This information was accessed on 20-2-2012 at: <http://pericles.ipaustralia.gov.au/ols/auspat/>

²⁰⁷ This information was accessed on 20-2-2012 at: http://www.pfizer.com/files/research/pipeline/2011_0228/pipeline_2011_0228.pdf

²⁰⁸ An example of such an analysis is DiMasi, Hansen et al. (2003).

market; ii) the price we pay for new drugs; and iii) the financial value of these new drugs in terms of their cost saving consequences (resource innovation).

Medical breakthroughs don't come cheap, though. For every successful drug, there are many, many more left on the lab-room floor--all of which, individually, cost millions or even billions to research and develop. These scientific breakthroughs never would have happened without a market that encourages and rewards fruitful scientific research. And while novel treatments may carry hefty initial price tags, they more than pay for themselves. Columbia University professor Frank Lichtenberg has shown that new drugs and treatments ultimately lead to lower health care costs. For every additional dollar in pharmaceutical expenditure, there is a reduction of \$3.65 in total hospital care expenditures. For every 100 prescriptions, expensive hospital stays declined by 16.3 days. (Pipes 2011)

3 Risks according to Pharma financial reports

3.1 Legal costs

The riskiness of the pharmaceutical industry could be experienced by an individual firm as large annual variations in return on equity. This could be attributed to a number of factors, one of which is costly legal battles. Consider the 2009 USD2.3B settlement by Pfizer Inc. relating, in part, to its promotion of off-label prescribing of drugs including Bextra and Geodon.²⁰⁹

These costs were reported as having a significant impact on Pfizer's profitability:

The (2008) payments made in connection with the resolution of certain legal matters related to Bextra and certain other products and our NSAID pain medicines of approximately \$3.2 billion (see Notes to Consolidated Financial Statements—Note 3C. Other Significant Transactions and Events: Legal Matters); Source Pfizer 2010 Financial Report p. 43

These legal costs of \$3.2B represent 41% of the total expenditure on R&D reported for 2008.

3.2 Is the pharmaceutical business inherently risky? The example of Roche

The biotech firms that require start-up capital are considered risky investments in that the return to the investor has a high probability of being zero and a low probability of being extremely high. While the risk for one firm is high, this risk can be managed by a portfolio of investments managed by venture capital firms. However Hall (2002) found no evidence that larger pharmaceutical firms face the same limitations in accessing capital markets; their portfolios of multiple potential drugs reduce the risk inherent in new drug development. One way of illustrating this issue is by reviewing a key ratio (net income payable to Roche shareholders) for one firm (Roche) and identifying the reasons for significant variations for five years of the twenty between 1991 and 2011.

²⁰⁹ http://www.pfizer.com/files/news/press_releases/2009/pfizer_doj_settlement_090209.pdf Accessed: 21-02-12

Net income as % of equity for Roche, 1991 to 2011

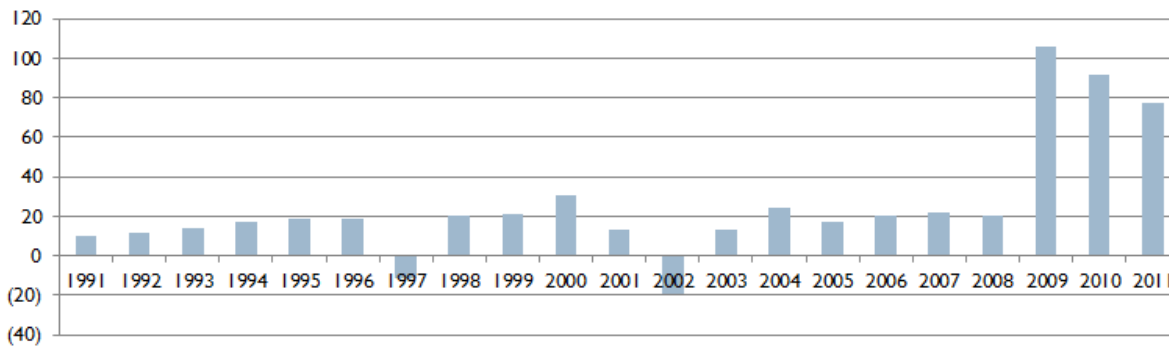


Figure 20 Net income as % of equity for Roche, 1991 to 2011

Source: Roche financial reports, from 1999, 2000 and 2011 Multi-year results available online at www.Roche.com Accessed: 21-02-12

In 2000, Roche reported a net loss (but a positive operating profit) for 1997, which was reported as a net positive income in the 1997, 1998 and 1999 financial reports. The reasons for this change in the 1997 income are not apparent from the financial reports but are most likely related to its financial relationship with Genentech and the drug Herceptin.

In 2002, Roche reported a net operating income that was positive but a net loss. This result was attributed to:

The sale of the Vitamins and Fine Chemicals Division, legal settlements with US direct customers in the vitamin case and an impairment of financial assets result in significant one-time charges and a substantial consolidated net loss. Source: Roche Annual Report 2002 p. 3

In particular, the impairment of financial assets was reported as follows:

The large equity holdings that earned significant returns for Roche in the 1990s involve risks that are making themselves felt in today's turbulent market environment. As a result of stock market developments over the past two years, the carrying value of our equity portfolio, which consists primarily of Swiss SMI securities, has declined sharply. In line with an anticipated change in international Financial Reporting Standards, we decided last year to revise our accounting policy and recognise impairment losses on financial assets if the assets' market value remains at least 25% below original cost for a period of more than six months. As a result of this decision, accumulated unrealised investment losses totalling 5,192 million Swiss francs as of the end of 2002 have been charged to income. Painful as the one-time impact of this measure is, it gives us the flexibility to allocate resources when and where they are needed for the strategic development of our operating businesses. (Roche Annual Report 2002 p. 5)

In 2009 to 2011, Roche reported a significant increase in income to equity ratio. This was a consequence of a dramatic reduction in equity, not an increase in income.

The Group completed the purchase of the non-controlling interests in Genentech effective 26 March 2009, as described in Note 3. Based on the revised International Accounting Standard 27 Consolidated and Separate Financial Statements' (IAS 27), which was adopted by the Group in 2008, this transaction was accounted for in full as an equity transaction. As a consequence, the carrying amount of the consolidated equity of the Group was reduced by 52.2 billion Swiss francs, of which 8.5 billion Swiss francs was allocated to eliminate the book value of Genentech non-

controlling interests. This accounting effect significantly impacts the Group's net equity, but has no effect on the Group's business or its dividend policy. (Roche Financial Report 2010 p. 115)

This very brief review of one ratio (net income as a percentage of equity) for one company (Roche) illustrates four sources of variability in the key ratio of net income to equity: legal costs; conditions in the financial market that lead to loss in financial assets portfolio; financial arrangements relating to the patent for Herceptin and Genentech, made after the drug was demonstrated to have a benefit for women with metastatic breast cancer; and changes in the equity structure of the firm as a consequence of its relationship with Genentech.

The underlying operating income for Roche and return on equity is essentially stable and high over this twenty year period. It is also possible to argue that this stability in operating income is a consequence of being able to access capital for R&D via internal funds, which, as discussed in Chapter 9, are costless (no interest and no repayment), except for the cost of lobbying. However, further research on this issue is outside the scope of this thesis.

4 Conclusion

Both of the methods for understanding risk referred to in the literature suggest that while pursuing one potential NME is a risky venture, if firms pursue a portfolio approach, the return on investment in the R&D portfolio could be reasonably stable and low risk (Reinhardt 2007 pp. 33-34). Therefore, the characterisation of the risk of pharmaceutical R&D as the risk of a loss in the investment in the R&D for one drug is consistent with the policy narrative (lobbying) but not consistent with the evidence. However, this inconsistency is not an obstacle for Game 2, which is about engaging with the narrative, first and foremost, and then exploring why this threat is a successful firm strategy.

This very brief review of the evidence does raise other issues about what the policy narrative means by the concept of uniqueness of pharmaceutical R&D and the implications of this for the apparent failure of capital markets to fund this R&D. If the uniqueness of this R&D is that many drugs need to be developed in order to achieve one drug entering the market, then this risk is managed in a large firm by maintaining a portfolio. If the uniqueness of the R&D process is characterised as the high costs of bringing one NME to market because the R&D attributable directly to a new drug is only part of the total costs, it would be difficult to argue that this point is too complex for the capital market to understand and hence is a source of failure for the capital market to finance R&D. In summary, regardless of the apparent uniqueness of pharmaceutical R&D, it is difficult to argue that it results in a unique argument for funding via economic rent (higher prices) rather than the capital market.

Appendix 9: The strong and weak compensation tests

1 Introduction

The strong and weak compensation tests are applied in Game 3, Chapter 10. The formal definitions of the terms strong and weak compensation tests are set out in Mas-Colell et al. (1995 pp. 829-831). In this Appendix I explain the distinction between these two tests, and justify their use in the context of Game 3, Chapter 10 even though the health economics community would be unlikely to accept the hypothetical compensation test as a policy rule in health.

2 Pareto improvement

Most economists are familiar with a potential Pareto improvement or compensation principle in the context of assessing the social welfare impacts of policy. A policy proposal passes the hypothetical compensation test if each individual made worse off by the policy could potentially be compensated by those who are made better off and, consequently, all individuals will be at least as well off as they were prior to the policy. It can be thought of as a “weaker” version of the Pareto improvement, which is a change that will result in no one being worse off after the policy change and some will be better off (without compensation) (Mas-Colell et al. (1995 p. 334).

The possibly perverse distributional outcomes of applying this criterion are also well known. This approach is not directly sensitive to the original distribution of wealth, therefore, a policy that makes the 5% wealthiest people in a population better off by \$200K each could be justified if it makes the remaining 95% worse off only by an average of no more than \$10.53K ($0.05 \times 200 = 0.95 \times 10.53$).

The hypothetical compensation test is a little more complex: it is based on the welfare implications for individuals of this payment, not the value of the payment. Therefore, to the extent that the decreasing marginal benefit of additional wealth is captured in assessment of individual welfare, an additional amount of \$5K, for example, will have a greater value to a poorer compared to wealthier person as welfare (rather than financial resources). This measurement of welfare gain rather than financial gain could magnify some of the perverse effects of hypothetical compensation as a policy criterion. If redistribution does not actually occur, other distributional issues emerge.

3 Strong and weak compensation tests

The idea of strong and weak versions of this test is probably less well understood than the hypothetical compensation criterion, at least in the health economic community. Whether or not a particular policy passes the strong criterion or only the weak criterion is determined by the nature of the social welfare function (SWF) post-policy change relative to the SWF pre-policy change. The two scenarios are presented in .

If the pre-policy SWF (A) is entirely within the post-policy SWF (B), then the strong test applies; there is no outcome in the post-policy change world where the compensating variation test is not met. (This assumes that the post policy world will be a situation on the SWF, that is, we have economic efficiency.) However, under the weak compensation test, the pre- and post-policy SWFs intersect. Therefore, there are some outcomes of the post-policy world where the hypothetical compensation condition does not apply; we could even end up in a situation where everyone is worse off compared to pre-policy.

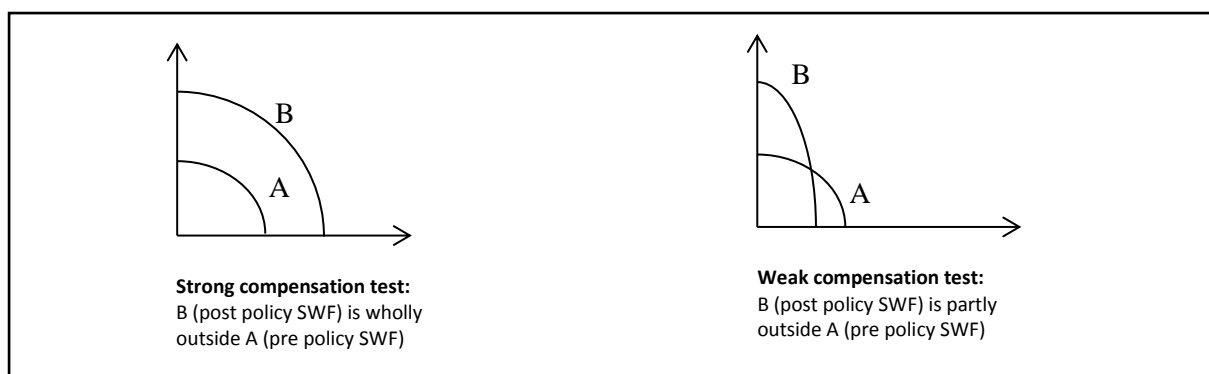


Figure 21 Strong and weak compensation tests

4 Why apply the strong and weak tests in this example?

The use of a potential compensation test is clearly inappropriate as a policy rule in health economics. However, in the situation of interest in Chapter 10 when we are testing the results found by authors such as Santerre and Vernon (2005) and Jenna and Philipson (2008) then it is appropriate to use these tests. The reason is that these authors are inferring that their policy proposals pass either the Pareto improvement test or the strong compensation test. (See discussion below) Therefore, in Chapter 10, we engage with their claims in a game theoretic model and establish:

- whether the policy of a price premium passes either of these tests;
- the conditions under which it passes the weak compensation test; and
- whether a contract can be established that will provide an incentive for the purchaser to enter into this policy of a premium by ensuring that the consumer can be compensated via an appropriate share of the surplus.

But first we consider how these two papers inferred that their policy proposals pass the strong compensation test.

4.1 Santerre and Vernon infer that the policy of no price regulation compared to price regulation passes the strong compensation test

Consider the case of Santerre and Vernon and their conclusion that the costs of price control policy in terms of loss in consumer welfare due to higher prices is outweighed (by 28 to 1) by the gain in social welfare.²¹⁰ Putting aside the issue of the overestimate of this ratio,²¹¹ which test does this result pass? The authors state that society will be better off as a result of no price regulation compared to price control. Santerre and Vernon do not identify any possible outcomes of a policy of no price regulation that would lead to a reduction in social welfare compared to price control. Hence they are suggesting that a policy of deregulation would pass the strong compensation test.

What about the distribution of this gain from deregulation of prices? Do the authors comment on this? And does it matter from the perspective of the strong and weak compensation tests? The distribution of this gain from deregulation between consumers and producers is determined by the price per QALY of these innovative health units; the higher the price per QALY, the less that is appropriated by consumers. The authors do not comment on the potential distribution of this surplus

²¹⁰ See Appendix 2 for a detailed discussion and re-simulation of their analysis.

²¹¹ Appendix 2 details the reasons why and demonstrates why their analysis overestimates this ratio.

across consumers and producers, hence we can infer that the authors are satisfied with the potential Pareto improvement as a criterion for acceptance of this policy. In other words, the authors are satisfied that there is no requirement for actual compensation provided that the net increase in social welfare is positive. Hence we can conclude that the authors are inferring, not only that this policy would pass the strong compensation test, but also, the compensation needs to be potential not actual. This point is important because the authors are comparing the cost of this increase in future health – entirely funded by consumers through higher prices – with the benefit. If the benefit is entirely appropriated by the firm via higher prices, then the return to consumers is zero even if the gain to producers outweighs the cost to consumers by 28 fold.

In a separate paper, Vernon has argued for full appropriation of the clinical innovation by full value pricing of the clinical innovation of new drugs in order to ensure optimal incentives for investments (Vernon, Goldberg et al. 2009). Given that Vernon has previously acknowledged that this R&D is financed through higher drug prices, this policy of full value pricing explicitly excludes the possibility of compensation for the group made worse off by the policy (Appendix 7, Section 4 p. 249).

4.2 Jena and Philipson infer that the policy of the optimal price premium passes the string compensation test

Jena and Philipson identified a policy of a premium over the “regular” threshold for new drugs in order to achieve the optimal incentive for R&D. The authors stop short of proposing full value pricing; they identify that there are situations when full appropriation by the firm is not justified such as the contribution of public sector medical research funding to the R&D costs of a new drug. The authors infer that no premium will always be worse than the optimal premium, where the optimal premium is greater than zero. However, they do not define what this optimal premium is, except that it is social welfare maximising.

We can infer that this optimal premium is assumed to pass the strong compensation test, not the weak test. How? Because the authors do not identify any conditions under which, at this optimal premium, which is always positive, there will be a social welfare loss.

The authors also make a strong distributional assumption. They do not refer to the possibility that consumers could be worse off under this policy because they are not compensated for their investment via higher prices. Like many US pharma-economic authors, it is sufficient to establish a potential Pareto improvement will follow from a policy, not to ensure an actual Pareto improvement via redistribution of the gains in social welfare between consumers (the funders of this investment) and producers (who appropriate some or all of the gain).

5 Conclusion

In Chapter 10, we test whether a policy of a price premium for new drugs above the health shadow price will pass the strong compensation test. We find that it fails the strong, but passes the weak compensation test. If it passes the weak compensation test there is a *prima facie* incentive to establish a contract which will redistribute a sufficient share of the gain in surplus to consumers to provide an incentive for consumers to pay the premium in Period 1.

Appendix 10: Adding an additional outcome of interest can reduce the maximum acceptable IPER for a new drug

1 Introduction

This Appendix looks at the problem of an argument for a premium over the shadow price due to reasons other than the relationship between price and innovation. Such reasons include characteristics of the patients (severity of disease), social objectives (improving equity), or outcomes of therapy beyond those measured by the QALY (productivity gains).

Whether it is reasonable to increase price due to the existence of “other things” depends upon the theoretical framework. When a non-economic approach is used, such as maxWTP, the idea that we would pay more for a good (a drug) because it has additional benefits compared to the best alternative drug is reasonable. We might even accept the argument that society should pay the maxWTP for those “other things”. When an economic approach is used to assess this question, four additional issues emerge. First, if we consider the opportunity cost, we would not pay more for this other thing than the least cost way of producing it; the maxWTP for the additional output is not the shadow price. Second, it is possible that there is another program or combination of programs that generates the same amount of QALYs as the new drug but more of the “other thing”, and at the same incremental cost of the new drug at the higher price. Third, the axiom of strict convexity of indifference curves is a consequence of the diminishing marginal return to increased consumption of a single good. There is a point when a bundle of goods that produces a little less QALY gains than the new drug but much more “other thing” compared to the drug, will be preferred to the drug. Fourth, if the firm introduces the possibility that there is an output other than QALYs that the health budget should pay for, there is no reason why for that decision further “other things” that this drug is not producing should be included.

The single observation tying these four issues together is that once we introduce a second possible outputs of health care, then micro-economic theory has a lot more to say about our preferences than what we need to solve the problem with only one type of output. That is, if we are saying that the outcome we are paying for is beyond QALYs, we need to revisit mainstream consumer theory to remind ourselves of the tools and theories developed by economists to address choice between alternative means of maximise utility. Indifference curves are a key tool.²¹²

In this Appendix, I show that, by introducing another outcome of value other than QALYs, for example, in order to justify a higher cost per QALY for a drug relative to the threshold, the consequence could be that the firm is then offered a lower price per QALY than the threshold price. I use a story to demonstrate these issues. The starting point for this story is the following series of observations:

- 1) There is a financial incentive for the collection of data on these “other things” otherwise firms would not invest in the development of this evidence.
- 2) The case for “other things” is made most frequently when, at the offer price, the drug is unlikely to be considered “value for money” in terms of its QALY gain alone. It is the additional piece of information that can justify reimbursing a drug.
- 3) If there are less “other things” for a new drug compared to the existing therapy, there is no incentive for the firm to produce this evidence as part of the reimbursement process.

²¹² For a discussion of the properties of indifference curves and the underlying axioms, see Jehle and Reny (2001) Section 1.2 and 1.3.

4) There is more than one type of “other thing”.

2 Background

A common practice in the drug reimbursement game is to argue that a new drug should be purchased at the offer price, even though its *IPER* is above the threshold price per QALY, because it has benefits beyond the additional QALYs. Typically this situation is framed as one of undervaluing the full benefits of a new technology by focusing only on the consequences that can be measured by QALYs.²¹³ However, in practice, this argument becomes relevant in a reimbursement process only when the *IPER* is above a given threshold; there is no value in investing in additional evidence to justify an *IPER* if it meets the necessary and sufficient condition of being at or below the threshold. In this Appendix we consider the possibility that under PEA, if this argument is used in the context of bargaining above a health shadow price, then the optimal result could be a lower rather than higher threshold, or no change in the threshold.

3 Example 1 – additional output of “other thing”

A new drug is offered to the Reimbursor at an *IPER* of \$30K per QALY. The Reimbursor is surprised because she has provided a signal of $\beta_c = \$5K$ per QALY. At prices above this, the health budget holder can purchase health effects more cheaply using other inputs. The Firm provides the equation it used to derive this *IPER*:

$$IPER = \frac{P_q \times Q + P_t \times T}{Q}$$

Where P_q is the maximum acceptable price per QALY ($=\beta_c$)

Q is the number of QALYs for the target patients.

P_t is the maxWTP per unit of other thing.

T is the number of units of other thing.

And by substituting in all the values in this equation, they found:

$$\begin{aligned} IPER &= \frac{\$5K \times 10 + \$20K \times 12.5}{10} \\ &= \frac{\$300,000}{10} = \$30,000 \end{aligned}$$

The “value” of the package or bundle (Health plus other thing) is \$300K. The total expenditure on the drug at this higher *IPER* is \$300K. However, because the Reimbursor requires a value is expressed in terms of QALYs, the Firm has divided this amount by the total QALYs (10).

The values of these estimates were derived using the most rigorous methods. These methods and hence the result can be replicated and validated. But can this approach to calculating a Health+

²¹³ For example see Goldman, Lakdawalla et al. (2010).

threshold be challenged? The Reimburser's question is: Should the threshold price be increased to account for this "other thing"?

4 The value of "other things"

Indifference curves, constructed with reference to two ways to improve consumers' welfare (other things and health measured as QALYs), are presented in Figure 22. These indifference curves join bundles of outputs (other things and QALYs), between which the consumer is indifferent and then ranks these indifference curves in terms of preferences. Different programs produce different bundles of outputs.

The first question is "whose indifference curves?" For the purpose of this Appendix, this could be the same group of people who the firm used to value "other thing". All that is necessary to note is that what is of interest in this example is the preferences across different mixed of health and other things, not their dollar valuation.

The bundle that represents the new drug is given by A. First we assume that the best alternative strategy (which will cost a total of \$50,000 or \$5,000 per QALY) is given by B and that just like the drug, the best alternative strategy also produces some of the other thing but less than Drug A. Hence it is on a lower indifference curve.

Program B only costs \$50,000 (\$250,000 less than Drug A). The Firm acknowledges this, and then says, because the Reimburser accepts that "other thing" is of value then a small premium would still be justified because the new drug generates more units of other thing; maybe an additional \$75,000?

The Reimburser then revisits her set of alternative strategies (See Chapter 6 Section 3 p. 84). She notices that there was another program, Program C, which had the same additional QALYs as Program B, and was the same incremental cost (\$50,000) but had more units of "other thing". Previously she had disregarded this program because she was indifferent between them (when only QALYS were considered). The Reimburser presents information about Program C to the Firm. She notes that for \$50,000 she has the same number of additional QALYs, but far more units of "other thing" compared to Drug A and Program B. She says to the Firm that in order to purchase Drug A instead of implementing Program C, she will require compensation to make up for the loss of these units of "other things". Therefore she will no longer pay \$50,000 for Drug A, instead she will pay less; the threshold will decrease.

Then she identifies a third option, Program D also at a cost of \$50,000, with slightly less QALYs compared to Drug A and Programs B and C. She notes there is a preference for this Program over the others. She now requires an even greater compensation for choosing Drug A rather than implementing Program D. The threshold price drops to \$2K.

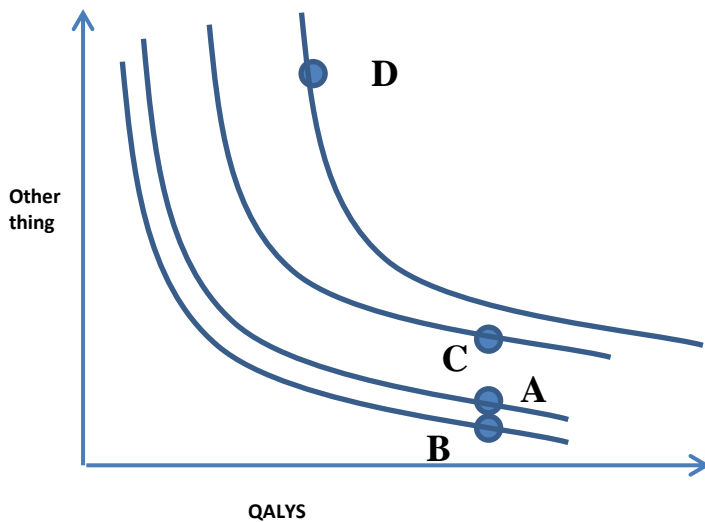


Figure 22 The value of "other things" - indifference curves

5 The value of "equity"

Now the clinicians start to lobby the Reimbursers. They say that their claim it is not about "other things", it is about characteristics of these patients. These 100 patients currently have no options available to them for treatment. Unlike the other 9000 patients with this condition, theirs is a rare form and current treatments available for the more common form are not effective for this subgroup. In the clinicians' view it is about equity; equity in access for the people who have the rare form of the disease compared to those with the common form.

The Reimbursers is concerned about equity. She widens her scope of alternative strategies again. She can still purchase Program B for \$50,000 and have the additional 10 QALYs, the same as those possible for the new drug. However, for that additional \$250,000 that the Firm is requesting for Drug A she can purchase Program E, podiatry services and new shoes and socks for a year for 250 homeless people who would otherwise have no access to foot care. Program E is about equity and she can achieve it for 250 people.

The clinicians say: "But there is no evidence that this program for homeless people will be effective in improving their health!"

The Reimbursers shrugs her shoulders. She asks herself: "Why is there no evidence?" If no organisation or individual can patent the resultant program, why would there be an incentive to develop evidence? She also notes that the investment by her country's publically funded medical research institute into research on Drug A was in the order of \$10M.

The Reimbursers points out that for the same total budget ($\$50,000 + \$250,000 = \$300,000$) she has gained some "equity" for 150 more people compared to Drug A and has the same gain in QALYs (10). Even if the homeless program is not effective in producing health benefits, compared with Drug A it will do no worse in terms of health benefits than the new drug and in terms of equity it will do much better.

6 The bottom line

The presence of benefits beyond health in the provision of health care is not disputed. What is disputed is the practice of allowing this “other thing” to be a lever for gaining higher price (or threshold) without considering the alternative ways of achieving the same or a better outcome, now that this outcome has been redefined.

The issue of whether the evidence of the full range of other things is available for non-drug health inputs is a barrier to applying this method in practice. However, this Appendix is intended to show why using conventional consumer theory we would not expect that introducing an “other thing” necessarily leads to a higher price for the drug. It is not intended to demonstrate a practical way of including “other things” in a valuation of a shadow price of a new drug.

At least three forms of bias are generated by providing a financial incentive for firms to generate evidence of the value of “other things”. First, firms have an incentive to provide evidence only for “other things” that will generate additional value, not “other things” that the new drug provides less of compared to the existing therapy. Second, by not correcting for the failure of the market to provide evidence of “other things” for patented and unpatented services, the preference for new technologies vs. existing technologies is reinforced if not magnified. Third, if previous drugs in that class were provided a premium for characteristics of patients, such as severity, then by paying this premium while the comparator drug is still on patent will result in this premium being double counted. (See Appendix 6 on appropriation of surplus.)

In the PEA framework, there is no scope for manufacturers or clinicians to use the idea of “other benefits” to bargain to a price above the shadow price, without taking into account alternative ways to reach these other outcomes and objectives. In being able to respond to these claims to a higher share of the innovative surplus by changing the set of alternative strategies, the Reimbursers becomes an active rather than passive participant in the drug price game, which ever version is being played. She may even chose to lower the threshold price per QALY.

Appendix 11: A presentation that might convince clinicians that opportunity cost is a real concept and displacement is not a proxy for opportunity cost

What is clinical innovation (ΔE) of Drug A for these patients, given the clinical context?

Options	Benefits	Harms	Net effect
Drug A (new drug)	10	4	6
Drug B (best alternative)	8	5	3
What is A's clinical innovation?	2	1	3 (= ΔE)

The clinical innovation of Drug A is 3- the net effect compared to the best alternative, Drug B

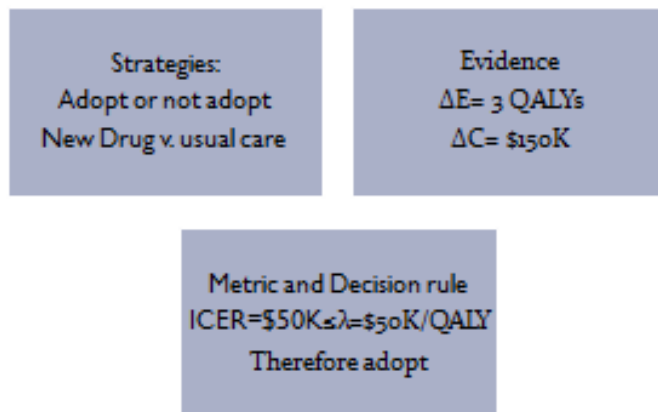
- Consider a new Drug A that has both benefits and harms compared to placebo and Drug B (the best existing therapy for that group of patients.)
- The clinical decision is the choice between two strategies: prescribe Drug A or Drug B.
- Clinicians are comfortable with the idea that the clinically innovative component of Drug A is not the same as the benefit of Drug A compared to placebo.
- In this example Drug A has a benefit of ten units compared to placebo and a harm of 4 units against placebo. Hence its net effect against placebo is 6 (=10-4) units.
- The corresponding figures for Drug B are 3(=8-5) units.
- Drug A also represents 2 units of benefits against Drug B and 1 less units of harm against Drug B, and hence has a net clinical benefit against Drug B of 3 (=10-8)-(4-5))
- The incremental effect of Drug A compared to Drug B is the ΔE that is used in an incremental cost effectiveness ratio. It is also the clinical innovation of Drug A.

What is resource innovation (ΔC) of Drug A for these patients, given the clinical and financial context?

Options	Costs of drug	Other costs	Costs
Drug A (new drug)	\$500K	\$200K	\$700K
Drug B (best alternative)	\$200K	\$350K	\$550K
What is net financial cost of adoption?	\$300K	-\$150K	\$150K (= ΔC)

- Clinicians and budget holders are also comfortable with the idea that the additional financial cost of the new drug is not the same as the financial cost of the new drug for the patient group, \$500K. It also includes the additional costs such as administration and hospital stays (\$200K).
- Drug A also represents \$300K of additional drug costs compared to Drug B and \$150K of less other resources used and hence has a net financial cost of adoption (replacement of Drug B) of \$150K = $(= (500K - 200K) - (200K - 350K))$.
- The incremental financial cost of Drug A compared to Drug B is the ΔC that is used in an incremental cost effectiveness ratio. It is also the resource innovation of Drug A.

Cost effectiveness analysis is SO simple



-
- So cost effectiveness analysis is simple, the ratio of the incremental cost of Drug A compared to Drug B to the incremental effect. In this case it is $\$150K/3QALY = \$50K$ per QALY.
 - In this case the decision threshold is also $\$50K$ per QALY and because the new drug is cost effective at the current price, it is adopted.

Price effectiveness analysis:

What is economic innovation of Drug A for the population given the economic context of the health budget?



- Cost effectiveness analysis compares the strategy of using Drug A with the best alternative strategy of using Drug B.
- Price effectiveness analysis compares the strategy reimbursing a new drug (adopt the new drug to achieve the additional health effects and displace to finance the additional costs) with the best alternative strategy which is to adopt or expand the most cost effective of existing programs and finance this by contracting the least cost effective of existing programs.
- Just as the net benefit of Drug A compared to placebo is the benefits less the harms, the net effect on the population of adopting Drug A and displacing services to finance the additional costs is -1 units (QALYs). This focus on the outcome for the population rather than the outcome for the patient group is consistent with the trend toward using impact on population health rather than the impact on specific patients targeted by the new drug as the maximand.
- There are two potential sources of inefficiency resulting from the strategy of reimbursement:
 - inefficiency in adoption, choosing to allocate the finances raised from displacing services to the least effective of the two services
 - inefficiency in financing, financing by displacing or contracting a program that is not the least cost effective
- The opportunity cost of the strategy to reimburse is 7 units (QALYs) – this is the net economic loss of adopting the new drug and financing its adoption by contracting another program. This is exactly analogous to the net clinical innovation of the new drug being assessed against the opportunity cost rather than the benefit against placebo – the foregone benefit of not using Drug B not the foregone benefit of placebo.

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Attachments

Attachment 1: The Nutrition Pill Manufacturer (Danzig, 1963)

This is an excerpt from Danzig (1963) . Permission was obtained from RAND to reproduce this excerpt in this thesis. It is a reminder of how basic and uncontroversial the core economic ideas behind PEA and the health shadow price are, particularly the idea that a monopolist producer of a patented input can still have competition in the market. Regardless of how much the Nutrition Pill Manufacturer has invested in the development of these nutrition pills, the manufacturer must still price with regard to the competition in the market for family nutrition, where this competition comes from ordinary food, much of which is unpatented and/or unpatentable. The last lines suggest that if housewives take a strict cost minimisation approach to their choices about food purchases, while meeting the criterion of a minimum supply of nutrients and calories, they might end up serving just nutrition pills – and that this outcome might not be desirable.

12-2. EXAMPLES OF DUAL PROBLEMS

A nutrition pill manufacturer wishes to supply the entire dietary requirements by marketing in the drug stores a pure calorie pill and a pure vitamin pill at prices that will not only compete with similar "foods" 1 and 2 offered in the grocery store but will be a cheaper source of nutritional needs than any food on the market. What prices should he charge in order to maximize his revenues?

Let π_1 be the price he charges per calorie pill and π_2 be the price per vitamin pill (each pill = 100 units). Then the dual problem takes the form shown in (6a). By substituting for π_i ,

$$\pi_i = -y_i$$

it takes on the form (6b) which is more convenient for plotting; see Fig. 12-2-I.

Dual Pill Problem

<p>(6a)</p> $\begin{aligned} -\pi_1 &\leq 20 \\ -\pi_2 &\leq 20 \\ -\pi_1 - 2\pi_2 &\leq 31 \\ -\pi_1 - \pi_2 &\leq 11 \\ -2\pi_1 - \pi_2 &\leq 12 \\ \pi_1 &\leq 0 \\ \pi_2 &\leq 0 \\ -21\pi_1 - 12\pi_2 &= v \text{ (Max)} \end{aligned}$	<p>(6b)</p> $\begin{aligned} y_1 &\leq 20 \\ y_2 &\leq 20 \\ y_1 + 2y_2 &\leq 31 \\ y_1 + y_2 &\leq 11 \\ 2y_1 + y_2 &\leq 12 \\ y_1 &\geq 0 \\ y_2 &\geq 0 \\ 21y_1 + 12y_2 &= v \text{ (Max)} \end{aligned}$
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In (6b) the sum of the terms to the left of the inequality (such as $y_1 + 2y_2$ in the third constraint) represents the cost to the housewife if she *simulates* the type of food in question by purchasing nutrition pills with equal amounts of nutritional elements; the quantity to the right represents the cost to her if, instead, she buys the food. In each case it is required that it cost no more to buy the simulated food.

The inequalities (6b) are plotted in Fig. 12-2-I, and it is evident that the optimum choice of prices is to charge 1 cost unit for the calorie pill and 10 cost units for the vitamin pill.

(7) Optimum Prices: $\pi_1^* = -1, \pi_2^* = -10$

Maximum Revenue: $v^* = \pi_1^*b_1 + \pi_2^*b_2 = -(-21) - 10(-12) = 141$

It should be noted that there is a built-in assumption that the drug manufacturer will supply all dietary needs. Granted this, it is clear that his prices must be competitive with the price of each food, for otherwise the housewife would buy part of the diet in the grocery store and part in the drug store. Another point worth noting is that foods 4 and 5 are still competitive with the pills; that is to say, no more costly than the pills, as can be seen by substituting these values of π_i^* in (6a). Thus, pill prices must

be set slightly below the optimum in order to overcome any residual bias toward pills and thereby guarantee the market. In the nutrition case, it is obvious from Fig. 12-2-I (and true in general when all $a_{ij} \leq 0$) that a slight

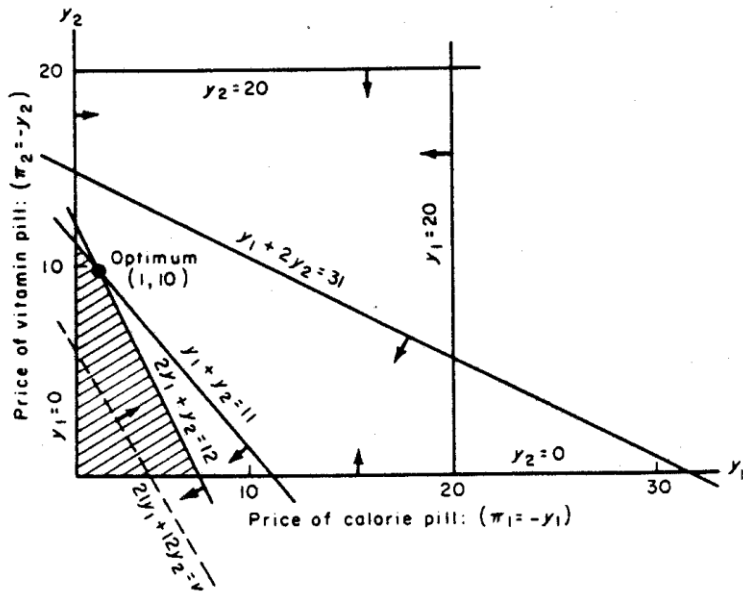


Figure 12-2-I. The dual pill problem.

decrease in all y_i (or increase in π_i) from the optimum is sufficient to guarantee the entire market, if the decisions of all housewives are determined strictly by minimum cost. Let us hope that this is not the case.

Attachment 2: Excerpt from the Joint Hearing of the Finance Committee of the US Senate April 2004

Word count: 5,000

STATEMENT OF GERARD ANDERSON, PROFESSOR, JOHN HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH, BALTIMORE, MD

Mr. ANDERSON. Thank you. Mr. Chairman, members of the Senate Finance Committee, my name is Gerard Anderson and I am a professor at Johns Hopkins University.

In my oral testimony this morning, I would like to make six points.

My first point, is that other industrialized countries have invested considerable resources and capital in developing the appropriate use of pharmaceuticals and monitoring pharmaceutical prices. Currently, however, the U.S. has no strategy for determining appropriate price or utilization for pharmaceuticals. Because we have done so little, it seems unfair to ask these other countries to change their programs.

My second point, is that our analysis shows that the U.S. pays twice as much for a market basket of 30 commonly prescribed pharmaceuticals as other countries. We are the outlier, not these other countries.

My third point, is that some other countries invest more on pharmaceutical research and development than the U.S. Recent data from the OECD shows that Sweden, Denmark, the U.K., and Belgium spend more on pharmaceutical R&D per capita than the United States does.

My fourth point is, even if these other countries paid more for pharmaceuticals, prices in the U.S. would not necessarily go down. You have talked about this today. This hearing talks about the advisability of the U.S. Trade Representative to negotiate with these countries to raise their pharmaceutical prices in order to equalize their support for research and development across industrialized countries. In order to implement this approach, the U.S. Trade Representative would need to have a target price level and encourage each country to pay this target price. This raises two important issues.

First, there would need to be an international standard to negotiate pharmaceutical prices. Two potential metrics that have been used in other countries are a desired level of research and development or a desired profit margin. What metric would be used to visualize the appropriate price? Second of all, I am not sure what price level would be used through the negotiation, what would be determined by the negotiation.

We are the outlier. We are paying twice as much as these other countries.

As part of a trade negotiation, would the U.S. be willing to accept a lower price for pharmaceuticals if international standards were adopted? I doubt it. In any case, my bottom line is that the trade negotiating strategy strikes me as pharmaceutical price fixing on an international scale.

Another approach is to rely on the free market. In my economics classes at Johns Hopkins, I teach about the free market and how it works best for certain goods and services. However, one situation where the free market does not work is when there is only one seller.

This is known as a monopoly.

Pharmaceutical companies are given patents on brand-name drugs. There is a legitimate reason for them to receive a patent, perhaps the most important being that they foster the pharmaceutical research and development.

However, because of this patent protection and the resulting monopoly for that specific drug, it is misleading to state that the brand-name drugs in the United States are purchased in a free market environment. Monopolies just do not respond to the market forces. Because pharmaceutical companies are given a government granted monopoly for a certain drug, they have no reason to lower their prices in the United States, even if these prices were raised in other countries. Generic drugs are different.

There is competition for generic drugs because other manufacturers can compete on the basis of price and quality. It is not surprising, therefore, that generic drugs are often much less expensive in the U.S. than other countries.

My fifth point, is that economic theories suggest, therefore, that even if the U.S. Trade Representative were able to negotiate lower prices in other countries, the pharmaceutical companies would still maintain their prices in the U.S. for these brand-name drugs.

My sixth, and final, point is that the U.S. should use prices in these other countries as the benchmark for the prices it pays for pharmaceuticals, especially in the Medicare program.

I would advocate, in fact, the approach that the Bush administration used in response to the anthrax scare. The Bush administration needed to purchase 100 million capsules of Cipro, and Tommy Thompson negotiated, on behalf of the government, a reduction from \$1.77 to 95 cents.

Does it matter that the U.S. pays higher prices for pharmaceuticals? A basic tenet of economics, is opportunity costs. If we pay higher prices for pharmaceuticals, we get beneficial pharmaceutical research and development. However, there are trade-offs. For example, lower prices for pharmaceuticals would allow the Medicare program to eliminate the donut hole in the Medicare drug benefit.

My written testimony shows how 50 percent lower prices for pharmaceuticals would allow the Medicare program to spend exactly the same amount of money and eliminate the donut hole, and this 50 percent is what the other countries are paying. So, Congress has a real choice: higher pharmaceutical prices and more research and development, or the elimination of the donut hole in the Medicare program.

Thank you, Mr. Chairman and members of the committee for the opportunity to testify this morning. I would be happy to answer any questions.

[The prepared statement of Mr. Anderson appears in the appendix.]

Senator THOMAS. Thank you both very much. Mr. Calfee, do you think trade negotiations can have some impact on the costs in the United States?

Mr. CALFEE.²¹⁴ I think that negotiations could have some impact on improving the R&D environment. Whether that will have a direct impact on prices in the U.S., I think, is fairly questionable.

I think in the short run, that what several people have said is basically correct, that if they relax the price controls in these other nations, if they provide greater rewards to R&D, that would not have much of a short-run effect on prices within the United States. It might have a pretty strong effect down the road because it means that new drugs would arrive more rapidly and you get more competition. In the short run, however, I am not sure we are going to get much price relief from dealing with the other nations.

Senator THOMAS. So you do not think the idea that we offset R&D by having higher prices here, but pick up a market by having lower prices somewhere else is the case.

Mr. CALFEE. No. I think what is happening, is that R&D is impeded. It is slowed down by the fact that the other nations are avoiding paying more for new drugs. Now, when you slow down R&D you get a lot of bad things happening. Especially, you do not get some new drugs you otherwise might get, but also you get less competition in the markets. So, you would get somewhat more competition, but it takes a little while for that to develop.

Senator THOMAS. Mr. Anderson, I get the impression that you believe the price setting by other countries would be something we ought to do in the United States.

Mr. ANDERSON. It is something that we ought to consider, yes.

²¹⁴ Mr Calfee is a Resident Scholar, American Enterprise Institute, Washington, DC and also made a statement to the Joint Hearing.

I think that we need to know how much we pay for different drugs that are therapeutically equivalent so that we can decide and give to the consumer the information about what are therapeutically equivalent drugs. That is what Senator Lincoln and Senator Graham were asking for, and I think that we should do, yes.

Senator THOMAS. Information is quite different than setting price.

Mr. ANDERSON. It is. And I think ultimately for the Medicare program, you have to look at the trade-offs. For me, the trade-off is elimination of the entire donut hole and lower pharmaceutical prices. Personally, I would rather have no donut hole and lower pharmaceutical prices, but that is the choice that you have to make.

Senator THOMAS. All right.

Well, let me ask the two of you, just in a short sentence or two, what would you do, if you were in charge of the world, about the costs of pharmaceuticals in the United States?

Mr. CALFEE. I think that there are some things the FDA could do that might help to some extent. There are some drug approvals that take longer than they should. Manufacturer regulations, I think, have become quite inefficient. I think that would have some short-run effect on pharmaceuticals. I think that liability reform would help with pharmaceutical prices.

Beyond that, I think that what we are really counting on is the development of new drugs and this huge wave of patent expirations that we are in the middle of, and the arrival of new generic drugs.

In almost every therapeutic category you can mention, we have either had, or are about to have, major blockbuster drugs going generic. There is a generic version of a statin drug. There are generics in some of the basic heart medication drugs, cancer drugs. Zocor is going to be going generic in a year or two. We are going to see a lot of prices going down, as well as new drug prices going up.

Senator THOMAS. Mr. Anderson?

Mr. ANDERSON. Essentially what we have done, is given these drug companies, for brand-name drugs, a monopoly. The way you handle monopolies is to try to control the prices through some type of rate setting. We have a whole variety of different rate setting systems to deal with monopolies, and I think we should explore those various options.

Senator THOMAS. Do you not think doing away with what you call a monopoly would take away the incentive to create new drugs?

Mr. ANDERSON. I think I would not want to get rid of patent protection at all. So, that is essentially what gives you the ability to create a monopoly.

Senator THOMAS. It sounds a little like you are contradicting yourself there. That is a monopoly.

Mr. ANDERSON. Essentially you have created a monopoly to develop research and development. What we are talking about is, what is the rate of return that you should receive? It is no different than if you deal with a utility like an electrical company. They have a monopoly, so the question is, what is the rate of return on their capital that is appropriate?

Senator THOMAS. If you have government control, like utilities.

Mr. ANDERSON. And when I worked in the Reagan administration I had an opportunity to help develop the Medicare prospective payment system, and that is essentially a rate setting mechanism that we developed.

Senator THOMAS. Senator Breaux?

Senator BREAUX. Thank you very much. I thank the panel members as well. It was really interesting. The one experience that we have had in this country in fixing pharmaceutical prices is in Part B under Medicare, where we fixed the price of the reimbursement rate to oncologists for cancer drugs.

We were over-paying them by a couple of hundred million dollars every year, so the last Medicare bill had to say, look, we have tried to fix prices for cancer drugs and we have screwed it up so bad, we

are going to have to eliminate it, because we were over-paying them. We were not under-paying them, we were over-paying them.

It was just a great example of how a price fixing mechanism at the government level does not work. It is interesting, I think, Mr. Calfee. I was looking at your statement. Of course, even without price fixing in lower income countries, the price of our product manufactured here is going to sell for less in that country than it does in this country. We sell cars that are made in the United States cheaper in Canada than we sell them in the United States. Why? Not because of price controls, but because the per capita income in Canada is substantially less than it is in the United States.

Open heart surgery in Mexico is probably a lot cheaper than it is in Houston or in New Orleans, or anywhere else in this country because that is what the market is going to bear. The problem becomes when it is also an additional fixed price because of government price controls that I think I am very concerned about.

Can you give me any concept as to why generics are so much more expensive in Europe, for instance, than they are in this country?

Mr. CALFEE. Well, most of those countries have not passed anything like the Hatch-Waxman Act here. The Hatch-Waxman Act gives a pretty smooth, open path for creating a generic drug and getting it on the market and manufacturing it. You can have several different manufacturers.

In some of the European countries, it is not that way. We do not have a law that says this is what you are allowed to do, these are the procedures you can follow, this is how you get a generic on the market. The result is that, in some cases, it is hard to enter the market.

It is intentionally made hard to enter the market by some of these countries because they want to preserve either a very small number of domestic generic firms or some of their domestic firms still have branded drugs in the market where they do not want to get generic competition.

So if those countries were to enact something like we have in the Hatch-Waxman Act and remove price controls, they would get cheap drugs very rapidly. One or two countries have moved in that direction, such as Canada and Britain, and they are getting a good generic market.

Senator BREAUX. Mr. Anderson, one of your recommendations, the fifth one, is that the United States should use prices in other countries as a benchmark price for the price we charge our consumers in this country.

Do you limit that to pharmaceuticals or would you say that the benchmark price of what we charge products in this country should be based on another country's price, even though that country may have a per capita income of 50 or 100 percent less than the United States? I mean, we could find some lesser developed countries that the price of the product is really very, very low. Should that become the benchmark price of what we sell that product for in this country? Mr. ANDERSON. Well, I think you have to look at it market by market. So if you are talking about hospitals or you are talking about physician service, most of the expenditures are for labor. So for a country that has very low labor costs, I would not expect the U.S. to have similar prices to those countries.

However, if we are talking a product like pharmaceuticals which is a product that you can buy, or computers, or something like that, I would expect that the United States would, in fact, pay similar prices.

Senator BREAUX. Why would we set our benchmark price on a country that has a 50 percent lower per capita income? How can we say that, because their per capita income is so much lower than the United States', that the price of that product in that country should be the benchmark for the price in the United States when their per capita income is half of what our country's is? Mr. ANDERSON. I think we could set it up so that it is similar to countries like Canada, like the U.K., like Germany, like Luxembourg, which have similar levels of income to us. If we want to pay 20 percent more to subsidize pharmaceutical research, that is fine with me. The question is, why should we be paying 100 percent more? Our incomes are not 100 percent higher than those other countries'.

Senator BREAUX. Well, why not try to get them to allow a market price to occur within their boundaries based on what their market would charge as opposed to what the government says it should charge?

Mr. ANDERSON. Well, I think when you do not have a monopoly— you have essentially given these countries a monopoly when we have given them a patent to sell drugs for a period of time—there is no alternative. If you have a problem with low blood levels, red blood cells, the only choice that you have got is Epo. It is a single monopoly and there is one company that sells it, and that is Genentech.

So, they have a monopoly to sell that product, and they do—and any economist would tell you should—sell it at the highest price they could possibly get it in a free market. So, the only way to negotiate with that is to have an equally powerful purchaser.

Senator BREAUX. My time is up.

Senator THOMAS. Thank you. Senator Santorum?

Senator SANTORUM. To liken a patent to monopoly, I think, misses what Senator Thomas suggested, which is, we have patents to encourage people to develop. If you are saying that we are going to give you a patent but the patent does not mean anything, then I can guarantee you, I do not know of anybody who is going to be applying for patents any time soon to create new medicines. But you said very clearly that that is all right with you, as long as you get maximum prescription drug costs covered.

I think that is a legitimate point to make, but I think you need to make it a little bit more explicitly than you have. You are willing to sacrifice a lot of new drugs and cures in the future to have cheap drugs today. If that is your point, I accept that point.

I think it is a legitimate point to make, and I think there are probably people here on the panel that agree with you. But I think couching a lot of terms that might not be as obvious to folks who are listening is not necessarily a clear statement of your position. But I think I have stated it clearly. Is it not?

Mr. ANDERSON. Yes. I think you also could get more research and development through expansion of the NIH. The NIH is a major research and development activity.

Senator SANTORUM. That is what you were talking about. You suggested earlier that other countries spend more money on R&D than the United States, but you are suggesting that countries spend more, not drug companies in those countries. Right?

Mr. ANDERSON. Drug companies in those countries spend more money, according to the data from the OECD, per capita—not total, but per capita.

Senator SANTORUM. Oh. Per capita.

Mr. ANDERSON. So it would not be fair for Sweden to spend more than the United States given that they have got about 10 million and we have 280 million. But on a per capita basis, they spend more. They spend about \$100 per person, and we spend \$46 a person on pharmaceutical R&D.

Senator SANTORUM. Again, I am not too sure that is a relevant comparison. It all depends on whether you happen to have a large pharmaceutical plant in your country, and whether one was started there. Obviously, you have consolidations and you have plants moving to and fro.

So, to pick out one of the few countries left in Europe, as you mentioned, just a handful that actually still have some sort of pharmaceutical research, maybe a better comparison would be to see what the EU spends versus what the United States spends, and take something with a similar market instead of taking a small country that may have one large research facility that skews the whole equation. So, I am not too sure that is a fair comparison.

I will ask you that question, for the record, since I assume you do not have the answer as to what the EU spends per capita versus the United States.

Mr. ANDERSON. I do have, on specific countries.

Senator SANTORUM. I understand that. But if you could give me, for the record, what the total EU spends per capita versus the United States, that would be helpful to me.

Mr. ANDERSON. Sure.

[The information appears in the appendix.]

Senator SANTORUM. Mr. Calfee, you mentioned that compulsory licensing was still a problem. If you heard the testimony from before, they suggest that compulsory licensing is no longer a problem. Who is telling the truth here?

Mr. CALFEE. What I was referring to, is the fact that, under the TRIPs agreement, compulsory licensing is still lurking in the background for so-called medical emergencies. People in the industry tell me that they fear that if they give some of these nations an ultimatum and say, we are not going to sell at the price that you specify, we are willing to sell at a higher price but not the price you specify, that at some point some of these nations could say, if that happens, we will declare a national emergency and we will engage in compulsory licensing. It has not happened. It is not clear that they could pursue that under WTO rules, but no one knows.

All I am suggesting, is that at some point these nations might say——

Senator SANTORUM. Those laws are still on the books in these countries, in other words.

Mr. CALFEE. The Canadian law is still on the books, the compulsory licensing laws. All I am suggesting is that they simply say explicitly, when we are negotiating prices, we will never resort to compulsory licensing in order to extort lower prices.

Senator SANTORUM. And they have not done that.

Mr. CALFEE. They have not done that.

Senator SANTORUM. I thought I read something around the time of the anthrax scare that Canada actually was threatening compulsory licensing with respect to Cipro.

Mr. CALFEE. I believe they did, and then they retracted that threat. But I believe they did do that.

Senator SANTORUM. So it is still a live threat.

Mr. CALFEE. Yes.

Senator SANTORUM. All right. Thank you, Mr. Chairman.

Senator THOMAS. Senator Kyl?

Senator KYL. Thank you. I appreciate both of you being here to testify.

When I went to Australia and New Zealand, one of the first things I had to dispel was that I was there as a representative of the pharmaceutical companies. I want to make it very clear, as a predicate to my question, that my concern is the health and wellbeing of American citizens, health care consumers, as well as people in other countries.

My motivation for being involved in this issue is to ensure that the best mechanism that we have for inventing and getting to market these new lifesaving drugs is preserved and protected as much as possible, not just for us here in the United States, but for people in other countries as well.

Of course, the means by which that research occurs is a combination of government support. We have doubled, we have more than doubled, the NIH funding. There is not any other part of the government where we have done that much increase.

I think that is great, because I think that, other than freedom, Americans primarily are concerned about their health care. Just ask anybody who has had a sudden illness in the family. They drop everything else and they will do anything to return their family member to health. It is the most important thing to us.

That being the case, I supported the Medicare bill, which puts a whole lot of money into availability of prescription drugs, with a lot of mechanisms to try to reduce the price of those drugs as much as possible.

But I see another area where we have got a problem, and that is that the American consumer is having to carry most of the burden of the research and development of the production of these new drugs. If that continues to happen, we will follow the lead of these other countries who have found it politically impossible to charge what the drugs really cost, so they fix the prices, number one, then they subsidize that, number two.

And you have already seen the hue and cry here in America to follow suit to do something to reduce the cost of drugs, including importation and price fixing. Of course, there is no free lunch.

That is certainly the case with the development of these innovative, very expensive to develop, new products. So, somebody has to pay for it, and fixing prices makes it impossible. As you acknowledged, there is a trade-off there. What I would suggest, is that we ought to be primarily concerned, and our number-one value here ought to be the highest quality medicine that we can possibly provide at a cost that is acceptable to people.

First of all, that assumes people should have a choice in the matter, that there just should not be a single payor government system that makes that decision for them, either as a specific matter or as a matter of pricing, and, second, that there be some choices involved, which implies competition. Now, what I found in looking abroad was the beginnings of a rationing system. It is just beginning, but it is taking some countries far longer than the United States to get certain new drugs to market.

It is impossible for some of these countries to pay the subsidized costs of some of the brand-new, more expensive drugs. As a result, they are not making them available to their citizens.

So, I want to ask a couple of questions in regard to that. One has to do with the new report by the Bain Company, which you may be familiar with, but another has to do with the Business Week article about a year ago which pointed out that, with regard to Europe, there is this lengthy listing pricing process, as a result of which, the article concluded, "European consumers are heading towards second-class citizenship when it comes to access medicines.

For example, in France, as many as 60,000 people have multiple sclerosis. An estimated 2,000 new cases are reported each year, yet less than half of the French patients diagnosed with MS are treated with life-saving medicines. So, it is not just American consumers, but people abroad that might be suffering under the policies of their government. I would like to ask you to comment on it. By the way, are either of you familiar with the Bain Company report? If not, I will just submit a question for the record on that.

Senator KYL. Mr. Calfee, let me start with you.

Mr. CALFEE. I have read a summary of the Bain report. In fact, I have read several summaries; I think they have marketed that report in several venues. But it does look like a very useful report.

I do not think there is any doubt that European patients are beginning to lose out on some of the new drugs, that the new drugs are arriving more slowly. I think that in some cases the reason it takes so long to negotiate a price is not because the two sides are having trouble agreeing on things, but rather that the health authorities are dragging their feet because they want to wait as long as possible before they pay for a new therapy.

I would emphasize that when we talk about a trade-off between getting new drugs or lower prices for the drugs that we already have, we have to really beware in moving too far in the direction of lowering the prices and waiting for new drugs. I mean, the Europeans are showing us that that wait can be quite some time. It will be a really, really long time if it turns out that the U.S. is no longer supporting new drug development.

I think that we ought to bear in mind how rapidly drugs are becoming generic, of the extraordinary promise of drug development that is now under way, and if we want to reduce prices, we ought to reduce prices for people who are relatively poor rather than for everyone, and make sure that R&D continues to flow. I think the Bain report has a lot of interesting comments to make about the trade-offs between these things.

Mr. ANDERSON. As a professor at Johns Hopkins University, research and development is our number-one product. So, I am absolutely in favor of research and development, as much as we can afford.

Senator Smith mentioned a Commonwealth Fund report, and let me highlight the results of that. It was a survey done in 2001, and it asked people in the U.K., Canada, Australia, New Zealand, and the U.S. if they could not fill a prescription due to cost in the last 12 months.

What they found, was that 26 percent of Americans said that they could not fill a prescription due to costs in the last 12 months; Australia, 19 percent; New Zealand, 15 percent; Canada, 13 percent; the U.K., 7 percent. So, yes, we spend twice as much. We get a lot more R&D. But our citizens are the ones who may be suffering.

They are the ones who are having difficulty filling the prescription drugs.

Senator KYL. Yes. If we do not end up paying the cost by imposing a system of price controls on this country, they are not going to be available to anybody at any cost.

Senator THOMAS. All right. Gentlemen, thank you very much. I think this has been very interesting. One of the things that has not been mentioned is the over-utilization of drugs. We might take a look at that one of these days as well. There may be some questions submitted to you in writing during the next few days. Thank you very much.

The committee is adjourned.

[Whereupon, at 12:35 p.m., the hearing was concluded.]