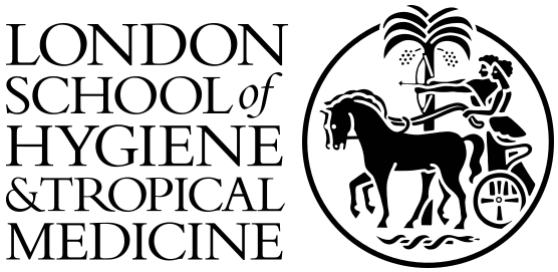

HEATH AND ECONOMIC IMPLICATIONS OF PATENT PROTECTION FOR PHARMACEUTICALS: A CASE-STUDY OF THAILAND

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DECLARATION OF CANDIDATE'S ROLES IN THE RESEARCH INVESTIGATION

I, Inthira Yamabhai, confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Inthira Yamabhai

ABSTRACT

Thai patent law was amended to comply with the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreementin 1992, eight years before the effective date required. Some 15 years later, during 2006-2008, Thailand issued compulsory licenses (CL) for seven medicines.Although this was allowed under TRIPS flexibilities, it has generated debate, both within Thailand and internationally, concerning whether, on balance, Thailand has benefitted from the restricted patent legislation resulting from TRIPS, or the unrestricting of it through CL. The debate arises because those concerned principally with health consider patents to lead to reduced access to essential medicines, and hence reduced health, whereas those principally concerned with trade see patents as the means to secure development and availability of new medicines and foreign investment. This thesis aims to understand better the implications of strengthening or weakening patent protection through systematically examining the relationships between price, access to current medicines, access to future medicines (through market entry of new medicines) and foreign investment in a more holistic fashion, both within the pharmaceutical industry specifically and the economy more generally.

To address this overall aim, four objectives were set. The first was to assess the impact of patents on pharmaceutical prices. The debate hinges on the relationship between price and patents, and hence it is imperative to first establish this relationship in Thailand. Ordinary least squares regression was employed to estimate the impact of patent upon price, while controlling for market and medicine factors. The findings show that patents are associated with a price increase of approximately 200%.Second, as price is argued to be the main restriction on access to medicines, it is important to assess the role of price in determining access to medicines. A probit model indicated that price is not a significant determinant of a medicine being listed on the National List of Essential Medicines (NLEM); however, price impedes access to non-NLEM medicines significantly.

Third, patent legislation will also affect the process for the launch of new medicines within a country. A Cox proportional hazard model was used to analyze the launch experience of new medicines to Thailand during 1982-2009.The empirical results

show that policy related to patent law has a significant and positive impact on the rapidity of the launch of new products in Thailand. Most importantly, CL is shown to have a significant and adverse effect on the speed of new medicine launches in Thailand.

The last objective is to examine the impact of stronger patent protection on foreign investment, both in the pharmaceutical industry specifically, and the wider economy more generally. The empirical estimation suggests that there is no significant change in foreign direct investment (FDI) inflows after the patent law amendment in 1992 and that weakening pharmaceutical patent protection using CL does not necessarily keep away foreign investors.

In conclusion, from this thesis there is little evidence of benefit from patent law change. Therefore, stronger patent protection should not be accepted. The evidence from this thesis highlights that the critical issue in determining whether the Thai population has gained from stringent patent protection or not is the tension between current and future access. Patents increase the price of medicines and impede current access. However, patients benefit from greater access to new medicines. These findings suggest that the price of patented medicines should be monitored closely to avoid undesirable effect on access, together with work on a system to more effectively stimulate local R&D activity.

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ACRONYMS

Acronym	Definition
ADBI	Asian Development Bank Institute
ADF	Augmented Dickey Fuller
AIC	Akaike Information Criterion
AIDS	Acquired immune deficiency syndrome
APEC	Asia-Pacific Economic Cooperation
ARVs	Antiretrovirals
ASEAN	Association of South East Asian Nations
ATC	Anatomical Therapeutic Chemical
BOI	Board of Investment
BOT	Bank of Thailand
BSA	Body Surface Area
CEA	Cost Effectiveness Analysis
CEPR	Centre for Economic and Policy Research
CIPIH	Commission on Intellectual Property Rights, Innovation and Public Health
CIPO	Canadian Intellectual Property Office
CL	Compulsory License
CSMBS	Civil Service Medical Benefits Scheme
DALY	Disability-adjusted life year
DDD	Defined daily dose
DIP	Department of Intellectual Property
DMSIC	Drug and Medical Supply Information Center
EFV	Efavirenz
EFW	Economic Freedom of the World

Acronym	Definition
ECM	Error correction model
EML	Essential Medicine List
EPO	European Patent Office
EU	European Union
FDA	Food and Drug Administration
FDI	Foreign Direct Investment
FTA	Free Trade Area
GATT	General Agreement on Tariffs and Trade
GDP	Gross Domestic Product
GIST	Gastrointestinal Stomal Tumor
GMM	Gaussian Mixture Model
GNI	Gross National Income
GNP	Gross National Product
GPGs	Global Public Goods
GPO	Government Pharmaceutical Organization
GSP	Generalized System of Preferences
HAI	Health Action International
HEED	Health Economic Evaluations Database
HITAP	Health Intervention and Technology Assessment Program
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
ICSID	International Council of Societies of Industrial Design
IGWG	Intergovernmental Working Group
ILO	International Labour Organization
IMF	International Monetary Fund

Acronym	Definition
IP	Intellectual Property
IPC	International Patent Classification
IPR	Intellectual Property Right
ISafE	Information, Safety, administration, frequency and Efficacy
MNCs	Multi-National Companies
MNEs	Multi-National Enterprises
MOPH	Ministry of Public Health
NBER	National Bureau of Economic Research
NCDs	Non Communicable Diseases
NCE	New Chemical Entities
NGOs	Non-governmental Organizations
NHSO	National Health Security Office
NICE	National Institute for Health and Clinical Excellence
NICs	Newly Industrialized Countries
NIEs	Newly industrialized economies
NLEM	National List of Essential Medicine
OECD	The Organisation for Economic Co-operation and Development
OLS	Ordinary Least Squares
PCT	Patent Cooperation Treaty
PhRMA	The Pharmaceutical Research and Manufacturers of America
PMPRB	Patented Medicines Prices Review Board
PReMA	The Pharmaceutical Research and Manufacturers Association
PWL	Priority Watch List
QALYs	Quality Adjusted Life Years
R&D	Research and Development

Acronym	Definition
SHI	Social Health Insurance
SMP	Safety Monitoring Programme
TNMSC	Tamil Nadu Medical Services Corporation
TPPA	Trans-Pacific Partnership Agreement
TRIMs	Trade-Related Investment Measures
TRIPS	Trade-related aspects of intellectual property rights
UC	Universal Coverage
UK	United Kingdom
UNCTAD	United Nations Conference on Trade and Development
US	United States
USD	United States dollar
USPTO	United States Patent and Trademark Office
WDI	World Development Indicator
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WL	Watch List
WTO	World Trade Organization

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CHAPTER 1 OVRVIEW OF THE THESIS

1.1 Introduction

International policies relating to patent protection have seen profound changes over the past two decades. During the Uruguay Round of multilateral trade negotiations, where the World Trade Organization (WTO) was established as a global body to promote liberalization of trade in goods and services, one of the main outcomes was the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). TRIPS Agreement is the comprehensive international agreement on intellectual property rights (IPRs) which established minimum universal standards concerning patents, copyrights, trademarks, industrial designs, geographical indications, integrated circuits and undisclosed information (i.e. trade secrets). Under the TRIPS Agreement all member states of the WTO are bound to amend their IPRs legislation in order to align them with the same standards of protection for intellectual property specified by TRIPS.

At its most basic, patenting is the legal system established to provide short-term exclusivity over the right to produce and sell the specific product patented; effectively granting the firm a short-term monopoly. Patenting was developed to achieve two objectives: (i) encourage innovation in the development of new products through guaranteeing a return on investment; and (ii) allowing widespread consumption of these products through alleviating concerns that the developer may have that other firms may replicate the product. The patent system allows the firm to sell the product at a price higher than that which would result from market forces in the absence of patenting. This is used in order to recoup the costs of research and development, since the competitive equilibrium price, reflecting marginal cost of production, would not encompass these earlier 'capital' costs (Love 2005).

However, there is concern that the patent price is not set to merely cover research and development costs, but set higher than this and thus used to achieve 'super-normal' profits (profits in excess of those required to recoup research and development costs and thus keep the firm in the market) at the detriment of wider access to patented products, resulting in a deadweight social welfare loss (Woodward

D and Smith 2003). It can be seen from the HIV/AIDS crisis in low income countries in 2000s and the majority of people lack access to available patented treatments due to their high cost (UNAIDS 2011).

In pharmaceutical industry, interest in patenting has climbed the global agenda since the establishment of TRIPS Agreement, which expanded the Western tradition of patenting to all members of the WTO, imposing patent protection for at least 20 years without discrimination as to place of invention or origin of product, and applied to both products and processes (Smith, Correa et al. 2009). This has generated especially heated debate within the health community concerning the implications that patent strengthening may have on the price of, and hence access to, medicines, affecting both availability and affordability.

The implications of patenting spread further, as innovation, technology and knowledge development are crucial drivers of economic development and of technology transfers resulting from international trade and investment and thus are significant drivers of the global economy. Recently, developing countries have initiated bilateral trade agreement with high income countries. To trade-off with trade and investment benefits offering from higher income countries, developing countries have to abide with more stringent intellectual property obligations than those required by the WTO TRIPS Agreement, as known as TRIPS-Plus (Frankel 2009). Arguments concerning patenting tend to take one of two sides: that patenting should be continually strengthened in the belief that this will encourage greater research and development, bringing new products to market, and enhancing trade and investment; or that patenting should be weakened to ensure that medicines are as cheap as possible in the belief that this will ensure greatest access by those in need of them.

Yet, although national policy makers need to judge evidence from both sides of the argument in order to strike a balance between affordable medicines, both now and in the future, and national trade and investment, seldom, if ever, do studies look at both sides. For instance, while continually strengthening patenting will likely lead to higher prices, further reducing affordability, weakening patenting may stifle future long-term access, since pharmaceutical companies might be reluctant to introduce new medicines into the market, and foreign investors may find other countries to

invest in where there is better protection of their products. In order to determine the appropriate balance in policy (such as the use of TRIPS-flexibilities), it is important to establish: (i) the impact that patent protection actually has on price (compared with other factors), since if price is unresponsive to patents than tackling patents will not affect price; (ii) what impact price has on current and future access (compared with other determinants of access), since if access is unresponsive to price (perhaps it responds more to physical location of chemists, for instance) then tackling patent/price will not affect access; and (iii) what impact patents have on foreign investment and innovation in national and international settings, since patenting may influence investment in local pharmaceutical industry, and also be subject to associated activities in the general economy.

This thesis addresses these issues together for the first time, through an empirical case-study concerning these areas, focused on Thailand. Thailand is an interesting case study as its experience with patent protection, patent challenges, using compulsory licenses (CL) for instance, and access to medicines under the universal coverage scheme, has been significant. Thailand changed its patent law to comply with TRIPS eight years before the agreement came in to effect, and some 13 years before the deadline for developing countries. There is no direct price control exercised for medicine price. The Thai medicine market depends heavily on imported medicines and Thailand perhaps pays more than it should when compared internationally; the public sector procured generics at 1.46 times their international reference prices, and innovator brands at 3.3 times their international reference prices (The Office of Food and Drug Administration 2007). Some cancer medicines were marketed in Thailand at very high prices compared with generics available elsewhere; for example, the original letrozole was sold at 30 times its generic price (Ministry of Public Health 2008). This has caused some to attempt to challenge and weaken the patent system as applied to medicines.

In this introductory chapter, section 2 first sets the stage by describing what a patent is and the implications of patents, including the important of patent for pharmaceutical industry. Section 3 briefly outlines the international agreements and their histories related to patent and their implications. The context of access to medicines, current health problems and IPR issues in Thailand are explained in

section 4 . Section 5 summarizes the key conclusions of previous studies focused on IPRs policies, which provides the basis for the research framework and thesis objectives as outlined in section 6. The final section provides a brief summary of each chapter and how this thesis is organized.

1.2 Public goods, knowledge and the role of patents

Most goods tend to be private in nature: their consumption can be restricted until a payment is made in exchange (they are 'excludable'), and consumption by one individual limits consumption of that same good by others (they are 'rival' in consumption) (Woodward and Smith 2003). For example, a private car seller can prevent other people from driving the car until a price has been paid to do so, and hence the car is excludable, and once the car is used by a buyer the same car cannot simultaneously be used by someone else, and hence it is rival in consumption.

Conversely, at the other end of the spectrum of goods, are public goods which are non-rival—the consumption by one individual does not detract from consumption by another—and non-excludable—it is not possible to exclude an individual from consuming the good. Often textbooks quote the example of lighthouses, where a ship cannot be excluded from the benefits of the warning it gives, and one ship benefitting does not prevent another from doing so. However, such properties are often subject to change. For example, television and radio signals which are non-rival (anyone with a receiver can use the signal without detriment to others using it) used to be non-excludable (anyone with a receiver could use them), but with advances in encryption technology it is now possible to exclude someone from using the signal, and hence charge a price. In this case, the good is excludable but remains non-rival and hence is what is termed a 'club good'. Cases where the good is non-excludable but rival, such as logging a forest, are termed 'common-pool goods' (Cornes R and Sandler T 1996).

Recently, the concept of global public goods (GPGs) has been gaining increasing attention in many areas, including health (Smith and MacKellar 2007). GPGs are considered to be goods exhibiting a significant degree of publicness (i.e. non-excludability and non-rivalry) but across time and space. They are public goods that are not limited geographically to a particular country, or to specific generations and

points in time, but are global in scope. For example, reductions in carbon dioxide emissions will slow global warming. It will be impossible to exclude any country from benefiting from this, and each country will benefit without preventing another from doing so. Similarly, the eradication of infectious diseases of global scope, such as smallpox or polio, provides a benefit from which no country is excluded, and from which all countries will benefit without detriment to others (Smith 2003).

Knowledge is arguably the archetypal public good (Stieglitz 1999). For example, once a new mathematical theorem is discovered then it is non-rival – anyone can use that theorem without disadvantaging others from using it – and non-excludable, since the information is not embodied in, or dependent upon, a product. Most knowledge tends to be a global public good: a mathematical theorem is consistent and true everywhere in the world, and is available and non-rival across all countries and across generations. However, the discovery and generation of knowledge is not costless, even though its subsequent dissemination may be at zero or a very small marginal cost. For instance, the time and effort involved in developing the mathematical theorem is borne by someone, yet publishing it in a journal, on the internet or even as a book makes it available for others to use at very low cost. This illustrates the economic problem concerning public goods – they generate a significant level of social welfare, but there is no incentive for one to be involved in producing them. When goods are non-excludable, individuals (or nations in the case of GPG) may free-ride (that is, may consume the good, and benefit from it, without reciprocation in contributing to the production of that good). This leads to under-supply, or non-supply, of the good and thus a societal loss of welfare. Thus, an individual firm or country has little motivation to generate new knowledge if the results of that investment can be cheaply imitated or used by others.

The implication of this is that the state must play some role in the provision of public goods (such as lighthouses, defence and street lighting). In the case of knowledge, the patent system was developed to ensure that knowledge is made legally excludable, and thus provide an incentive for individuals and firms to invest in knowledge creation (Smith, Thorsteinsdottir et al. 2004). Patents present a legal system to provide short-term exclusivity (or monopoly rights) over the production and sale of a specific product resulting from R&D, thus turning a public good in to a private good (or at least a common-pool good). Patenting thus provides an incentive

to bring a new product to market by giving legal authority for short-term exclusivity over the right to produce and sell the products. It is built around a fundamental tension: ideas are public but creators need private returns. The benefits that have accrued from the development of the transistor, the laser or the mathematical algorithms that underlay the modern computer have been enormous, extending well beyond the benefits accruing to those who made or financed these innovations and discoveries. However, without the premium that the patent allows it is argued that these advances would never have been produced. Thus, there is an understanding that patents may generate some short-term reduction in social welfare, but generate much larger longer-term social welfare from ensuring that products are discovered in the first place.

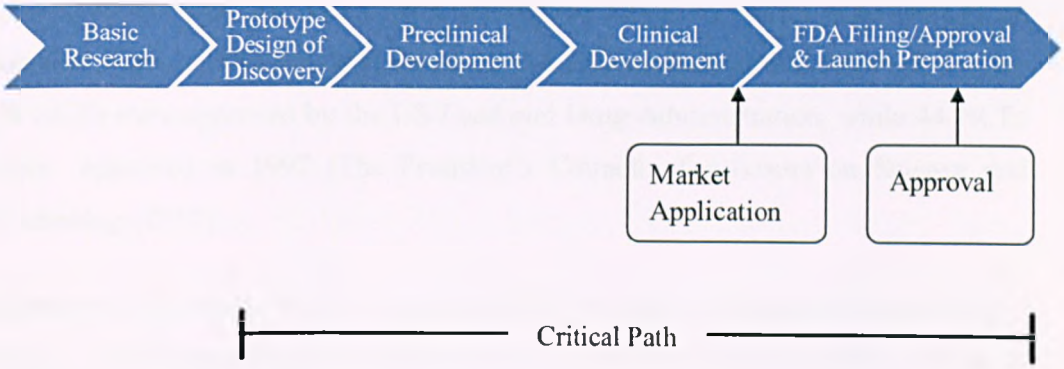
1.2.1 Pharmaceutical patent

There is much knowledge creation within health care, the most high-profile of which is that which goes into the creation of medicines. Patents for pharmaceuticals are considered vital as invention and innovation involve many risky, timely and costly processes. It is reported to take an average of 13 years for a new medicine to move from the initial discovery into the marketplace as a final product, and the cost for the development of a new drug could be as high as USD$884 million cash and USD$1.8 billion capitalized (Paul, Mytelka et al. 2010; Morgan, Grootendorst et al. 2011). Out of 5,000 compounds that are discovered, only five will perform well enough to move into human testing, and only one of these five compounds will be approved by the Food and Drug Administration (FDA) (Colvin and Maravelias 2008). No firm will invest this time, effort and resources, if the final product may then be cheaply copied and sold by rival firms.

Figure 1 shows a stylized "critical path" that encompasses the medicine development processes (U.S. Department of Health and Human Services 2004). At the far left, ideas coming out of basic scientific research, which is the fundamental understanding of biology and disease processes, enter into an evaluation process (prototype design or discovery). The "discovery" process seeks to select or create a molecule with specific desired biological activities. They then undergo a sequence of protocols including preclinical development, clinical development and filing for approval to be ready to launch. Preclinical evaluation seeks to examine the safety

and effectiveness of medicine within animals, while clinical development involves human trials in three phases: phase I, II and III. Phase I concerns safety and how the medicine is absorbed, phase II is concerned with optimal dosage in order to maximize beneficial effect and minimize harmful side effects, and phase III, involving a very large participant group who have the relevant disease, determines if the drug's benefits outweigh the risks in a larger patient group, and also compares the new potential drug with commonly used treatments that are already on the market.

Figure1.1 The Critical Path for Medical Product Development



Source: US FDA, Innovation or stagnation: challenge and opportunity on the critical path to new medical products

From the "discovery" process moving from left to right along the path, the new knowledge related to that medicine, new molecule, new process or new use, can be discovered. The patent system is designed to provide one patent for one invention. Therefore, if company X invents a new chemical compound, company X may be entitled to a single patent to protect the newly invented compound and how it is manufactured. If company X then also discovers new forms of the compound, or invents new ways to deliver or manufacture the compound, they may be entitled to a separate patent for each invention. As a result, a single medicine may be covered by many separate patents claiming the chemical compound (the active ingredient or base compound), polymorphic forms of the compound, salts, and formulations, one or more for the medicines or processes and methods for manufacturing the active ingredient. It is worth noting that although a patent grants monopoly rights for 20 years, by the time the medicine is ready to launch there may only be around 11 years

of the patent left to run. This is because a new molecule or new compound is patented once it is discovered, and thus starting the patent time-clock running at a very early stage, prior to the various stages of clinical trails and final medicine registration process (Dickson and Gagnon 2004).

The pharmaceutical industry is facing challenges on several fronts. There is increasing demand from healthcare systems for new high-efficacy products, provided they are appropriately priced, and especially those associated with 'personalised medicine' which are seen as conferring the maximum efficacy on the target population. However, trends in R&D productivity show the opposite. The last two decades has witnessed a declining trend in new chemical entities (NCEs). In the 1990s, on average, 34 NCEs were introduced while 25 NCEs were introduced annually during 2000s. In 1997, the lowest NCEs introduction was observed, as only 18 NCEs were approved by the US Food and Drug Administration, while 44 NCEs were approved in 1997 (The President's Council of Advisors on Science and Technology 2012).

Moreover, it is taking longer to get new drugs to market (Thomson Reuters 2011). Since a lower percentage of candidates entering preclinical development survive to the market application stage, it is imperative for pharmaceutical companies to be secured the exclusive right to ensure that, if it passes all trials and it then enters the market, profits are significantly larger than development costs. Of course, it is the ability to set this initial, patented, price at high levels that creates the controversy highlighted earlier, which this thesis intends to explore. Critical in this is the change in patent law that has happened at the global level over recent years, to which we now turn.

1.3 International agreements related to patent law

This section focuses on the political economic forces driving WTO provisions, inbilateral and regional trade and investment agreements, and the implications for multilateralism and access to medicines in developing countries.

1.3.1 TRIPS

By the 1990s variance between countries in the protection and enforcement of IPRs was a growing source of tension in international economic relations (World Trade Organization). The ad hoc system in place had resulted from a combination of unilateral pressure and pressure from bilateral agreements. It possessed little order or predictability, and weak systems to implement patent legislation and to resolve disputes. Throughout the 1980s, but gaining significant momentum in the 1990s with the increased importance of the digital environment, intellectual property became an important business tool,and new internationally-agreed trade rules for intellectual property rights were seen as a way to to cope with the international economic tension. Based on intense lobbying by industrialized countries, led by the US and supported by the European Union, Japan and other developed nations, as well as campaigns of unilateral economic encouragement under the Generalized System of Preferences (GSP) and coercion under Section 301 of the Trade Act favouring developing countries, the TRIPS Agreement was born during the Uruguay Round trade negotiations of the GATT (General Agreement on Tariffs and Trade). The Uruguay Round took place from 1986 to 1994, and aimed to link trade policy to intellectual property standards (Braithwaite and Drahos 2000).Key provisions of the TRIPS agreement are addressed in Box 1.1.

The main aim of the TRIPS agreement is to strengthen and harmonize certain aspects of the intellectual property protection at the global level. It covers both categories of intellectual property: industrial property (patents, trademarks, geographical denominations, industrial designs and models and unpatented know-how) and literary and artistic property (copyright and neighbouring rights). It sets out minimum levels of protection that each government has to give to the intellectual property of all WTO members, without discrimination as to place of invention or origin of product. It seeks to strike a balance between the long term benefits and possible short term costs to society. Society benefits in the long term when intellectual property protection encourages creation and invention, especially when the period of protection expires and the creations and inventions enter the public domain. The WTO's dispute settlement system is available when there are trade disputes over intellectual property rights. To achieve this standard, WTO members

are required to modify their intellectual property laws to make them consistent with the new WTO standards. For instance, the TRIPS Agreement states that all patents shall be available for at least 20 years from the filing date, whereas before TRIPS the patent term varied greatly among countries (7, 10, 17 or 20 years). All WTO Members have to incorporate this 20-year patent term in their own patent law.

Box 1.1 Major characteristics of the TRIPS Agreement

Objectives: The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.

Minimum standards: The TRIPS Agreement establishes minimum standards for the protection of IP. States are free to introduce systems of protection not referred to in the Agreement, for example, to protect informal knowledge, or the rights of indigenous communities. They are also free to set higher standards of protection for existing rights.

Enforcement: The Agreement establishes general principles that are applicable to IPR enforcement procedures so that IPR holders can effectively enforce their rights. In addition, it contains provisions on court procedures, court orders, suspension of custom clearances for goods and criminal penalties.

Dispute settlement: The WTO includes a procedure for settling disputes between Members. Any Member can bring proceedings against another Member. A panel of specially appointed trade experts interprets the various agreements of the WTO, including the TRIPS Agreement. Once the panel issues its report, it is adopted unless one of the parties to the dispute appeals the decision or there is a consensus by WTO Members not to adopt the decision. If a party to a dispute fails to abide by a decision of either a Panel or the Appellate Body, the other party can impose trade sanctions on that Member.

Developing countries' transitional periods: While developed countries should have complied with the obligations under the TRIPS Agreement by 1 January 1996, developing countries and countries with economies in transition had until 1 January 2000. Least developed countries had until 2006 to implement the Agreement.

Built-in agenda: The TRIPS Agreement includes a built-in agenda of review. Specifically, Article 27(3)(b) provided for the review in 1999 of certain provisions relating to the patentability of plants and animals, and the protection of plant varieties. In the area of geographical indications, Article 23(4) provides that, in order to facilitate the protection of geographical indications for wines and spirits, negotiations shall be undertaken in the TRIPS Council on the establishment of a multilateral system of notification and registration. Preliminary work in this area has already begun. Article 71(1) provides that the TRIPS Council shall review implementation of the whole Agreement from 1 January 2000 and every two years after that.

Source: (Walker 2001)

In the pharmaceutical sector, prior to the TRIPS Agreement, pharmaceutical patents were not widely recognized in many developing countries. As there were no international standards on the scope of patent protection, countries had very different regulations on IP protection according to their own needs. Some 40 countries did not provide patent protection for pharmaceutical products at all (Boulet, Perriens et al. 2000). Many countries provided only process patent. Product patents provide for absolute protection of the product, whereas process patents provide protection in respect of the technology and the process or method of manufacture (WHO/EDM 1999). Critically, protection for process patents do not prevent the manufacture of patented products by a process of reverse engineering, where a different process or method from that which has been invented (and patented) is used but the final product is the same. For example, manufacturers in certain countries are able to make generic versions of patented medicines since national legislation only permits process patent protection (WHO 2005).

Therefore, copies of medicines protected by a patent in other countries were widely available, usually at a lower price than the original patented drug. The copies were either manufactured by local companies or imported, without the permission of the patent holders. This practice ended following the TRIPS Agreement. All WTO members have to make patents covering both products and processes available for pharmaceutical inventions in their countries. A company that has invented a new pharmaceutical product or process, since 1 January 1995, is able to apply for at least a 20-year patent protection in any WTO member country.

1.3.2 TRIPS flexibilities

The inclusion of pharmaceutical patents in the WTO TRIPS agreement brought concern to many that it would exacerbate the problem of access to medicines in developing countries, as it sought to limit, or even disable, direct competition (generics) to new medicines until the relevant patents expire (unless licences are granted). However, as concessions to these concerns, TRIPS was amended to contain provisions that allow a degree of flexibility and sufficient room for countries to safeguard the social benefit of access to medicine. These 'flexibilities' including transition periods, CL, public or non-commercial use of patents, parallel importation, exceptions to patent rights and exemption from patentability, and limits on data

protection (Musungu and Oh 2005). A short description of these categories is provided in Box 1.2. This means that countries have a certain amount of freedom in modifying their regulations and various options exist for them in formulating their national legislation to ensure an appropriate balance between the goal of providing incentives for future invention of new drugs and the goal of affordable access to existing medicines.

Box 1.2: Important TRIPS flexibilities

Compulsory licences: These are mechanisms used by public authorities to authorize use of a patent-protected invention by the government or third parties without the consent of the patent-holder. Patent-holders are to receive adequate compensation, usually in the form of a royalty. WTO Members are free to determine the grounds upon which compulsory licences may be granted. Practice shows that they may be issued on various grounds of general interest, such as public health, and are a common feature of patent law in both developed and developing countries.

Parallel imports: Companies often charge lower prices for a medicine in one country than in another, taking into account a range of market factors. This means that a country with limited resources can sometimes afford more of a patented medicine by purchasing it abroad at a lower price and importing it, rather than buying it directly in its domestic market at the higher price. In legal terms, the patent owner has "exhausted" its property rights in the product actually sold – it maintains the exclusive right to manufacture the product, but it cannot use its intellectual property rights to prevent resale of those units it sells.

Bolar provision/regular exception: This permits the use of a patented invention without authorization from the patent owner in order to obtain marketing approval of a generic product before the patent expires. This allows a generic product to enter the market more quickly after patent expiry, which in turn facilitates access to cheaper medicines.

Transition period: This allows developing and least-developed countries extra time in the implementation of their TRIPS obligations. Three transition periods provided for in the Agreement were: 1) the 1995-2000 period, at the end of which developing countries were obliged to implement the TRIPS Agreement; 2) the 2000-2005 period, which provided an additional period of 5 years to put in place product patent protection pharmaceuticals or agro-chemicals for those countries without such protection; 3) the 1995-2006 period for least-developed countries, later change to until 1 January 2016 according to paragraph 7 of the Doha Declaration.

Sources: (1) UNAIDS, WHO and UNDP (2011)(UNAIDS 2011)

(2) (Musungu and Oh 2005)

In practice, however, only a few developing countries have made use of these 'flexibilities' (Commission on Intellectual Property Rights Innovation and Public Health 2006). The lack of IPR management capacity at the national level and of appropriate institutional mechanisms are some of the reasons the TRIPS flexibilities have been infrequently used (Correa 2001). Although flexibilities such as CL are written into the TRIPS Agreement, some countries were unsure of how these would be interpreted, and how far their rights to use them would be respected (Oliveira, Bermudez et al. 2004). The debate culminated at the Doha World Trade Organization Ministerial Conference (9-14 November 2001), where WTO Members expressed their agreement that the TRIPS Agreement should be interpreted and implemented so as to protect public health and promote access to medicines for all. This marked a watershed in international trade demonstrating that a rules-based trading system should be compatible with public health interests.

The Doha Declaration on the TRIPS Agreement and Public Health, adopted by the WTO Ministerial Conference in November 2001, affirms and clarifies the right of WTO Members to make full use of the safeguard provisions of the TRIPS Agreement to protect public health and enhance access to medicines (WTO 2001). The confirmation that the TRIPS Agreement has provided room for flexibilities at the national level has important political and legal implications (Correa 2002). It indicates that the pressure to impede the use of available flexibilities run counter to the purposes of the TRIPS Agreement. In legal terms, it means that individual Members are able to adopt laws and regulations to implement it in light of public health needs. In addition to other provisions clarifying the nature of TRIPS flexibilities, the Doha Declaration extended the transition period for least developed countries to implement protection of patents and undisclosed information, as well as their enforcement for pharmaceutical products until January 2016 (World Trade Organization 2003).

1.3.3 TRIPS-Plus

Clearly these flexibilities are not in the interests of the pharmaceutical industry, as they weaken the legal right to temporary monopolies, and hence to charging higher prices in the short-term. While a tension remains between fostering patent protection, as required by the WTO-TRIPS Agreement, and providing access to medicines that

may be out of reach for many people in various countries, more recently 'TRIPS-Plus' model, which requires stronger protection of IPR than that agreed on in TRIPS, has been coined to describe what is happening in bilateral trade negotiations. The TRIPS-Plus concept covers both increasing the level of protection for right holders beyond that which is given in the TRIPS Agreement, and reducing the scope or effectiveness of exceptions and limitations to rights. These practices have the effect of reducing the ability of developing countries to protect the public interest and may be adopted at the multilateral, plurilateral, regional and/or national level (Musungu and Dutfield 2003). Free Trade negotiations are being used as forums to promote trade and investment between trade partners while simultaneously enhancing the protection of IPR beyond the levels agreed on in the TRIPS agreement (Sell 2007). As part of trade agreements with the United States or the European Union, some countries such as Brazil, China and several Central American states have been required to adopt stronger IPR protection (MSF 2011).

Common examples of 'TRIPS-plus' provisions include extending the term of a patent longer than the 20 year minimum, or introducing provisions that limit the use of compulsory licences or that restrict generic competition. More generally, 10 areas of negotiation relating to the pharmaceutical sector that go beyond TRIPS have been noted: (1) protection for test data exclusivity; (2) linkages between medicine registration and patents; (3) patent term compensation for granting delays; (4) patent term compensation for delays in marketing approval; (5) strengthening intellectual property law enforcement; (6) restricting CL to public non-commercial use in national emergencies; (7) limitations on parallel importing through contracts with the patent holders; (8) prohibition of the revocation of patents on the grounds of public interest; (9) the ability to patent new uses of products; and (10) the ability to patent animals and plants (natural sources of medicines) (Fink C 2005; Correa 2006).

These have an impact on access to medicines. For example, data exclusivity protection refers to exclusive rights granted over pharmaceutical test data submitted by companies to regulatory authorities to obtain market authorisation. This information has to be kept confidential for a period of time determined through negotiations. If a generic manufacturer wants to register a drug in that country, it is not allowed to merely show that their product is therapeutically equivalent to the

originator product. Instead, it must either wait until the exclusivity period has expired, or repeat lengthy clinical trials in order to demonstrate the safety and efficacy of the medicine. Data exclusivity and the other TRIPS-plus provisions are frequently pushed as a part of free trade agreements between developed and developing countries (Smith, Correa et al. 2009)

In conclusion, most countries that have had different rules in the past are now harmonizing their minimum levels of IPRs protection, as required by the TRIPS agreement. Measures to safeguard a country's access to medicines exist under this Agreement and the rights to exercise these measures have been affirmed at the global level. However, many countries that trade with the US or the EU may enter into bilateral trade agreements that commit them to more stringent IPRs rules than the TRIPS Agreement (TRIPS-Plus) in exchange for concessions in other areas of trade—often access to the US market for agricultural or manufactured goods. This is a crucial area for the health community to influence the trade agenda and for decision-makers to be aware of the consequences of signing these FTAs and trying to implement the safeguards in the TRIPS flexibilities. This is especially true for Thailand, which has a history of early compliance with TRIPS, using flexibilities to enable its universal coverage system to be affordable and feasible, and of experiencing trade repercussions from enacting such flexibilities.

1.4 TRIPS, trade and access to medicines: Thailand as a case study

1.4.1 Access to medicine system in Thailand

Thailand is a lower-middle-income economy in Southeast Asia with a 2011 per capita GNI of US$4,440 and total population of 64 million (Ministry of Interior) (World Bank 2012). Medicine cost is the most significant proportion of total health expenditure; 46% of overall health expenditure and 3% of GDP in 2008 (Ministry of Public Health 2011). Medicine price setting is generally not regulated in Thailand; although there is a consumer protection law under the Prices of Goods and Services Act B.E. 2542, this Act only applies when the product owners sell at prices higher than the labelled price.

At present, universal health care is delivered through three schemes: Civil Service Medical Benefits Scheme (CSMBS) for government employees and their

dependents; Social Security Scheme (SSS) for private business employees; and the Universal Coverage Scheme (UC) for any persons not covered by CSMBS or SSS. UC is the largest insurance program covering approximately 75% of the population while CSMBS and SSS cover 25% of the population (Patcharanarumol 2008).These three public health schemes provide medicines at zero cost to the patient provided that they are on the National List of Essential Medicines (NLEM) (National Drug Committee 2008).

The NLEM was adopted from the WHO concept of essential medicines in 1981. The current NLEM version was issued in 2008 and consists of 637 medicines, with 17 therapeutic groups, which aim to treat and prevent all major health problems among the Thai population. The main objective of the NLEM is to provide medicines that are necessary, effective and safe at an affordable level through government hospitals and other health stations (National Drug Committee 2008). Payment for prescribed medicines outside the NLEM is the responsibility of individuals under the SSS and UC schemes, but not the CSMBS, which allows three medical doctors to co-endorse the use of medicines outside the NLEM (Tangcharoensathien 2003).

A scoring system has been used to select medicines for inclusion on the NLEM since 2004 (Sripiroj A, Tantivess S et al. 2000). The members of working groups representing each therapeutic group acquire information concerning each medicine from secondary data sources (e.g., Pubmed, BMJ clinical evidence, Cochrane library, Micromedex Drugdex Drug Evaluation, Medscape Druginfo Database, or Gold Media Clinical Pharmacology 2004 CD ROM). They then use four criteria as the basis for a scoring calculation: Information (quantity and quality of evidence), Efficacy, Safety (precautions, severe adverse effects and medicine interaction) and Ease of use (administration restriction score and frequency of medicine administration). The scoring system is known as ISafE – the acronym of all the criteria used in this method. Each criteria is scored from 0 to 1, where 0 represents unreliable evidence, least efficacy and unsafe profile and 1 represents high quality and rich evidence, high efficacy and safe profile. The ISafE score is then the product of a simple multiplication of the four criteria divided by 4. The maximum score using this method is 1 and the minimum score is 0. At this point the price of the medicine is excluded from the criteria to make sure that the NLEM considers all possible medicines. Medicines in the same therapeutic area are sorted by the ISafE

scores, with half of the medicines chosen for further processing. Next, the Essential Medicine Cost Index (EMCI) is calculated, which is the treatment cost for a medicine divided by the ISafE score. The medicines with the lowest EMCI are recommended for inclusion in the NLEM; deemed to be providing acceptable quality at low cost. Procurement regulations in the public sector attempt to then encourage the use of the NLEM medicines; the National Essential Medicine Policy requires that public hospitals spend at least 60–80% of their government medicine budget on medicines that are on the NLEM.

In addition, it is required that at least 80% of the medicine budget allocated to all government health facilities must purchase medicines from the Government Pharmaceutical Organisation (GPO), except where the GPO's price is 3% or more expensive than private suppliers. If the GPO cannot provide the needed medicines, the lowest price of the maximum procurement will be used as a reference with the exception of monopoly medicines which can use a higher price (Lerttiendamrong, Tangcharoensathien et al. 1998). As a result, patented medicines have always been excluded with this indirect price control policy.

Also, although public facilities are required to procure medicines from the NLEM, the specific medicine lists in public hospitals may differ from the NLEM list according to the size of hospital, where smaller hospitals have a medicine list typically smaller than the NLEM while the bigger hospitals not only have the NLEM medicines but also have a more extensive list of medicines since their role as tertiary care facilities means that they have to deal with complex medications necessary for uncommon diseases. Typically, rural, general, central and university hospitals have a proportionate split between medicines from NLEM and medicines not on NLEM of 82:18, 81:19, 71:29 and 57:43 respectively (Sripiroj, Tantivess et al. 2000).

Each hospital also has the authority to negotiate directly with the seller, thus providing the potential for further differences in price between institutions for the same medicine. Several efforts have been made to remove this anomaly, such as reference pricing and bulk purchasing at the provincial level for generic medicine procurement to get the minimum price; generally 4-21% less expensive (Waning 2009).Tiered pricing and co- payment systems have not been introduced in Thailand yet. Two -thirds of medicine consumption follows the advice of health professionals

(Wibulpolprasert 2007). Access to the medicine is thus mainly through the hospitals accounting for 70%, with relatively little through clinics (7%) and drugstores (15%) (IMS Health 2010). There are a limited number of studies that examine in detail the supply chain system of medicine distribution, in terms of lead-time or inventory management. Medicine distribution in Thailand is through manufacturers or agents. The distributors for multinational firms are logistics companies, and there is therefore no information of lead-time or inventory management; however public hospitals are generally recognised to keep a 2-3 month supply in stock (Pitaknetinan, Tangcharoensathien et al. 1999).

1.4.2 TRIPS, trade and access to medicines: Thailand as a case study

In 1979 Thailand's Patent Act (B.E.2522) established the first legal protection for inventions in the country. This Act only allowed process patents for pharmaceuticals. As mentioned, Thailand, as officially a developing country, was not required to provide patent protection before 2000. However, during the mid-1980s, many developing countries, such as Thailand and Brazil, were subject to trade pressure from the US government for increased IPRs protection (Wilson, Cawthorne et al. 1999). In contrast with Brazil, the Thai government was not able to resist the pressure from the US Trade Representative after a complaint by the US Pharmaceutical Manufacturers Association claimed that the patent protection for pharmaceutical products in Thailand was inadequate (von Schoen-Angerer and Limpananont 2001). As a result, Thai patent law was amended to include protection for pharmaceutical products in 1992, eight years ahead of the requirement in the TRIPS Agreement and 13 years ahead of the end of the transitional flexible period for developing countries (Markandya 2001).

The 1992 Patent Act, however, included a provision intended to protect consumers from the impact of high prices by establishing a Committee on Pharmaceutical Patent to monitor and compare medicine prices, and dispense corrective measures where inappropriate price behaviour was found. Thai patent law was revised again in 1999, and again in response to US economic pressure (Sweeney 2000). The major changes were the dismantling of the Committee on Pharmaceutical Patent, and amendments to allow for the protection of petty patents for six years, which allows simple inventions with industrial applicability, but which is not necessarily of a

groundbreaking nature, to enjoy the benefits of patent protection. The intuition behind these amendments was that they would offer a key incentive to promote the foreign investment needed for technology and knowledge transfers.

Thailand is a lower-middle-income economy with a 2007 per capita Gross National Income (GNI) of US$3,400 and total population of 63.3 million (Worldbank 2007). Prior to 2002, around 30% of the Thai population were uninsured and had to pay their own medical bills (Tangcharoensathien 2007). Universal Coverage (UC) was achieved in Thailand in early 2002, meaning that all Thai people are insured under one of three national health insurance schemes which are the Civil Service Medical Benefits Scheme (CSMBS) for government employees and their dependents, the Social Health Insurance (SHI) for private business employees and the UC scheme for any persons who are not covered by CSMBS and SHI.

During the past decade, the overall pattern of morbidity in terms of disability-adjusted life year (DALY) loss has been dominated by Non-Communicable Diseases (NCDs) (The Thai Working Group on Burden of Disease and Injuries 2002). Although NCDs are preventable or mitigatable by reversing lifestyle trends, medicines also play a significant role in reducing the damage caused by premature ill health. Given universal coverage, a holistic health system to provide adequate access to NCD medicines is vital for the Thai government. All Thai people are able to access medicines on the National List of Essential Medicine (NLEM) free of charge. However, some essential medicines are not selected for this list, and it has been argued that price is a major barrier to NLEM medicine selection (Ministry of Public Health 2008). Therefore, for non-NLEM medicines, patients are responsible for meeting the full price.

The Thai medicine market, as in most developing countries, depends heavily on imports. The proportion of imports rose with an accelerating rate during the period of high economic growth in the mid-1990s. Notably, this increase coincided with the amendment to the Thai Patent Act which effectively introduced patents for pharmaceuticals products. From 1992, when the new Patent Act went into effect, the rate of growth in the share of imported medicines in the Thai market increased by approximately 30% to 60%.The prices of medicines in Thailand are set mainly by the manufacturer, with no policy related to price regulation (Sooksriwong C 2009).

Therefore, the price of medicine is relatively high compared with other countries at similar levels of economic development. A survey by the World Health Organization (WHO) and Health Action International (HAI) found that, on average, Thai patients pay 2.5 times more for generic medicine and 4.4 times more for branded medicines than 36 other similar developing countries (Sooksriwong C, Yoongthong W et al. 2009). Patenting has always been highlighted by those in public health as a major factor contributing to the high price of medicines, and therefore as a significant barrier to access to medicines (Love 1999; Songkhla 2009; Kessomboon, Limpananont et al. 2010).

The debate over patent implications on access to medicine reached a peak in 2005 when the rise of HIV/AIDS as a major health problem, and concern over the rising costs of anti-retrovirals (ARV), coincided. HIV/AIDS was a major health problem during the period from 1994 to 2004. There were 25,000 new cases and 5,000 AIDS deaths per year in this period. A comparison of anti-retroviral prices in January 2005 showed that patented medicine prices in Thailand were much higher than generic prices from Indian manufacturers. For example, original EFV(200 mg) 100 capsules sold in 2006 at 3,192 baht per bottle, while a generic equivalent sold at 1,292 baht (Medecins Sans Frontieres 2006). Similarly, Lopinavir/Ritonavir (LPV/r) (180 capsules) from Abbott was sold at 17,762 baht per bottle, whereas Hetero sold at 5,930 baht or 33%of patented price (Medecins Sans Frontieres 2006).

Yet, although HIV/AIDS is a focus of attention, it is cancer that is the major cause of death in Thailand, with nearly 30,000 deaths annually and more than 100,000 new cases reported each year (Wibulpolprasert 2007). The number of cancer patients under the universal coverage scheme has increased from around 18,600 in 2004 to 341,000 in 2010. Most new anti-cancer medicines are patented, costly, and inaccessible to the middle class as well as the poor in Thailand. They are neither included in the NLEM nor covered by the National Health Insurance system. Therefore, patients have to pay for these medicines out of their own pockets. As a result many patients drop out of treatment when they cannot continue to afford the medicine (Ministry of Public Health 2008). Since the government failed to meet the goal of full access (Ministry of Public Health and National Health Security Office 2007), the Sub-committee on selecting essential medicines under the National Health Insurance scheme proposed measures to increase access, including CL for seven

patented medicines; two ARVs, EFV and LPV/r, one cardiovascular, clopidogrel, and four anti-cancer medicines, letrozole, docetaxel, erlotinib and imatinib, during 2006-2008 (Ministry of Public Health 2008).

The seven CL issued by the Thai government for these medicines provoked particularly strong reactions from pharmaceutical companies. For instance, Abbott Laboratories withdrew its registration application for seven new medicines in protest of the government use license on the LPV/r combination. Strong reactions were also forthcoming from the US and European governments since Thailand was the first developing country to issue CL for medicines not only for the treatment of HIV/AIDS but also other diseases, including heart disease and cancer (Tantivess, Kessomboon et al. 2008).The implications of CLs are also not confined to the pharmaceutical industry. In 2007 the Office of the United States Trade Representative elevated Thailand's ranking from the Watch List (WL) to Priority Watch List (PWL), indicating concerns over deficiencies in IPR protection and enforcement (USTR 2007), and announced that privileges under the Generalized System of Preferences would be removed for three Thai products: gold jewellery accessories, polyethylene terephthalate, and flat screen television sets.

In 2003, during the Asia-Pacific Economic Cooperation (APEC) Summit in Bangkok, the governments of Thailand and the United States initiated negotiation on a Thai–US FTA, to conclude in 2006. Like other FTAs, one of the 23 negotiation issues was TRIPS-Plus, which requires higher level of intellectual property protection than those agreed to in the TRIPS agreement: for example, protection for test data exclusivity, linkages between medicine registration and patents, the strengthening of intellectual property law enforcement, and restricting CL to public non-commercial use during national emergencies (Rossi 2005; Correa 2006).

This negotiation still has not been concluded, due to unstable political conditions, although it is expected that Thailand would benefit both economically and politically from the FTA. In economic terms, Thailand is very concerned that its exports to the United States have been losing market share in recent years to other countries, such as Mexico and China. Eliminating US tariff and non-tariff barriers to Thai exports through the FTA could increase the competitiveness and market share of Thai products in the US market. In addition, Thailand would receive greater US

investment as has occurred in other countries that have entered into similar agreements. Modernization and the diffusion of higher levels of technology are essential for the Thai economy to remain competitive in the face of competition from other lower-wage, emerging market economies such as China, Vietnam, and Laos. In addition, a closer political and economic relationship with the United States would bestow political and economic leverage to Thailand in Southeast Asia (Ahearn and Morrison 2006).

Given the experience of pharmaceutical patent protection in Thailand during 1992-2008, patent protection combines both health and trade issues. Product patent protection for pharmaceuticals was enforced in Thailand prior to the introduction of TRIPS to the WTO, which represents one of the longest experiments in setting high patent standard protection for pharmaceuticals in the developing world. Stronger patent laws might attract trade flows and foreign investors. However, their drawbacks for health are significant. Making use of the available safeguards to protect the health of the Thai people could make the country worse off in other ways, in terms of access to new medicines and reduced levels of foreign investment and access to export markets. In order to support the development of national policies which respond to international initiatives that affect patent laws (notably future government use license or FTA negotiations, including TRIPS-Plus) it is necessary to consider the impact that the level of patent protection has on the country as a whole.

1.5 What have we learned from past research?

Policy makers struggle to balance health with trade policy objectives, in the pharmaceutical sector as elsewhere (Smith, Lee et al. 2009). Tensions arise over medicine pricing in particular. What those in health view as necessary to maintaining equitable and wide access to medicines, industry views as inimical to R&D and innovation. Empirical evidence concerning the static and dynamic impacts of pricing is therefore essential since the net social welfare effect of any patent policy innovation may be either positive or negative. Patent policy not only has a direct effect on the current uses of existing technology but it may also have an effect on incentives to develop new technologies in the future. For example, with stringent patent protection, people may have less access to medicine due to higher monopoly

prices. However, overall social welfare may benefit in the long-term from being able to access a higher "quality" product (i.e.increased social marginal benefit or decreased social marginal cost).

Though it has been 20 years since the Thai Patent Act was amended to comply with TRIPS in 1992, there has been little emphasis on assessing the implications of the Agreement, or the subsequent use of flexibilities, on health or trade; which is the aim of this thesis. The purpose of this section is to outline the context for this in terms of the existing empirical evidence concerning patent protection, both in Thailand and internationally. This evidence will be explained in more detail in the appropriate chapters.

With respect to patent implications in general, the economic literature has focused on the implications of patent policy on static and dynamic welfare effects, since one of the basic justifications of a patent protection is to foster dynamic innovation as compensation to the static losses caused by granting temporary monopoly rights. There is a level of consensus among economists that developing countries will suffer a loss in static welfare in the short run with reinforcement of IPRs (Chin and Grossman 1988; Nogués 1993; Zuniga and Combe 2002). Contrary to the consensus regarding negative static effects, the assessment of the dynamic effects of strong patent protection is less clear. Some hypothetical studies predict that an increase in patent protection unambiguously promotes innovation (Kamien and Schwartz 1974; Diwan and Rodrik 1991). However, a number of empirical studies suggest that there is a significant probability that stronger IPR protection may slow down technological progress in the long run (Chin and Grossman 1990; Deardorff 1992).

Empirical studies in Thailand, and other similar countries, are rare. The findings illustrate the role of patent protection in four areas: price, present access, future access, and international trade and investment. Overall, patent protection appears to increase price by around 26%-277% depending on which of three estimation approaches is used: demand estimation before the patent came to effect, regression during the time the patent is active, and observation from before and after the patent expires (Watal 2000; Fink 2004; Magazzini, Pammolli et al. 2004; Boersma and et al. 2005; Borrell 2007). With respect to price and access, most studies describe how patenting increases price (as above) and then 'assume' that price affects access; there

is no study looking at the direct association between the extent of price increase and the extent of changes in access, controlling for other influences. While the specific analysis of the seven medicines for which Thailand implemented CLs showed that the generic equivalent price increased utilization rates by around three times (Yamabhai, Mohara et al. 2009), another study demonstrated that switching all medicines under a patent system to a no patent system would have increased the percentage of AIDS patients with access to new medicines only from 0.88% to 1.18%, due to other factors (Borrell and Watal 2003). This supports Attaran (2004) who suggests that the main obstacles to access are associated with the country's socio-economic status such as the lack of manufacturing capacity or a poor health care system (Attaran 2004).

With respect to the effect of price on future access, Lanjouw (2005) determined the effects of patent policy and price control policy on market entry, and showed that extensive price control and process-only patent protection lowers the probability of having a new medicine launched to market in lower-income countries by 30% (Lanjouw 2005). An implication of removing patent protection to gain increased current access is that this might result in patients foregoing the opportunity to get a new medicine in the future, as it would not be discovered (at the extreme this would be true globally, due to an overall reduction in industry income) or not marketed in a country (or, more likely, at the local level) (NOGUÉS 1993). This clearly generates trade-offs between benefits now and in the future (Grootendorst and Matteo 2007). Indeed, one study estimated that for every dollar in consumer benefit realized from providing greater access to current medicines, future consumers would suffer at a rate of three dollars in present value terms from reduced future innovation (Hughes, Moore et al. 2002). However, such studies lack a direct link between profitability and actual investment in R&D. They illustrate the effect of patents on profit and, again, 'assume' that this translates directly to R&D.

With respect to the broader impact, five studies which looked at the impact of patents on trade were found. Based on a Computable General Equilibrium model, it was estimated that the Thai-US FTA would increase the export and import levels for Thailand by 3.4% and 4.7% respectively (Thailand Development Research Institute Foundation 2003). Other studies suggest that IPR protection more generally has a

positive influence on overall trade flows in both small and large developing economies (Ferrantino 1993; Maskus and Penubarti 1995; Fink and Braga 1999). These results are in line with results that patent protection had a positive impact on Indian pharmaceutical exports (Pradhan 2007).

However, the impact of patents on foreign direct investment (FDI) is less categorical. Most studies here use regression to analyze the effect of IPRs on FDI. Additional variables are included in the regression to control for different country-specific factors, although all compare IPR risk with proxy indicators for 'economic risk' and/or 'political risk'. Most studies focus on the role of national patent protection policy to attract US investors. Ferrantino (1993), Markus and Penubarti (1995), Kondo (1995) and Primo Braga and Fink (1999) find that the protection of patent rights does not influence the location choices of foreign investors (Ferrantino 1993; Kondo 1995; Maskus and Penubarti 1995; Fink and Braga 1999).However, other studies suggest that the volume of FDI in a country tends to be inversely related to the weakness of IPR protection (Maskus 1998; Nunnenkamp and Spatz 2004; An, Maskus et al. 2008).

In terms of pharmaceutical FDI, a strong patent system was found to have caused a considerable flow of investment into the American pharmaceutical industry (Lehman 2003). However, some studies show a negative correlation between the levels of protection and foreign investment. This is supported by conclusions elsewhere that the exclusion of pharmaceuticals from patent protection was a significant factor leading Italy to become a base for export-oriented production of generic medicines (Weisburst and Scherer 1995). Supakankunti (2001) showed for Thailand that there had been little foreign investment in the pharmaceutical sector since the strengthened patent law in 1992 (Supakankunti, Janjaroen et al. 2001). From 1992 to 1998, only around $60 million was invested in new pharmaceutical companies in Thailand. It has been suggested that this is because foreign investors consider Thailand an unsuitable destination due to the insufficiency of well-trained human resources, technology and equipment, and the inadequacy of the registration system for new medicines (Kuanpoth 2007).

In sum, patenting does increase price, although the effect differs according to methodology and country, and weakening patent rights could increase present access

to medicine for Thailand. However, international evidence reveals that patenting may benefit future access, although this is based on complex assumptions and estimations. Patent protection appears to have a positive impact on trade flow. However, the implication for FDI is equivocal.

The preceding review reveals that the link between strong patent protection and the social welfare impact of pharmaceuticals in developing countries has not been well established. While it is less contentious that patent protection leads to static inefficiency (i.e. increased price in the short-term), the dynamic benefits associated with stronger patent protection seem uncertain. Specifically, some weaknesses can be identified in the existing studies. Studies of the impact of patents on prices and innovative activity focus almost exclusively on developed economies, and empirical evidence regarding the impact of the TRIPS Agreement is rather limited. Arguments concerning the effect of patenting on trade and investment tend to be considered in the economics literature, and arguments concerning access tend to be the focus of health literature. Clearly the impact of patenting is of interest to both audiences, and for national policy the key is to compare the issues and evidence for both sides: current and future access, and trade and investment. While continually strengthening patenting will likely lead to higher current prices, further reducing current access, weakening patenting may stifle long-term access, since pharmaceutical companies might be reluctant to introduce new medicine into the market, and foreign investors may find other countries to invest in where there is better protection of their products. Without patents products would be imitated and sold on the local market.

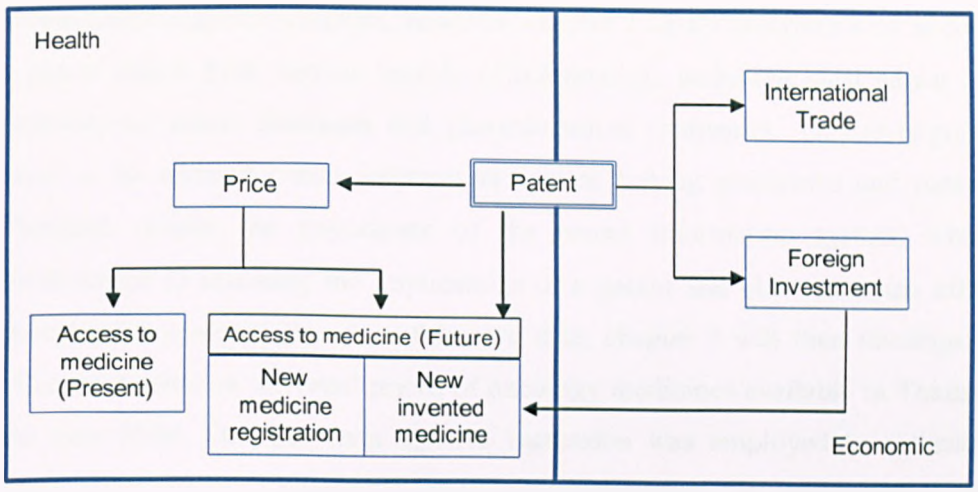
1.6 Framework and thesis objectives

This thesis studies the effects of IPRs, in particular pharmaceutical patent protection, on medicine prices and access to medicines both currently and in the future, and considers holistically the economic implications for trade and FDI. A case study of Thailand will be employed since Thailand has a unique history of IPRs law and implementation of CL to safeguard public health. This thesis further focuses on cancer medicines, in the health context. This is because cancer is currently one of the leading health problems in Thailand, and also because cancer medicines are expensive and subject to numerous patents.

It is apparent that patent protection has both health and economic consequences. A conceptual framework developed to illustrate the broad implications of patent protection is provided in figure 1. Patent protection affects the price of pharmaceuticals, where price is a component in determining affordability and affordability is then a component in determining access to existing medicines. Price is also a component in determining industry investment in introducing or developing new medicines. A higher price is likely to reduce current access, but stimulate the development of new medicines through a higher R&D budget enabling patients to benefit from access to new medicines in the future. Patent protection is also accompanied by foreign investment in domestic facilities for the production of pharmaceuticals. Finally, as indicated in the literature above, there are wider trade relationships that may be affected by patent decisions, which are not related to medicines at all.

However, the patent is only one determinant of the price of medicine. There are a range of supply and demand conditions that affect price. There is also, within health care, the added issue that most recipients of medicine do not directly pay the full price. For instance, in the Thai context, 97% of the population is covered under the public insurance schemes and can therefore access medicines on the NLEM without payment. Stronger patent protection could have the effect of amplifying FDI. A significant amount of such investment may stimulate the growth of local drug manufacturers or public institutes through technology and skill transfers.

Figure 1.2 Conceptual framework



The 1992 Thai patent law changes caused issues around the price of patented medicines, access to those medicines and its effect on the national economy. On the one hand, the government is concerned about drug expenditure since Thailand depends on imported medicines and 97% of the population is covered by national insurance. TRIPS-plus obligations would make this worse. On the other hand, the national economy also depends upon exports and foreign investment, which is expected to benefit from trade agreements. The specific objectives of this study are to:

1. assess the impact of patents on pharmaceutical prices;
2. assess the role of price in determining access to medicines;
3. assess the role of patents and price in determining future access to medicines not yet introduced in to Thailand; and
4. assess the role of patents on FDI (in the pharmaceutical sector specifically and in the economy as a whole).

Each chapter of the thesis focuses upon one of these objectives. They were designed and written as stand-alone papers, each encompassing an introduction, literature review, methods, results and discussion sections. The evidence gained from these four component studies will then be used, together with the conceptual model above, to comment upon the overall implications of patent policy for Thailand in the final chapter.

1.6.1 Thesis outline

Before these empirical chapters, however, chapter 2 firstly describes how to conduct a patent search from various sources of information, including local patent office, international patent databases and pharmaceutical companies. This is required as there is no updated patent information system linking medicines and patents in Thailand, despite the importance of the patent information system, which is fundamental to assessing the implications of a patent and also underpins effective procurement systems. Based on this core data, chapter 3 will then investigate the effect of patents on the retail prices of oncology medicines available in Thailand in the year 2008. Ordinary least squares regression was employed to estimate the explanatory power of patents on price, while controlling for market and medicine factors. The main finding of the model will show how much prices may be inflated by patents, and if there are other influential factors affecting price.

Universal coverage allows Thai people to access medicines on the NLEM free of charge. Chapter 4 presents a probit model to assess the role of patent and price in determining NLEM medicine selection. It also considers the affordability of non-NLEM medicines. The model employed includes those aspects of the market and medicine characteristics that are regarded as important factors in medicine selection. This chapter also estimates the number of medicines that would have been selected if generic prices were available.

Patent protection can encourage pharmaceutical companies to introduce their products to Thailand quickly. CL might therefore discourage companies from launching new products in the market and thus reduce future accessibility. Chapter 5 focuses on the impact of strengthening or weakening pharmaceutical patent policy on the availability of new medicines. This chapter employs a Cox proportional hazard model to analyze the launch experience of 86 active ingredients, with 248 trade names, treating cancer in Thailand covering the years 1982-2009.

The role of patents on FDI is presented in Chapter 6. The purpose of this chapter is to address what happens if a country decides to strengthen the patent system by allowing product patent protection earlier than the TRIPS Agreement requires, or to weaken the patent system by implementing CL. It also considers the role of stronger

patent protection on FDI, both in the pharmaceutical industry and the wider economy, and on innovation. A structural break, time series analysis and error correction model were employed to test if there is evidence of the impact of pharmaceutical patent related policy on FDI. This chapter also considers if there is a dramatic change in the rate of innovation in Thailand after the patent law change in 1992. A brief discussion regarding R&D in the pharmaceutical industry is also presented in this chapter.

Finally, chapter 7 summaries the findings from these four research sub-questions to address the broad research question of the thesis, which is whether Thailand is better off strengthening or weakening its patent policy concerning pharmaceuticals. This chapter discusses the main contributions of the thesis to knowledge and policy, as well as the study's limitations. Areas of further research which could extend the findings of this thesis are also mentioned in this chapter.

CHAPTER 2 BALANCING THE RIGHT TO KNOW AND THE PRIVACY OF THE PATENT SYSTEM: A CASE STUDY OF ONCOLOGY MEDICINES IN THAILAND

2.1 Introduction

According to the TRIPS Agreement, developing counties which are member states of the World Trade Organization required to provide patent protection on medicines by 1 January 2000 (World Trade Organization 2002). A patent aims to promote innovation by rewarding inventors with the exclusive right to produce and sell a good, for a limited time, to prevent others from making, using, selling, or distributing the patented invention without permission. Social benefit is derived not only from being able to access a new technology as it comes to market, but also from access to the information disclosed within the patent system, which is a source of valuable technical knowledge that can be reproducible without unnecessary burden. These aims coincide with the objectives of the TRIPS Agreement to promote technological innovation and to transfer and disseminate technology; a balance of rights and obligations.

Patent information, whether it has been filed, granted, is pending or has expired, is important to public health in a number of ways. Local health authorities and procurement bodies need to have patent information to help them choose cheaper medicines from alternative sources without the risk of patent infringement (World Health Organization 2004). Research institutions and originator and generic pharmaceutical firms, need to know about the patent information of specific products in specific countries in order to determine their freedom to operate in research and development, manufacturing and procurement without infringing upon patents, and to understand which licenses might have to be negotiated (Yancey and Stewart 2007). In addition, this information enables an overview of trends over time in terms of medical research and development, the changing directions of established players, and the growing role of new players in medical research and development (Liu and Shyu 1997; Ernst 2003).

However, given the critical nature of this information, identifying thepatent for each medicine is surprisingly difficult, even in countries with a high level of technology

(World Health Organization 2008). First, a single medicine can be protected by a large number of separate patents. Each patent can be related to an invention concerning the product (e.g. a specific molecule), a process (e.g. the process to manufacture this molecule), a medical indication (e.g. the effect of this molecule on a human body), or a combination of products (e.g. a fixed dose combination of two molecules). This is because patents protect the invention, not the medicine as such. Second, patents on medical products commonly involve very technical claims that are comprehensible only to those with substantial scientific training. Third, the fact that searching for a patent by the active ingredient name yields no results does not mean there is no patent related to that medicine, since patent specifications typically do not reference end products, in significant part because the invention was discovered before the product name was known.

In developing countries the problem is worse as there are substantial capacity and resource constraints in national patent offices, a lack of communication between the relevant authorities, and language barriers (World Health Organization 2011). As a result, developing countries usually buy patented products instead of seeking a generic equivalent version, since they assume that a medicine patented in the USA is also patented in their country. The avian flu pandemic in late 2005 is a good example which shows that the governments in developing countries could have provided this medicine for their population faster and more cheaply if the patent information of oseltamivir[1] was prepared and known. After the Philippines government planned to implement CL, the owner of the medicine declared that there was actually no patent covering oseltamivir filed in the Philippines (Requejo 2005). Also, Thailand had been purchasing the original of sertraline, a depressive disorder treatment, and risperidone, a schizophrenia treatment, for many years until the use of CL for these medicines was considered and it was found that there were no patents for these medicines in Thailand (Thaipost 2009).

In light of this, the proposal of a global pharmaceutical patent database was considered by the World Health Organization's Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) at the 2008 World Health Assembly. The proposal was to create a user-friendly, public, global database

[1]Whose tradename is Tamiflu

on the status of health-related patents in all countries which could meaningfully advance public health objectives, including efficient pharmaceutical procurement, in developing countries. However, at the time of writing, the progress of this database cannot be found.

With regard to patent information related to medicines for specific diseases, some patent landscape reports on various topics have been published by different international organizations (World Health Organization 2004; World Intellectual Property Organization 2007). For example, the Médecins Sans Frontières initiated a project collaborating with selected national or regional patent offices to undertake the verification of the patent information of 18 ARV treatment products in 29 countries (Boulet, Perriens et al. 2000). Covering other diseases, a project determining the patent of the medicines on the WHO Model Lists of Essential Medicines is on-going (World Health Organization 2010). These projects aim to help developing countries obtain patent information, as undertaking a patent search is costly and time-consuming.

The patent landscapes mentioned are specific to communicable diseases. However, the burden of disease in low- and middle-income countries is now turning to non-communicable diseases, especially cancer (World Health Organization 2011). Cancer has been an important health problem in Thailand with more than 100,000 new cases diagnosed and more than 30,000 deaths each year (Wibulpolprasert 2007). Medicines treating cancer are generally expensive. The prices of new-to-market treatments, targeted therapies and those with limited toxicity are set very high. It is claimed that most of the high price chemotherapy agents are patented and it is further argued that patents lead to unaffordable prices (Ministry of Public Health 2008). Surprisingly, this claim was made without knowing exactly which medicines are under patent protection.

At present, there is no literature determining the patent of oncology medicines in developing countries generally, or in specific countries like Thailand. Numerous considerations come into play when discussing the impact of patents on public health. A fundamental part of assessing the impacts of patents is to first discover which medicines are actually covered by patents. Only then it is possible to estimate the impact of patenting on access to those medicines. Identifying which medicines

are patented in one country, like Thailand, and then estimating patent impact on access may seem simple. However, it requires many processes. The number of patented medicines may be less than one expected due to the misapprehension that monopoly medicines or those medicines patented in the US are also patented in the considered country. Patent information helps to inform procurement agencies in Thailand about whether to purchase or manufacture generic versions, or whether they must obtain voluntary or CLs to legally purchase or manufacture generic versions. As mentioned previously, Thailand has been slow to seek generic versions of some products because of the misunderstanding that they were patented in Thailand. This chapter aims to shed light on the processes to identify the patent of oncology medicines in order to be able to estimate the likely impact of patents.

Following this introduction, the next section describes the pharmaceutical patent system, including medicine patent databases in USA, Canada and Thailand. This is followed by the method of patent search employed in this study. Part 4 presents the results and Part 5 concludes and discusses the patent information system in Thailand with lessons also for other developing countries.

2.2. Pharmaceutical patent and patent search guideline

A patent is an exclusive right granted to individuals who invest in the creation and dissemination of knowledge, providing them with an incentive to produce a new and useful product or a new way of doing something or of solving a problem (World Intellectual Property Organization 2011). A patent for a specific invention is national and the application for a patent is filed in the country where protection is desired; there is no worldwide protection. When a company invents a new product or process, the Paris Convention allows this company one year to file patent applications in any other Member State of the Paris Convention (World Intellectual Property Organization). This one-year period is to preserve the novelty of the invention during the time the company decides in which countries it wants to seek patent protection. A pharmaceutical company will file patent protection in countries where potential competitors could replicate product development of either its R&D or other research institutes(Bhat 2005).

As mentioned in the introduction chapter, the pharmaceutical industry is inherently risky and costly since it faces a rapidly evolving science of discovery, as well as changing economic, legal and regulatory environments. Hundreds of millions of dollars invested in a new drug can take a decade or more to pay back, as scientific and technical barriers produce a high failure rate (DiMasi, Hansen et al. 2003). It is said that patents for the pharmaceutical industry are especially important compared with other industries, given that the actual manufacturing process is relatively easy to replicate and can be imitated with a fraction of investment of that required for the new entities investigation and effectiveness testing (Scherer 1993). Moreover, the pharmaceutical industry is demanded by government agencies for the safety and quality assurance of product before the product can be launched in to market. Without the degree of financial protection patenting secures, many argue that the innovative good or process would never be created (Nogués 1993).

Since identifying patent information on each pharmaceutical product is very complicated, there are some manuals published by WHO and World Intellectual Property Organization (WIPO) which provide a guide on how to identify if relevant patents relating to a medicine exist in the country of interest (World Intellectual Property Organization 2007; World Health Organization 2010). The manuals suggest using the US FDA Orange Book and the Health Canada Patent Register as a starting point, given the difficulties in identifying and matching patents to relevant products, since US FDA and Health Canada also provide patent information for 'approved for sale' medicines. However, locating patents in developing countries through the extended searches described in Box 2.1, is not a straightforward process. One reason is that the patent family and national phase data available in esp@cenet and Patentscope do not cover all countries where the patent may have been filed (World Health Organization 2010). Also, even where developing country patent offices offer an online searchable database key data may be omitted, incorrectly inputted or out of date, all of which can lead to an unsuccessful search (Limpananont, Kuanpotch et al. 2004). Finally, as complete specifications and claims for patents filed or granted in developing countries are rarely available online, in many cases they will have to be requested directly from the concerned national or regional patent office.

Box 2.1: Summary of steps to search for patents on medicines

Step 1

The first step is to identify patents that relate to marketed medicines. One efficient way of obtaining this information is through public databases made available online by the US FDA (the Orange Book) and Health Canada (Patent Register). These databases match some key US and Canadian patent numbers to medicines that are marketed in these countries, but that may also be sold in other countries.

Step 2

Once US and/or Canadian patent(s) number(s) relating to a medicine have been identified, the next step is to obtain the bibliographic details of the patent(s). It is also recommended to obtain the specification(s) of the US and/or Canadian patent(s) found. Having access to the bibliographic data and full details of the identified patents is not only useful for identifying priority data relevant to equivalent patents filed in other countries, but also for finding keywords that may be used to expand the search to other related patents. The EPO's esp@cenet database is a source to obtain bibliographic data.

Step 3

As the Orange Book and Health Canada Patent Register do not provide information on all relevant patents relating to a particular medicine, further searches are necessary. It is recommended to expand patent searches using various techniques including keywords, applicant/assignee name, patent classification, citations and date range information. The WIPO public database and Patentscope offer more search fields than other public databases and provide information on international patent applications, as well as national phase data.

Step 4

Taking the techniques and information obtained through steps 1 to 3, the next step is to apply them to finding patents in the country of interest.

Source: WHO (2010)

2.3 Thai patent database

Although this thesis aims to assess patent implications, the first important task is to know which medicines are actually patented in Thailand. The possible approach to obtaining information on patents in Thailand is to establish the application date of the first patent protecting the chemical entity of the patented medicine found from the US and Canada databases, then add one year to this date, since those patents for the same invention should have been filed within the one-year priority period referred to earlier. This allows one to get an approximate sketch of when the same patent granted for the same chemical entity in other countries will likely commence and expire. However, this applies only to countries where a patent has been filed and where the patent owner pays the maintenance fees to keep the patent active. Moreover, it depends on the specific patent and country, since patent owners themselves may not file or maintain all patents. In addition, one medicine is likely to be covered by more than one patent. It is possible that the patent owner will choose to file one of the patent families. This then leads to an incorrect assumption of patent information and leads to risk of infringement. Patent analysis therefore should be done on a country specific basis.

In Thailand, there is no legal link between medicine registration and patent information. The patent database in Thailand is maintained by the Department of Intellectual Property (DIP), under the Ministry of Commerce. DIP provides an open-access database to search for patent applications and documents that patent holders in all fields, including pharmaceuticals, may have filed. The patent documents are provided in the Thai language; with terms stemming from foreign languages translated into Thai, including technical terms and the names of persons and organizations. However, searching for pharmaceutical patents with this database is not straightforward, since it is linked with name of the medicine, and often patents are filed under chemical name. Thus, searching for patents by active ingredient name is likely to yield no results. The inconsistency in translation of patent documents from English to Thai further exacerbates the problem.

In an attempt to resolve these problems, 2002 saw the launch of a Pharmaceutical Product Patent Database Development Project (PPDD) undertaken by the Social

Pharmacy Research Unit,[2] Chulalongkorn University. This project examined the patent documents filed in Thailand in the international code of A61K (preparations for medical, dental, or toilet purposes (World Intellectual Property Organization), during the period 1992-2002 in order to develop a more consistent and comprehensive database of patented drugs. This database[3] is user-friendly and may be searched either by active ingredient or trade name. Unfortunately, it has not been updated since the project finished and thus has no record of medicines since 2003. Moreover, in undertaking a patent search for oncology medicines, only two medicines were found to be covered by patents in Thailand compared with 47 medicines found to be patented medicines from the US FDA and Health Canada databases. If this information is correct and up to date, it would be a great opportunity to procure the cheaper generic versions of 45 medicines. However, some of these medicines were introduced in Thailand after 2003 and hence the patent information of these medicines will not be able to be found from this database.

Patent information is often inaccurate and incomplete. All patent databases always indicate that the information may not be complete. It is therefore suggested that patent owners be contacted in order to verify medicine patent. As a result, an innovative method of cooperating with related authorities, patent offices and public health offices, as well as pharmaceutical companies to update patent information related to medicine is needed. In the next section, the process of identifying patented medicines undertaken for this thesis is outlined in more detail.

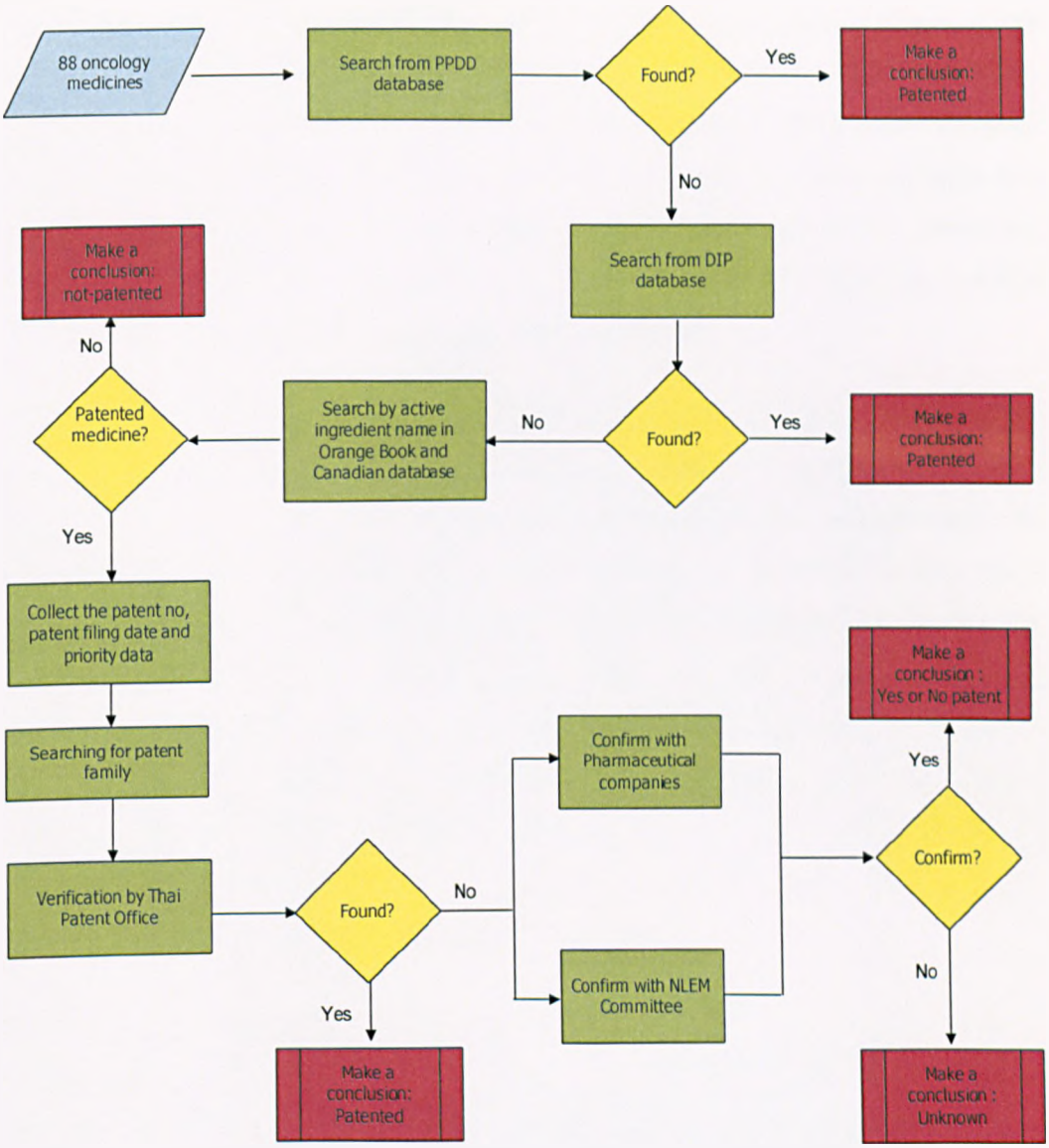
2.4. Methods

As mentioned in the introduction chapter, this thesis focuses on cancer medicines. All cancer medicines marketed in Thailand in 2008, the year this study was conducted, were obtained from the Thai FDA. This resulted in 88 active ingredients to conduct patent searches for. Mixed methods were used as recommended by the WHO guideline and other sources available in Thailand. Figure 2.1 presents the process to search for medicine patent employed in this study. In short, all active

[2] The Unit aims at conducting studies involving the social aspects of drug, health and pharmaceutical technology in order to gain better understanding of, and to propose alternatives for solving social problems pertaining to these topics. The research emphasizes the integration of knowledge from a multiplicity of disciplines such as pharmaceutical science, economics, political science, law, ethics and behavioral sciences.
[3] Available at http://wwwappl.fda.moph.go.th/patent/homepage.html.

ingredients were initially searched for in the DIP public database and PPDD databases, as mentioned in the previous section. For the medicines with a status of 'not-found', the patent status and information (patent number and filing date) of their active ingredients were searched for in the U.S. FDA Orange Book and Health Canada databases. Further searches were conducted to identify the priority and family information for the Thai patent office to verify relevant patents in Thailand. Active ingredients that were found to be patented in USA or Canada, but where patent information was not found in DIP, were then confirmed with the relevant pharmaceutical companies and the NLEM committee. The next section describes each step in details.

Figure 2.1 Patent search process



2.4.1 Identification of patented medicines by Thai patent office

The critical information required to search for relevant patents of each medicine is identifying the 'priority data'. The priority data are the application numbers and dates provided when the first patent application claiming an invention is filed (World Health Organization 2010). These numbers are referred to when subsequent patents or related subject matter patents are filed. This 'priority data' can therefore be used to connect related patent documents across national or regional patent offices,

through databases and computerized search systems. Hence, the priority application number functions as an identifying code in the world intellectual property system. WIPO considers the availability of correct priority application numbers to be extremely important and has requested that "the standard be implemented by industrial property offices as soon as possible" (World Intellectual Property Organization 2007). The Thai patent office is compliant with this standard and requests applicants to provide priority data of every patent filing at DIP. Therefore, by providing the priority number(s) for a patent relating to each medicine, a patent office may be able to match it to a patent filed in Thailand.

In theory, the priority application numbers can be used on their own to request applications and granted patents from the Thai patent office. However, in practive, a , 'patent family' searching step, which includes all related patents, can help make the patent search more comprehensive. A 'patent family' is a list of similar patent documents linked by priority application numbers from throughout the world that derive their origin from the priority patent (Hingley and Park 2003). Identifying the patent family generates a group of hundreds of patents all originating to a specific priority application number. For this thesis, patent family information was retrieved through the European Patent Office's (EPO) Esp@ceNet.[4] As a result, a family of patent numbers and filing dates of each patent is recored and used as another source of information to search for patents filed in Thailand.

In short, the first step is to identify patented medicines from the Orange book and/or Health Canada databases (Generic Pharmaceutical Industry and Intellectual Property Section 2008; World Health Organization 2010). These two databases also provide the patent(s) listed by the proprietor in relation to the market product. All patent numbers for each product were recorded. For each patent number, the priority data were retrieved from US and Canadian patent information through the online patent office databases: the United States Patent and Trademark Office (USPTO)[5] and Canadian Intellectual Property Office (CIPO)[6] for US and Canadian patents

[4] Available at http://www.epo.org/searching/free/espacenet.html

[5] Available at http://patft.uspto.gov/

[6] Available at http://brevets-patents.ic.gc.ca/opic-cipo/cpd/eng/introduction.html

respectively. A search for the relevant patent families for each patent was then conducted.

Table 2.1 Example information used to search for patents of amifostine

1	2	3	4	5	6
Patent number	**Application number**	**Filing date**	**Priority data**	**Patent family (filing number and date)**	**Priority date of patent family**
5424471	08/099,298	July 29, 1993	US19930099298 19930729; US19920922929 19920731	EP0655917 (A1) - 1995-06-07 EP0655917 (A4) - 1995-08-02 EP0655917 (B1) - 2004-03-17 EP1243272 (A2) - 2002-09-25 EP1243272 (A3) - 2003-01-22 EP1764103 (A2) - 2007-03-21 US5424471 (A) - 1995-06-13 US5591731 (A) - 1997-01-07	1992-07-31
5591731	08/389,386	February 16, 1995	US19950389386 19950216; US19930099298 19930729; US19920922929 19920731	EP0655917 (A1) - 1995-06-07 EP0655917 (A4) - 1995-08-02 EP0655917 (B1) - 2004-03-17 EP1243272 (A2) - 2002-09-25 EP1243272 (A3) - 2003-01-22 EP1764103 (A2) - 2007-03-21 US5424471 (A) - 1995-06-13 US5591731 (A) - 1997-01-07	1992-07-31
5994409	08/987,550	December 9, 1997	US19970987550 19971209	EP1039887 (A1) - 2000-10-04 EP1039887 (A4) - 2003-01-15 EP1039887 (B1) - 2006-05-24 EP1537861 (A2) - 2005-06-08 EP1537861 (A3) - 2005-06-15 US5994409 (A) - 1999-11-30 US6586476 (B1) - 2003-07-01 US2002132795 (A1) - 2002-09-19 US7105575 (B2) - 2006-09-12	1997-12-09
2120133	66440	July 30, 1993	US19930099298 19930729; US19920922929 19920731	EP0655917 (A1) - 1995-06-07 EP0655917 (A4) - 1995-08-02 EP0655917 (B1) - 2004-03-17 EP1243272 (A2) - 2002-09-25 EP1243272 (A3) - 2003-01-22 EP1764103 (A2) - 2007-03-21 US5424471 (A) - 1995-06-13 US5591731 (A) - 1997-01-07 US2006040903 (A1) - 2006-02-23	1992-07-31

An example of patent data retrival for one medicine, amifostine, is illustrated in Table 2.1. From Orange book and Health Canada databases, there are four patents reported. Each patent, application number and date and priority data were recorded as shown in column 2 to 4. Each patent number was then used to search for patent family in Esp@ceNet to get the information in column 5. Thai patent database[7]

7 http://110.164.177.243/DIPSearch/PatentSearch/SearchComplex.aspxData

allows users to search with flexible fields such as by patent number, application date, priority patent number, priority patent date. Data in column 4, priority data, were used as priority to search in the DIP internal database. If no patent information was found, the data from column 1 to 3 was used. The search was then finalised by searching by patent family data, column 5 and 6, respectively. To sum up, for one medicine, it could reach to a hundred of search terms.

In conclusion, verification was provided by the Thai patent offices by using key sets of information to identify if the medicine is patented , which are:

- US and/or Canadian patent number, application number and date;
- the priority application data of each patent; and
- patent application numbers and dates identified through the patent family search.

2.4.2 Identification of patented medicines by other authorities

For those medicines found to have patent(s) in the US and/or Canada but not found by the Thai patent office, confirmation was sought directly from the relevant pharmaceutical companies on their patent status: examination process, adverstisement process, granted patent or others. The names of companies selling suspected patented medicines (from Orange Book and/or from the monopoly medicine status from the FDA drug registration database) are listed in Appendix 1. A questionnaire was developed to survey medicine patent information from these companies, including application number, types of patents (product, process, or petty patent), date of the application, patent status (filing, examination, advertisement or granted) and patent expiry date. An example is shown in Appendix 2. Since the time available to collect information was limited, 14 weeks, the survey was done via the Association of Pharmaceutical Research & Manufacturers (PReMA) who cooperated and distributed the questionnaire from October 2010 to January 2011.

Pharmaceutical patent information may also be obtained from the NLEM committee. The NLEM is a list of medicines, vaccines, radioactive substances, and disinfection agents that are necessary for the prevention and control of major health problems in Thailand. The NLEM is referred to by the three public health schemes as the 'pharmaceutical reimbursement list' (Teerawattananon, Tantivess et al. 2009).

Applicants for pharmaceutical patents have to submit the "Por.Tor.Yor. 14 Form" to the NLEM committee. There is one section with regard to patent information. It requests product owners to provide patent information for the medicine concerned. However, submitting patent information is requested, not required, since there is no law or regulation to force the applicants to provide the patent information. Therefore, there is much missing patent data and some information is incorrect.

In parallel to questionnaires being administered to pharmaceutical companies, as outlined, a request was made to the NLEM committee to access the forms to retrieve the patent information part of the form submitted by pharmaceutical companies. Data were then cross-checked with the data provided by the pharmaceutical companies.

2.5. Results

Figure 2.2 shows the results from the patent verification process. From 88 active ingredients selling in Thailand in 2008, four patented medicines were found from PPDD and DIP. It was found that 47 medicines have been filed for patent protection in USA or Canada. All relevant data, including priority patent data and patent family data of each patented medicine were sent to the patent office in Thailand to search for the patent application or patent granted to those 47 medicines. Twenty-one medicines were found to have patent protection from the DIP internal database and through verification by a patent officer. For the rest of the medicines, the Por.Tor.Yor. form was requested from the NLEM, in parallel with a survey of pharmaceutical companies. Another six medicines were confirmed to have been subject to filed patents in Thailand; three of which were retrieved from the NLEM. A number of pharmaceutical companies refused to complete the questionnaire survey, claiming that they did not have the information or that it was company policy to keep the information requested confidential. Therefore, for eight medicines (Appendix 3) there is no information concerning patent status. Appendix 3 also shows non-patented medicines, of which twelve were confirmed as such by pharmaceutical companies.

Figure 2.2 Step by step results of patent status verification

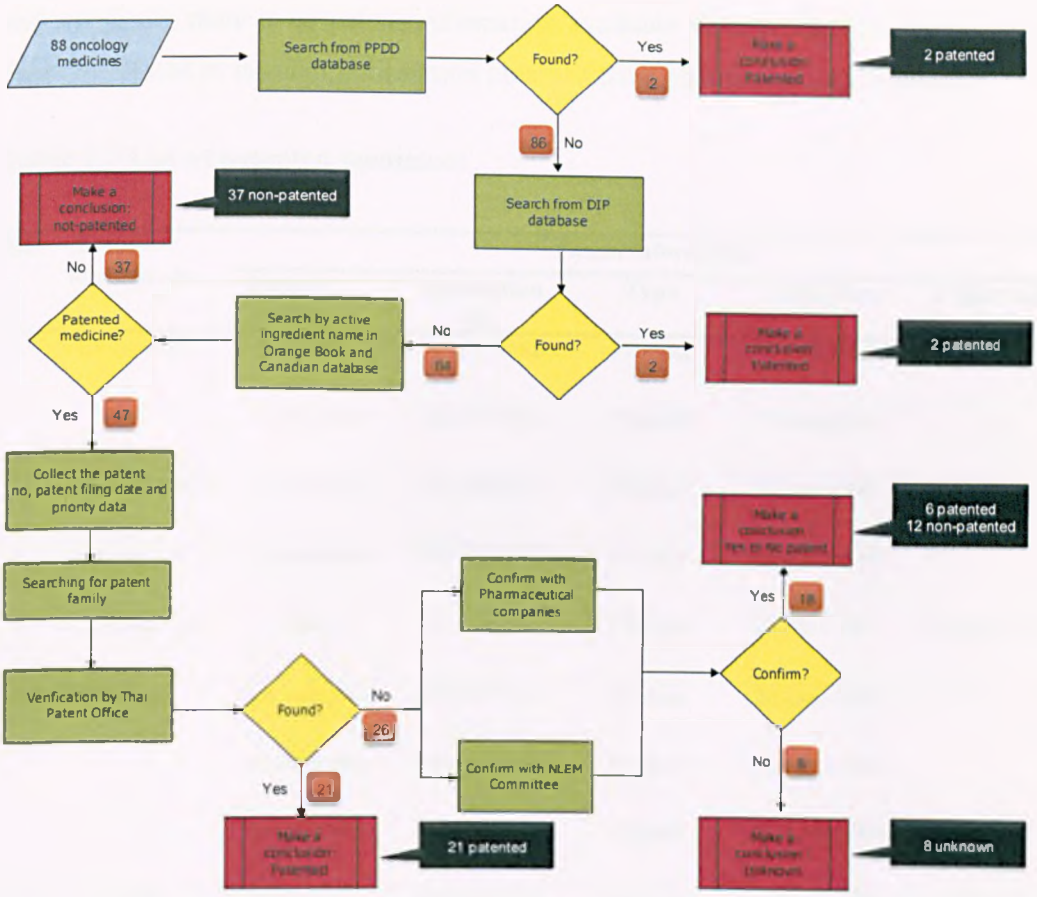


Table 2.2 shows patent information for 31 active ingredients that the patent owner filed for patent protection, either for product, process or new use protection, in Thailand over the period 1993-2008. It also provides their patent number, application number, filing date and expiry date. As can be seen from the table, most medicines are protected by product patents. Only two process patented medicines, docetaxel and gemcitabine, and one new use patented medicine, ondansetron, were found. There are some medicines that are still under the examination process. 14 medicines that have a patent status of 'examination' still have to await the examination process to be finished.

Patents of four medicines are under the 'filing' status. The patent details of medicines that currently remain in the filing process are not known. DIP regulations state that "applications for patents which are not published or issued are not generally open to the public, and no information concerning them is released".

Therefore, the details of patents filed for four medicines (dasatinib, etoposide, oxaliplatin and trastuzumab) cannot be obtained. For granisetron, ibandronic acid and sorafenib, there is no patent information available through the Por.Tor.Yor. 14 Form of NLEM or through information obtained from pharmaceutical companies.

Table 2.2 List of patented medicines

No.	Active ingredients	Patent information				
		Patent number	Application No.	Type	Filing date	Expiry date
1	Aprepitant	17690	9801002488	Product	1-Jul-1998	1-Jul-2018
		Examination	0201004524	Product	3-Dec-2002	-
2	Bevacizumab	Examination	0501004920	Product	20-Oct-2005	-
3	Bortezomib	Examination	0501001443	Process	29-Mar-2005	-
4	Capecitabine	9441	9301002157	Product	26-Nov-1993	26-Nov-2013
5	Cetuximab	Examination	0201004785	Product	20-Dec-2002	-
		Examination	0401004678	Product	25-Nov-2004	-
		Examination	0401004701	Product	26-Nov-2004	-
6	Dasatinib	Examination	0501005150	New use	2-Nov-2005	
				Filing process		
7	Docetaxel	12332	9501001641	Process	7-Jul-1995	7-Jul-2015
8	Doxorubicin			Filing process		
9	Epoetin beta***	Examination	101001782		10-May-2001	
10	Erlotinib HCl	Examination	9601000814	Product	19-Mar-1996	-
11	Etoposide			Filing process		
12	Fludarabine phosphate	Examination	0201004766	Product	19-Dec-2002	
13	Gefitinib	27686	9601001252	Product	24-Apr-1996	24-Apr-2016

No.	Active ingredients	Patent information				
		Patent number	Application No.	Type	Filing date	Expiry date
14	Gemcitabine*	Examination	19307	Process	21-Jun- 1993	-
		10145	19308	Process	21-Jun- 1993	21-Jun- 2013
15	Goserelin	Examination	0101000493	Product	14-Feb-2001	-
16	Granisetron**	No patent information disclosure				
17	Ibandronic acid**	No patent information disclosure				
18	Ibritumomab	9595	9301002057	Product	12-Nov-1993	12-Nov-2013
19	Imatinib	Examination	9801002650	Product	13-Jul-1998	
20	Irinotecan	Examination	0501002510	Product	31-May-2005	-
21	Lapatinib	Examination	9901000064	Product	11-Jan-1999	-
22	Letrozole	Examination	0801000497	Process	31-Jan-2008	-
23	Medroxyprogesterone	9157	9501003476	Product	26-Dec-1995	26-Dec-2015
24	Nilotinib	Examination	0301002355	Product	25-Jun-2003	
25	Ondansetron *	9938	9401001016	New formula, New use	23-May-1994	23-May-2014
		Examination	0501000228	Product	20/01/2005	-
26	Oxaliplatin	Filing process				
27	Paclitaxel*	Examination	030658	Product	27-Mar-1996	-
		Examination	034883	Product	20-Dec-1996	-
		Examination	063343	Product	31-Jan-2001	-
		Examination	072446	Product	20-Jan-2002	
28	Rituximab	9595	9301002057	Product	12-Nov-1993	12-Nov-2013
29	Sorafenib***	No patent information disclosure				

No.	Active ingredients	Patent information				
		Patent number	Application No.	Type	Filing date	Expiry date
30	Trastuzumab**	Filing process				
31	Tretinoin	Examination	1003953	New use	16-Oct-00	16-Oct-20

* from FDA patent database ,** from pharmaceutical companies, *** from NLEM

In conclusion, in figure 2.3, 35% of oncology medicines in Thailand in 2008 were patented, 57% were unpatented, and 8%were unknown. The list of unknown patent status and non-patented medicines are shown in Appendix 3. The pie chart below shows that DIP is the main source of patent information. Pharmaceutical companies are also an important source to confirm that the medicines are not patented in local markets.

Figure 2.3 Patent status and sources of patent information

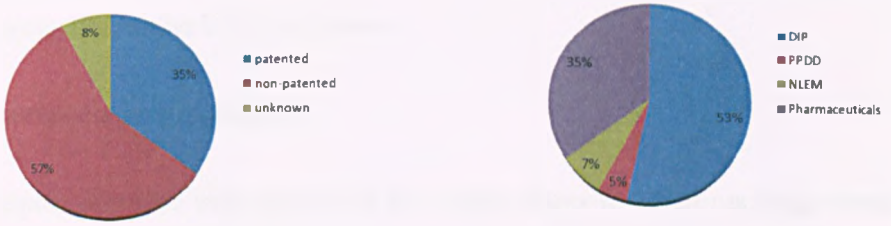


Table 2.2 presents the list of 13 active ingredients that were found to be unpatented in the USA or Canada. Each medicine has only one seller marketing it in Thai market. The sales value of these medicines in the year 2008 was approximately 262 million baht (8.7 million $US).

Table 2.3 List of monopoly status medicines found to have no patent in US or Canada drug patent database

No.	Active ingredients	No.	Active ingredients	No.	Active ingredients
1	altretamine	6	Dactinomycin	11	ramosetron hydrochloride
2	asparaginase	7	hydroxycarbamide	12	tegafur + uracil
3	azacitidine	8	Idarubicin	13	thioguanine
4	buserelin	9	Lenograstim		
5	chlorambucil	10	Melphalan		

Three main sources of patent information have revealed that there are 31 medicines that product owners requested patent protection for in the Thai market. The number could be higher if the medicines with unknown patent status are included, which yields 39 medicines out of 88 medicines, but this is still well under half of medicines in the Thai market. When comparing this number with the figure of patented medicines either in the US or Canada, 49 of these 88 medicines were found to have patent protection in the USA or Canada.

2.5. Conclusion and discussion

This chapter provides information on the patent status for each oncology medicine marketed in Thailand in 2008. Given that there is no good system to identify whether a medicine is patented or not in Thailand, this chapter shows how patent information can be searched for in Thailand. By tracing the medicine's origin from the US, Canada and Espacenet patent databases, and continuing to investigate with the Thai patent office, the FDA and pharmaceutical companies, 31 medicines were found to have patent protection.

The national patent office is the most obvious source to identify patents. However, the process takes considerable time since their capacity to deal with requests is limited. Although the guidelines for assessing patents are very useful, patent information for some medicines were not able to be found using this process. There are three possible reasons for this. First, product owners may decide that the patent filed in Thailand will not be shown in the patent family as it may have subsequent

patents granted later on to protect; for instance, an improved manufacturing process or improved formulation with fewer side-effects, which have not yet been linked together. Second, the applicant might submit the wrong priority data, for example instead of 630.224, writing 630,224, which would mean that the electronic database would not be able to identify it. Third, it may be the case that pharmaceutical companies might choose not to file a patent in Thailand if they think the capability to produce that medicine is limited.

Aso, the decision to choose which patent will be filed in any country depends on its owner assessing the cost, scope of protection, law enforcement or any potential negative consequesnces (Borrell and Watal 2003; Pavento, Greene et al. 2003). Four medicines, bortezomib, docetaxel, gemcitabine and letrozole, were found to have process patent protection instead of product patent protection. Process patent means that local manufacturers or other suppliers can produce or find similar products that have a technically different production process without incurring patent infringement. This might be because a patent is typically filed when the invention is found and it takes considerable time to bring that product into the market. Since Thailand changed its patent law in 1992, the first product patent of a medicine filed elsewhere may already have expired by 1992, or it may not be possible to file a patent in Thailand, i.e. it cannot be counted as 'novelty'. Therefore, relatively important patents, that still have patent life, maybe considered filing in Thailand.

The USA and Canada account for a significant market share of world pharmaceutical sales (International Union Against Cancer 2008). Product owners will try to seek patent protection in these countries. There is an assumption that if a medicine is patented in the US, it is likely to be patented in a developing country as well. This might not be the case since it depends on company's decision to file a patent application in the country. This study confirms this argument since the results show that 15 active ingredients patented in the USA do not have a patent in Thailand. With lower technology capability and performance, pharmaceutical companies may not consider it worthwhile to protect their products with patents in some developing countries. Developing countries may therefore find that they pay more than they need to for some medicines simply due to this misinterpretation.

Identifying patented medicines is very simple in developed countries like the US and Canada since there is a direct linkage between the FDA and patent office. Patent linkage refers to the communication process between the Health Ministry and the Patent Office to prevent marketing approval of generic drugs until after the expiration of patents covering the drug product or approved use. This system requires product owners to file patent information related to medicine within 30 days of approval. Despite the fact that it helps in identifying patented medicines and opens the door to access to technical knowledge related to those medicines, it causes problems since it could delay entry of generic medicines to the market since the manufacturer of the generics must provide notice to the original manufacturer of its submission of an application, thereby allowing the patent owner the opportunity to seek enforcement of its patent rights (MERCK 2011; Knowledge Ecology International 2011).

In many developing countries, however, this option is not available, and pharmaceutical patent information is effectively secret from all but the patent holder. Private services may not cover these countries, or may be prohibitively expensive for public organizations. As a result, many guidelines concerning how to conduct a pharmaceutical patent search have been published, although often systems cannot be navigated easily to work out precisely what is patented. Thus, international organizations have tried to provide examples of how to find a patented medicine in some countries (World Health Organization 2004; World Intellectual Property Organization 2011). These efforts have demonstrated the appropriate means to identify patent landscapes in developing countries.

Establishing a user friendly health related patent database for developing countries was proposed by the WHO's IGWG (World Health Organization 2008). However, although it is feasible, this establishment could consume huge effort and considerable time, expertise and funding to overcome the barriers. Some patent mapping in developing countries has been done but this can only focus on specific medicines, as this study focuses on oncology medicines. In addition, the patent review reports always state clearly that the patent information in the report may not be used as a comprehensive and an approved source of patent information. It is

recommended to confirm with the patent office or pharmaceutical companies directly before medicine procurement is made.

This makes an obvious imbalance in the patent system visible. A government grants a monopoly right to exclude others from making, using or importing the invention throughout that country, in exchange for the disclosure of the invention to the public to meet the objective of the patent system to encourage inventive activity, as well as technology transfer. Yet the exclusive right protection is reached while the disclosure is still confidential in developing countries, impeding strategic procurement. This chapter reveals that a lack of patent information could lead to missed opportunities in the cost-effective procurement of generic medicines, since not every monopoly medicine is patented. The difficulties in obtaining such information make it very difficult to establish what price should be paid, and what the implication of a patent on price is. It is impossible to estimate the impact of patenting on price or other factors if the patent status itself is not known. Indeed, ironically, patenting might actually not hinder public health if, as is the case in Amir'sstudy, only 2% of essential medicines listed on the WHO Essential Medicine List are patented (Amir 2004).

This study reveals the oncology medicine patent landscape in Thailand with the verification of patent statuses at the national level. The next level of inquiry is whether granted patents cover inventions that affect the use of and access to some medicines. In this case, analysis of national patents is needed to determine the scope of the patent with respect to a commercial product made, used, sold or imported into Thailand. Further studies need to be done to answer this question.

CHAPTER 3 TO WHAT EXTENT DO PATENTS LEAD TO HIGHER PRICES: A CASE STUDY OF ONCOLOGY MEDICINES IN THAILAND

3.1. Introduction

Recent years have seen increasing attention being paid to the rising cost of health care in low- and middle-income countries (LMICs), where treatment prices are often especially high as a proportion of income (Niëns, Cameron et al. 2010). This cost pressure is often linked to the increasing price of medicines faced by these countries. This is particularly true for the treatment of cancer, which has seen tremendous progress in prevention, treatment and palliation, albeit largely through technological developments which entail increasing costs of care, more than doubling over the past two decades in the US for example (Tangka, Trogdon et al. 2010), and nearly doubling in the UK over the past decade, from £3 billion to£5 billion (Sullivan, Peppercorn et al. 2011). Such expense is clearly a barrier to many, but is especially pronounced within LMICs, where two-thirds of the global burden of cancer mortality exists (International Agency for Research on Cancer 2008).

The increased stringent use of patents has been argued to be a key driver for this increased cost of cancer care. A patent grants a temporary legal monopoly on a product to provide a return to expenditure on the research and development embodied in that product, as a form of payment for knowledge generation. Without this, the public good characteristics of such knowledge would mean that the product could be easily replicated, and thus no market incentive would exist to produce it. The higher price that can be charged during the patent period is therefore supposed to reflect the incorporation of the high fixed costs related to the process of research and development surrounding new chemotherapeutic compounds. The concern is that patents are used to generate a much larger gap between the actual medicine price and the price required to recoup these research and development costs, thus generating 'super-normal profits.' It is certainly true that patented medicines are priced several times higher than equivalent generic prices. For example, in China, some patented medicines are priced at 18 times that of the lowest generic price (Sun 2004). Similarly, patented cancer medicines in Thailand are between 3 and 35 times higher than generic equivalents sold in India (Ministry of Public Health 2008). In

Kenya and Guatemala, the price of fluconazole is the same as in the US, at US$12.20, whereas the generic version produced in Thailand is only US$ 0.29 (Perez-Casas, Chirac et al. 2000).

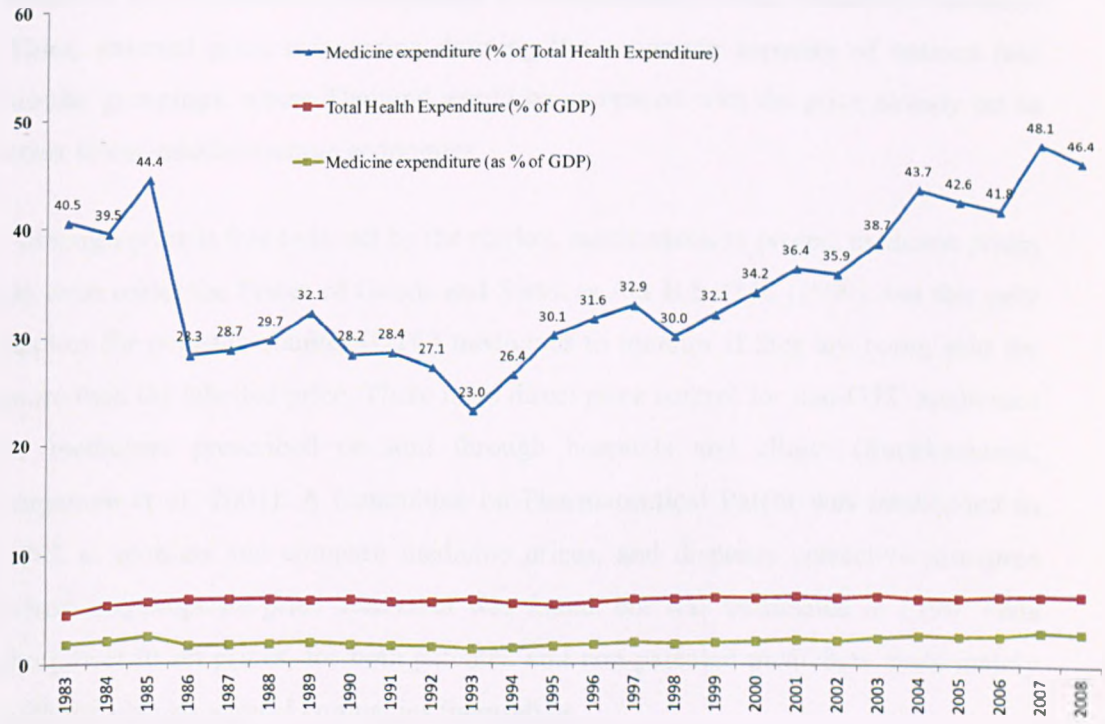
This concern over the impact of patents on price led the Thai Ministry of Public Health (MOPH), in 2008, to issue CLs for four anti-cancer medicines: letrozole, docetaxel, erlotinib and imatinib (Ministry of Public Health 2008). However, this was criticised by pharmaceutical companies on the basis that, unlike HIV/AIDS where previous CLs were issued, cancer, as a non-communicable disease, was not seen to constitute a national emergency, as required under the TRIPS Agreement (Johnson 2011). From the survey of attitudes towards the CL, it was also found that Thai and international respondents who were decision makers, health workers, academia and activists agreed significantly less with the issuance of CL on anti-cancer medicines than on HIV/AIDS medicines (Yamabhai, Mohara et al. 2009). It is also not clear to what extent the patent actually affects price (and hence the benefit to be derived from issuing a CL) since half of cancer medicines selling in Thailand in 2008 were not patented; despite this they remained expensive. As policy concerning medicines appears to be largely driven by an assumption that price is the major determinant of access, and that price is largely determined by patent status, it is critical to determine the extent to which price is actually determined by patent status, as if it is not, then CL may be an inappropriate policy lever, possibly leading to more harm than benefit. If it is the most significant determinant of price then this confirms the importance of measures focused on patents (subject to the discussion in chapter 5 on wider implications).

This chapter is organised as follows. An overview of the Thai medicine pricing system and the empirical evidence concerning the impact of patent on price is presented in sections 2 and 3 respectively. In section 4, the methods used in this study are outlined, including the variables and model employed. The results of an estimation of patent and other market characteristics impact on price are provided in section 5, and section 6 concludes.

3.2. The Thai medicine price setting system

In 2006, the Thai pharmaceutical market was valued at US$ 2.75 billion, accounting for 0.35% of the world pharmaceutical market,[8] with a 10-13% annual growth rate (Hill and Chui 2009; IMS Health 2010). As shown in Figure 3.1, medicine expenditure accounted for 46% of overall health expenditure in Thailand in 2008, which is rather high compared with similar countries, or even developed countries, where medicine expenditure accounted for some 12% of total health expenditure in the United Kingdom, 14% in the USA and 21% in Japan (OECD. Stat 2011). Regarding sources of medicine expenditure, the greatest proportion was from the household sector (58%) (Wibulpolprasert 2011).

Figure 3.1 Overall health and medicine expenditures in proportion to GDP and proportion of medicine expenditure to health expenditure, 1995-2005



Source: Thailand Health Profile (2009)

The Thai medicine market depends heavily on imports. The proportion of imported medicines has been increasing gradually from 30% in 1992 to 60% in 2006

[8]Valued at $773 billion in 2008.

(Wibulpolprasert 2007). At present, a system of patent linkage, linking patent status and the registration of medicines, has not been implemented in Thailand; as a result, it is difficult to estimate the proportion of patented medicines contained in imported medicines. With respect to oncology medicines more specifically, 99% were imported in 2008, with a market value of US$342 million, which accounted for approximately 7% of the total value of medicines consumed in the Thai market.[9] Patent requests were made for around 64% of those oncology medicines that were already patented in the USA or Canada.[10]

Generally, medicine pricing in Thailand is freely set by product owners, with free competition among medicines under the same category. In setting this price on entry to the Thai market, three main factors are suggested as being involved in the decision (PReMA). First, the costs incurred in bringing the product to market, from production to marketing. Second, an analysis of the value of the new medicine in terms of its incremental effectiveness in comparison to other available therapies. Third, external price referencing defining the economic capacity of nations into similar groupings, where Thailand would be compared with the price already set in other lower-middle-income economies.

Although price is free to be set by the market, mechanisms to protect medicine prices do exist under the Prices of Goods and Services Act B.E.2542 (1999), but this only applies for over-the-counter (OTC) medicines to monitor if they are being sold for more than the labelled price. There is no direct price control for non-OTC medicines or medicines prescribed or sold through hospitals and clinics (Supakankunti, Janjaroen et al. 2001). A Committee on Pharmaceutical Patent was established in 1992 to monitor and compare medicine prices, and dispense corrective measures where inappropriate price behaviour was found, but was terminated in 1999. Thus the power to set prices, for both patented and non-patented medicines, rests mainly with the pharmaceutical companies themselves.

Strong guidance from the government for the purchasing of medicines, however, is found. For example, reference pricing systems and co-purchasing have been introduced to encourage generic medicine procurement and to ensure that medicines

[9] Authors' calculation based on IMS data
[10] Chapter 2 results

are obtained for the minimum price (Lerttiendamrong, Tangcharoensathien et al. 1998; Jirawattanapisal, Kingkaew et al. 2009). The MOPH also has policies to indirectly control medicine prices and expenditure in the public sector. The NLEM was developed and individual public hospitals in Thailand are encouraged to purchase medicines from this list. However, many new chemotherapy medicines are not listed there since the prices are not deemed to be affordable by the government (Ministry of Public Health 2008). Cancer patients will therefore need to pay out of their own pocket for non-NLEM medicines, shown in appendix 5. Another related policy ensures that at least 80% of the medicine budget allocated to public hospitals must be used to purchase from the Government Pharmaceutical Organization (GPO), unless the GPO's price is 3% more expensive than private suppliers, which further encourages generic usage.

In conclusion, Thai cancer patients depend heavily on imports. Although patented and monopoly medicines are expensive, there is an absence of direct regulatory and procurement measures to control price, and indirect measures are used instead. Although it is suggested that pharmaceutical companies set prices according to cost, cost-effectiveness and international reference, it is not clear how patent rights are utilised in setting medicine price. Inspite of market power also depends on the existence of therapeutic substitute products that may offer patients an alternative medical treatment, in the Thai market, where the government does not intervene in price determination, a patent may provide substantial market power to set the price far above that indicated by the three factors mentioned above.

3.3. Extensive literature review: patents as a determinant of medicine price

An extensive literature review was performed to assess the scope of empirical research that had examined the role of patents as a determinant of medicine price. A three stage strategy was used to search and select articles to be included in the literature review. First, a computerized search using multiple keywords across four databases: namely Econlit, Embase Classic and Embase, Global Health and OVID Medline, as the most relevant to public health and economics (see Appendix 4 for further detail of searches). Second, the results from stage 1 were then filtered for publications reported in the English language and published between 1 January 1990 and 31 December 2011 to cover the implementation of international patent

protection in 1995. Finally, the reference lists of those articles retrieved for final review were manually searched, especially for grey literature, including technical reports from government agencies or scientific research groups, working papers from research groups or committees and white papers.

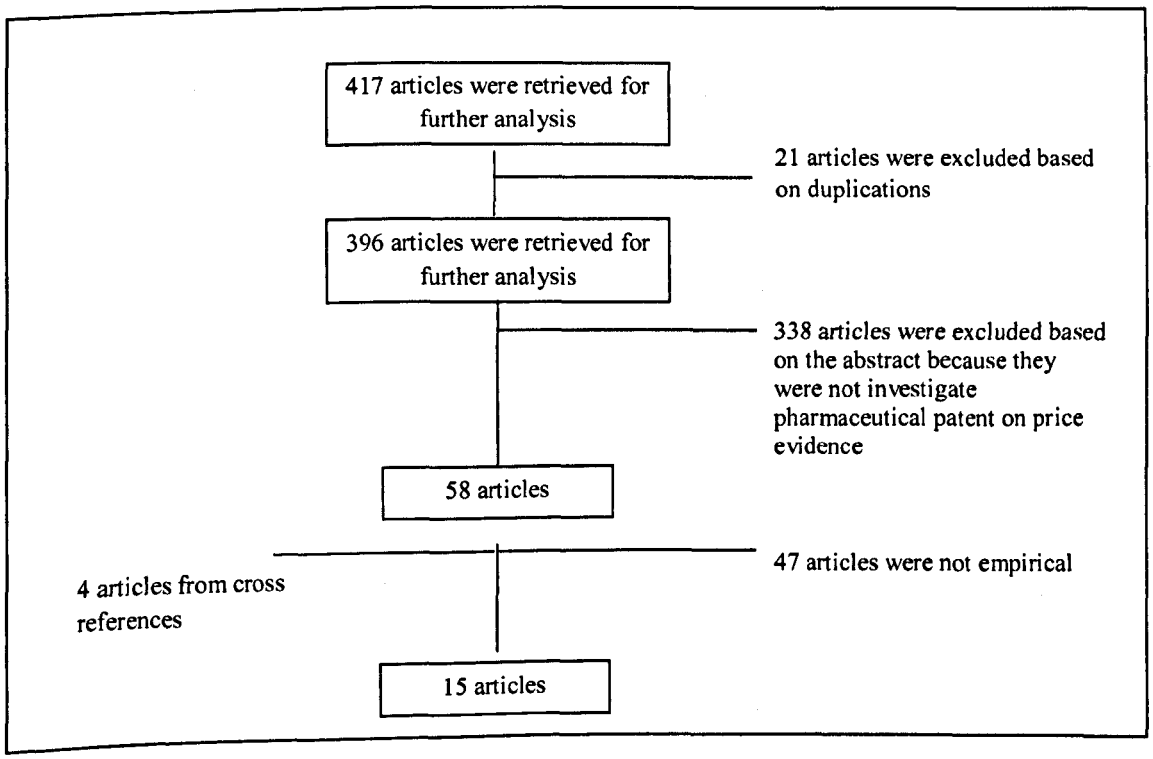
The search resulted in 417 potential articles for the literature review. All these articles were entered in to a Microsoft Excel database that contained each article's reference, setting (i.e. medicine therapeutics, year conducted and countries), objectives of studies, the statistical method used for data analysis and the conceptual model and explanatory variables included in the analysis. Two criteria were then used to select potential studies for full review. To be included in the literature review, a study had to:

1. Deal empirically with the implications of pharmaceutical product/processpatent on price. Studies dedicated to other types of innovations (i.e. motor vehicles, electrical equipment innovations, etc.) and to other types of implications (i.e. access or research and development) were not retained.
2. Include an empirical study, allowing for both descriptive statistics and econometric methods. Theoretical and conceptual studies as well as discussion studies were not retained.

3.3.1 Extensive literature review: results

The combined searches and other data sources found 417 potential titles. After the exclusion of duplicate publications, 396 abstracts were left for analysis, as outlined in figure 3.2. Applying the above two criteria to title and abstract review yielded exclusion of 338 papers which did not meet the first inclusion criteria, i.e. not investigating patent impact on pharmaceutical price. Further review of the remaining 58 full papers led to the exclusion of 47 articles which did not meet the second inclusion criteria above (e.g. discussion of the effect of patent on price).

Figure 3.2 Flow-chart of literature review



This left a total of 11 studies which matched both criteria. The bibliographies of these publications were then examined for additional relevant studies, which resulted in four additional studies included, making total of 15 articles for review. Table 3.1 gives the characteristics of these 15 studies included in this analysis.

Table 3.1 General characteristics of included studies

No.	Authors and Reference no.	Study period	Setting (Country/ medicines)	Objectives	Patent impact	Study type	Method
1	Watal (2000)	1985-1992	India,22 patentable medicines in mailbox (varied in wide therapeutic areas)	The effect of product patents, price control and CL on medicine prices and welfare.	+26-+242%	Demand function estimation	Comparing effect from different demand functions, the constant elasticity demand and the linear demand function, and estimation price as the composite of demand function.
2	Fink (2004)	1992	India, two therapeutic groups, quinolones and synthetic hypotensives	The impact of product patents on medicine price and pharmaceutical company's profit	+30-+277%	Demand function estimation	Modelling a demand function as two-stage decision-making process (chemical entity and brands under that chemical entity). Then estimating price and profit under each substitution elasticity among chemical entities and among brands.
3	Kessomboon et.al. (2010)	1992-2042	Thailand/ all medicine spending	To assess the impact of the TRIP-Plus proposal, patent extension and data exclusivity, of Thai-US Free Trade Agreement on access to medicines	+32-+67%	Demand function estimation	The Model of Impact of Changes in Intellectual Property Rights (MICIPR) comparing two specific scenarios, baseline (TRIPS) and TRIPS-Plus scenarios. It is based on assumption of constant price different between two scenarios, a constant price elasticity demand function, constant market share entire product life and constant market share of domestic and the innovative industry. The model then calculates impacts on expenditure of each scenario.
4	Grabowski and Vernon (1992)	1983-1986	USA, 18 expired patent medicines	The pricing and competitive behaviour after patent expiration	+7% one year and +11% in two years after patent expiration	Observational study and Regression analysis	Descriptive statistics of price index of overall market, original medicine and generic medicine. Regression of the determinant of generic entry

No.	Authors and Reference no.	Study period	Setting (Country/ medicines)	Objectives	Patent impact	Study type	Method
5	Griliches and Cockburn (1994)	1987-1990	USA, two anti-infective drugs: cephalexin and cephradine	The pricing and competitive behaviour after patent expiration	+60% in three years after patent expiration	Observational study	Calculation of the aggregate price indexes for a simple two-goods world where consumers buy either the brand or the generic version of a drug
6	Challu (1995)	1987-	Italy, 38 medicines	The impact of the 1978 patent law change	+163% compared to pre-1978 price	Observational study	Comparing new drug prices in Italy before and after the 1978 patent law. Using US prices as a reference
7	Boersma et.al. (2005)	1996 to 2001	The Netherlands, three medicines which patents expired between 1996 and 2001	To observe price and share prior to and after patent expiration.	+51-+69% in one year after patent expiration	Observational study	Trend analysis of volumes and price (measured as defined daily doses (DDD) prior to and after patent expiry were calculated.
8	Jones et al. (2001)	1981-1994	Canada, 82 medicines from the British Columbia Pharmacare Programme.	The impact of the Canadian Patent Act in 1987 on price	Make price index pre-1987=0.940 Post-1987=1.057	Observational study	Descriptive statistics of prices before and after 1987 and log regression of generic market share, one factor, to predict market price
9	Supakankunti et. al. (2001)	1987-1998	Thailand, six therapeutic categories were chosen to represent the patented market	The effect of new patent law on price	Nominal value show stable and likely to decrease	Observational study	Since the Thai patent law was changed in 1992 and there were no patented medicines at the time of study, medicines included in this study were monopoly medicines that suspect that the owners would file for patent protection once the patent law allow.. Descriptive statistics were used to report the price movement or trend of real price and nominal price of branded and generic medicines.

No.	Authors and Reference no.	Study period	Setting (Country/ medicines)	Objectives	Patent impact	Study type	Method
10	Suh et al. (2000)	1984-1987	USA, 35 chemical entities which patents expired between 1984 and 1987	The effect of generic medicine entry on price after patent expiration	+5% in 1 year +20% in 3 years after patent expiration	Observational study and Regression analysis	Descriptive statistics of price after patent expiration and analysing the influential factors that affect price, which are number of multiple-source medicine, market growth, market size, profitability, severity of illness, duration of treatment, number of year after patent expiration.
11	Limpananont et. al. (2004)	2001-2004	Thailand, antiretroviral therapy medicines	Price differences of patented and generic medicines	+150-+300%	Observational study	Comparing and calculating price ratio of patented and generic DDD prices
12	Magazzini et al. (2004)	July 1987-December 1998 (Quarterly data)	USA, UK, Germany, and France, all medicines which patents expired within study period	Price and determinant of price after patent expiry	-5%-+5% -20%-+10% (3 years after patent expiration)	Observational study and Regression analysis	Descriptive statistics of prices before and after patent expiration. Regression of the price with controlling of market share of patented products, market size, % of sales to the hospital segment, the average market growth, the number of brand names, ratio of the average price of original products, etc.
14	Borrell (2007)	1995-2000	34 low and middle income countries in 14 antiretroviral therapy medicines.	The impact of patents on medicine bundle prices across developing countries	+16-+70%	Regression analysis	Developing a price function as a composite function of number medicines in patent and non-patent systems, number of generics after patent expiration, number of doses per day, efficacy, adverse reactions, number of year in the US market
15	Kelton et al. (2008)	2001-2002	USA, 5,000 individual drug products purchased by the Buyer during 2000 to 2001	To determine factors associated with percentage of change in price	+78-+86%	Regression analysis	Dependent variable is price change. Explanatory variables are brand, dummy variables of shortage 2000-2002, dummy variables of patent expiration in 2000-2002 and log of expenditure.

Fifteen studies looked at the effect of patent on price, including two Thai studies. Most focussed on the patent expiration effect in the USA. Overall, patent protection appears to increase price by around 26%-277% depending on which of three approaches to estimation is used. The first method uses elasticity of demand to calculate price. Most studies have used this method to estimate the likely effects of patents on the price of medicines not currently under patent protection but eligible to be once TRIPS was introduced, and then extrapolated the results of this exercise to the situation of those medicines being under TRIPS obligations. By this methodology the entire patentable medicine price in India would increase by a mean of 26% with linear demand and 242% with constant price elasticity of demand (Watal 2000). Similarly, by accounting for different products through trademarks and advertising, this approach estimates that price would increase by 30-277% if these medicines came under patent protection (Fink 2004).

As an example, Kessomboon et.al. (2010) estimated the impact from TRIPS to the TRIPS-Plus obligation from the Thai-US Free Trade Agreement on price by using a model developed by Joan Rovira and jointly produced by the World Health Organization and the Pan American Health Organization. The paper is light on methodology, with heavy reliance on assumptions including a constant price difference between patented price and price under competition, and a constant price elasticity demand function. This model estimated that a 10 year patent extension would cause a 32% increase in the price index for medicines in Thailand. The impact could be as high as 67% when adding patent linkage and data exclusivity on patent extension (Kessomboon, Limpananont et al. 2010).

This approach would be useful if the price elasticity of demand is known and correct. For the pharmaceutical market, the consumption decision commonly involves participation by a physician and a third-party payer (government or hospital committee). The consumer may or may not bear some part of the price depending on a country's specific regulatory and reimbursement regimes. The pharmaceutical market's demand function is thus often distorted. Therefore, a model based on price elasticity of demand might not present the real world situation of the complexity of the pharmaceutical market. This is also not appropriate for analysing the current situation in Thailand, as stronger patent protection has been implemented since 1992,

and there seems to be no effect from the introduction of product patent protection at this time on the price of patentable medicines in the market before 1992 (Supakankunti, Janjaroen et al. 2001).

Second, the observation of price before and after patent expiration is used to infer the price effect of patent protection. The maximum price reduction was found in the Netherlands, where the price fell by 51-69% after patent expiry, compared with the last year of patented price (Boersma and et al. 2005). Less reduction was found in Germany, the UK and France; three years after patent expiration the price index decreased approximately 20% in Germany and the UK while for France the price index was stable. Conversely, two US studies showed that an original product can have an increase in price of 7% after one year and 11% after two years following generic entry (Grabowski and Vernon 1992; Suh, Manning et al. 2000). Another study showed a 60% price increase after three years expiration while the generic price decreased by 30% (Griliches and Cockburn 1994). However, the effect in each country will differ since each nation has a different medical tradition, policy for financing and supporting generic entry and brand royalty of physicians, pharmacists and customers. The marketing strategy of pharmaceutical companies also differs, and often they spend more heavily on advertising intensity once the patent has expired which could explain at least some of the price increase. Nonetheless, the evidence is equivocal.

This approach is also not suitable for the current Thai situation since product patents have been allowed since 1992, so the first product patent expiration will not happen before 2012. Moreover, while these studies are able to isolate the likely impact of patent enforcement on prices, they are limited by the fact that they do not provide any sense of the magnitude of the patent effect, and there may be selection bias concerning medicines analysed, reducing generalizability (i.e. price sensitivity is not equal across every medicine). Only three studies were able to assess the impact with or without (before-and-after) patent introduction concurrently with market competition from generic medicine. One study in Thailand compared the price of patented and generic HIV/AIDS medicines from 2001-4 and found that the patented price was approximately 1.5-3 times higher than the generic price in 2001 (Jiraporn Limpananont, Vithaya Kulsomboon et al. 2004). The experience in Canada and Italy corresponds with that in Thailand. A study of the impact of the 1987 Canadian

Patent Act, delaying the exercise of compulsory licences to manufacture and/or import the patented pharmaceuticals , found that after 1987 medicine prices, in general, increased relative to pre-1987 prices (Jones, Tanya et al. 2001). Similarly, after a patent law in Italy came into effect in 1978, new medicine prices were 163% higher than new drug prices before 1978 (Challu 1995).

Third, studies perform regression analysis of possible explanatory factors on medicine price, of which patent status is one factor. One study estimated the impact of patent protection of 14 ARV molecules in 34 low- and middle-income countries which have different patent systems, where patenting was eligible or ineligible between 1995 and mid-2000. This showed that combination therapy containing at least one patented medicine was on average priced 70% higher than combination therapy containing only generic medicines. Combination therapy containing at least one original medicine were priced 16% higher than local copies even when introduced in no-patent systems (Borrell 2007). However, these studies did not include market characteristics, showing supply and demand factors which are major determinants of price, in their models. The consequences of not including a relevant independent variable in the model are that OLS regression generally produces biased and inconsistent estimates.

From three approaches employed in previous studies, multiple regression analysis is the most reliable since it allows researchers to establish objective measures of relationships between independent and dependent variables. However, previous literature shows the importance of regression analysis including independent variables that consist of relevant variables that determine price to avoid omitted variable bias.

3.3.2. Research gap

The literature review revealed that little empirical research has been undertaken on the extent to which patent rights affect price. Most studies that are undertaken investigate price after patent expiration. The setting of these studies are very mixed, across therapeutic areas and medicines. The literature generally shows that the size of impact varies across a huge range, depending on what methods are employed in the studies. Current evidence therefore makes it difficult for a country, such as

Thailand, to come to a conclusion on advice to national policy makers to make decisions which trade-off health or access impacts with wider economic issues. The high price of medicine may not be related to patent rights. Furthermore, price may not be related to access either. This latter issue is tackled in chapter 4, and the former in the remainder of this chapter. This paper adds to the literature in several ways: (i) it is an empirical study on the impact of patent on price concerned with a non-communicable disease, cancer; (ii) it is focussed specifically upon Thailand, which is a unique case study as patent law was changed to comply with TRIPS obligations at a very early stage and there is no price control or government committee to monitor patented price; and (iii) it incorporates a series of demand and supply factors, in addition to patent, as explanatory factors.

3.4. Methodology

This study seeks to assess the relative impact of patent status as a component of pharmaceutical prices while controlling for other factors. In general, patenting gives the patentee an exclusive legal right authorising monopoly power to set price much higher than the marginal cost. However, as with other products, medicine price also depends upon other supply and demand factors. From the literature review discussed previously, some common factors of note in setting medicine prices were identified: therapeutic value of the new compounds (degree of novelty), manufacturing cost, market share, price control system, tax, exchange rate, patent system and patent duration, purchasing power and willingness to pay, reimbursement, and substitutes. These factors drive the conceptual model underpinning the analysis conducted here, as outlined below

3.4.1 Price determinants: conceptual framework

Pricing behaviour is a complex issue, and one which is highly dependent on manufacturing, marketing, and distribution costs, medicine characteristics, market competition characteristics and the economic goals of the parent company (Monaghan and Monaghan 1996). Economic theory suggests that in regular markets important determinants of price relate to a series of supply and demand side factors. From the supply side, there are four important factors determining price. First, increasing competition may lead to lower price. This factor reflects the availability

of substitute goods: the more and closer the substitutes available, the cheaper the price is likely to be. If no close substitutes are available, the supplier of a product has more flexibility over the price they can charge. Scholars testing the influence of the number of competitors on medicine price have indeed found that a higher number of competitors leads to a lower price (Pérez-Casas, Herranz et al. 2001; Kanavos, Costa-Font et al. 2008), and that increasing the number of substitutes from one to two leads on average to a 38% reduction in the price and increasing from two to three to a 19% reduction (Lu 1993).

Second, the product age (the number of years that the product has been on the market). This factor is used to represent the therapeutic effectiveness, assuming that more recent compounds are generally more effective. The newly introduced medicine, displaying improvements in efficacy compared with existing ones, will be priced at a premium. This variable may also reflect life-cycle pricing strategies in unregulated markets and age-related regulation. With increasing years on the market, the supplier may decrease the price in order to cover the mature stage of the product life-cycle; Danzon and Chao, for example, found a sharp decline of price with molecule age (Danzon and Chao 2000). However, although some evidence suggests that longer product life is associated with lower price (Kanavos and Vandoros 2011), other evidence finds no evidence that product age has an impact on price (Berndt, Griliches et al. 1992). This might be because of the different setting and treatment of variables.

Third, recent studies have focused on the impact of the number of medicines presented on price (Reiffen and Ward 2005; Regan 2008). The number of forms or strengths available provides the prescriber with greater flexibility to prescribe the product that most suits their patients'need. Recently, Ellison and Ellison (2007) have suggested the use of presentation proliferation as a strategic tool of entry deterrence. By increasing the number of presentations available the branded firm increases the cost to the generic entrant of reproducing the entire product line thereby deterring entry, which allows the branded firm to charge a higher price (Ellison and Ellison 2007). Fourth, the cost of production. It is recommended that price should be determined at least in part by the cost incurred during the manufacturing process (Mrazek 2002).

Demand side factors also determine price level. The higher the sales volume (the higher the number of cases) the lower the drug price (Hornbeck 2005). Scherer and Watal found that drug prices decreased with the number of HIV/AIDS cases, although the magnitude of the effect was small (Scherer and Watal 2005). With respect to quality-adjusted price, therapeutically innovative medicines are found to be priced higher than existing substitutes (Weston 1982; Lu 1993).

On the basis of existing literature and in order to study the determinants of medicine price, a price function was developed. Here prices are assumed to be set by profit-maximizing firms, taking the effects of supply and demand and patent rights into consideration. This price determination function is depicted in equation (1):

$$P = f(S, D, Pa) \quad (1)$$

where price, P, is a function of the supply characteristics, S, demand characteristics, D, and the nature of monopoly right, whether on- or off-patent (Pa).

3.4.2 Literature review: medicine price determinants

From the papers reviewed, it appears that medicine price, in general, depends on several supply and demand factors. For example, therapeutic advantage and number of substitutes are significant price determinants; as the number of substitutes increased in one study from one to two there was an average 38% decline in the ratio of the new drug price to the average existing market price (Lu and Comanor 1998). Kanavos and Vandoros (2011) also found that product age has a significant and negative effect on prices (Kanavos and Vandoros 2011). However, there are some variables absent, such as the prescribing patterns of doctors, tax, exchange rate, reimbursement and subsidy, and duration and conditions for exclusive rights. Based on the literature review, Table 3.2 lists factors that have been shown to influence price. These influenced factors will be described in detail in the next section.

Table 3.2 Key factors influencing medicine price and correlation sign.

Influence factors	Correlation sign	References
Therapeutic value of the new compounds, product efficacy or less adverse effect	+	(Lu 1993; Danzon and Chao 2000; Borrell 2007)
Molecule age, representing a novelty or high efficacy of new molecule and pricing strategy by product life cycle	+/-	(Innovation ; Danzon and Chao 2000; Kanavos and Vandoros 2011)
Number of forms as showing choices and convenience available to patients	+	(Danzon and Chao 2000; Reiffen and Ward 2005; Regan 2008)
Number of competitors	-	(Danzon and Chao 2000; Suh, Manning et al. 2000; Adriaen, Witte et al. 2007; Kanavos, Costa-Font et al. 2008; Regan 2008)
Manufacturing cost	+	(PReMA)
Market share, market concentration and market power	+	(Suh, Manning et al. 2000)
Price control or reference price system	-	(Danzon and Chao 2000; Kanavos, Costa-Font et al. 2008)
Country mean income, purchasing power	+	(Borrell 2007)
Price control policy, reimbursement and subsidy	-	(Adriaen, Witte et al. 2007; Kanavos, Costa-Font et al. 2008)

3.4.3 Data and Sources

As described in chapter 2, all medicines in the therapeutic class of oncology were retrieved from the Monthly Index of Medical Specialities (MIMS) Thailand database, and these were then confirmed against the Thai FDA to verify the availability and completeness of medicines marketing in Thailand in 2008, when this study was conducted. At this time there were 88 chemical substances, contributing to 249 products in 418 forms for oncology treatment. These medicines are categorised into four therapeutic groups: cytotoxic chemotherapy, hormonal chemotherapy, immunological chemotherapy and supportive care therapy. For each medicine, price data and other data related to pricing behaviour were collected from various sources described in the following section.

Dependent variable: Price

The price data for all oncology medicines in 2008, in each form, were obtained from the Intercontinental Medical Statistics (IMS) Health database. This database provides retail pricing for over-the-counter medicines at drugstores and wholesale prices at hospital, as well as sales volume, date of launches and market growth for all instances of a medicine. Price at the hospital level was chosen for the analysis since the hospital is the major channel for medicines in Thailand, accounting for 71% (IMS Health 2012). IMS price is calculated form the results of a survey of purchase price from 276 general and 22 specialized hospitals.

Alternative sources of medicine price at hospital level are FDA and DMSIC, however both sources have limitations. FDA provides manufactured or imported price reported by product owners. This ex-factory price from FDA is surprisingly higher than the wholesaler price, showing the transfer pricing strategy of MNCs. The second source, DMSIC, also provides the purchase price facing government hospitals; the limitations of different standards of drug identity codes makes it impossible to have a comprehensive list of medicine price and volumes through this route. Also, it is set up by voluntary basis; there are no rules and regulations that government hospitals have to submit purchasing price to DMSIC or any government authorities. Large hospitals which are likely to have procurement of oncology medicines do not follow the system (Holloway ; Tangcharoensathien 2008).

Therefore, the sample size of DMSIC database is relatively small and many medicines are 'missing'.

It is said that price data from IMS are audited and adjusted to represent the whole market (Joncheere 2003). The limitation of IMS price is that the price at hospital level does not include mark-up by hospital; however, the majority of patients who are insured will received medicines free at the point of delivery. As a result, price from the IMS database is the most standardized data available and will be used in this study.

This private database provides retail pricing, sales volume, date of launches and market growth for all instances of a medicine. Price is the retail price set by the pharmaceutical company. However, patients or hospitals may not actually pay that price. Free-cost medicines, medicines provided without payment, are a common practice; however, it would be extremely difficult, if not impossible, to determine the exact buying price of hospitals. This data are the most standardized data available for price.

Prices were calculated on the price per daily maintenance dosage adapted from the defined daily dose (DDD) as suggested by WHO guidelines (WHO 2011). The DDD is an average dose per day for a medicine used in adults to standardize the comparison of medicine usage between different medicines or between different health care environments. However, the data for DDD is not available for anti-cancer medicines, since treating cancer patients, for the majority of chemotherapy drugs, is dosed based on body surface area (BSA) or the patient's weight. As a result, the cumulative dose received during treatment in cycles needed were calculated based on the average BSA at 1.51 m^2 and patient's weight at 60.88 kg (Sinawat and Chiyabutra 2004; Nedphokaew, Aphinives et al. 2007).

The recommended dose for each medicine in each indication was retrieved from MICROMEDEX, a database of drug indication, dosage, interactions and side effect information. It covers all FDA approved medications. Based on this information, the cumulative dose received during the cumulative number of days that the patient received that medicine was estimated. The price per daily maintenance dose was computed at the average daily dose and at product level using the volume-weighted

average of all forms available in 2008. There were 88 active ingredients contributing to 249 products in 418 forms. In each product, price was calculated at a weighted average price; therefore, it has 249 observations (sum of a product of quantity and price of each strength divided by quantity).

Explanatory variables

Patent information for each medicine was obtained from the patent survey presented in Chapter 2. As indicated in table 3.3., the cytotoxic chemotherapy group appears to have the largest number of patented medicines; 21 patented medicines or 23 medicines likely to have patent protection out of 58 medicines. The group of supportive care therapy is found to have six patented medicines and there are four patented medicines in the hormonal chemotherapy group. For the immunological chemotherapy group, although there is no patented medicine based on patent information available, it is likely that two medicines are on-patent medicines since they have monopoly status and are under patent protection in the USA and Canada. To sum up, there are 27 patented medicines and seven medicines that are suspected to have patent protection. From the patent data available, patent expiry date was collected and was estimated as the number of years to expiry; from this the average patent life from 2008 is estimated to be 11.30 years. In general, a product that has monopoly rights would use a high price initially to recoup the investment (Ferrell and Hartline 2011). Borrel (2007) also confirm this pricing strategy of HIV/AIDS medicines in developing countries (Borrell 2007).

It is hypothesized that a patent shifts price up, and that price is also higher the greater the number of years remaining of patent protection. Therefore the null hypothesis is that there will be a significant positive association between patent status of medicines, or number of years of patent remaining, and the price.

Table 3.3 Number of oncology medicines in each therapeutic group by monopoly and patenting status

Therapeutic group	No. Of medicines	Patented medicines	Patent information not available	Average years to expiry
1. Cytotoxic Chemotherapy	58	21	2	11.4
2. Hormonal Chemotherapy	14	4	3	11.5
3. Immunological Chemotherapy	7	-	2	-
4. Supportive Care Therapy	9	6	-	10.83
Total	**88**	**27**	**7**	**11.30**

Data concerning other supply and demand side characteristics of the market were obtained from IMS. The IMS provides launch year, market growth, sales and sales volume of each product across all its versions available in the market. These data allow calculation of product age, market size and number of competitors in each active ingredient. To avoid the duplication of number of competitors in the same active ingredient, the patented medicines were checked and found that there was only one seller in each patented medicine.

The marginal cost of production represents the complete process of production and cost of material in manufacturing. Generally, in a perfect market, one could expect that entry and competition would push generic medicine prices down to a level approaching the marginal cost of production. Some studies have therefore employed the lowest unit cost of a generic medicine on the market as a proxy of marginal cost (Grabowski and Vernon 1992). However, often there is no generic competition on the domestic market since the market is protected by a patent. Therefore, the Indian procurement price was selected as a benchmark to represent the marginal cost variable. This is because not only is India a leader in generic medicine production, but medicine pricing in India can also represent the manufacturing cost with

exclusion of monopoly right exercised on price since, prior to 2005, there were no product patents on Indian medicines, just process patents. Indian pricing, with adjustment for the same strength, was mainly obtained from the Tamil Nadu Medical Services Corporation Ltd., (TNMSC) (TNMSC 2010), a public sector organisation in India with the primary objective of ensuring the availability of essential medicines in government medical institutions. For medicines not available from this source, the average price from Medindia[11] was used. The average exchange rate for 2008 at 0.82 Baht per Indian Rupee was used to convert into Thai currency.

The price of a medicine should, in theory, represent the marginal health gained from taking that medicine. Quality-adjusted life years (QALYs) are a measure of health in terms of length of life and quality of life. The QALY has been widely used to value the benefits of interventions as they provide a single index of outcome for use in cost-effectiveness analysis. Although treatment as chemotherapy can extend life for a period of time by killing or stopping the process of cancer cells growth, it does create adverse side effects to health at the same time. Since the QALY is a function of life extension and quality of that life, QALYs gained is a good proxy to represent both life year gained and adverse effects. However, the availability of 'QALY gained' is scarce. Information concerning other outcomes associated with medicines could add another level in the search for the relationship between quality and quantity of life obtained from that treatment. Defining the benefit of anti-cancer medicines is challenging since surrogate outcomes have not always been established (Vera-Badillo, Al-Mubarak et al. 2013). The amount of time a new drug prolongs life was found as the most important factor in choosing among treatment options (Hare J 1992). It is also found that medicine price is determined by life-prolonging; a longer life-extension treatment, considered high value, would be priced higher (Martin 2010; Kantarjian and Zwelling 2013). Life years saved (LYS) is thus chosen to be a proxy for the benefit of anti-cancer medicines.

Chemoherapy has a range of side effects that depends on the type of medications used. Nausea and vomiting are common side effects that can frequently be reduced or eliminated with less costly self-care measures. This study includes two severe complications of chemotherapy, neutropenia (low white blood cell counts) and

[11]http://www.medindia.net/buy_n_sell/pharm_industry/ph_drugprice.asp

thrombocytopenia (low platelet counts), although some chemotherapy drugs can also cause damage to other cells, such as the bone marrow cells. It is expected that both of these indicators would have a negative impact on price since they are life-threatening and also costly to manage.

QALYs gained, life year gained and important adverse effects were selected to represent medicine characteristics. To avoid the problem of multicollinearity – since QALY combines quantity and quality of life – there would be interaction effects between QALY and LYS and side effects variables. Therefore at the analysis step, when choosing independent variables to include in the analysis, the QALY variable and LYS and side effect variables were chosen separately. For example, if QALY variable is included, LYS and side effect variables were excluded from that model.

Life year saved and Quality Adjusted Life Years (QALYs) gained were selected to represent the health benefit of taking the treatment while the probabilities of severe thrombocytopenia and neutropenia were selected to represent adverse effect. The number of life years saved and QALYs gained are expected to have a positive effect on the price of a medicine as they reflect the benefits obtained, and thus a higher QALY would imply, ceterus paribus, a higher price able to be set by the pharmaceutical company.

The Health Economic Evaluations Database (HEED) and Cost-Effectiveness Analysis Registry at the Centre for Reviews and Dissemination were databases used to find QALYs gained and life years saved which are gained when compared with best supportive care available on the market. Data for the percentage of severe neutropenia and thrombocytopenia were retrieved from DRUGDEX database which reports the percentage of adverse effect of particular medicines.

3.4.3 Model specification

A model of price as a function of factors indicated above was developed and data fitted to establish the relationship and the sensitivity of price to these different factors. Two factors related to the patent were whether or not there is a patent in place and, where there is, the number of years before patent expiration. The other selected factors consist of efficacy and adverse effect reduction (proxy of novelty),

Indian price (proxy of cost of production), quantity purchased, number of substitutes and market size. The final set combined in a multiple regression model, as illustrated below.

$$P_i = \alpha_i + \beta_i x_i + \varepsilon_i$$

Where P_i is the price for daily dose of medicine i, x_i is a vector of observable characteristics of the individual medicines (i.e. patent status, market share, sales, number of seller and form available, QALYs, etc.) and ε_i is the effect of the unobservable. The definitions of all variables are listed in Table 3.4. Price per daily dose, sales volumes and Indian price were transformed on a logarithmic scale, as this was more manageable as the data covers a large range of values. It also tends to convert exponential (compound growth) trends to linear trends to comply with linear regression analysis. Hence, the coefficient estimates are interpretable as elasticities, serving as an approximation of the elasticity of price to the interested variables (Wooldridge 2002; Dougherty 2011).

Table 3.4 Definitions of variables

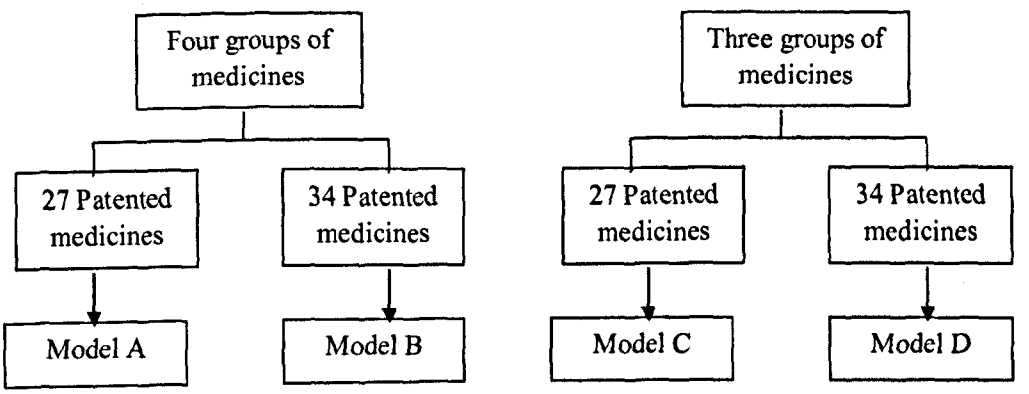
Variables	Description	Number of observation
Dependent variable		
Price per day	Log of price per average dose needed for one day.	249
Explanatory variable		
Patent status	1 for patented medicine and 0 for non-patented medicine	241
Patent expiry	Number of years to patent expiration	249
Log of sales volume		
Number of competitors	Number of sellers selling the product in the same active ingredient	249
Number of forms	Number of forms available for each brand name	249
Product age	Number of year that product has been on market, from the registration year to 2008	243

Variables	Description	Number of observation
Log of Indian price	Log of Indian price	194
Life year saved	Number of life year saved gained	54
Thrombocytopenia	Percentage of severe Thrombocytopenia event	170
Neutropenia	Percentage of severe Neutropenia event	109
QALYs	QALYs gained compared with best supportive care	57

There are two plausible options for analysis depending on the medicine group and patent information input in the model. As shown in table 3.1 there are four main groups of medicines used to treat oncology; however, the group of cytotoxic medicines is the majority of the sample, 160 out of 249 products. The sample sizes of hormonal therapy and immunotherapy are relatively small, 38 and 13 respectively. As a result, the analysis included these three groups together since they are all cancer treatments aiming to destroy or halt the growth of cells from dividing, multiplying and spreading throughout the body. The fourth group is supportive care therapy which is the prevention and management of the adverse effects of cancer and its treatment. It lightens the symptoms and complications of cancer and reduces or prevents toxicities of treatment. The analysis therefore has two options, including all four groups or including the three groups which aim to destroy cancer cells.

Another important scenario concerns the patent. Since patent information for seven medicines is unidentified, there are two possible alternatives in conducting the analysis: (i) analysing without those seven medicines with missing patent statuses; and (ii) analysing with an assumption that those seven medicines are patented medicines. The year of expiration for these seven medicines is calculated from the latest year of expiration in the USA and adding one more year for the patent application process. As a result, there are four different models, Model A to D, with mixed variables to estimate the price setting determinants, as shown in Figure 3.3.

Figure 3.3 Four models based on four different scenarios to analysis



For each model in Figure 3.3, different specifications were estimated to present a pricing equation reflecting the groups of relevant explanatory variables; market characteristics, medicine characteristics and market and medicine characteristics together. Since the variable of manufacturing cost was proxied by the Indian price, resulting in a biased underestimate of manufacturing cost, two specifications were estimated (model 1 and 2), inclusion and exclusion of the marginal cost variable. Model 1 represents the influence of market characteristics variables but excludes this marginal cost variable, whereas model 2 includes the marginal cost variable. The second group of specifications, models 3 and 4, representing medicine characteristics which separate QALYs gained and life years saved. The last group of specifications (model 5-8) include all explanatory variables, accounting for the different manufacturing cost and medicine benefit variables.

3.5. Results

A correlation test among variables was undertaken to avoid multicollinearity. Given linear model specification, it would be expected that there is an interaction between a number of forms and price and between product age and number of competitors. The correlations are small: -0.06 and 0.18 respectively. Also, when testing the model for the multicollinearity by variance inflation factor (VIF), the maximum mean VIF appears at the 7^{th} regression specification at 4.2 while the VIF values of other models were found at around 3. As a rule of thumb, if VIF values are higher than 10, then

there is a problem with multicollinearity and it needs further investigation(Kutner MH, Nachtsheim CJ et al. 2004).

Results for model A, outlining the determinants of price from most available patent data and including all four therapeutic groups, can be found in Table 3.5. In the first specification, sales volume and number of competitors have a negative and statistically significant coefficient at $\alpha = 1\%$. For example, a one percentage increase in purchased volume would decrease price by 0.2%, and entrance of a new seller would decrease price by 20%. As expected, patent status and product variety have a positive and significant effect on prices at the same level. Patented products are priced 190% higher than non-patented medicines. However the number of exclusive years left has an effect opposite to that expected. It seems the more patent life a medicine has, the cheaper it is; one year less in patent life leads to a price increase of approximately 5%.

The number of competitors has a negative and significant effect on price, as expected; only in the 7th regression specification is this variable not significant and this seems likely to be because of the small observation numbers. In general, if there is one more competitor, the price would decrease by around 13%-30%. The coefficient estimates on the number of forms available is positive and statistically significant in column 2 and 6 suggesting that the more variety in choices, the higher price. However, this variable is a more consistently significant regressor in models C and D. The estimated coefficient on product age is negative and statistically significant in the 2nd specification in model A and B and shows significance in the 1st and 2nd specifications in model C and D. This suggests that the longer the product is on the market the lower the price. However, the impact is minimal.

When the marginal cost variable was included in the model (Column 2), results remain very similar to Model 1. Although, the number of observations dropped to 182, the sign of every variable was unchanged and followed from theory. However, the magnitude of explanatory variables was less significant than the Model 1 results. The impact of patent on price dropped to 135%. Marginal cost has a positive significant impact on price: one percent increase of cost would increase price by approximately 0.2%. In the third specification, with a very small sample size , investigation toward how medicine efficacy and adverse effects affect the price of

medicines, suggests that life years saved has a positive and significant coefficient: one life year saved could increase price by around 90%. The event of thrombocytopenia has a negative, but not significant, effect on price. The percentage of severe neutropenia shows a positive relationship with price which is not as expected. With a small R^2 in model 4, QALYs gained has a positive correlation with price; however, this variable is not a significant price determinant. Surprisingly, rather than an adverse effect, neutropenia shows asignificant positive effect on price; a percentage increase in chance to severe neutropenia would increase price by 3-6%. This maybe because of the colinearity between neutropenia and thrombocytopenia (r=0.36).

When including both market and medicine characteristics, Models 5-8, some of the market characteristics turn out to be insignificant but still show the expected signs. Although Models 6 and 8 show high R-square, this is from a very small data set, determined by the availability of QALYs information, as shown in table 3.4. Most of the medicines included in these models are not patented medicines. It is therefore suggested that models 1-3 be seen as the core, most reliable, results.

For Model B, with the assumption of patent information, the results, as shown in table 3.6, show minimal differences to Model A. The number of observations increase and signs and significance level of each explanatory factor are similar to Model A. However, the percentage of thrombocytopenia now becomes a significant price determinant. When analysing data for only three chemotherapy groups (Models C and D), the results are almost identical to those of Models A and B, as shown in Table 3.7 and 3.8.

In conclusion, with regards to the effect of patent on price, monopoly rights protection from a patent for the particular medicine generates a price of patented medicines some 130-200% higher than medicines without a patent. This effect is statistically significant and shows an expected sign. However, pharmaceutical companies appear to use a penetration pricing strategy rather than skimming strategy as expected to launch new products in Thailand. Over time, as brand loyalty increases, the low introductory price is often raised. Price is negatively correlated with patent year left, as seen from the experience in the US(Grabowski and Vernon 1992; Suh, Manning et al. 2000).

Table 3.5 OLS coefficient (SE) of pricing regressions of Model A: four groups of medicines with patent information available

	(1) lnpddd	(2) lnpddd	(3) lnpddd	(4) lnpddd	(5) lnpddd	(6) lnpddd	(7) lnpddd	(8) lnpddd
Patent status	1.902***	1.355***	1.529***	2.001***	1.353***	0.957*	0.988**	0.338
	(0.583)	(0.390)	(0.320)	(0.569)	(0.387)	(0.564)	(0.410)	(0.565)
Years to patent expiration	-0.052	-0.059*	-0.048*	-0.007	-0.046**	-0.061*	-0.065***	-0.061
	(0.046)	(0.031)	(0.028)	(0.046)	(0.018)	(0.034)	(0.021)	(0.037)
Log of sales volume	-0.219***	-0.074*			-0.088	-0.255***	0.014	-0.099
	(0.042)	(0.043)			(0.065)	(0.066)	(0.060)	(0.063)
Number of competitors	-0.186***	-0.131***			-0.139**	-0.308***	-0.002	-0.199***
	(0.019)	(0.022)			(0.058)	(0.036)	(0.060)	(0.033)
Number of forms available	0.062	0.280***			0.253	0.394**	0.112	0.243
	(0.086)	(0.081)			(0.159)	(0.193)	(0.133)	(0.184)
Product age	-0.026	-0.039***			0.002	-0.010	0.015	0.013
	(0.016)	(0.014)			(0.033)	(0.040)	(0.030)	(0.033)
Log of Indian price		0.253***					0.310***	0.283***
		(0.045)					(0.106)	(0.087)
Life year saved gained			0.908***		0.523**		0.716***	
			(0.194)		(0.238)		(0.210)	
% of severe Thrombocytopenia			-0.022		-0.019		0.001	
			(0.016)		(0.011)		(0.009)	
% of severe Neutropenia			0.062***		0.037***		0.033***	
			(0.006)		(0.011)		(0.010)	
QALYs gained				0.371		-0.077		-0.003
				(0.225)		(0.158)		(0.126)
_cons	8.685***	5.903***	3.289***	5.448***	5.774***	9.988***	2.426*	6.724***
	(0.396)	(0.507)	(0.450)	(0.505)	(1.236)	(0.630)	(1.295)	(0.800)
N	232	182	43	54	40	51	39	42
R^2	0.458	0.600	0.883	0.135	0.905	0.829	0.927	0.889
adj. R^2	0.443	0.584	0.868	0.083	0.876	0.801	0.901	0.862

Notes: Robust standard errors in parentheses. Significant at (*) 10%, (**) 5% or (***) 1%

Table 3.6 OLS coefficient (SE) of pricing regressions of Model B: four groups of medicines with assumption for the missing patent information

	(1) lnpddd	(2) lnpddd	(3) lnpddd	(4) lnpddd	(5) lnpddd	(6) Lnpddd	(7) lnpddd	(8) lnpddd
Patent status	1.439***	1.448***	1.742***	2.065***	1.660***	1.058**	1.085**	0.248
	(0.509)	(0.387)	(0.390)	(0.581)	(0.440)	(0.504)	(0.465)	(0.551)
Years to patent expiration	-0.022	-0.076**	-0.043	-0.023	-0.061	-0.076**	-0.086**	-0.076*
	(0.040)	(0.034)	(0.051)	(0.048)	(0.043)	(0.034)	(0.041)	(0.038)
Log of sales volume	-0.225***	-0.082*			-0.153*	-0.283***	-0.015	-0.099
	(0.041)	(0.042)			(0.080)	(0.069)	(0.061)	(0.062)
Number of competitors	-0.182***	-0.127***			-0.160***	-0.304***	0.003	-0.192***
	(0.019)	(0.021)			(0.055)	(0.035)	(0.075)	(0.035)
Number of forms available	0.076	0.305***			0.309*	0.399**	0.120	0.216
	(0.090)	(0.080)			(0.176)	(0.193)	(0.144)	(0.179)
Product age	-0.026	-0.038***			0.003	-0.001	0.021	0.027
	(0.016)	(0.014)			(0.036)	(0.041)	(0.032)	(0.034)
Log of Indian price		0.256***					0.391***	0.310***
		(0.045)					(0.130)	(0.090)
Life year saved gained			0.645**		0.267		0.521**	
			(0.241)		(0.221)		(0.227)	
% of severe Thrombocytopenia			-0.029**		-0.018**		0.005	
			(0.013)		(0.009)		(0.010)	
% of severe Neutropenia			0.063***		0.030***		0.025**	
			(0.006)		(0.010)		(0.010)	
QALYs gained				0.267		-0.163		-0.026
				(0.251)		(0.188)		(0.145)
_cons	8.676***	5.861***	3.538***	5.534***	6.762***	10.189***	2.647*	6.568***
	(0.388)	(0.508)	(0.381)	(0.503)	(1.177)	(0.671)	(1.540)	(0.860)
N	240	186	46	57	43	54	41	44
R^2	0.451	0.596	0.815	0.124	0.857	0.810	0.904	0.883
adj. R^2	0.436	0.580	0.792	0.075	0.818	0.781	0.871	0.856

Notes: Standard errors in parentheses. Significant at (*) 10%, (**) 5% or (***) 1%

Table 3.7 OLS coefficient (SE) of pricing regressions of Model C: three groups of medicines with assumption for the missing patent information

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	lnpddd	lnpddd	Lnpddd	lnpddd	lnpddd	lnpddd	lnpddd	lnpddd
Patent status	2.395***	1.343***	1.529***	2.001***	1.353***	0.957*	0.988**	0.338
	(0.512)	(0.448)	(0.320)	(0.569)	(0.387)	(0.564)	(0.410)	(0.565)
Years to patent	-0.068*	-0.038	-0.048*	-0.007	-0.046**	-0.061*	-0.065***	-0.061
expiration	(0.035)	(0.031)	(0.028)	(0.046)	(0.018)	(0.034)	(0.021)	(0.037)
Log of sales	-0.250***	-0.086*			-0.088	-0.255***	0.014	-0.099
volume	(0.041)	(0.048)			(0.065)	(0.066)	(0.060)	(0.063)
Number of	-0.168***	-0.096***			-0.139**	-0.308***	-0.002	-0.199***
competitors	(0.019)	(0.020)			(0.058)	(0.036)	(0.060)	(0.033)
Number of forms	0.446***	0.391***			0.253	0.394**	0.112	0.243
available	(0.094)	(0.081)			(0.159)	(0.193)	(0.133)	(0.184)
Product age	-0.060***	-0.043***			0.002	-0.010	0.015	0.013
	(0.016)	(0.015)			(0.033)	(0.040)	(0.030)	(0.033)
Log of Indian price		0.334***					0.310***	0.283***
		(0.048)					(0.106)	(0.087)
Life year saved			0.908***		0.523**		0.716***	
gained			(0.194)		(0.238)		(0.210)	
% of severe			-0.022		-0.019		0.001	
Thrombocytopenia			(0.016)		(0.011)		(0.009)	
% of severe			0.062***		0.037***		0.033***	
Neutropenia			(0.006)		(0.011)		(0.010)	
QALYs gained				0.371		-0.077		-0.003
				(0.225)		(0.158)		(0.126)
_cons	8.620***	5.133***	3.289***	5.448***	5.774***	9.988***	2.426*	6.724***
	(0.400)	(0.591)	(0.450)	(0.505)	(1.236)	(0.630)	(1.295)	(0.800)
N	194	159	43	54	40	51	39	42
R^2	0.575	0.680	0.883	0.135	0.905	0.829	0.927	0.889
adj. R^2	0.562	0.665	0.868	0.083	0.876	0.801	0.901	0.862

Notes: Standard errors in parentheses. Significant at (*) 10%, (**) 5% or (***) 1%

Table 3.8 OLS coefficient (SE) of pricing regressions of Model D: three groups of medicines with assumption for the missing patent information

	(1) lnpddd	(2) lnpddd	(3) lnpddd	(4) lnpddd	(5) lnpddd	(6) Lnpddd	(7) lnpddd	(8) lnpddd
Patent status	1.737***	1.424***	1.742***	2.065***	1.660***	1.058**	1.085**	0.248
	(0.510)	(0.437)	(0.390)	(0.581)	(0.440)	(0.504)	(0.465)	(0.551)
Years to patent expiration	-0.027	-0.056*	-0.043	-0.023	-0.061	-0.076**	-0.086**	-0.076*
	(0.037)	(0.034)	(0.051)	(0.048)	(0.043)	(0.034)	(0.041)	(0.038)
Log of sales volume	-0.252***	-0.093*			-0.153*	-0.283***	-0.015	-0.099
	(0.040)	(0.047)			(0.080)	(0.069)	(0.061)	(0.062)
Number of competitors	-0.165***	-0.091***			-0.160***	-0.304***	0.003	-0.192***
	(0.019)	(0.021)			(0.055)	(0.035)	(0.075)	(0.035)
Number of forms available	0.473***	0.411***			0.309*	0.399**	0.120	0.216
	(0.095)	(0.080)			(0.176)	(0.193)	(0.144)	(0.179)
Product age	-0.060***	-0.042***			0.003	-0.001	0.021	0.027
	(0.016)	(0.015)			(0.036)	(0.041)	(0.032)	(0.034)
Log of Indian price		0.340***					0.391***	0.310***
		(0.047)					(0.130)	(0.090)
Life year saved gained			0.645**		0.267		0.521**	
			(0.241)		(0.221)		(0.227)	
% of severe Thrombocytopenia			-0.029**		-0.018**		0.005	
			(0.013)		(0.009)		(0.010)	
% of severe Neutropenia			0.063***		0.030***		0.025**	
			(0.006)		(0.010)		(0.010)	
QALYs gained				0.267		-0.163		-0.026
				(0.251)		(0.188)		(0.145)
_cons	8.552***	5.076***	3.538***	5.534***	6.762***	10.189***	2.647*	6.568***
	(0.394)	(0.589)	(0.381)	(0.503)	(1.177)	(0.671)	(1.540)	(0.860)
N	202	163	46	57	43	54	41	44
R^2	0.562	0.677	0.815	0.124	0.857	0.810	0.904	0.883
adj. R^2	0.548	0.663	0.792	0.075	0.818	0.781	0.871	0.856

Notes: Standard errors in parentheses. Significant at (*) 10%, (**) 5% or (***) 1%

3.6. Conclusion and discussion

This study investigates the relative role of patents, compared to other market and medicine characteristics, in determining the price of medicines treating oncology in Thailand in the year 2008. This is to get a figure on the effect of patent on price to inform the impact of patent, via price, on access, analysed in the next chapter. Fewer empirical studies have investigated the price of medicines for non-communicable disease, even fewer of which explicitly take patents into account. The strengths of this study are that the study design is focussed only on one specific market and that the variables input in the model covered various factor known to affect price from both economic theory and empirical evidence.

The result in a qualitative sense is not surprising; patenting is associated with higher prices relative to a regime where patents are not available. However, from literature reviews the impact could range anywhere from 26-277%. This study shows that the impact of patent on the price of oncology medicines in Thailand is within this range, 130-212%, but although far less, itself still forms a considerable range. This relatively high patent impact in Thailand could be the result of pricing freedom, with no patented price monitoring and control in Thailand. Many countries that regulate manufacturer prices, either directly or indirectly, are likely to have a patent impact on price that is lower (Magazzini, Pammolli et al. 2004). Although the Thai health system provides universal coverage to the Thai population, the cost of some medicines will be the responsibility of the hospital, each of which purchases medicine separately. Therefore, the range of price between hospitals is high, depending upon negotiations. Moreover, most patented oncology medicines are not supported by universal coverage, and pricing of these medicines is likely to depend more on market characteristics and market power.

Another aspect of importance, in addition to having a patent or not, is the length of the patent life of the product. This study found that the lower the patent life, the higher the medicine price is. This could be due to the 'generic paradox,' suggested by Scherer (1993), that price of off-patent medicine increases after patent expiration, specifically in the US market. This might be because the pharmaceutical company uses that increased price strategy, with retention of their loyal customers, to compensate for losing market share when generics enter the market, or because

pharmaceutical companies might use entry with lower price to build loyalty and then increase price subsequently. However, this factor has unstable significance in four models, only showing significance in some specifications. Another factor that has a high impact on price is the benefit obtained from life years saved. A product extending life by one more year could shift price approximately 100%. Although the source of life year saved, as well as adverse effect, is obtained from a clinical trial conducted directly by the company holding the patent, patients would choose an expensive chemotherapy even though it has a small benefit on health (Matsuyama, Reddy et al. 2006; Baker 2008; Harrington S 2008).

Since QALYs area well-known tool to estimate outcomes for assessing the benefit of medicines, it should have a positive relationship with price. The findings presented here reveal the opposite. This maybe because the newly introduced and expensive medicines provide fewer QALYs gained than one that has already been in the market for a long time (diminishing marginal returns); the average QALYs gained for newly introduced drugs in 2008 is 0.29 while the average QALYs gained for those 10 years old is 1.36. This is consistent with an empirical study that concluded that the improved therapeutic gains do not account for the higher prices that have been set (Suslow 1992).

In addition, the adverse effect of neutropenia was found to have a positive relationship with price while thrombocytopenia shows a negative sign. Although chemotherapy kills fast dividing cancer cells, it also ends up killing some fast dividing cells in bone marrow that eventually cause white blood cell counts to fall. However, white blood cells will reach their lowest number 10 to 14 days after chemotherapy and then increase steadily and usually return to normal before the next cycle is due. While thrombocytopenia causes bleeding from the nose or more serious haemorrhage can occur at the back of the eye (retina), sometimes threatening sight (Ignoffo 2011).

This study has three potentially significant limitations, due to lack of data. First, prices input in this model do not take discounts or promotions from pharmaceutical companies into account. Therefore, the patent effect may be overestimated. However, the most available data source that represents the price was used and this study aims to assess the intent of the patent owner to exploit the monopoly. Second,

the method employed in this study is cross-sectional, which looks at price at a specific point of time. It does not take the price trend into account if the product owner decreases or increases price during the period from introduction to the year 2008. This was because it was not possible to obtain a time series of medicine prices in Thailand. However, market growth and product age were chosen to proxy price trend to capture the relationship between price and time. Third, there is a lack of systematic data on the benefits and adverse effects from medicines. This information was retrieved from clinical trials that were performed on specific indications. However the results of the same medicine in different indications yield different results. Of course, the population samples included in clinical trials also differ. As a result, this factor might not represent the actual benefits and costs of treatment by that medicine.

Hence, directions for future research include investigating the real purchase price at government hospitals, which are responsible for the access to medicines for the majority of the Thai population, investigating patented price setting behaviour over time, and a more appropriate assessment of benefit. Because the cost of providing a full range of treatments for cancer could potentially be high, prices and financing are inescapable factors in determining access to cancer treatment. Further study should therefore examine the effect of these patented prices on access to medicine.

Some have suggested that companies are hesitant to lower prices in poorer countries for fear of causing a backlash in richer markets (Hornbeck 2005).When price range scan be reviewed and compared, lower prices can be obtained through skilful negotiation, in locating new supply sources, and in assessing the efficiency of local procurement systems. If the medicine is an important therapeutic advance with no close competitors, the degree of monopoly power can be large, with corresponding profits for the manufacturer or patent owner.

Many medicine policies have major implications for access to, and utilization of, treatments for cancer patients. With respect to market characteristics, most of them have a significant impact on price. For instance, the higher the sales volume, the more suppliers selling the same medicine in the market and the longer time that product has been on the market, the cheaper prices medicines are. However, the magnitude of their impacts is minimal, i.e. a policy related to market characteristics

would have a small impact on oncology medicine use. Therefore, this study reveals that policies relating to patenting are effective options to decrease the price of oncology medicines. The use of TRIPS flexibilities (CL, parallel importation, limits on data protection, use of broad research and other exceptions to patentability, etc.) may be needed, although the adverse effect of CL policy needs to be considered and is the subject of investigation and discussion in Chapters 5 and 6.

This study has investigated the determinants of the price of oncology medicines, across market competitiveness and the characteristics of the medicine, taking into account their sales volume, number of providers, patent status and years to patent expiration, product age, production cost, benefits gained and adverse effects. The evidence shows that patent status, most of the market characteristic factors and the benefits of the medicine in terms of life years saved are significant, and the sign of correlations are shown as expected. Patent status is the most significant price determinant, and so policies affecting patent status could be considered as effective measures to bring down the price. The next chapter considers the impact of the patented price on access to medicines.

CHAPTER 4 THE IMPACT OF PATENT AND PRICE ON ACCESS TO ONCOLOGY MEDICINES IN THAILAND

4.1. Introduction

The rapidly rising cost of health care, and high medicine prices for non-communicable diseases (NCDs), especially cancer, are growing concerns worldwide (Marquez and Suhrcke 2005; World Health Organization 2005). Approximately 80% of premature mortality resulting from NCDs occurs in low- and middle-income countries (World Health Organization 2003). Cancer now constitutes a huge health and economic burden for developing countries (Kanavos 2006). Also, since 2006, cancer has been the major cause of death in Thailand, responsible for nearly 30,000 deaths annually and more than 100,000 new cases reported each year (*Wibulpolprasert 2007*). A significant proportion of morbidity and mortality could be prevented if treatments are made more widely accessible. Unfortunately, oncology medicines, which comprise a substantial proportion of the cost of organising and delivering cancer treatment programmes, are generally expensive (Featherstone and Whitham 2010). For example, in 2007 the average cost of chemotherapy treatment for 10 common cancer types where chemotherapy is a key treatment modality ranged from some $17,212 to $27,494 in the US (Fitch and Pyenson 2010). As a proportion of income, these modern medicines are even more expensive – and often prohibitively so – in low- and middle-income counties (Quick JD, Hogerzeil HV et al. 2002).

There are concerns that the patenting of medicines makes them unaffordable and that this is the driver which makes them ultimately inaccessible and hence underutilised. The exclusiveness in selling a medicine conferred by a patent to a particular manufacturer discourages competition among manufacturers, and makes generic competition illegal. This makes it difficult for countries to implement effective and sustainable policies to bring down the price ('t Hoen 2003). Of course, pharmaceutical companies stress that the prices secured in the period of the patent are necessary to recuperate the initial investment in R&D. They argue that without substantial investment in R&D the discovery of new more efficacious products

would not be possible. The patient therefore would lose out on the benefits of a more efficacious drug yet to be developed, as a result of decline in funding for R&D, if they were to benefit from lower present prices (a subject returned to in the next chapter).

However, despite the focus and emphasis placed on patents as a root cause of inaccessibility to modern medicines, empirical evidence directly linking patented price and access is rare. Most studies describe how patenting increases price, and then *assume* that price is the driver of access and so, by deduction, the patent must prohibit access. A number of studies have discussed how patents might do more harm than good in terms of access to medicines, and that the World Trade Organization (WTO)'s agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) has exacerbated this situation (Schulz 2000; Scherer and Watal 2002; Forman 2009). Several studies have also examined the availability, price and affordability of medicines on the WHO essential medicine list (WHO-EML) in several countries including Thailand (Babar, Ibrahim et al. 2007; Kotwani, Ewen et al. 2007; Mendis, Fukino et al. 2007; Suh 2011). However, none have focused specifically on medicines used to treat cancer or empirically on the contribution of price to access and the contribution of patent to price (which was the subject of the previous chapter). Recently, WHO initiated a global initiative to improve the care of chronic diseases in low- and middle-income countries (World Health Organization-Health Action International 2008). However, the project focused mainly on diabetes and cardiovascular disease. There were only two palliative cancer treatments,[12] codeine and morphine, included in the survey list. Moreover, these studies lack information concerning the direct association between the extent of price increases and the extent of changes in access, controlling for other influences. It is this issue that this chapter seeks to address.

In Thailand, the NLEM adopted the WHO-Essential Medicine List (EML) concept (World Health Organization. 2002). This specifies a set of medicines which the Thai population will not have to pay out-of-pocket for, but will be covered by the state. Therefore, in principle, the NLEM determines the extent to which a medicine will be widely accessible to the Thai population. The process of selecting a medicine for this

[12] A treatment designed to relieve symptomsrather than cure an illness.

list is important, and correspondingly complex, including factors related to health need, safety, efficacy, efficiency, equity, treatment cost, national affordability, availability, compliance and quality (Chongtrakul P 2005). Many new anti-cancer medicines are not included on the NLEM, and a reason often stated is because of their high price (Ministry of Public Health 2008). For these medicines, not on the NLEM, patients have to pay out-of-pocket. It is therefore important, for Thailand, to understand the role of patent and price in getting a medicine listed on the NLEM, and to understand how, where it is not on the NLEM, price impacts access to that medicine.

Specifically, this study is to determine:(i) whether patented medicines are available on the NLEM, and the extent to which patent status and the price of the medicine affect its selection; (ii) whether non-NLEM medicines, both patented and non-patented, are considered to be affordable to the Thai population; and (iii) the extent to which, from i and ii above, price determines access to NLEM and non-NLEM medicines.

The paper is organized as following. The next section describes how the medicine system in Thailand determines access. Section 3 presents literature review of the impact of patent status and price on access to medicines. Section 4 describes the data and presents an econometric specification of the probit model used in this study to estimate the impact of price on access, and section 5 presents the results. Finally, further steps are discussed in the concluding section.

4.2. Access to medicines in Thailand

Access to health care in Thailand is provided by both public and private insurance schemes. Thailand achieved universal coverage for the entire population in 2002 by introducing a new public insurance to cover the approximately 47 million people who were not beneficiaries of two major existing public insurance schemes: the CSMBS and SHI (Tangcharoensathien, Patcharanarumol et al. 2010). These three public health insurance systems together comprise a comprehensive free benefit package that includes ambulatory care, hospitalization, surgical operations disease prevention, health promotion and many expensive medical services.

The NLEM adopted from the WHO concept of essential medicines was developed to provide medicines that are deemed necessary, effective and safe for Thai people through government hospitals and other health stations. Also, the NLEM aims to be used as a tool to encourage the rational use of medicines (National Drug Committee 2008). The first version was launched in 1981, and is revised periodically; the current version was issued in 2008, the 9th edition. The NLEM includes 637 items, in 17 therapeutic groups. The NLEM is referred to as the pharmaceutical reimbursement list by the three public health schemes, so that prescription medicines that are on the NLEM are also free of charge. The cost of prescribed medicines not on the NLEM is the responsibility of individuals under the SHI and UC schemes, but not under the CSMBS. The CSMBS allows three medical doctors to co-endorse the use of medicines outside the NLEM (Tangcharoensathien 2003). The CSMBS scheme is a primary driver for growth as it is a free market and there are no restrictions for out-patient use. It covers 8 percent of the population but accounts for 40-50 percent of branded pharmaceutical sales (Wibulpolprasert 2007).

The NLEM directly involves medicine availability for the government sector. Procurement regulations in the public sector attempt to encourage the use of medicines listed on the NLEM by requiring public hospitals to spend at least 60–80% of their government medicine budget on medicines on the list. However, the medicine listed in public hospitals is different from the NLEM list, and varies by the size of hospital. Medicine management is the responsibility of a hospital pharmaco-therapeutic committee, and medicine procurement carried out by the pharmacy department (Pitaknetinan, Tangcharoensathien et al. 1999). Large hospitals, especially central and university hospitals, generally have broader medicines and bigger lists than the NLEM, since the diseases are on average more complex. The proportions of medicines that are on the NLEM and not on the NLEM in rural, general, central and university hospitals are 82:18, 81:19, 71:29 and 57:43 respectively (Sripiroj, Tantivess et al. 2000). Each hospital individually manages its budget to procure and manage its medicine inventory. Medicines on the "Jor 2" sublist of the NLEM, a special category for expensive or closely monitored medicines for safety reasons, which are mostly high price medicines, will be reimbursed or provided from the National Health Security Office directly. This

policy allows doctors to prescribe expensive medicines to patients in need without concern for burdening hospitals.

As two of the main components of access are affordability and physical availability, access to medicines in Thailand depends heavily on whether a medicine is on the NLEM, as the NLEM provides a medicine free to the patient at point of use. Moreover, the National Health Security Act of 2002 ensures all Thai citizens the right to health care and access to medicines listed on the NLEM, if they are needed, with no cost sharing. The determinants of medicine selection to the NLEM are therefore a crucial determinant of access. Generally the NLEM committee consists of 17 working groups according to therapeutic area. Several factors are applied before a medicine can be included on the NLEM, concerning disease severity, efficacy, costs, compliance, prevalence and incidence of the disease. It also has to have been cleared by the safety monitoring programme (SMP) implemented by the Thai Food & Medicine Administration (FDA).

Since 2004 a scoring system has been used for medicine selection (Sripiroj A, Tantivess S et al. 2000). The score is based on four criteria which cover Information (quantity and quality of evidence), Efficacy, Safety (precautions, severe adverse effects and medicine interaction) and Ease of use (administration restriction score and frequency of medicine administration), which is known as the ISafE score. The maximum score for each of the four components is 1, and the minimum is 0, and the overall ISafE score is the result of simple addition of the four individual scores, although any 0 scores will lead to immediate rejection of the medicine. Due to this, the ISafE system is not applicable to anti-cancer medicines as the medicines' adverse reactions mean that they would be classified as unsafe and hence their safety (S) score would be zero, and the medicine would be excluded automatically despite its high scores in other criteria.

The NLEM therefore do not use the ISafE score for oncology medicines, but rather make a decision based on health need, relative safety, efficacy, compliance, quality, total treatment cost, cost-effectiveness, equity, and national affordability (Yoongthong, Hu et al. 2012). According to the secretariat of the Health Economics Working Group under the Subcommittee for the Development of NLEM (personal communication) , from approximately 40 oncology medicines proposed, less than 10

medicines are accepted. Even where medicines are cost-effective they may not be selected if they need a significant budget to be able to provide them (Ministry of Public Health and National Health Security Office 2008).

Patents on medicines, which are tied to market prices as shown in the previous chapter, have been clearly shown as a factor in determining whether a medicine is listed on the NLEM. For example, prior to 2003, patented antiretroviral (ARV) medicines were not included in the NLEM due to their high prices (Tantivess and Walt 2006). In October 2003, the government declared its commitment to provide universal access to triple ARVs for HIV/AIDS treatment. EFV was therefore put in the NLEM. However, this commitment required a significant budget to ensure universal access to ARVs for all patients in need. Since EFV was under patent protection, CL was used to reduce its price and this enabled the MOPH to provide this medicine to an additional 20,000 AIDS patients (Ministry of Public Health 2008). Four patented anti-cancer medicines were finally listed on the NLEM following CL in 2008. This suggests that some patented medicines currently not on the NLEM might be included if there were generic versions available. Although CL can decrease price significantly, it raises the wider question of the role of price specifically as a determinant of access.

4.3. Extensive literature reviews

An extensive search of the literature was performed to search for empirical evidence concerning price as a factor determining access to medicines in any country. Econlit, Embase Classic and Embase, Global Health and Medline were the four databases searched, selected because they cover journal articles, books, and dissertations, as well as articles in collective works, such as conference proceedings and collected essay volumes in the areas of economics and health. Keywords were identified from published work related to the research question. The search strategy involved a combination of three search steps which individually addressed the price, pharmaceuticals and access or affordability. These were combined as follows: (*patent OR TRIPS OR price*) AND (*medicine OR drug OR pharmaceuticals)* AND (*access OR afford OR utilization*). The combined search, limited to English publications between 1990 and 2011 to cover the TRIPS agreement era implemented

during mid-1990s, yielded 744 articles.Three criteria were used to select and assess the potential studies. To be included in the literature review, a study had to:

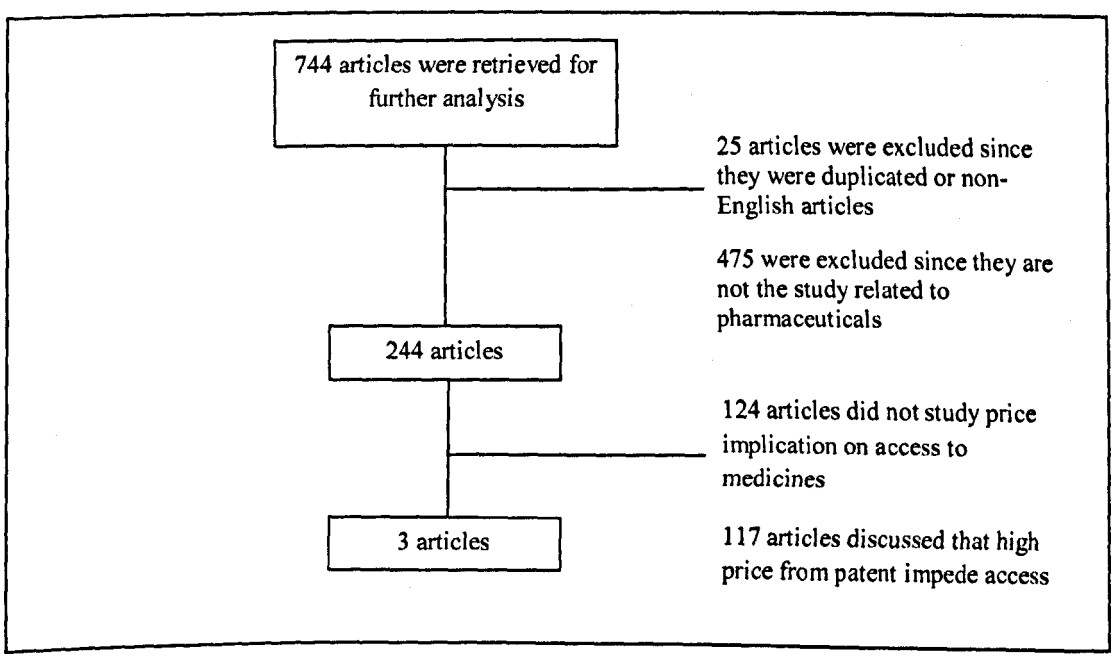
1. Focus on the issue of the implications of pharmaceutical patents, patented price or policies favouring pharmaceutical patent protection or patenting on access to medicine. Studies dedicated to other types of innovations (i.e. motor vehicles, electrical equipment innovations, etc.) were not retained;

2. Include an empirical study, either descriptive statistics or econometric analysis. Theoretical and conceptual studies as well as discussion studies were not retained; and

3. Define access (usually in terms of a utilization rate).

The identified articles were screened (Figure 4.1). After the exclusion of non-English and duplicate publications, a first assessment based on title and abstract resulted in 475 papers which did not meet the first inclusion criteria, i.e. not investigating impact of pharmaceutical patents. Following a review of the text of the remaining papers, a further 124 articles were excluded which did not focus on patent implications on access to medicine and 117 articles were excluded for not meeting the second and third inclusion criteria above.

Figure 4.1 Flow-chart followed when performing a systematic review



Empirical evidence directly linking (patented) price and access is rare. Most studies describe how patenting increases price and then *assume* that price affects access, but do not measure the direct association between the extent of price change and the extent of changes in access, controlling for other factors. Only three studies were found which did this, two of which are about the Thai setting but reported in English.

Akaleephan et al. (2009) examined the effect of patent life extension from a TRIPS-Plus proposal on access to medicines in Thailand. Using two datasets from the FDA, providing import or produced price and volume, and the Drug and Medical Supply Information Centre (DMSIC), providing purchased price of some government hospitals, the top 74 items which accounted for 50% of market value were selected. With no information concerning patent verification in Thailand provided, of these 74 medicines, 18 were grouped as patented items and 14 as monopoly items. However, these two groups were then combined later in the analysis since the authors were unsure if these medicines were actually patented items. Nonetheless, the authors regressed market share of generics based on year of entry and used this to predict the additional expense when there is an extension of market exclusivity. The results illustrated that a period of extension of 10 years would generate an additional expenses of around 13.4-86.9 $US million. This study also estimated that expected expenses only patented brands constituting the consumption volume in 2003 (i.e. no generics) would have been $US 517 while the actual expense (with generics) was $US 264 million. Under the assumption that the national budget for medicines is fixed, the increasing expense from lack of generic competition could reduce the consumption volume of medicines, from 2,538 million DDD to 1,653 million DDD The authors concluded that, the availability of generics would help to save 105% of actual government expenditure, and accessibility – defined as expected utilization rate–would increase by 54% (Akaleephan, Wibulpolprasert et al. 2009). However, the model employed in this study was a static model and it estimated the monopoly status effect rather than the patent effect since almost half of medicines included in the model were monopoly status medicines, not patented medicines per se. Therefore, the results of this study are overestimated.

The second study (Yamabhai, Mohara et al. 2009) focused on CL implementation in Thailand, which enabled generic manufacturers to offer generic equivalent versions

of medicines at some 3-38% of the branded price. By a regression of increased access on time only, as a result, it was estimated that approximately 8,000 extra patients could utilize efavirenz (EFV), and over five years suggested that the increased number of patients with access to EFV would be 17,959.The study also considered anti-cancer medicines, where four CL were granted in January 2008 for letrozole, docetaxel, erlotinib, and imatinib (which are used in the treatment of breast and lung cancers, gastrointestinal stromal tumors (GIST) and leukaemia).The estimated increases in the five-year period are as follows: 8,916 patients for letrozole; 10,813 for docetaxel, 1,846 for imatinib; and 256 for erlotinib. A limitation of this study is that, unlike estimating from the trend of real numbers of increased access as in the HIV/AIDS case, the increased utilization of anti-cancer medicines was estimated from expert opinion since there was no importation of generic equivalents at the time of the study.

The last study focused on access to HIV/AIDS medicines in low- and middle-income countries more broadly from 1995 to 1999. By estimating a sample selection model to examine the impact of patents on sales, the authors estimated two key simultaneous relationships to tackle the question under study: (1) the relationship between the likely entry decision across drug-country-year divisions and patents; and (2) the relationship between market coverage (i.e. mean coverage of patients under annual treatment with a specific ARV drug) and patents, conditional on drug entry decisions and patent regimes. The authors estimated access by multiplying the probability of having a medicine available with the conditional expected access to that medicine, and showed that switching all medicines under a patent regime to a no-patent regime would have only increased the percentage of AIDS patients with access to new medicines from 0.88% to 1.18% between 1995 and 1999 (Borrell and Watal 2003). However, with reference to individual countries, it suggested different magnitudes of impact. For example, in Thailand, where most of the relevant medicines were under patent, around 10,000 additional prescriptions were felt to have likely been prescribed if all patents were waived, generating an increase in access of some 50%.

It is clear that evidence on the role of price on access, especially with respect to anti-cancer medicines, is limited, inconclusive, and problematic; estimated data and the

use of expert opinion are some of the issues involved. This suggests that a more holistic assessment of the impact of high prices, due to patent rights, on access to oncology medicines with specific focus on the Thai health system, in which access to medicine is dependent on its NLEM status, is required.

4.4. Methodology

The critical issue of access to medicines for the majority of people in Thailand can be divided into three main groups. First, how price affects whether or not the medicine is on the NLEM. If that medicine is chosen to be on the list, patients who need that medicine have a right to be treated without cost. If that medicine is not chosen, patients face the full price. This suggests that assessing the role of price on the probability of a medicine being listed on the NLEM is important. Second, in the case of non-NLEM medicines, affordability is a critical issue (that is, medicines not under patent may be cheaper but not cheap enough to significantly increase access). Third, there will be other factors, such as a sufficient supply chain infrastructure, which will also affect access, and it is important to understand how much price, relative to these other factors, is a determinant of access. This section describes the methods used to examine these three questions.

4.4.1 Assessing the role of price on NLEM status: Probit model

This section describes the analysis undertaken to investigate factors that influence whether or not a patented medicine is selected by NLEM, focusing on the role of price. The outcome variable has only two possible values: selection or non-selection, suggesting that a binary choice or qualitative response model[13] is suitable. A linear regression probability model cannot be used to fit factors influencing this choice since the outcome variable causes problems with the disturbance term, as it consists of only two values, i.e. it is neither continuous nor a normal distribution. This means that the standard errors and the usual test statistics are invalidated. Moreover, the predicted probability may be greater than 1 or less than 0 for extreme values of X. These problems are dealt with by fitting the model with a technique known as maximum likelihood estimation and elaborating the model as a sigmoid function of

[13] The model is binary with the outcome, which is always denoted Y, being assigned a value of 1 if the event occurs and 0 otherwise.

Z, a linear function of the explanatory variables. The two most popular forms are the logistic function, which is used in logit estimation, and the cumulative normal distribution, which is used in probit estimation. According to one of the leading authorities on the subject, Anemiya (1981), both give satisfactory results most of the time and neither has any particular advantage.

Model

This study assumed that the unobservable term is normally distributed with the same mean and variance, and thus a probit model was selected. This uses the cumulative standardized normal distribution to the sigmoid relationship F(Z), zero mean and unit variance. Z is a linear function of the variables that determine the probability:

$$Z = \beta_1 + \beta_1 X_2 + \ldots + \beta_k X_k. \quad (1)$$

F(Z), the cumulative standardized normal distribution, gives the probability of the event occurring for any value of Z:

$$p_i = F(Z_i). \quad (2)$$

Maximum likelihood analysis is used to obtain estimates of the parameters. The marginal effect of Xi is $\frac{\partial p}{\partial Xi}$ which, as in the case of logit analysis, is best computed as

$$\frac{\partial p}{\partial X_i} = \frac{dp}{dZ}\frac{\partial Z}{\partial X_i} = f(Z)\beta i. \quad (3)$$

Now, since F(Z) is the cumulative standardized normal distribution, f(Z), its derivative, is just the standardized normal distribution itself:

$$f(Z) = \frac{1}{\sqrt{2\pi}} e^{\frac{-1}{2}Z^2} \quad (4)$$

Though logit and probit analysis generally yield similar marginal effects, the shapes of the tails of the logit and probit distributions are different and so logit and probit can give different results if the sample is unbalanced. A logit model is therefore

employed to test if the results from both models are different, with the same set of data and variables.

Variable definitions and sources of data

To estimate the probability of medicine selection as a function of a set of relevant variables, this study selects all medicines treating oncology marketed in Thailand in 2008. The NLEM version 2008, the most recent version when this study was conducted, was used as the outcome of decision making. The list of medicines is available on the Thai Food and Drug Administration website.[14]The outcome variable (Y_i) has only two possible values: select or not select. Y_i is the variable that captures various reasons for which a medicine is accepted into the NLEM. The dependent variable takes on the value of one if medicine i has been selected for the NLEM, and zero if that medicine has not been selected.

The characteristics of these medicines will then be explored, in terms of sales, patent status, cost of treatment, number of patients needed and QALYs gained. The explanatory variables of the model are explained in detail below. The range of factors included is outlined in table 4.2.

This study considers price in terms of annual cost of treatment. It is an important factor for policy makers since it directly affects the government budget, and thus the affordability of other medicines. Cost of treatment per course was estimated by the unit price multiplied by the volume needed for each cycle suggested for each medicine, as obtained from MICROMEDEX, a database providing evidence-based medicine information. Price in this case was the average price that government hospitals procured the medicine at in 2008. Though in the NLEM selection process, pharmaceutical companies submit the price to consider, only 16 medicine owners submitted their prices to the NLEM committee in 2008.Moreover, most of them were higher than the market price, and thus did not seem reliable and reflective of practice. In practice, if NLEM working groups are interested in putting a medicine on the list, negotiation will be undertaken in order to bring down the price to an acceptable level. This study therefore employed the 'real' prices paid by government

[14]http://www.thaifda.com/ed2547/?pg=result

hospitals since they include discounts and promotions. This cost was then log-transformed to reduce wide-ranging quantities.

Patent status of a medicine could possibly be a reason that a medicine is not proposed for consideration, since the committee might use this as a proxy for affordability. Patent status takes a value of one if the individual medicine is patented and a value of zero where it is not patented. The patent statuses of medicines were obtained from various sources (see Chapter 2). Correlations between variables were checked and none of them show severe correlation; the maximum correlation was 0.55, found for product age against patent status. However, the previous chapter demonstrated that price is significantly determined by patent, and thus multicollinearity could occur. The correlation between the two factors was checked, and does not show a high correlation (r=0.39), and multicollinearity checking was done by the variance inflation factor (VIF) test and the Collin test in STATA. The test statistic of VIF is 1.18 and the condition number[15]is 9.65 indicating no multicollinearity problem. It is suggested that a large VIF, 5 or more, and condition number, 30 or more, is an indication of multicollinearity problem (Carlsson and Lundström 2002; O'Brien 2007).

Number of patients needing the medicine is an influential factor on the selection process since it shows the size of the potential burden. It is expected that the government would prioritise diseases of higher prevalence in choosing medicines for the NLEM. From the MICROMEDEX database, the indications of each medicine were noted and then used to find the code of International Statistical Classification of Diseases and Related Health Problems, 10th Revision (known as ICD-10). Each medicine's ICD-10 code was recorded and matched with the number of patients which were recorded with the ICD-10 code, obtained from the National Health Securities Office which manages the universal coverage scheme and accounts for 75% of the population. This study selected the average number of patients during the period 2004 to 2007, since the previous version of the NLEM was issued in 2004 so the number of patient during the period before the NLEM 2008 version was launched is considered as the influential factor. However, as each medicine has a slightly different indication, and not every patient is treated with the medicine since

[15] A commonly used index of the global instability of the regression coefficients.

there may be more suitable treatments available, such as surgery or radiotherapy, the number of patients by ICD-10 was adjusted using the National Cancer Institute of Thailand data on the numbers of patients undergoing specific methods of treatment each year.

Table 4.1 Percentage of treatment by therapeutic group from 2004-2007

Therapeutic group	2004	2005	2006	2007
1. Cytotoxic Chemotherapy	27.6%	38%	25.5%	27%
2. Hormonal Chemotherapy	0.2%	0.3%	0.5%	7%
3. Immunological Chemotherapy	0.1%	0.1%	0.1%*	0.1%*
4. Supportive Care Therapy	4.6%	13%	24.5%	10%

Source: Cancer Registry 2004-2007

*estimate from the previous year since the data are not available

There are wide variations in choosing chemotherapy regimens that are based on doctor preferences (Shabaruddin, Elliott et al. 2010). Sales and market share represent the 'doctors' favourite' medicine (Morgan MA, Dana J et al. 2006). This could reflect a view that a specific well-known medicine is accepted as a first line or first choice therapy. This data was obtained from IMS. Product life also indicates the possible reliability and safety of a medicine, and the number of years from registration year was employed in the model to reflect this.

It is said that the NLEM 2008 version was the first version that used pharmaco-economic evidence in designing reimbursement (Akaleephan, Wibulpolprasert et al. 2009). Economic evaluation is mainly conducted by the Health Intervention and Technology Assessment Program (HITAP), a health technology assessment agency under the MOPH. HITAP developed national guidelines for economic evaluation and uses a cost-effective threshold set at average GDP per capita, as suggested by the WHO (WHO Commission on Macroeconomics and Health 2001; Ngorsuraches, Meng et al. 2012). Results of economic evaluation studies are considered by the Subcommittee of NLEM when they make decisions on whether to include or exclude a medicine (Jirawattanapisal, Kingkaew et al. 2009). It estimated that cost-

effectiveness analysis (CEA) would therefore be a relevant factor in decision making. However, not every medicine was assessed by CEA, and often it applies only to expensive medicines (Ngorsuraches, Meng et al. 2012). Nonetheless, although CEA data for each medicine are not available, QALYs gained are always used as an outcome measure (Harper 2011). This measures the change in life expectancy and in quality of life resulting from treatment, i.e. it captures the benefits and adverse effects of the medicine in question. Moreover, it allows comparison across disease areas. Medicines that provide a high level of QALYs would be expected to have a high chance of being selected to the NLEM. The HEED, the Cost-Effectiveness Analysis Registry, and the Centre for Reviews and Dissemination were databases used to find QALYs gained and life years gained for each medicine, when compared with the best alternative supportive care available on the market.

Table 4.2 Definitions of variables

Variable	Definition
NLEM	1 for NLEM medicine and 0 for non-NLEM medicine
Patent	1 for patented medicine and 0 for non-patented medicine
Cost of treatment	Log of cost of treatment per course
Cancer cases	Registered cancer patients by type of cancer specified for that medicine (average from 2004-2007)
Sales value	Sales in Thailand in the year of 2008 (Baht)
Market share	Market share within the same therapeutic area
Product age	Number of year from the registration year (year)
QALYs gained	QALYs gained

4.4.2 Affordability of non-NLEM medicines

This section outlines the methods used to assess the affordability of those medicines which are not on the NLEM. Generally, affordability is always assessed as the cost of treatment in relation to peoples' income. The number of days the lowest paid unskilled government worker would have to work to pay for one treatment course was employed by the WHO/HAI study referred to earlier (Sooksriwong C, Yoongthong W et al. 2009). Since the lowest paid unskilled government worker pay

in Thailand varied from 148 to 203 Baht/day, depending on province, this part of study uses the average wage of the Thai population in 2008, equal to 297 Baht/day, which is more reasonable, as obtained from the National Statistics Office. This figure is then used to estimate the number of days this worker would have to work to purchase various treatments that were not on the NLEM. It is also conservative, knowing that a considerable number of people will of course fall below this level.

Cost of treatment was estimated as the cost per day. This is because chemotherapy is not usually a single treatment, but a course of treatments. It is typically given in cycles, with rest periods between the cycles. A cycle can last one or more days. Therefore, the cost per day is selected to estimate affordability. First the cost of one cycle is estimated. This is then divided by the number of days in that cycle.

Selection probability of patented medicines not on the NLEM

The best model developed from section 4.4.1 was used to estimate the probability of a medicine being put on the NLEM from the pool of patented medicines that were not already on the NLEM list. This probability will be compared with the simulated probability of being put on the NLEM when that patent is removed. However, with the removal of patent protection, the replacement with generic equivalent version is possible, which will discount the price. This analysis will therefore simulate discount schemes at 50% and 80% of the original price and to see the extent to which the chance of those medicines being selected forth NLEM changes. The model relating to equation (4), replacing the patent status factor with the cost of treatment, is estimated.

4.4.3 Price Sensitivity of demand for prescription drugs

Finally, analysis was undertaken to estimate the responsiveness of prescription demand by exploiting exogenous variation in the prices of oncology medicines. A dependent variable representing prescription demand was developed. A number of patients (Access) in each year was also estimated by dividing sales volume of each medicine by the average volume needed for one patient in one year. This variable was regressed on the independent variables shown in table 4.2 which are price, number of cancer cases, market share, product age and QALYs gained. Price here is

the median price of medicines purchased from government hospitals obtained from the Drug and Medical Supply Information Center (DMSIC). For the missing values, mostly monopoly medicines, prices were retrieved from the IMS. To summarise, this section investigates whether demand for prescription drugs is sensitive to price, through OLS regression in the following functional forms.

$$Access_i = \beta_0 + \beta_1 Price_i + \beta_2 Cancer_i + \beta_3 Market\ share_i + \beta_4 Product\ age_i + \beta_5 QALYs_i + \varepsilon_i \quad (5)$$

These functions were also estimated for subgroup analysis: NLEM and non-NLEM. This was done to determine whether medicine prescription treatment differs among these two groups.

4.5. Results

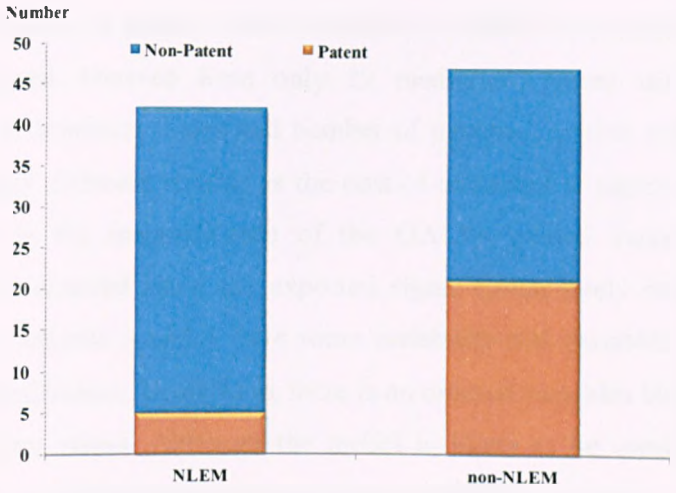
In 2008 version of NLEM, 43 of the 88 available active ingredients for treating cancer were chosen to be put on the NLEM (see appendix 5). With respect to each therapeutic group, around 43-50% of active ingredients available on the Thai market were chosen to be put on the NLEM. Table 4.3 shows the number of medicines selected for the NLEM in each of the four main categories outlined previously.

Table 4.3 Number of medicines on market and NLEM

Group	Medicine on market (No.)	Medicine on NLEM (No.)	%
1. Cytotoxic Chemotherapy	58	29	50
2. Hormonal Chemotherapy	14	6	43
3. Immunological Chemotherapy	7	3	43
4. Supportive Care Therapy	9	5	50
Total	88	43	49

Figure 4.2 compares the number of NLEM and non-NLEM status medicines which are patented to those which are not patented. It can be seen clearly that the number of patented medicines on the NLEM was relatively small compared with non-NLEM medicines; only five patented medicines were selected for the NLEM, while 21 patented medicines were excluded.

Figure 4.2 Number of medicines treating oncology by NLEM and patent status



4.5.1 The role of patent and price on medicine selection

With the aim of estimating the overall effect of individual variables, including patent and price, on the selection of medicines for the NLEM, a binomial probit model was fitted to the data available. Obviously, price affects the affordability of medicines for the government. However, a patent may or may not affect the decision-making process. As a result, this section will estimate two main models. The first model includes both patent and price factors while the second model excludes patent variables. Since QALY data availability was limited to only 24 medicines, models 3 and 4 were created to test the impact of costs and benefits from treatment. Including all variables together, the program failed to run since there was an insufficient sample.

Table 4.4 shows the results of the estimation by the probit model. The majority of the sample was included in models 1 and 2, while there were only 22 and 24 medicines included in models 3 and 4 respectively. Beginning with model 1, all explanatory variables show the expected signs. Patent, sales and product age are

statistically significant determinants of medicine selection. Having patent status decreases the probability of being selected by 36%. A 10% increase in sales and a product that is one year older could increase the probability of being selected by 2% and 7% respectively. The annual cost of treatment and number of patients requiring treatment are not significant determinants of the NLEM status decision. The estimates of the marginal effects at the sample means of model 2 are virtually the same as those obtained from model 1.

Model 3 consists of patent, cost of treatment, number of patients, sales value and QALYs gained. Derived from only 22 medicines, patent still seems to be a significant determinant. Sales and number of patients are also significant. Model 4 shows slightly different results, as the cost of treatment is significant. A surprising result here is the insignificance of the QALYs gained variable, although the coefficients estimated show the expected signs. Given likely bias from the small sample size, models 3 and 4 have some instability and variables with inconsistent signs and significance. In addition, there is an omitted variables bias, such as product age and patent status. Although the model is likely to be unreliable, sales value seems to be a relatively robust factor affecting NLEM selection.

With respect to the number of observations, Chi-square and pseudo-R^2, model 1 represents the most robust model of selection of medicine to NLEM. NLEM status is explained by patent status, cost of treatment, number of patients, sales and product age. Patenting has a strong and significant effect on the selection decision. Sales and product age have a positive relationship to the probability to be selected. However, price is not a significant independent determinant of medicine selection.

Table 4.4 Determinants of the medicine selection into NLEM: Probit models

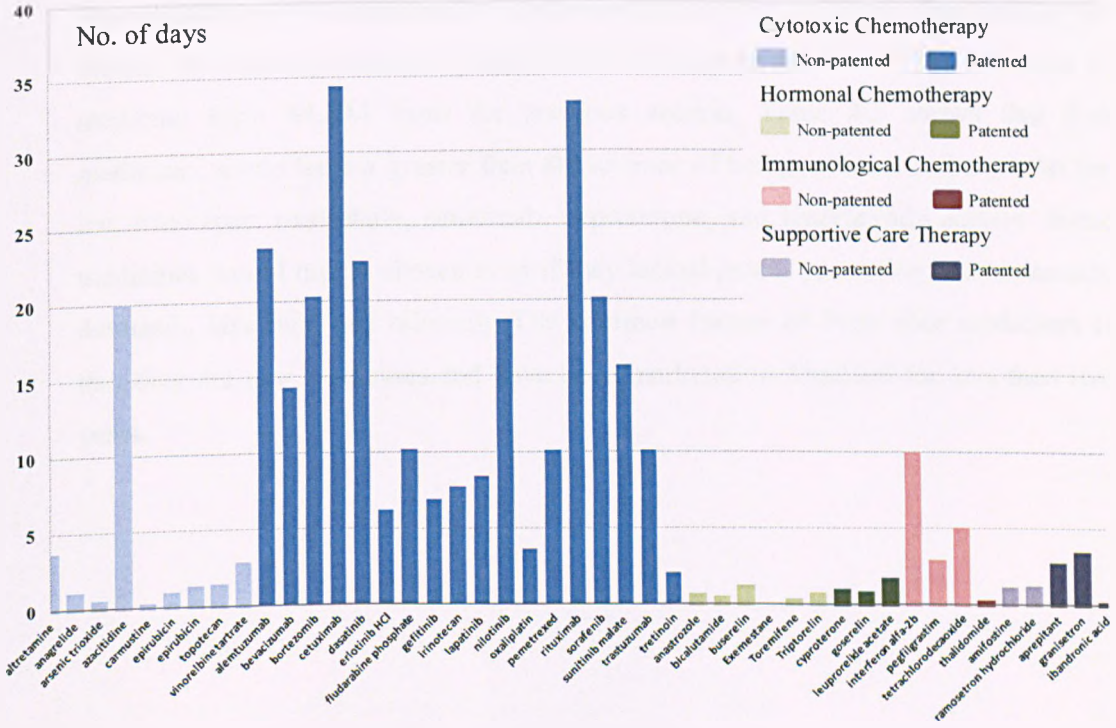
Variable	Model (1)		Model (2)		Model (3)		Model (4)	
	Coefficient	Marginal effect	Coefficient	Marginal effect	Coefficient	Marginal effect	Coefficient	Marginal effect
Patent	-0.936*	-0.360**			-3.795*	-0.821***		
	(0.488)	(0.175)			(2.274)	(0.274)		
Cost of treatment	-0.149	-0.059	-0.137	-0.055	-0.971	-0.202	-1.064**	-0.295**
	(0.125)	(0.049)	(0.108)	(0.043)	(0.643)	(0.152)	(0.530)	(0.123)
Log of No. of patients	0.041	0.016	0.112	0.045	-1.109*	-0.230	-0.608	-0.168
	(0.108)	(0.042)	(0.093)	(0.037)	(0.623)	(0.159)	(0.373)	(0.104)
Log of sales value	0.522***	0.205***	0.370***	0.147***	2.073*	0.430*	0.978*	0.271**
	(0.146)	(0.058)	(0.119)	(0.048)	(1.210)	(0.249)	(0.536)	(0.112)
Product age	0.167***	0.065***	0.171***	0.068***				
	(0.039)	(0.015)	(0.035)	(0.014)				
QALYs gained					0.097	0.020	-0.029	-0.008
					(0.112)	(0.020)	(0.056)	(0.016)
N	85	85	93	93	22	22	24	24
pseudo R^2	0.544	0.544	0.498	0.498	0.687	0.687	0.487	0.487
Log likelihood	-26.755	-26.755	-32.307	-32.307	-4.520	-4.520	-7.839	-7.839
Chi-squared	63.749***	63.749***	64.215***	64.215***	19.801***	19.801***	14.875***	14.875***

Notes: Standard errors in parentheses. Significant at (*) 10%, (**) 5% or (***) 1%

4.5.2 Affordability of non-NLEM medicines

This section presents the results of analyses concerning the affordability of treatment, estimated by the number of day's wages that the average Thai worker would be required to pay to purchase the medicine that is not on the NLEM list at the lowest price available. There were 47 medicines not on the list, of which 43% were not patented. Analysis was conducted by the group of medicine; non-patented and patented across four main therapeutic areas. Figure 3 shows how many days that an average Thai worker needs to work to pay for a daily dose of that medicine. There are 10 medicines, of which one is a patented medicine, that cost less than one day's wage to buy. In cytotoxic chemotherapy, patented medicines are clearly less affordable compared to non-patented medicines. It is interesting to note that azacitidine, which requires the highest number of days to pay for it (20), is the only non-patented medicine with monopoly status, where there is only one seller in the Thai market.

Figure 4.3 Affordability of non-patented medicines that are not on NLEM



Hormonal chemotherapy seems affordable compared with the other three therapeutic groups. On average it needs approximately two days' wage to purchase. The affordability of patented and non-patented medicines is not substantially different. It is interesting to see that patented medicines in the immunological therapeutic group are more affordable than non-patented medicines, although of the three non-patented medicines in this category, one is a monopoly and the other two have only two suppliers. Within supportive care therapy, medicines need, on average, 1.2 days' wages to afford on-patented medicines and 2.1 days' wages for patented medicines.

In conclusion, patented medicines in cytotoxic chemotherapy create a high burden of payment for patients who need them. Some of the non-patented medicines also, however, show a high burden if they have a small number of suppliers.

4.5.3 Probability of patented medicine selection

This section presents analyses of how the probability of selection to NLEM changes if the medicine were no longer under patent protection. Removing a legal monopoly right would allow the Thai government to procure cheaper medicines (notwithstanding the relationship between patent and price already discussed in the thesis). By deriving from the probit model of the determinants of the selection of medicine forth NLEM from the previous section, Table 4.5 shows that five medicines would have a greater than 80%chance of being selected to be put on the list; irinotecan, oxaliplatin, rituximab, cyproterone, and leuprorelide acetate. Some medicines would not be chosen even if they lacked patent protection; alemtuzumab, dasatinib, lapatinib, and nilotinib. The common feature of these four medicines is that they are new medicines and have been marketed in Thailand for less than two years.

Table 4.5 Probability to be on the NLEM with the original price, with 50% and 80% discounted price.

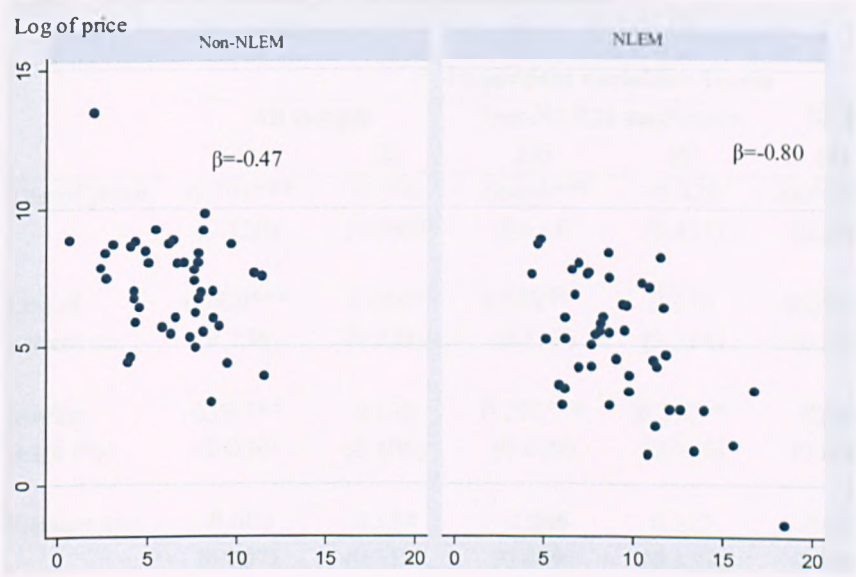
No.	Generic name	Original price (Baht)	NLEM probability with original price (%)	NLEM probability with 50% discount (%)	NLEM probability with 80% discount (%)
1	Alemtuzumab	70,000	0.0	0.02	0.03
2	Bevacizumab	19,591	7.0	33.10	38.22
3	Bortezomib	56,500	1.3	11.61	14.51
4	Cetuximab	14,935	1.9	15.08	18.48
5	Dasatinib	144,000	0.0	0.00	0.00
6	Erlotinib HCl	82,497	6.3	31.14	36.14
7	Fludarabine phosphate	28,168	4.0	29.59	34.50
8	Gefitinib	28,168	5.8	33.79	38.88
9	Ibritumomab tiuxetan	700,000	0.39	0.55	0.80
10	Irinotecan	10,982	47.8	83.69	86.82
11	Lapatinib	35,000	0.0	0.02	0.03
12	Nilotinib	39,000	0.0	0.00	0.00
13	Oxaliplatin	8,294	53.0	86.71	89.44
14	Pemetrexed	42,000	3.7	22.89	27.21
15	Rituximab	61,096	45.7	82.33	85.66
16	Sorafenib	89,700	0.9	9.05	11.47
17	Sunitinib malate	49,000	0.1	2.28	3.13
18	Trastuzumab	76,358	16.5	52.63	58.05
19	Tretinoin	8,840	0.6	7.05	9.07
20	Cyproterone	2,429	49.2	84.65	87.64
21	Goserelin	23,005	12.6	45.73	51.20
22	Leuprorelide acetate	6,811	68.7	93.65	95.19
23	Thalidomide	15,400	3.4	21.65	25.84
24	Aprepitant	681	1.0	9.97	12.60
25	Granisetron	5,178	18.7	55.96	61.30
26	Ibandronic acid	1,510	23.3	62.27	67.36

Source: Authors calculations based on table 4.4 estimates

4.5.4 Price determinants of medicine prescriptions

This section presents the results concerning the responsiveness of medicine consumption to changes in price. Figure 4.4 shows the relationship between price and number of treatments prescribed (as a proxy of demand and consumption). Both groups show that the demand for oncology medicines is inelastic, which would be expected given their unique, and life-saving, properties. In addition, the elasticity of demand for the NLEM listed group is greater than the non-NLEM listed medicines, i.e. prescription of NLEM medicine is more responsive to price changes than non-NLEM medicines.

Figure4.4 Dstribution of price and number of treatment by group of medicines



To illustrate the role of covariates in the estimations, Table 4.6 shows all sample and subgroup analysis. Since the availability of data on QALYs gained is limited, two specifications were estimated for each group of medicines, one with and one without QALYs gained information. For example, models 1 and 2 are the estimates of the utilization of all oncology medicines without QALYs gained and with QALYs gained respectively. In general, the analysis confirms that price has a significantly negative effect on the number of prescriptions, especially in the medicine in the no cost-sharing group, i.e., a 10% percentage price decrease leads to 8% increase in prescription. Price sensitivity for NLEM medicine was nearly twice that of non-

NLEM medicine (-0.81 versus -0.48). As anticipated, cancer epidemiology and the 'doctors 'favourite' (proxied by market share) are also positively related to the number of prescriptions for the non-NLEM group where patients spend privately. In contrast, these variables have less or no significant effect on medicine utilization in model 2. The coefficients for product age bear positive signs and are not significant, at least at the five percent level. With a lower sample size due to lack of QALYs information, models 2,4 and 6 find price not to be a significant determinant on number of treatments. Surprisingly, the coefficient of QALYs shows a negative sign in the all sample and non-NLEM groups. For NLEM medicines, this coefficient shows a positive sign, i.e. the higher QALYs gained, the more utilization of the medicine.

Table 4.6 Determinants of medicine utilization

	Dependent variable=Access					
	All sample		Non-NLEM medicines		NLEM medicines	
	(1)	(2)	(3)	(4)	(5)	(6)
Log of price	-0.701***	0.076	-0.484***	-0.429	-0.813***	0.118
	(0.130)	(0.369)	(0.154)	(0.421)	(0.159)	(1.081)
Log of patient no.	0.609***	0.449*	0.539***	0.035	0.651**	0.913
	(0.136)	(0.221)	(0.157)	(0.354)	(0.254)	(1.032)
Market share (%)	0.087**	0.172	0.193***	0.290**	0.042	0.078
	(0.039)	(0.105)	(0.059)	(0.114)	(0.036)	(0.306)
Product age (Year)	-0.007	0.154	-0.066	0.212	-0.092	0.116
	(0.037)	(0.126)	(0.059)	(0.139)	(0.059)	(0.364)
QALYs gained		-0.016		-0.060		0.070
		(0.063)		(0.089)		(0.221)
_cons	10.271***	3.818	8.583***	8.937	12.771***	2.375
	(1.221)	(4.353)	(1.456)	(5.278)	(1.699)	(12.279)
N	93	24	45	16	48	8
R^2	0.528	0.531	0.394	0.536	0.523	0.663
adj. R^2	0.507	0.400	0.334	0.304	0.478	-0.179

Note: Robust standard errors in parentheses
* p<.1, ** p<.05, *** p<.01

4.6. Conclusion and discussion

This study investigated the impact of patent and price on access to, and the affordability of, oncology medicines to the Thai government and Thai population. With respect to the government, around 50% of oncology medicines on the Thai market are able to be provided by the Thai government and made available to everyone based on need and free at point of use. The results of this study confirm that price is not the significant rationale determining whether a medicine is put on the NLEM (Chongtrakul P 2005). However, whether medicines are patented does significantly decrease the probability of the medicine being listed, and hence available to the Thai population.

One reason why patent status, independent of price, may affect whether a medicine is listed is that patented medicines are new to the Thai market, and hence information on safety and efficacy might not be enough to outweigh the expense. In the case of the most clinically effective new patented medicines, a CEA study would need to be conducted and it usually takes longer to get consensus among stakeholders who are policy makers, economic evaluation working groups and patient groups. If there were no patents, then five more medicines would be likely to have been put on the list. With respect to affordability to the Thai population of non-NLEM medicines, most are considered unaffordable to the average Thai worker.

This study also suggests that medicine utilization is mainly determined by price. Utilization for NLEM medicine is more responsive to price than for non-NLEM medicine. This is because the system of NLEM is at the national level, while medicine delivery occurs at the local level, and this mainly depends on the procurement system of each hospital. Whether medicine deemed essential and expensive will be prescribed will depend on physicians. In the case of government hospitals or private hospitals in the UC system, physicians are imperfect agents for patients since their prescription choices may reflect their own direct financial or nonfinancial incentives due to insurers' reimbursement and cost control strategies (Danzon and Ketcham 2004). Therefore, prescription of medicines on the NLEM is more responsive to price. This agrees with the findings of Liu and Chollet(2006) that in low-income populations, the price elasticity of demand for prescription medicines may be particularly high (Liu and Chollet 2006). This is also supported by the CL

implementation of HIV medicines in Thailand. Though EFV was already on the NLEM, due to its high price physicians tended to prescribe it to severe patients only. After CL implementation, a significant increase in the number of EFV prescriptions was observed (Yamabhai, Mohara et al. 2011).

Conversely, as shown in this chapter, most non-NLEM medicines are unaffordable by the majority of the Thai population. These medicines tend to be prescribed in private hospitals to rich patients, regardless of price. Therefore, utilization of non-NLEM medicine is price-insensitive. A study by the RAND Corporation shows that price elasticities of around -0.2 are expected for all types of medical care (Meyerhoefer and Zuvekas 2010). Price responsiveness for medicines used for more acute conditions is higher (-0.3 to -0.6) (Goldman, G. F. Joyce et al. 2004; Landsman, W. Yu et al. 2005). In this study, the price elasticity of oncology medicines in the Thai market, specifically in the out-of-pocket market, is in this range, at -0.4.

This study has limitations. First, it focuses on access only affordability for the Thai government and population. Other factors such as access to hospital and medicine availability are also important factors affecting access (Kanavos P, Lim JY et al. 2002). Despite the fact that public hospitals should use NLEM as a reference and there is a regulation requiring hospitals to procure medicines that comply with the NLEM, needed medicines may not be available at the health care facilities close to the patient's home. This is because some chemotherapy treatments need complicated technology and a skilled health workforce, so the Pharmacy and Therapeutic Committee at rural hospitals might exclude those medicines from the hospital's medicine list. As a result, although the policy has provided affordability, the system may fail to deliver access to them. The availability of NLEM oncology medicines and to what extent Thai patients have to pay in order to reach to the point of service where they can get the 'free medicine,' depends on the price and physical access to medicine. There is a clear need for further investigation at the hospital level, where physical variables, including logistics and supply chain variables, are included in order to assess whether the NLEM can meet it objectives for all of the Thai population.

Second, the analysis presented here failed to estimate the size of the impact that patenting has on access, defined as the number of patients. Data are available to estimate the number of patients on an overall disease basis. For example, a patented medicine is suggested for treatment of colorectal cancer in patients for whom first-line based therapy has failed, and who are intolerant to other therapies. Data on the number of colorectal cancer patients are available. However, information on the number of patients who have failed with the first-line based therapy and who also are intolerant to other therapies is unknown. This may be the reason why the number of patients in the model is not significant, since it could be a redundant factor.

The relationship between access and the price of non-NLEM medicines is a challenge for future study. Since there are no systematic data showing the number of patients that would have received non-NLEM medicine but have received the NLEM medicine instead, the effect of patented non-NLEM medicines on access is subject to debate. This suggests that the further exploration of the demand estimation for non-NLEM medicines would be useful. This is important since for some medicines the number of patients requiring the medicine is relatively small. In addition, the demand for a patented medicine may be a static demand curve, as chemotherapy always has adverse effects (i.e. though there is a decrease in price, the doctor might not prescribe it since it might lead to severe adverse effects). Therefore, the effect of the patent status of non-NLEM medicines on access may not be as high as expected.

The burden of NCDs is already significant in Thailand, and yet universal access remains out-of-reach for most non-NLEM medicines. Calculating affordability in this study based on the average wage of a Thai worker may, however, lead to an overoptimistic result, since a significant proportion of the population earns less than this amount. This study thus confirms the unaffordability of cancer treatments which are not on the NLEM. From this study, patent status is assumed to be a barrier to access, given that it decreases the probability of being on the NLEM by around 36%.

Overall, it is clear that patents determine the listing of medicines on the NLEM, which in turn affects the affordability of the medicines, and ability of the Thai population to access them. In this case, appropriate measures could be introduced to help the poor access medicines they require. Since Thailand, as a member of the WTO TRIPS Agreement, is free to use various means to withdraw exclusive rights

for a particular medicine, such as CL, then these might help improve public health. However, this all refers to medicines currently on the market, and it has been suggested that such measures may prevent new medicines being released and hence disadvantage the Thai population in the future (The Nation 2007). It is to this issue that the next chapter turns.

CHAPTER 5 TO WHAT EXTENT DO NATIONAL PATENT POLICIES IMPACT ON NEW PRODUCT LAUNCHES

5.1. Introduction

There continues to be widespread debate over the implications of increasingly stringent international patent legislation, following the WTO-TRIPS Agreement, and recent TRIPS-plus developments (Mercurio ; El-Said 2005; Smith, Correa et al. 2009). The patent system is used to ensure that pharmaceutical R&D has the necessary income to support it, by granting exclusive rights over products to set a price higher than the marginal cost of production in order to recover expensive and high risk R&D costs (DiMasi, Hansen et al. 2003). However, although the higher prices sustained by patents finance the search for new innovations, higher prices also mean that fewer consumers can purchase goods incorporating those innovations in the period of the patent – usually 20 years (Guennif and Lalitha 2007). Granting inventors patent rights thus unavoidably involves a trade-off between two equally important public health goals: widespread access to existing medicines and the maintenance of incentives to create and make available new ones (Borrell and Watal 2003).

The 'access to medicines' discussion tends to focus upon the first of these goals, centred around affordability of existing medicines. Clearly patent status and price are important elements of access but, as we saw in the previous chapter, they are not the only elements. More importantly, the most fundamental requirement for access to a medicine is for the medicine to first exist. This 'existence' is expressed in two ways. First, and most basic, is that the product is actually discovered and marketed. Without adequate income for R&D arguably no new medicines would be developed at all, which would be a global welfare loss and the precise reason for the development of the patent system in the first place (Nogués 1993). However, there is a second, and more subtle but equally important expression of 'existence' and that is availability in the patient's domestic market and health system to be purchased. This is important given that fewer than 50% of the new pharmaceutical molecules marketed worldwide are sold in any given country (Lanjouw 2005). Even those

medicines that are eventually marketed in one country frequently appear in other countries some six or seven years after becoming available to consumers elsewhere (Lanjouw 2005). This 'diffusion rate' for new, or patented, medicines depends on the strategies implemented by product owners, which in turn is affected by local patent and pricing policy (Borrell and Watal 2003; Danzon, Wang et al. 2005). Indeed, it was the aim of the TRIPS Agreement to standardise patent legislation, making medicines more likely to be quickly diffused and hence available to a wider population (Lanjouw 2005).

This chapter seeks to understand the role that patents have as a determinant of the launch of all medicines in to the Thai market. Although, it would seem intuitive that weaker price regulation would facilitate entry, by virtue of increasing flexibility in price setting and securing returns on the product, the degree of patent protection, either provided by national patent law or acquired from the patent status of the product, is also important for medicine launches. Where it lacks patent protection, a pharmaceutical company may refuse to make a medicine available in a country. This was the experience in Brazil for example, where Boehringer Ingelheim refused to register tipranavir because of a lack of guarantees of protection from national patent law (Lotrowska 2008). Similarly, in India, when patent law had not been amended to comply with TRIPS, there were only two original anti-retroviral products marketed locally, while eight other molecules were not made available (Dhamija, Bansal et al. 2009).

In addition, monopoly control over medicines gives enormous power to pharmaceutical companies. While stringent patent law makes local markets more attractive, multinationals may delay or even avoid launching medicines in lower-priced countries because they are concerned about the implications for pricing in other markets (and the possibility of international (illicit or legal) trade in medicines, including parallel importing). On the one hand, the owner may want to market a patented medicine as quickly as possible to benefit from a local monopoly. On the other hand, as the product is already protected from duplication by local patent law, the owner may want to wait for some time after the global launch to avoid price discrimination which could damage the higher prices that the firms enjoy in high-income countries (Kyle 2006; Kyle 2007). For instance, Bayer introduced its new

antibiotic ciprofloxzcin in India eight years after the drug's global launch (Lanjouw 2005), and Roche refused to make Fuzeon available in South Korea since the Ministry of Health, Welfare and Family Affairs listed it at US$18,000 a year while Roche charged US$25,000 a year elsewhere (Weissman 2008).

In Thailand, the medicine market depends heavily on imports. The proportion of imports rose with accelerating rates during the nation's period of high economic growth in the mid-1990s, coinciding with the amendment of the Thai Patent Act, which effectively introduced patents for pharmaceutical products in 1992. Most medicines treating cancers are therefore also imported. Only one substance, out of 88, is produced locally and it is not a medicine intended to kill cancer cells but a supportive care therapy. As a result, access to medicines for cancer patients in the future depends heavily on whether multinationals or local subsidiaries decide to launch their products in the Thai market.

As indicated, Thailand provided significant pharmaceutical patent protection from 1992 until 2006, which was when the Thai government decided to issue CL. Although explicitly specified in the TRIPs agreement, countries that have implemented CL have usually faced a form of retaliation from the pharmaceutical company owning the patent for that medicine (Correa 2002). For instance, the CL on lopinavir/ritonavir, a second line treatment for HIV/AIDS patients, led Abbott, the patent owner, to state that, due to the CL, the company would no longer register seven products in Thailand. These seven withdrawn medicines were the heat stable form of lopinavir/ritonavir, a high blood pressure medicine (trandolapril/verapamil hydrochloride ER), a painkiller (ibuprofen), an antibiotic (clarithromycin), a blood clot medicine, (reviparin sodium), an arthritis medicine (adalimumab), and a Kidney disease medicine (paricalcitol) (Baker 2007).

There were many campaigns from activists to boycott Abbott's products. Although, these products were launched in the Thai market eventually, almost two years later, the CL implementation created a concern about future access to new products if pharmaceutical companies would stop launching new medicines in Thailand, or delay their introduction to the Thai market. In this situation, it is very challenging for policy makers to choose between the benefits of increasing access to current medicines at the possible cost of reduced access to medicines not yet on the market.

Previous studies have paid close attention to the market entry of generic medicines after patent expiration (Torres, Puig et al. ; Kanavos, Costa-Font et al. 2008; Laursen 2009; Granier and Trinquard 2010) and the barrier that patents present to generic entry (Rudholm 2001; Ellison and Ellison 2011). To date there has been little analysis of the determinants of international medicine launches. Some empirical studies focus on the effects of price regulations and price implications on New Chemical Entities (NCEs). They suggest that higher prices and larger markets have a significantly positive effect on the likelihood and speed of launch (Danzon, Wang et al. 2005). Only two studies specifically concerned with the effects of patent protection were found (Borrell and Watal 2003; Lanjouw 2005); these are described in the next section.

This chapter seeks to analyze the role that patents, including patent policy and patent status, have on the launch pattern across a range of cancer treating medicines over the period 1982-2009 in Thailand by using a duration analysis of the likelihood and speed of launch. Explanatory variables determining speed of launch include those related to the attractiveness of markets, patent protection and price setting rigidity. Section 2 presents the findings of the prior literature on the implications of patents on medicine launches. Section 3 describes the model used to estimate medicine launches in Thailand, and Section 4 presents the role of patents compared with other determinants of product launches. Finally, section 5 discusses the results and draws the main conclusions which lead to the policy implications that arise.

5.2. Extensive literature review

In order to assess how future access, through product launches, may be affected by patent policy, it is important to establish what factors influence the market entry decision and, in particular, to what extent patent status and price influence it. Literature relating to this issue was obtained through search of four relevant databases to cover the literature of trade and health: Econlit, Embase Classic and Embase, Global Health and Medline. Keywords were identified from papers related to this area published in peer reviewed journals. The search was then conducted using the following expression: (patent* or intellectual propert*).af. AND (public health or health* or drug* or pharmaceutical* or medicine*).af. AND (availabilit* or entry or launch).af. The full search strategy is shown in Appendix 4. Six hundred and

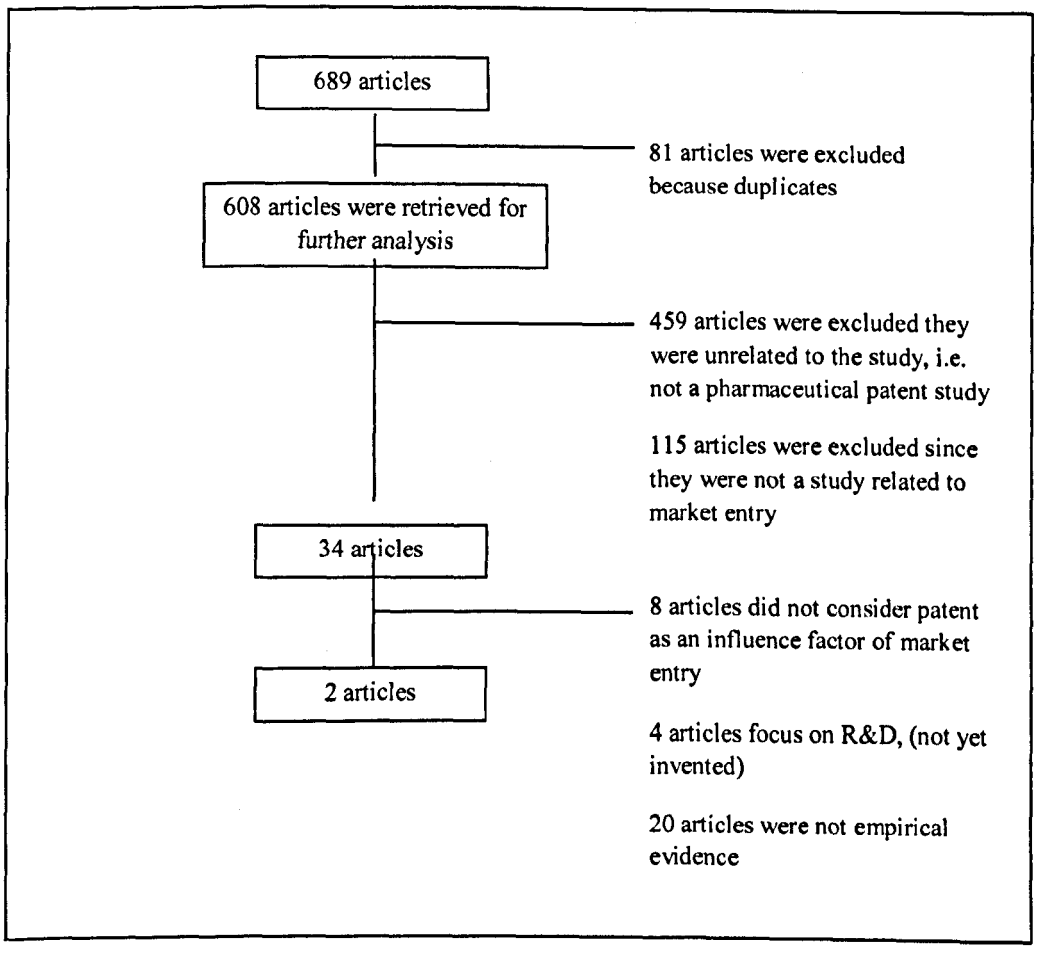
eighty nine articles written in English, and published between January 1st, 1990 and December 31st, 2011 were retrieved.

All the references were screened and 81 excluded as duplicates, leaving 608 for further analysis. To be included in the literature review, a study had to:

1. investigate the pharmaceutical industry. Studies looking at other types of innovation (i.e. energy, electrical equipment) were excluded;
2. deal with the issue of the implications of patent policy on medicine entry. Studies providing patent information of inventions or assessing the implications of patent on other topics (i.e. the implication of patent on price or access) were excluded; and
3. be an empirical study, either descriptive statistics or econometric methods. Theoretical and conceptual studies, as well as discussion studies, were not retained.

A flow-chart of the review is presented in figure 5.1. From the above databases, there were 34 journals and grey literature reports passed the first criteria. Twelve studies were excluded by the second criteria and 20 studies were excluded since they were not empirical work.

Figure 5.1 Flow-chart followed when performing a systematic review



It is surprising, given how much access is discussed, that such little attention has been devoted to studying the impact of patent rights on the introduction of medicine to domestic markets. There are only two empirical studies employing patent legislation as an explanatory factor for market entry. These studies estimated how intensively national patent enforcement speeds up or slows down the introduction of new medicines. Both studies were interested in the relationship between the entry decision across drug-country-year divisions and the patent factor. The first study used sales data on 15 patented ARVs filed in the US in a sample of 34 low- and middle-income countries providing or not providing patents to eligible drugs before 1st January 1995. Controlling for relevant market characteristics (dosage, efficacy and adverse reaction) and also adjusting income for purchasing power parity and income equality, the results from their probit model suggested that patent legislation increased the marginal probability of new drug launches from 28% to 33%. In

addition, the positive effect of patenting appears only to apply to a product that was launched in the US three years previously. For newly introduced medicines in the US, less than three years old, the patent legislation reduces the probability of having medicine in the local market of low- and middle-income countries (Borrell and Watal 2003).

With a broader scope of medicines, a similar question was explored by Lanjouw (2005), who investigated NCE global launches by year in 68 countries at all income levels, including Thailand, in the period 1986-2002. A probit and a log-logistic hazard model estimation were used to estimate the probability and speed of medicine launch in a given country within either two years or ten years of the medicine's first appearance on the global market. Patent variables include whether the patents are issued for a short or long period, and whether they are process or product patents. This study also considers the level of patent protection, which is a variable that takes on values between 0 and 1, with a higher value indicating that a country has more limits on how patent rights can be curtailed. Other control variables are whether the country has moderate or extensive price control, and whether the medicine is on an essential list, with control for other socio-economic variables. The observed probability that a drug is launched in a low- or middle-income country within two years is about 9%. The estimates suggest that going from a regime with only short process patents to one with long process patents significantly encourages rapid entry. A long process patent regime still allows for possible generic entry and this appears to be important. The marginal effect is to raise the probability of launch within two years by 2-3 percentage points (or about a 30% increase). However, the individual incremental effects of adding short and then long product protection are insignificant (Lanjouw 2005). This study also presented a policy simulation in some countries by using the empirical implications of the econometric model discussed. For Thailand, this study suggested that the probability of launch within two years, with a long patent term and no price control policy, is 43%, compared with a scenario in which there are no product patents and price control policies exist, in which the probability of launch is 26%.

The model employed in these two studies was multi-country, including high-income and low-income countries. Although the results are more generalizable, they

sometimes mislead. Under some circumstances and model assumptions patent protection has a positive effect for some countries, while under other circumstances it has a negative effect. Single country studies are particularly effective at maximizing their explanatory leverage by exploiting the availability of comparable units of analysis, whether over market or medicine characteristic variations within the country (Pepper D. Culpepper 2005). Therefore, an analysis should be performed to determine how patent protection will affect market entry in depth in a single country. This would be especially beneficial to Thailand where the patent and health system is different from general middle-income countries.

5.3. Method

Duration analysis is a well-known tool used to analyse transition time-to-event data. It is also known as survival or hazard model analysis (Heckman and Singer 1984).Though this technique is widely used in the medical and biological sciences, it is also applied in engineering (as an analysis of reliability and failure time), as well as in social and economic sciences (John P. Klein and Goel 1995). The benefit of this method is that it takes time into account, by adjusting for the period at risk automatically and incorporating time-varying covariates, or explanatory variables that change with time (Kiefer 1988). While each product has a time series of annual observations, static models are estimated only with each firm's last observation. Duration models, by estimating a 'hazard function', take advantage of much more data; they can be thought of as a binary logit models that includes each product year as a separate observation (Jones and Branton 2005). Therefore, the hazard model was chosen to analyse the speed of drug launch since it accounts for the fact that firms change through time and the need to determine the product launch probability at each point over that time.

5.3.1 Estimating the hazard function

In practice, many hazard models are difficult to estimate because of their nonlinear likelihood functions and time-varying covariates (Jenkins 2004). Essentially, each hazard model is different based on the nature of the underlying distribution of the dependent variable. There are four major techniques to estimate the hazard model:

exponential regression, normal and log-normal regression, stratified analysis and Cox's proportional hazard model.

Exponential regression is a model that assumes that the survival time distribution is exponential. In the normal and log-normal regression model, it is assumed that the survival times come from a normal distribution; the resulting model is essentially identical to ordinary multiple regression. Stratified analysis is used to test whether the relationships between the independent variables and survival are identical in different groups. Cox's proportional hazard model is not based on any assumptions concerning the nature or shape of the underlying survival distribution (Wu and Tuma 1994). The model assumes that the underlying hazard rate is a function of the independent variables.

A Cox's proportional hazard model, as known as the Cox model, was employed in this study. This model, proposed by David R Cox in 1972, is the most-often cited in survival analysis (Henderson 1995). The Cox model is the most general of the regression models because it estimates the relationship between the event rate (i.e. launch of drug in Thailand) and explanatory variables without having to make any assumptions about the shape of the underlying survival distribution. The Cox model presumes that the ratio of the hazard rate to a baseline hazard rate is an exponential function of the parameter vector. The hazard function can be estimated using the following equations:

$$\frac{h(t)}{h_0(t)} = e^{X'B} = e^{b_1x_1+b_2x_2+b_3x_3+\cdots+b_nx_n} \quad (1)$$

$$h(t) = h_0(t).e^{b_1x_1+b_2x_2+b_3x_3+\cdots+b_nx_n} \quad (2)$$

Where *h(t)* denotes the resultant hazard, given the values of the *n* covariates for the respective case and the respective survival time (*t*). The quantity $h_0(t)$ is called the *baseline hazard* or *underlying hazard* function and corresponds to the probability of reaching an event when all the explanatory variables are zero. The base line hazard function is analogous to the intercept in ordinary regression (since $\exp^0=1$). The regression coefficients β_1 to β_n give the proportional change that can be expected in the hazard, related to changes *n* in the explanatory variables. The assumption of a constant relationship between the dependent variable and the explanatory variables is

called a proportional hazard that remains the same for all analysis periods. To estimate a hazard model, each product contributes only one launch observation ($y_{it} = 1$) to the Cox model. Time-varying covariates are incorporated simply by using each annual data for their product-year observations.

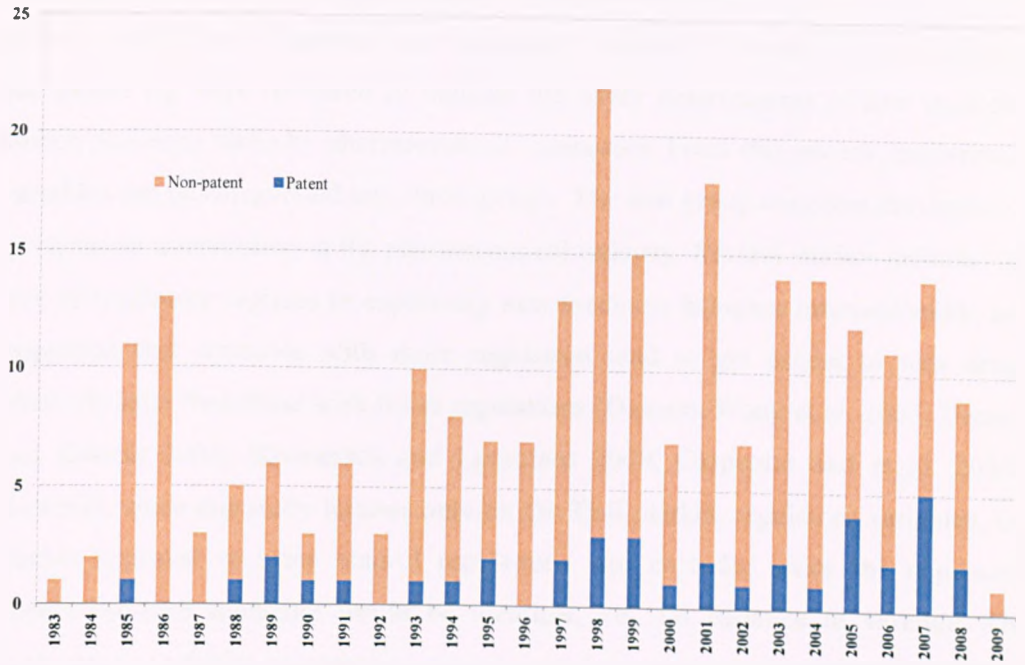
5.3.2 Data

Dependent variable: The launch and lag data

The Thai launch data are drawn primarily from the Thai Food and Drug Administration database.[16] The database identifies the registration number which shows the year that a product owner requested a market approval from the Thai FDA. For missing data, the launch data are obtained from IMS identifying the month and year that a product first had retail sales in Thailand. For each product, IMS provides the trade name, active ingredient, and the firm making the product. Coverage includes entry of cancer medicines during 1982-2009 in the retail sector and also the hospital sector in Thailand. The Thai data cover a broad set of therapeutic classes treating cancer launched in the Thai market during that period. The combined dataset covers 248 samples, from 88 active ingredients, of all medicines launched. The number of medicines launched in each of the years covered is shown in figure 5.2. The first medicines was registered in Thailand in 1983 and, on average, nine medicines, whether original or generic, are registered annually thereafter, although the number is higher in later years.

[16]http://wwwapp1.fda.moph.go.th/consumer/conframe.asp

Figure 5.2 Number of new oncology medicines in Thailand by year of registration



A recent study of the introduction of NCEs worldwide from 1982 through 2003 suggests that the US was the leading market for first launch choice (Citeline Drug Intelligence ; Grabowski and Wang 2006). Thus the US approval date is used as a reference to indicate how quickly a product comes to launch in the Thai market. The set of medicines available in Thailand in 2008 were searched for by propriety name in each chemical substance in the US FDA/Center for Drug Evaluation and Research[17] to find the approval date given for sale in the US market. For products with the same trade name that were not selling in the US market, the first product with the same generic name sold in the US market was used as the reference launch date in the US. This information indicates how long it takes for an approved medicine from the US to be available on the Thai market. The dependent variable, launch lag, is a constructed dummy variable. It takes the value of 1 if it is introduced in to Thailand within two years after US approval, and 0 if it is introduced in to Thailand more than two years after.

[17] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Explanatory variables

This section describes the independent variables influencing the lag in launch between the US and Thailand (the dependent variable). Previous studies analysing the launch lag were reviewed to indicate the likely determinants of new medicine launch decisions taken by pharmaceutical companies. From this review, explanatory variables can be categorised into three groups. The first group concerns the degree of government intervention in the pharmaceutical industry. Several studies included the role of regulatory regimes in explaining new medicine launches internationally, and suggested that countries with more regulation tend to get access to new drugs relatively later than those with fewer regulations (Danzon, Wang et al. 2003; Danzon and Epstein 2008; Stremersch and Lemmens 2009; Carpenter and et al. 2010). However, since this study focuses only on the Thai market, regulatory variables, i.e. market approval or price control regulations, are excluded since the regulatory impact on each medicine would be identical, i.e., no variance in variable. The explanatory variables representing government intervention were constructed based on four important policies favouring the pharmaceutical industry during 1990 to 2008. Four dummy variables were created to examine whether these policies affect the speed of new medicine entry or not. The first variable reflects the amendment of Thai patent law in 1992 (variable **PALAW92)** to increase the level of patent protection, either a product or a process patent for inventions in all fields of technology. The second variable represents the withdrawal of the Committee on Pharmaceutical Patent in 1999 (variable **PALAW99)**. This committee was intended to protect consumers from manufacturers' rights to market exclusively, through monitoring and comparing international medicine prices, and dispensing corrective measures where inappropriate price behaviour was found. Therefore, the amendment in 1992 secured pharmaceutical companies from duplication and the amendment in 1999 confirmed their right to price-set.

The third variable indicates the introduction of a universal health-care coverage scheme in 2002 (variable **UC02)**. This scheme offered comprehensive health care that included not just basics, such as free prescription drugs, outpatient care, hospitalization and disease prevention, but more expensive medical services, such as radiotherapy, surgery and critical care for accidents and emergencies. This shifted

the market from individual based financing to government financing. The fourth variable is the CL policy implemented during 2006-2008 (variable **CL06**). As mentioned previously, stringent patent policy might attract product owners to introduce a medicine quickly, and withdrawing patent rights of some medicines, under CL, might make a patent owner reluctant to launch a new patented medicine in that market. These four dummy variables (**PALAW92, PALAW99, UC02, CL06**) take a value of 1 after the policy implementation year of 1992, 1999, 2002 and 2006 respectively to capture the effect of these four policies.

The second group identifies market-driven characteristics. The larger the potential sales, the more likely that the product owner would launch with shorter delay. Lanjouw (2005) investigated launch patterns of new medicines in 68 countries over two decades, 1982-2002. The results suggested that GDP per capita and size of population, representing market opportunity, are significant determinants in high income countries (Lanjouw 2005). Specifically focusing on oncology treatment in Thailand, this study selected two variables, percentage of medicines imported (**DIM**) and number of patients (**NOP**) to represent market opportunity. As mentioned previously, most cancer medicines selling in Thailand are imported, so the high proportion of imported medicines shows potential market encouraging market entry. Therefore, the percentage of imported medicines was chosen to represent market attractiveness. The health problem presented by cancer also denotes the need for treatment. Number of cancer patients could represent the level of the problem, with data taken from the Thai National Cancer Institute. This institute has collected data for more than ten years through five cancer registries in Thailand (Sriplung, Wiangnon et al. 2006). Three-year cancer incidence in Thailand covering the years 1990-2008 has been regularly reported in 'Cancer in Thailand' reports. The trend in incidence for the 1980s was estimated by using an equation derived from the actual trend from 1990 onwards. This variable could hasten drug entry because it is expected that an increasing trend will denote higher demand and hence generate higher sales. These two variables are all expected to have a positive effect on the launch speed.

The last group of variables represents market structure and product characteristics. Sales, sales volume, and price were found to be significant determinants of market

entry in previous literature (Danzon, Wang et al. 2003). Unfortunately, due to budget limitations, this study was able to acquire data of the year 2008 only, not the data when the products were introduced. Therefore, the expected profit of each product in the year 2008 had to be constructed by accumulating profit margin, price and cost, and sales volume. Since the opportunity to charge a price greater than the marginal cost to get higher profit may stimulate firms to introduce products into Thai market more quickly, this study uses price set by the pharmaceutical companies from IMS and assumes that the price was equivalent to the introduction price, and was stable during the study period. This is likely to be more true for the original products where discounts on price are rare (Borrell and Watal 2003). To be able to measure this profit earned, the marginal cost of production is estimated. This study employed the Indian price as a proxy of marginal cost. Profit margin of each product was calculated by subtracting IMS price from Indian price. The information on sales volume of each medicine was also obtained from IMS. Expected total profit earned, **EXPRO**, was derived from multiplying the profit margin and sales volume in 2008.

Two other important factors are that large firms always gain advantages in pharmaceutical regulation (Carpenter, Brian Feinstein et al. 2000). This is because large firms have economies of scope from sharing R&D cost and experience gained across many products available for sale in the same therapeutic area (Singh A, Gilbert JK et al. 2003). Kyle (2003) used discrete-time hazard models and found evidence that multiple launches in a given market and market competition situation were significant determinants of new medicine launches from 1980 to 2000 in G7 nations (Kyle 2003). Pharmaceutical companies gain experience from several market launches, enabling them to come up with more efficient launch strategies leading to faster introduction of new products, while intense competition may slow down market entry as the expected return would be diminished (Lichtenberg and Philipson 2000).

This study therefore uses the total number of products (**TP**), within the same company, sold for cancer treatment as a proxy of economy of scope and market experience. The hypothesis is that the higher the number of products being sold the more likely the launch of a new product, as the company faces a lower cost of

market entry. The number of products from different firms previously on the market in the same therapeutic area, **(PM)**, indicates the level of market competition.

The variable of interest that this study wants to test is patent, **PAT.** Borrell and Watal (2003) concluded that patents have a positive impact on medicine availability. The hypothesis of this study is that stronger patent status speeds up the market launch of a medicine in Thailand. Thus, it takes a value of 1 if the medicine is patented and zero if not. However, patents may slow product entry if the product owner wishes to wait after the global launch of a new product to enter a developing country market with a lower price, which will allow them to capture market share to avoid price discounting (Borrell and Watal 2003). All explanatory variables are defined in Table 5.1 with summary statistics.

Table 5.1 Variables used in estimation and their definitions

Variable	Definitions	Data sources
Patent law amendment in 1992 (PALAW92)	Dummy=1 if launches after 1992	
Patent law amendment in 1999 (PALAW99)	Dummy=1 if launches after 1999	
Universal coverage policy in 2002 (UC02)	Dummy=1 if launches after 2002	
CL policy in 2006 (CL06)	Dummy=1 if launches after 2006	
Drug imported (DIM)	Share of imported medicines from total medicine consumption	Thailand Health Profile
Log of number of patients (NOP)	Number of patients diagnosed as cancer	NHSO
Prior number (PM)	Number of products, with the same ATC code, on market prior introducing	Thai FDA
Total products (TP)	Number of products, with different brand in the same ATC code within one seller	IMS
Log of expected profit	Multiplying between profit	IMS

Variable	Definitions	Data sources
(EXPRO)	margin and sales	
Patent status (PAT)	Dummy=1 if that medicine is patented medicine	Chapter 2

5.4. Results

5.4.1 Lag in introduction of patent and non-patented medicines

The lag between approval dates of cancer medicines in the US and the registration year and launch date in Thailand is shown in Figure 5.3. The average lag is 5.31 years for non-patented and 3 years for patented medicines. Fifty-seven products were introduced in Thailand *before* they were approved in the US.

When the samples with negative lag length were excluded, the average lag is 9.1 years for non-patented medicines and 4.5 years for patented medicines. Patented medicines were introduced to Thailand significantly faster than non-patented medicines. Although there were 248 products at the beginning, for this chapter the total number of observation is 231 since 17 products were not found in the US market and thus excluded from analysis. Table 5.2 shows the two groups mean comparison of non-patent and patented medicines. On average, patented medicines were launched in Thailand 2.3 years before non-patented medicines were significant at the 10% level. Patented medicines were launched even faster when considering only positive lags; the length for non-patented medicines to be introduced in Thailand was twice as fast as the launch lag of patented medicines, significantly different at the 0.1% level.

Figure 5.3 Lag (years) of overall medicines and patented medicines

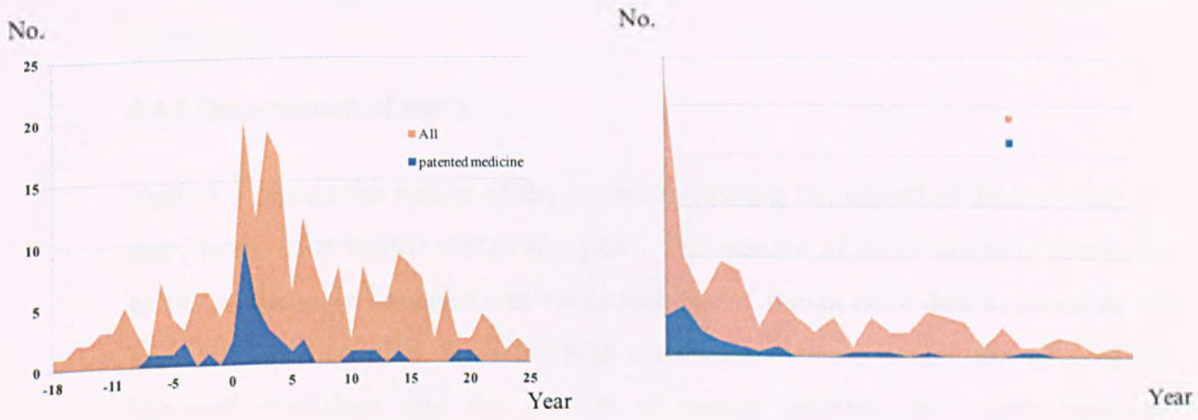


Table 5.2 Mean comparison of lag between non-patent and patented medicines

Group	All		Positive lag only	
	Non-patented	patented	Non-patented	patented
N	194	37	149	31
Mean (years)	5.31	3	9.10	4.51
Min (years)	-18	-8	0	0
Max (years)	25	20	25	20
Mean comparison test	t = 1.458, (P = 0.0731)		t = 3.668, (P= 0.0003)	

There could be three possible reasons that non-patented medicines, on average, are introduced in the market later than an original patented medicine. First, patent owners may have an incentive to distribute a patented medicine more quickly since market exclusivity usually means higher prices and greater income flows which, in turn, may encourage patent holders to launch new product in Thailand soon after they are launched in the US, provided the price can be set close to the target price in the major market (since the pharmaceutical market in Thailand is not regulated). Second, some medicines in this study may be currently patented, or previously patented, in the countries where the generic pharmaceutical companies are capable of manufacture. It could take considerable time until all patents covering a medicine expired and bioequivalent test data were ready to register in Thailand. Third, patented medicines generally has a higher competitive advantage, as it promises higher efficacy or more convenience, which may attract higher demand from customers compared with non-patented medicines which are likely to be considered 'inferior' in some way and also face price competition. The next section will investigate if a patent has a role in market entry, compared with other important determinants.

5.4.2 Determinant of entry

Table 5.3 reports the results of the models estimating the impact of determinants on entry to the Thai market within two years. The number of observations is decreased to 147 as there are limitations in the availability of Indian price data to establish the expected profit variable. Since the high correlation between policy, the value of the imported medicines and the number of cancer patients, they were analyzed

separately to avoid possible multicollinearity. However, the model with all variables is also shown as model 4 for completeness. The correlation table among variables is shown in Appendix 8.

Starting with model 1, the first three dummy variables indicate whether Thailand offers policies that positively affect pharmaceutical entry. They are the patent law amendment to protect product patents in 1992, the removal of the Committee on Pharmaceutical Patent and amendments to allow for a six years of protection for petty patents in 1999, and the introduction of universal coverage in 2002. It can be seen that these policy variables encouraged rapid entry. In model 1, the marginal effects of the increase in the probability of launch within two years are 6.5, 2.8, and 1.6 times for the structural break variables of 1992, 1999 and 2002 respectively. However, the dummy variable corresponding to the introduction of universal coverage is not statistically significant.

The next three variables capture the size of market, as shown in models 2 and 3. They are percentage of imported medicines, number of cancer patients and market size. These first two variables are significant and positive determinants of medicine launch. An increase in the share of imported medicine leads to an 11% increase in the probability of the entry of a new drug to Thailand. The number of cancer patients increases the probability of entry by 3.5 times. Market size is, however, not significant as a determinant of launch.

As expected, the dummy variable of CL shows a negative impact on rapid entry. It decreases the probability of a rapid launch by 55%. This effect is statistically significant at the 5% level in model 1 and at the 1% level for models 2 to 4. The last four variables indicate firm and medicine characteristics. They are the number of products on the market before that product enters, total number of medicines by the same manufacturer in the market, expected profit and patent status. There is a decline in the likelihood of entry if there are many medicines in the same ATC market. For example, if there is product already on the market, it decreases the probability of entry of new comers by around 10%. This determinant is significant and robust in all models. Firms that have many products for sale in the same ATC group choose to introduce new medicines some 6% more quickly. This variable is also significant at the 5% level in the model 1, and at the 10% level in models 2-4.

The surprise results were found in the last two variables, expected profit and patent status. Although they do have a positive impact on medicine entry decision, they are not significant determinants of entry.

In conclusion, it seems that policy variables have a strong and significant impact on rapid entry, as do market-based factors. Stringent patent protection, by changing the patent law to protect product patents and weakening patent protection, affects the launch lag significantly. In contrast, product-driven factors are weakly significant and have minimal impact on the rapidity of launches.

Table 5.3 Hazard model estimates of probability of launch within two years

	Model 1: Policy		Model 2: Drug imported		Model 3: Number of patients		Model 4: All variables	
	Coefficient	Hazard ratio	Coefficient	Hazard ratio	Coefficient	Hazard ratio	Coefficient	Hazard ratio
Patent law amendment in 1992	1.859***	6.420***					-1.132	0.322
	(0.698)	(4.480)					(1.060)	(0.342)
Patent law amendment in 1999	0.913	2.492					-0.462	0.630
	(0.568)	(1.416)					(0.716)	(0.451)
Universal coverage policy in 2002	0.668	1.951					-0.790	0.454
	(0.456)	(0.888)					(0.659)	(0.299)
Drug imported (percentage)			0.109***	1.116***			-0.040	0.960
			(0.016)	(0.018)			(0.065)	(0.063)
Number of patients					1.322***	3.752***	2.648**	14.128**
					(0.204)	(0.765)	(1.114)	(15.732)
CL	-0.791**	0.453**	-1.150***	0.317***	-1.048***	0.351***	-1.121***	0.326***
	(0.389)	(0.176)	(0.397)	(0.126)	(0.390)	(0.137)	(0.408)	(0.133)
Prior products (number)	-0.090**	0.914**	-0.101***	0.904***	-0.106***	0.900***	-0.110***	0.896***
	(0.037)	(0.033)	(0.037)	(0.033)	(0.037)	(0.033)	(0.037)	(0.033)
Total product	0.065**	1.068**	0.058*	1.059*	0.062*	1.064*	0.059*	1.061*
	(0.032)	(0.034)	(0.033)	(0.035)	(0.032)	(0.034)	(0.033)	(0.035)
Expected profit	0.062	1.064	0.013	1.013	0.001	1.001	-0.039	0.961
	(0.074)	(0.079)	(0.075)	(0.076)	(0.074)	(0.074)	(0.077)	(0.074)
Patent status	0.386	1.471	0.360	1.434	0.454	1.574	0.523	1.688
	(0.385)	(0.567)	(0.399)	(0.571)	(0.390)	(0.615)	(0.400)	(0.675)
N	147	147	147	147	147	147	147	147
Log lik.	-200.496	-200.496	-199.056	-199.056	-196.484	-196.484	-195.447	-195.447
Chi-squared	73.397	73.397	76.931	76.931	82.076	82.076	84.149	84.149

5.5. Conclusion and discussion

This study examined factors that might determine the entry of new medicines to the Thai pharmaceuticals market, specifically those for cancer care. The theoretical model is based on the assumption that possible entrants will launch more quickly when there is a supportive patent policy and the market is attractive and profitable. The empirical results show that policies related to patent law have a significant and positive impact on the rapidity of new product launches in Thailand. These results contrast with the previous studies of Borrell(2003) and Lanjouw (2005), which showed that providing patent protection has a minimal impact on medicine launches on a cross-sectional, cross-country basis. This might be because the data set included in both studies covered different health systems which the models cannot capture adequately. The study presented here also found that policies favouring price setting, a large market and high demand are also positive and significant determinants of a rapid launch.

There is little evidence, however, that expected profit enhances the likelihood of quick entry into the Thai market, which contrasts with the study of Rudholm (2001) who found that the profit opportunity has a positive impact on entry to the Swedish pharmaceutical market. This might be because multinational companies do not see Thailand as a significant profit making country as the market size is very small. They might expect more marginal profits from marketing in Thailand or price positioning for other regional markets.

There are, of course, limitations to the study presented here. For instance, that the estimates of the delay are based solely on the products that were launched in Thailand, and that it focuses only on cancer medicines. These both affect generalizability to other countries and therapeutic areas.

Most importantly from the perspective of this thesis, CL is shown to have a significant and adverse effect on the speed of new medicine launch in Thailand. It is likely that this will slow access for patients to new medicines available in other countries. This will have implications for public health and social welfare. If, for example, five percent of new drugs are no longer marketed in a country due to CL, this may be damaging, or not, depending on which drugs were in that five percent. A

new superior antibiotic medicine, for instance, could save society approximately $4.6 billion by 20 years after approval (Spellberg, Miller et al. 2007). The implication is that removing patents to gain increased access now, would result in patients foregoing the opportunity to get this new medicine in the future, as it would not have been launched. The balance to be assessed in this example is whether the increased access now was worth more than $4.6 billion opportunity cost; if so, CL is a pareto-optimal policy, if not, it has resulted in a second best situation. In the extreme case of patent termination, the study of Huges et al. (2002) identified that for every dollar in consumer benefit realized from providing greater access to current medicines, future consumers would be harmed at a rate of three dollars in present value terms from reduced future innovation (Hughes, Moore et al. 2002).

Future research to expand this area is therefore essential to address more precisely the costs and benefits of CL to current and future health and welfare. For example, to investigate the forgone health cost, in terms of QALYs or DALY, from the seven new medicines withdrawn from the Thai FDA registration process as retaliation to the introduction of CL. This figure will need to be compared with the health gain, in QALYs and DALYs, from increasing access to current medicines subject to CL over the period until the patent licence expired and/or the price would have fallen in any case. This is essential if decision-makers are to evaluate policy options relating to patents and access to medicines which balance the full health and welfare needs of the Thai population over time.

Further, pharmaceuticals often have acceptable substitutes, and some "lifestyle" drugs may not be of great clinical importance. Future research is required to explore the therapeutic significance of pharmaceuticals that are launched slowly, or not at all, and the extent to which this failure is associated with substitutes being available in the market. Therefore, the lack of new medicine being introduced to local markets might not lead to adverse effects as expected. Clearly, multi-national pharmaceutical companies are not the only source of new medicines, as evidence suggests that 20% of new breakthrough patented medicines were developed by public institutes (Bhaven 2009). It is also estimated that of the total global medical R&D funding of $100 billion in 2010, approximately 44% was provided by the public sector in the form of funds flowing to government research bodies or government grants provided

to private bodies (Bird and Cahoy 2008). This means that access to medicines in the future might not depend so heavily on the private pharmaceutical sector, if the public sector is able to develop and distribute their own products.

Stringent patent protection might encourage quicker entry of innovative products, and at the same time stringent patent protection will protect local capacity, and also cause the country to lose that capacity. In the longer term that same local capacity could be an alternative source of entry, and the country offering extensive patent protection may lose the benefits of that activity and have fewer new products in the market overall as a result (Maskus 2000). Finally, giving innovators the strongest patent protection might be viewed as worthwhile irrespective of its effect on entry, on the grounds that it might boost R&D and the discovery of new NCE.

A final implication of CL worth mentioning is that CL might come with another price: that industry more generally may mistrust a licensing nation's promises to protect and enforce patent rights (Vaughan 2001). As a result, industries that find the security of property rights lacking in a given nation may avoid engaging in FDI with that nation (Bird and Cahoy 2008). FDI is a major potential source of economic growth for recipient nations, withdrawal of which might arise as a reaction to CL practices, which could force developing nations to pay a particularly heavy cost for providing needed medicines for its citizens. The next chapter will examine the implications of strengthening and weakening patent protection for FDI.

CHAPTER 6 THE EFFECT OF PATENT PROTECTION ON FOREIGN INVESTMENT AND INNOVATION

6.1.Introduction

The TRIPS Agreement established international agreement on minimal standards for IPR protection for WTO members. TRIPS requires a minimum patent protection of 20 years for inventions in several areas, including the pharmaceutical sector. TRIPS clearly states that "*the protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations*" (World Trade Organization 1995). Although technology diffusion can take place through a variety of channels that involve the transmission of ideas and new technologies, such as importation of high-technology products, adoption of foreign technology and acquisition of human capital through various means, FDI has been suggested to be the most important channel for technology transfer (Borensztein, De Gregorio et al. 1998). Therefore, the strengthening of IPR protection through the amendment of patent law to comply with TRIPS by low- and middle-income countries should motivate foreign investors to invest capital in these countries (Wade 2003). The benefit to the host country is not limited to the direct monetary benefit this brings to stimulate their national economy and labour market, it is also the indirect benefits of the transfer of knowledge and the improvement of labour skills (Wu 2000; Lee 2004).

To promote a country as the best place to invest, several policies maybe introduced, such as de-regulation, liberal investment rules and operational flexibility (Kumar 1998). Strengthening IPR protection is one policy promoted. Firms for which such rights are crucial, especially pharmaceutical companies, are unlikely to invest in manufacturing or research and development activities directly in countries where patent protection is weak (Mansfield 1994; Saggi 1999). This can be seen from the many developing countries that changed their patent laws to comply with the TRIPS Agreement earlier than the agreement required, in order to attract FDI (Morin 2009).

It was believed that these countries would benefit from new knowledge and more advanced technology.

In Thailand, the main justification in favour of the 1992 IPR strengthening, which included pharmaceutical patenting, was to encourgae multinational companies to invest in Thailand (Kuanpoth 2007). The other expected benefit of strengthening patent protection for medicines is that this could increase domestic capabilities and strengthen the local pharmaceutical industry through the transfer of new technologies to the country (Howard A. Kwon 1995). It certainly appears as if this amendment to the patent law has worked, since Thailand has been one of the fastest growing economies in the world for more than two decades and was ranked among the top twenty countries in the world as a place to do business (Ismail and Yussof 2003).

Although this strengthening of patent protection is designed to lead to greater technology transfers through the inflow of FDI, the TRIPS Agreement is also suggested to be an obstacle to access to patented medicines. However, this agreement has a passage, reaffirmed in the Doha Declaration of 2001, that allows countries facing a public health emergency to grant CL for patented pharmaceutical products. The CL allows the country to either manufacture or distribute the product itself, or to import medicines manufactured overseas. However, the removal of a patent owner's rights often provokes retaliation by the pharmaceutical industry, as well as wider international investment sources. The crucial question is whether pharmaceutical companies, and other investors, may mistrust the licensing nation's promises to protect and enforce patent rights once CLs are issued, and whether industries that find the security of property rights lacking in a given nation may avoid engaging in direct investment with that nation, within the pharmaceutical and chemicals sector specifically, or the wider economy more generally.

The purpose of this chapter is to address the question: what impact has stronger patent protection had on FDI and innovation, and what happens to FDI and innovation if a country decides to weaken its patent system through the implementation of CL? The experience of Thailand in dealing with patenting and FDI issues is used as the context, as it has significant experience with IPR. On the one hand, IPRs protection in Thailand is considered extensive when compared with other countries in the region, as the amendment of the Thai patent law in 1992 was

eight years before the effective date, or 13 years before the transition period allowed for developing countries, to comply with the TRIPS Agreement of WTO (Kuanpoth 2007). On the other hand, during 2006-2008, Thailand issued CLs for a number of HIV/AIDS retroviral drugs, a heart medication and four cancer medicines, becoming the country with the highest number of CL issuances in Asia. After the Thai government introduced CL on seven medicines, the Office of the United States Trade Representative (USTR) elevated Thailand's ranking from a country on the Watch List (WL) to one on the Priority Watch List (PWL) in the USTR's Special 301 Report. In another move by the USTR, duty-free access to the US market for three Thai products under the US GSP was withdrawn in July 2007. This has raised concerns in Thailand that such trade sanctions and policies may undermine FDI, or that their effect might outweigh the expected benefits of the CL.

Although it has been 18 years since the patent law amendment, empirical evidence of the impact of patent policy on FDI is absent, meaning that several critical questions have yet to be answered, including whether inward FDI increased after the amendment of the Thai patent law and whether innovation activity (i.e. patents registered in Thailand by national patent owners) has increased. Since the current bilateral free-trade agreement (FTA) discussions between the USA and Thailand have caused great concern over the ability of the Thai government to issue further CL, such questions are critical to inform policy makers on the appropriate balance between public health and the wider investment and trade impacts of free-trade negotiations.

This paper consists of six sections. Section 2 summarises the previous findings relating to the impact of IPR on FDI. Section 3 describes the background of the FDI promotion and trade policy in Thailand since the 1970s. The data and estimation procedures, econometric model specification and other methods are described in Section 4. Section 5 presents the empirical results, and section 6 draws some conclusions and provides recommendations related to patent policy based on this empirical work.

6.2. Empirical evidence concerning the impact of IPR protection on FDI

This study focuses on issues of attracting FDI, with a particular emphasis on the role of patent legislation in this process. There is a lot of discussion about the benefits of strong patent protection as an incentive to foreign investors to invest in developing countries, but this study wants to establish what the *empirical* evidence is of the role of patent legislation on FDI. Therefore, an extensive literature review of empirical evidence concerning what extent patent law helps determine investment was conducted.

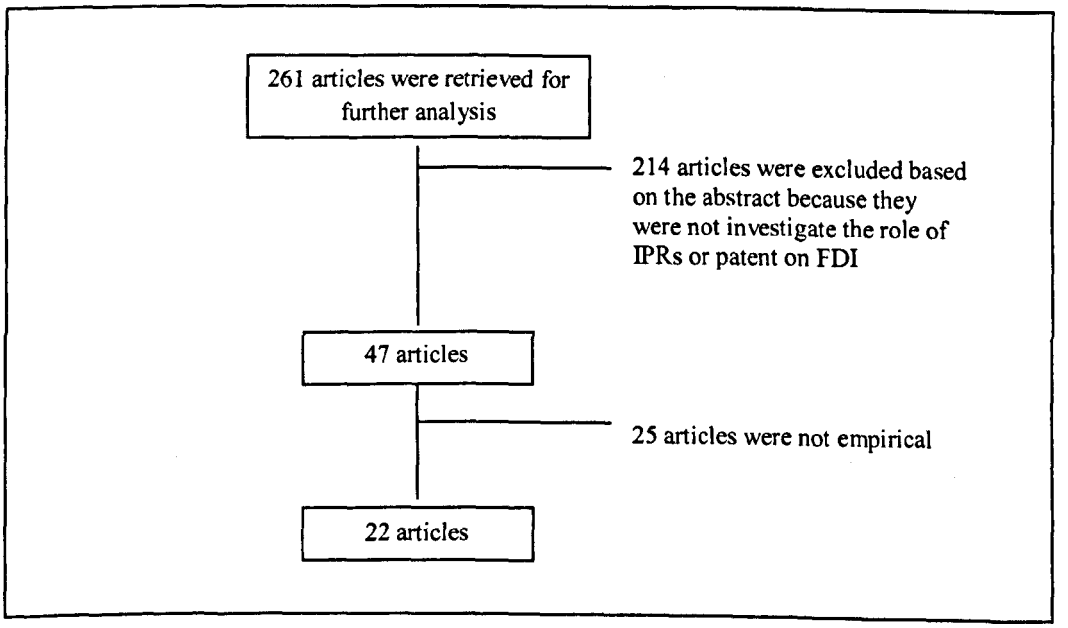
A three stage strategy was used to search for and select articles included in the literature review. First, a computerized search by using multiple keywords (see Appendix 9) in four databases, namely Econlit, Embase Classic and Embase, Global Health and OVID Medline, which are the most relevant databases to public health and economics. In the second stage, English language papers and those published between 1 January 1990 to 31 December 2011 were retrieved to identify literature published around the time of the implementation of the TRIPS Agreement. Finally, a manual search of the reference lists of the articles retrieved was done to include journal articles, and grey literature including technical reports from government agencies or scientific research groups, working papers from research groups or committees and white papers, not already identified. By doing so, 261 potential articles for the literature review were identified. Two criteria were then used to select and assess the potential studies. To be included in the literature review, a study had to:

1. deal with the issue of the implications of IPRs or patent protection on FDI. Studies dedicated to other types of implications (i.e. access or research and development) were not retained; and,
2. include an empirical study, using either descriptive statistics or econometric methods. Theoretical and conceptual studies as well as discussion studies were not retained.

6.2.1 Extensive literature review: results

The combined searches and other data sources found 333 potential titles. Titles and abstracts (where available) were scanned. The screening process is shown in figure 6.1. After the exclusion of duplicated publications, of which there were 72, 261 abstracts were left for analysis. For each one of these articles the title and abstract was first reviewed and assessed according to the inclusion criteria. This resulted in the exclusion of 214 papers which did not meet the first inclusion criteria and 25 which did not meet the second inclusion criteria.

Figure 6.1 Flow-chart of literature review



There were 22 papers which examined empirically the role of patent or IPRs protection on FDI. These papers, as indicated below, have reached inconclusive conclusions. A brief summary of each paper and variables employed, are presented in Tables 6.1-6.3.

No relationship between IPRs protection and FDI

There are seven empirical studies found in this category, as shown in Table 6.1. Most of them use regression analyses on cross-sectional data to analyse the effect of IPRs on FDI. Additional variables were included in the regression to control for the difference in country specific factors, although most used some estimate of economic

risk and/or political risk. Some regression analyses for FDI in the 1980s based on research by Ferrantino (1993), Kondo (1995) and Primo Braga and Fink (1999), found no significant link between IPR protection and FDI (Ferrantino 1993; Kondo 1995; Primo Braga and Fink 1999). These three studies employed different approaches to IPR protection. The first study used dummy (0/1) variable to reflect differences in national IPR protection schemes. The second study developed its own patent index. The last study employed the Ginarte and Park (1997) index. These studies then regressed these patent indices and other macroeconomic variables on FDI.

Using FDI data from the 1990s, the above results were confirmed with the study by Pfister and Deffains (2005) who investigated the role of patent protection, using the Ginarte and Park index, on location choices of French firms in 17 developing countries from 1994 to 1995. Analysed using a tobit model and controlling for market competition factors and macroeconomic differences, patent rights protection was not found to influence the location choices of French firms (Pfister and Deffains 2005).

Recently, Seyoum (2006) who developed a new patent index to include scope, patent life, and provision from weighted point survey firms did not find statistically significant correlation between patent index and FDI (Seyoum 2006). One study which more specifically focuses on the chemical industry, Fosfuri (2004), did not find IPR protection playing any significant role in fostering international activity or conditioning its mode after controlling for several country characteristics (Fosfuri 2004). An observational study of FDI inflows to Thailand from 1988 to 1998 also revealed that there had not been much foreign investment in the Thai pharmaceutical sector since the strengthened patent law in 1992 (Supakankunti, Janjaroen et al. 2001).

These studies have employed a wide range of approaches. The most common method used is regression, taking macroeconomic and policy factors into account. However, these analyses only cover the period before TRIPS came into effect, 1995 for developed countries and 2000 for developing countries, so one might expect that the impact of strengthening IPR protection has not yet taken effect. In addition, the boom period of globalization in the 1990s means that emerging economies had a

strong and growing interest in attracting trade, FDI, and technological expertise and high income countries also sought to reallocate their resources into areas of greatest comparative advantage and growth, fuelling the expansion of trade and investment. These reasons might support the findings of no relationship between FDI and the level of patent protection.

Table 6.1 Summary of literature reviews by methods and variables employed: No relationship

No	Authors	Period	Setting	Objectives	Method	Variables
1	Ferrantino (1993)	1982	US firms, US affiliated in 45 countries	The effect of IPR on trade and investment flows	Gravity model	Using dummy (0/1) variables to reflect differences in national IPR protection schemes and control for economic risk (distance, phone, landlock, colony and European countries), political risk (Paris convention member, restriction on foreign firms, number of international agreement membership, duration of patent), labour cost, population and GDP while dependent variables are total exports, royalty fees, and sales of affiliates.
2	Kondo (1995)	1976-1980	US outward FDI in 33 countries	The effect of patent protection on FDI	Survey (for IPR index) and Multiple regression of FDI testing	Developed their own patent index, including scope, patent life, retrieved from weighted point survey firm. Then controlled for GDP per capita, population, education, English language, GATT membership and ICSID membership.

No	Authors	Period	Setting	Objectives	Method	Variables
3	Primo Braga and Fink (1999)	1989	89 countries from developed to least developed countries	The effects of increased protection on intellectual property	Gravity model	A gravity model of bilateral trade, FDI, and technology licensing, which estimates the effects of increased protection on a cross-section of 89x88 countries. Index on national IPRs systems developed by Park and Ginarte (1996),estimating the effects of explanatory variables (such as IPRs, GDP and population of both countries, geographical distance, a common border, language)
4	Pfister and Deffains (2005)	1994-1995	The location choices of French firms in 17 developing countries	The role of the patent rights in the host country	A conditional logit model	The independent variables are number of French competitors, number of subsidiaries, openness, GDP, GDP per capita, consumer price index, the status of EU membership, national R&D investment over GDP, education, democracy, corruption, patent protection index (Ginarte and Park index), dummy variable of the exceeding patent protection index.

No	Authors	Period	Setting	Objectives	Method	Variables
5	Seyoum (2006)	1990 and 1995	63 countries	The impact of patent protection FDI	The OLS regression	The patent index by Ginarte and Park (1997), controlling for other variables such as market size, GDP growth, exchange rates, population, corruption, unemployment, trade/GDP, scientists and engineers, GDP growth
6	Fosfuri (2004)	four time periods: 1981–1983, 1984–1987, 1988–1991, 1992–1996.	75 countries received investments in chemical plants during the period 1981–1996	The impact of IPRs protection compared with country risk on the determinants of international activity through wholly owned operations, joint-ventures and technology licensing,	OLS, Tobit and GLS random effect	Income per capita, population, weighted distance of country, averaged schooling years in the total population, (exports + imports)/GDP, global index of risk, composite index of risk (political, financial and economic), dummy variable for number of scientists and engineers per million of population, time fixed effect, IPR index by Ginarte and Park
7	Supakankunti et. al (1999)	1988-1998	Thailand	The impact of patent law change in 1992 on FDI in pharmaceutical industry Thailand	Observation	Providing the trend of FDI in overall and chemical industry in Thailand

Positive impact of IPR protection on FDI

There are a number of studies which suggest that the volume of FDI in a country tends to be inversely related to the weakness of IPR protection. This section begins with literature focusing on the determinants of US investment, and investment in China, and concludes with studies which deal with post-TRIPS implications on FDI in developing countries. A brief summary of each study is provided in Table 6.2.

Five studies looking at FDI determinants were found that focused on the activities of US Multinational Enterprises (MNEs). First, Lee and Mansfield (1996) calculated an IPR protection index from the perceived weakness of protection in 14 countries, obtained from survey results of 94 US firms. The authors then regressed the total US FDI as a whole in those countries over the period 1990-1992 with the IPR index and the specific variables of some countries. The results show that weaker IPR protection has a significant negative impact on US FDI: a one percent rise in the perceived weakness of IPRs protection would reduce US FDI in that country by 14%. In a sample of chemical firms, the weakness of IPR protection in a particular country would cause firms to allocate their investment to sales, distribution and simple production activities rather than to manufacturing the final product or R&D facilities (Lee and Mansfield 1996).

With recognition of the joint decisions made by MNEs in choosing to export, invest or license, Maskus (1998) used a seemingly unrelated regression to capture these joint impacts, controlling for country specific variables. This is done for a panel of US MNEs investing in 46 countries from 1989-1992. The index of patent strength was one developed by Rapp and Rozek (1990).[18]The results suggest that a one percent rise in the extent of patent protection would increase US investment in that country by only 0.45% (Maskus 1998).

The third and fourth studies used cross-sectional FDI data. Nunnenkamp and Spatz (2004) used US FDI at the industry level in 166 countries in 1995 and 2000. The IPR protection indices used were mainly from Ginarte and Park and World Economic Forum (WEF) data. Using a gravity model and controlling for country specific

[18]A score based on the sum of five national patent law components: (1) extent of coverage, (2) membership in international patent agreements, (3) provisions for loss of protection, (4) enforcement mechanisms and (5) duration of protection. Each of the categories is assigned a value between 0 and 1, and the unweighted sum of these values constitutes the patent rights index.

variables, IPR protection turned out to be insignificant in the base run; however, the estimation results for IPR protection interaction with host-country characteristics showed significant impact. IPR protection appeared to positively affect transportation equipment and machinery industries and negatively affect the food industry. Surprisingly, it was seen to have a negative impact on the chemical industry but this was not statistically significant (Nunnenkamp and Spatz 2004). An et.al. (2008) examined US FDI decisions in 52 manufacturing industries investing in 62 countries in the year 1995. The IPR index was shown to have a positive impact on FDI and licensing. The results revealed that strengthening IPRs, by extending the monopoly period, would increase the chance that firms would choose FDI as a mode of entry (An, Maskus et al. 2008).

Fifth, a similar message was found in the study of Awokuse and Gu (2010). The authors employed a Gaussian Mixture Model (GMM), controlling for various country specific variables, to examine the effect of IPR protection on the investment of US firms in 53 countries from 1994-2006. The IPR index used was from Ginarte and Park study and the Economic Freedom of the World (EFW) index. The results illustrate that countries that strengthen their IPR protection can attract more international transactions from US multinational firms, and that countries with strong imitative ability can attract more US FDI after strengthening their IPR protection (Awokuse and Gu 2010)

There are four studies concerning the location attractiveness of Eastern Europe and China. First, Javorick (2004) surveyed more than 1,405 global firms. The survey recipients were asked whether they had undertaken FDI in any of the 24 countries in Eastern Europe and the former Soviet Union and, if so, what type of projects they were engaged in, whether they were investing in manufacturing projects or a solely in distribution related projects. The authors adapted the Park and Ginarte index and created a new set of indices based on the descriptions of IPR regimes provided by the International Intellectual Property Alliance in their recommendations for countries to be placed on the US Special 301 Watch List. Host country variables and firm specific variables were controlled for. The results indicated that weak protection of intellectual property rights deters foreign investors in four technology-intensive sectors: (1) drugs, cosmetics and health care products; (2) chemicals; (3) machinery and equipment; and (4) electrical equipment. In addition, foreign investors in all

industries tend to set up distribution facilities rather than to engage in local production in a country with weak IPR protection (Javorcik 2004).

The next three studies focus on China as a recipient of FDI. Du et al. (2008) investigated the FDI location choice of 6,288 US firms investing in various regions in China from 1993-2001 and Kawai (2009) undertook the same but for Japanese investors. Both of these studies used the logarithm of the number of approved patents per capita as a proxy IPR index. Though the former employed the gravity model while the latter employed a conditional logit model, these studies yield similar results: that US and Japanese MNEs prefer investing in the regions that have higher protection of intellectual property rights (Du, Lu et al. 2008; Kawai 2009). Awokuse and Yin (2010) assessed the impact of China's IPR laws on its ability to attract FDI from 38 countries, after it had amended its patent law to align it with the TRIPS Agreement. The authors applied the IPR score of Ginarte and Park as well as that of EFW. The results also confirmed that the strengthening of IPR protection in China had a positive and significant effect on FDI (Awokuse and Yin 2010).

The last study describes the implication of global IPR protection on FDI inflows in developing countries which have amended their law to comply with the TRIPS Agreement. Lesser (2002) examined the determinants of foreign investment in 44 developing countries in 1998. With a multiple regression methodology, he concluded that an increase in the IPR index, developed by the author, by one-point would boost FDI by $1.5 billion (Lesser 2002). The study by Adam (2010) employed seemingly unrelated regressions to analyse the effect of strengthening IPR protection in four separate 5–year periods (from 1985-2003). The Ginarte and Park patent index was used to measure IPR alongside controlling for country specific variables. The results of the study indicated that strengthening patent protection has a positive impact on FDI. Additionally, the impact on FDI following the TRIPS Agreement is higher than before it came to effect (Adams 2010). However, this study used 1995 as a TRIPS implementation date for developing countries, whereas the deadline for developing countries was actually 2000 and some countries might have changed their patent law to comply with TRIPS before 1995.

Table 6.2 Summary of literature reviews by methods and variables employed: Positive relationship

No	Authors	Period	Setting	Objectives	Method	Variables
1	Lee and Mansfield (1996)	1991	U.S. firms and investment in 14 developing countries	The effect of IPR protection level on U.S. firm's FDI and the role of IPRs protection in chemical industry	1.Survey for IPRs protection perception 2.OLS regression 3. Tobit model for the chemical industry	Surveying weaknesses in IPR protection perceived by 94 US firms and developing two regression models to find the influence of IPRs protection level on overall US FDI and levels of technology transfer in the chemical industry. For OLS of overall US FDI, independent variables are: weakness of IPR, size of market with control for firm specific and country specific factors, IPR index, dummy for Mexico, FDI in the previous year, degree of industrialization, and openness and time dummy variables. For a Tobit model from 14 US chemical industries, the independent variables are: the percentage of firms that perceived weaknesses in IPR protection, and GDP and dummy variables for firms, while the dependent variable is percentage of firms that will invest in facilities to sell and distribute.

No	Authors	Period	Setting	Objectives	Method	Variables
2	Maskus (1998)	1989-1992	US FDI in 46 countries	The effect of patent protection on U.S. patent applications filed in host country, total sales of foreign affiliates of U.S. parents, U.S. exports shipped to affiliates and total assets, foreign affiliates of U.S. parents	Seemingly Unrelated Regression corrected for heteroskedasticity and autocorrelations	Estimating a simultaneous set of equations to capture these joint impacts, controlling for market size, tariff protection, the level of local R&D by affiliates, distance from the US, and investment incentives (proportion of affiliates that received tax concessions in host country and in any of the countries) and disincentives (proportion of affiliates that employ a minimum amount of localpersonnel in host country and in any of the countries).
3	Nunnenkamp and Spatz (2004)	1995 and 2000	US FDI and US FDI at theindustrial level in 166 countries	The relationship between IPR protection and overall FDI and by industry	Gravity model regression	FDI determinants by a regression of FDI on GDP per capita, population, distance to U.S., the cost of living abroad, average years of schooling and IPRs index, using Ginarteand Park for the year 1995 and World Economic Freedom (WEF) index for the year 2000. Testing the industry characteristics by adding industry dummies in the previous independent variable set.

No	Authors	Period	Setting	Objectives	Method	Variables
4	An et.al. (2008)	1995 (for FDI or licensing) and 1994 (for exportin g)	U.S. FDI in 52 manufacturing industries invested in 62 host countries	Examine the effect of strengthening IPR protection on the mode of technology transfer: exporting, FDI or licensing	A multinomial logit model of three mode of entry choices	The explanatory variables covering national characteristics, GDP, absorptive capacity (share of national exports from high-technology industries and the proportion of the labor force with tertiary education), distance, cultural distance (English and index developed by authors), FDI fixed costs (economic freedom index), market capitalisation and investment cost index, IPR index from Ginarte and Park 1990. The industry characteristics variables are industry R&D intensity and capital intensity (the ratio of total real capital stock to total industry sales).

No	Authors	Period	Setting	Objectives	Method	Variables
5	Awokuse and W.G. Gu(2010)	1994-2006	53 countries, including developed and developing countries	how the interaction between IPR protection and imitative abilities of host countries impacts exports or FDI from the U.S.	A Gaussian Mixture Model	Independent variables are IPR index from WEF and Ginarte and Park.IPR index and control for distance, exchange rate, openness to trade and investment, foreign tax rate and imitative ability (a composite index developed by the authors, using data of government education expenditure, education enrolment, number of R&D researchers, patent applications, patents in force, railways traffic passengers and freight, literacy rates aged 15-24, primary education completion rate, telephone lines and cellular subscribers per 100 population, internet users per 100 population and personal computers per 100 population). Dependent variables are export and FDI.

No	Authors	Period	Setting	Objectives	Method	Variables
6	Javorcik (2004)	1995	1,405 global firms invested in Eastern European countries	The impact of intellectual property protection on the volume of FDI	Survey and Probit model	A questionnaire on decision to enter and mode of entry was developed. Tobit regression of the decision and mode of entry on GDP per capita, population, corporate tax rate, legal effectiveness, corruption, privatization, openness, the overall progress in reform, effectiveness of the legal system, corruption level, privatization policies and openness to trade. For testing the mode of entry, the author included firm specific variables such as firm sales, R&D outlays as a percentage of net sales, selling, general & administrative expenses as a percentage of net sales, the number of four-digit SIC codes describing a firm's activities and a dummy variable of investor's regional experience with the region before 1989.

No	Authors	Period	Setting	Objectives	Method	Variables
7	Du et al. (2008)	1993-2001	6288 US firms invested in various China's regions	The impacts of four economic institution variables, including property rights protection, the degree of government intervention in business operations, the degree of government corruption and contract enforcement, on the location choice of FDI	Discrete choice model	A survey of private enterprise in China to create three indices which are the degree of government intervention in business operations, the degree of government corruption and contract enforcement. The other concerned variables are the agglomeration, dummy for the presence of US Embassies or Consulates and dummy for government promotion policies, wages, infrastructures (length of highway per square kilometre in a region) and education (percent of higher education student in the region). IPR index is the logarithm of the patent per capita approved number.

No	Authors	Period	Setting	Objectives	Method	Variables
8	Kawai (2009)	1998-2006	1839 Japanese manufacturing firms investing in China	The determinants of Japanese manufacturing firms' location decisions in China	A conditional logit model	The empirical models are developed and tested. The dependent variable is choice of investment (1= Yes, 0= No). The independent variables are the natural logarithm of the number of Special Economic Zones, IPRs index, the natural logarithm of the share of total investment in fixed assets by state-owned units in relation to total investment, GDP, labour costs, road infrastructure and the natural logarithm of the number of Japanese manufacturing. All explanatory variables are lagged by one year.
9	Awokuse and Yin (2010)	1992-2005	A panel data for 38 countries including 24 high-income countries and 14 low-income countries that have invested to China	The impact of China's IPR laws, amended in 1992 to comply with WTO's TRIPS agreement, on its ability to attract FDI from 1992–2005	A gravity model, random-effect	IPR indices employed are: (1) Annual foreign patent applications as a measure of the strength of IPR protection in China and (2) IPR index developed by Ginarte and Park (1997). The gravity model consists of IPR protection, GDP, distance to China, average trade cost and investment cost in China, regional dummy of Asia and a ratio of industrial value-added to GDP (proxy for the level of industrialization) were analysed in a gravity model.

No	Authors	Period	Setting	Objectives	Method	Variables
10	Lesser (2002)	1998	FDI in 44 developing countries	The effects of stronger IPR protection in the areas of imports and Foreign Direct Investment (FDI)	Multiple regression	The variables includes income per capita, past FDI, exchange rates, tariffs, the proportion of previous year FDI to GNP of pervious year and the degree of industrialization. A new index was developed that uses membership in international treaties to measure the scope and efficiency of IPR.
11	Adam S. (2010)	1985-2003	75 developing countries	The impact of intellectual property rights (IPR) protection on FDI. The impact of TRIPs Agreement on FDI inflows	The Seemingly Unrelated Regressions (SUR)	Using the Ginarte and Park index as a measure for IPR protection and controlling for real GDP, real GDP per capita, inflation, openness, population, mainline telephone per 100 people, return on investment and a composite index of the risk variable including political, financial and economic risk.

The inconclusive results

There are four studies, as shown in Table 6.3, with regression analyses that yielded inconclusive results. Park and Ginarte (1997) created their own patent protection index, as mentioned, for a panel of 60 countries from 1960–1990 and estimated a system of equations to identify the effect of patent protection and other national characteristics on economic growth, such as R&D activity, investment, and education. The result showed that the benefit of patent protection with respect to investment and R&D occurred only in the top 30 economies (Park and Ginarte 1997).

Athukorala and Kohpaiboon (2006) examined US MNEs decision patterns concerning the location of investment in R&D activities. The authors regressed the ratio of R&D expenditure to total sales, along with country and firm specific variables. IPR was found to have a positive impact on R&D investment, significant at the 10% level, yet a negative impact for a developing countries subgroup (Athukorala and Kohpaiboon 2006).

However, the converse results were shown by Blyde and Acea (2003). They explored the determinants of the decisions of OECD investors to invest in developed and developing countries in 1985, 1990 and 1995. The authors employed a gravity model and controlled for macroeconomic situations, the IPR protection index from Ginarte and Park, and infrastructure level. The results suggest the positive impact of national patent laws in developing countries but their negative impact in developed countries (Blyde and Acea 2003).

Qian (2010) investigated the impact of national patent law reform on inward FDI in 26 countries that established national pharmaceutical patent laws during the period 1978-2002. After controlling for a list of country- and industry-level variables that are likely to affect innovative potentials and technology transfer, there is no statistically significant relationship between national pharmaceutical-patent protection and innovation or FDI. However, when combining national patent protection with economic freedom and higher education level, they are positively related to increases in US and Japanese MNC subsidiaries and British FDI (Qian 2010).

Table 6.3 Summary of literature reviews by methods and variables employed: Inconclusive relationship

No	Authors	Period	Setting	Objectives	Method	Variables
1	Park and Ginarte (1997)	1960–1990	60 countries from developed to least developed countries	The impact of IPR protection on economic growth (GDP growth)	Regression	Created an IPR index and estimated a system of equations to identify the effect of IPR protection and other national characteristics on economic growth such as R&D activity, investment, and education.
2	Athukorala and Kohpaiboon (2006)	1990-2001 (three-year intervals)	168 US-based MNEs that have invested internationally (42 countries)	The determinants of the international location of R&D activity by foreign affiliates of US-based MNEs	Regression analysis	Included control variables are real GDP, distance, percentage of domestic sales in total affiliate sale turnover, technology intensity index, R&D personnel per million population, wages of technical personnel, tax incentives for firm-level R&D activities, Intellectual property right index (from World Economic Forum, Global Competitiveness Report), capital stock of US firms, an index of R&D potential of output mix, dummy variable for developing countries other than NICs, newly industrialized countries in East Asia, financial crisis dummy, and a vector of time dummy variables

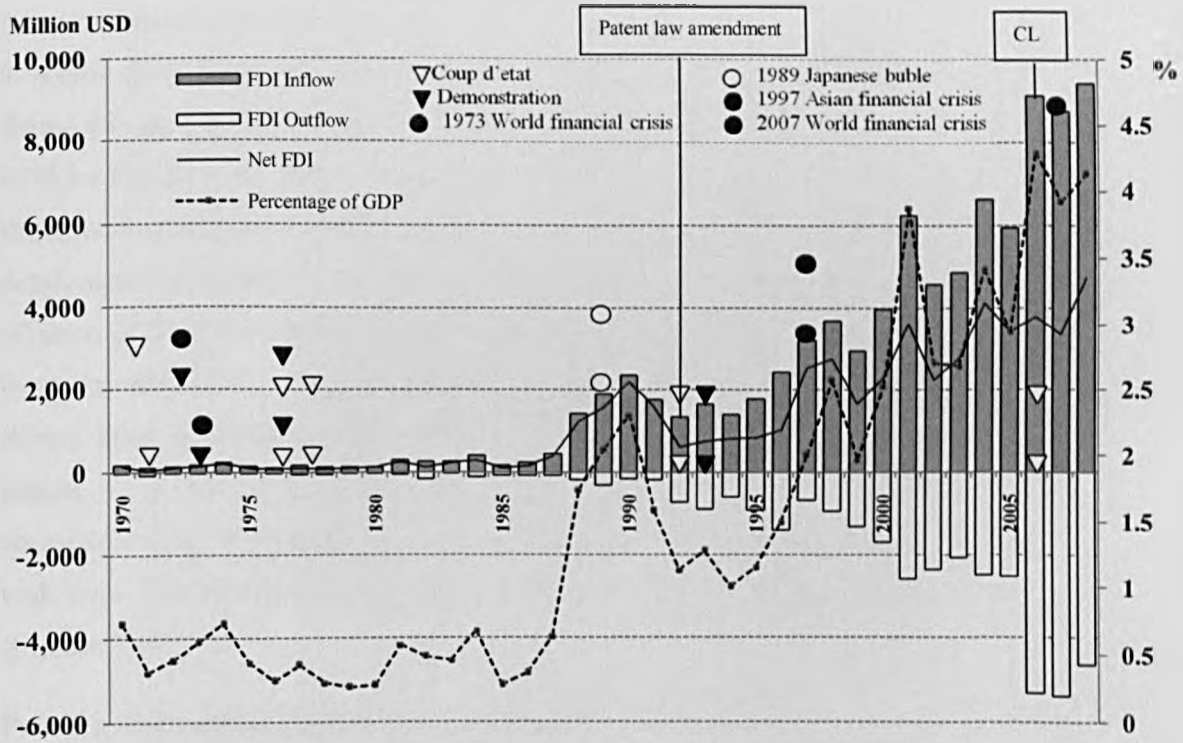
No	Authors	Period	Setting	Objectives	Method	Variables
3	Blyde and Acea (2003)	1985, 1990 and 1995	The sources of FDI are 19 OECD countries and 40 countries as the recipients of FDI, 8 of which are from Latin America.	The inflows of FDI to Latin America and developing countries after TRIPS	The gravity model	The independent variables are GDP per capita, population, dummy of common language, past colonial links and region, distance between country, Ginarte and Park IPR index
4	Qian (2010)	1978-2002	26 Countries that established national pharmaceutical patent laws during that period	Patent reform on inward FDI	Regression	The formal regression model is estimated on the two groups of matched pairs (Set 1: non-patent and new patent pairs; and Set 2: always-patent and new-patent pairs) separately. The included variables are GDP, freedom, education, IPR score, price control, economic freedom, innovative potential, labor, pharmaceutical exports to the US, dummy variables for time periods

In conclusion, there are a number of empirical investigations pointing to an uncertain relationship between IPR protection and FDI distributions, which depend upon the country samples included, FDI sources, data from opinion surveys or secondary data, and the approach used tocalculate the level of IPRs or patent protection scales. The answer of how important IPR protection is for FDI is still unsettled. Some evidence indicates that there is a positive impact of patent law on FDI overall, and in the phamaceutical industry more specifically, while some indicates that weak patent protection on pharmaceuticals was a main factor in making the country a manufacturing base for these pharmaceutical companies. However, it is worth noting, for the context of this thesis, that Bird and Cahoy (2008) illustrated that developing countries who issue CL would face *additional* risks in attracting global capital or could trigger the loss of significant FDI (Bird and Cahoy 2008). As both country-specific and regional factors influence the effect of IPRs on FDI, more regional and country–specific studies should be done to validate the findings of this study. As noted by Lesser (2002), the effectof IPR on FDI may only be possible on a country-by-country basis.

6.3. FDI history and policy in Thailand

Thailand transformed from an absolute monarchy to a constitutional monarchy in 1932. It has undergone a dynamic political situation with a long series of military coups d'état, rebellions and unstable political situations (Dhiravegin 2010). Since the 1960s, when the political scene became relatively more stable, the Thai government focussed more attention toward international trade (Chritensen, Dollar et al. 1993). The Board of Investment (BOI) was established in 1966 to transition the country from trade policies that were focused on import substitution, to become one of the world's leading export-dedicated economies (Board of Investment 2006). The BOI was given a mandate to attract and stimulate foreign investment in the country by image building and investment services which help relationship building and providing consulting related to doing business in Thailand. Over the past four decades, the Thai Government has been actively promoting the country as an investment location by means of liberalizing laws and regulations for the admission and establishment of foreign investment projects. Figure 6.2 shows the amount of inward and outward FDI Flows in Thailand from 1970 to 2008.

Figure 6.2 Inflation adjusted value of FDI inflow, FDI outflow, net FDI and FDI inflows as a percentage of GDP of total industries from 1970-2008 (million USD at 2005 price)



Source: Bank of Thailand

The value of FDI inflow had more or less stabilised at an annual average of US$ 114 million during the 1970s. As a percentage of GDP, the flow of FDI in Thailand was relatively small and fluctuated throughout this decade, due to the world financial crisis in 1973 and the political unrest in Thailand. As a result, a major policy shift towards import substitution took place to promote local industrial development and attract investment through a high protection rate and a set of incentives provided by BOI (Shujiro Urata and Kazuhiko Yokota 1994).

The year 1985 was an important turning point for Thai inward FDI. Having maintained policies of economic liberalization since the start of the 1980s, falling oil prices and the dramatic appreciation of the yen in the mid-1980s (Linda Lim and Fong 1991), together with recovering industrialized country economies investing in FDI in the Asian region of Japan and the Asian Newly Industrialised Economies (NIEs) (Shujiro Urata and Kazuhiko Yokota 1994), FDI inflows into Thailand

increased considerably from US$ 160 million in 1985 to US$ 2,542 in 1990 (from 0.2% of GDP to 2.3% of GDP).

After the financial crisis in 1997, the Thai Baht was devalued. FDI inflows recovered to steady from a low of US$ 3.2 billion in 1997 to US$ 3.9 billion in 2000, and during this period FDI inward flow as a percentage of GDP increased from 1.5% in 1995 back to 2.5% in 2000. As the economy began to improve, Thailand experienced strong economic growth during the 2000s (Sally 2007). Despite political unrest from demonstrations against Prime Minister Thaksin Shinnawattra, followed by a military takeover in 2006, it remains an attractive investment. FDI inflows during this decade increased dramatically compared with the previous decade. The escalating FDI started from US$4billion, 3.8% of GDP, in 2000 and headed to above US$ 9.5 billion, 4.1% of GDP, in 2008. The growth of FDI in the post-crisis period was characterized by a dramatic increase in mergers and acquisitions as foreign firms took over Thai companies that faced severe debt and liquidity problems (Peter Brimble 2002).

Patent policy relating to FDI in the phamaceutical industry

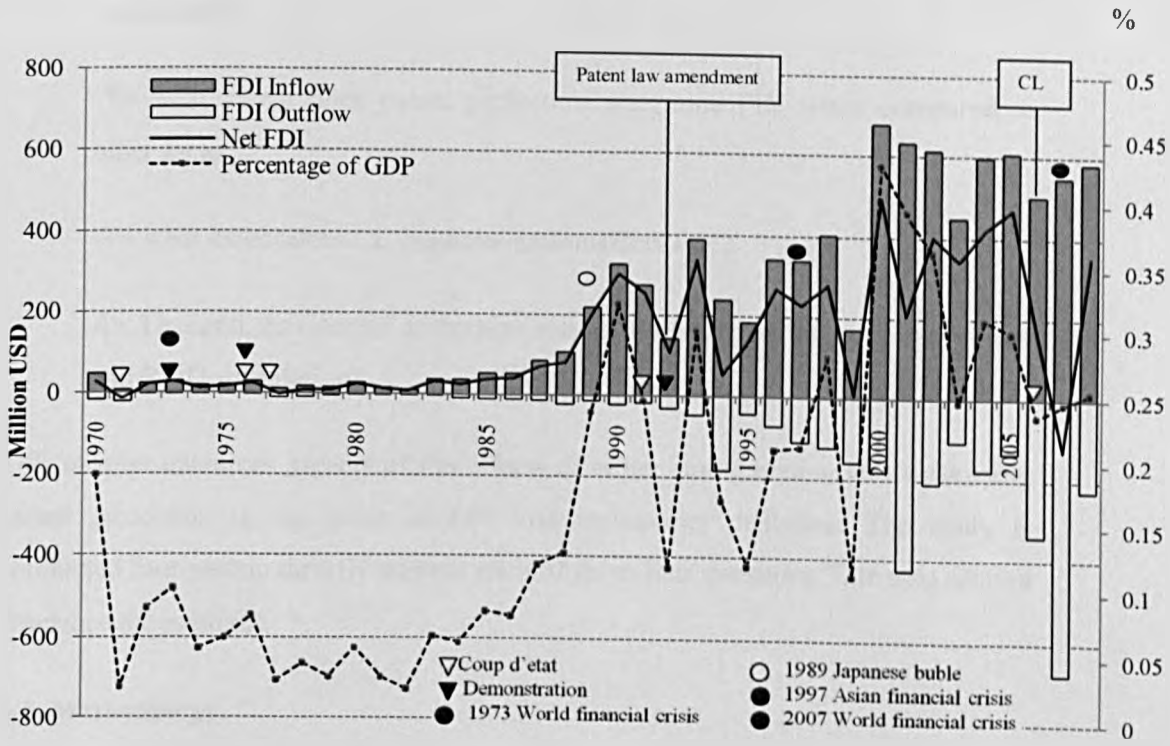
The first Thailand Patent Act B.E.2522 (1979) included only process patents for pharmaceuticals, a weak system which provided the opportunity for rival firms to arrive at the same product with a different process. In 1986 a "White Paper" illustrating how US pharmaceutical companies in Thailand were being harmed by the inadequate Thai patent system was submitted to International Trade Association, US Chamber of Commerce. Moreover, the Pharmaceutical Research and Manufacturers of America (PhRMA) filed a petition with the US Government to withdraw benefits under the GSP to Thailand in 1987 (Markandya 2001). Although the Thai government stressed that providing patent protection at the same level as developed countries would not be possible for the level of social, economic and industrial development of Thailand, the Office of USTR determined that the Government of Thailand's protection of patents was unreasonable and that action was appropriate (Kuanpoth 2007). As a result, to avoid trade sanctions, the new Thai Patent Act came into force in September 1992. It, however, included a provision intended to protect the public from the impact of high prices by establishing a Committee on Pharmaceutical Patent to monitor and compare medicine prices. This

committee was given powers to acquire cost and pricing information and issue CL on the grounds that a product is priced excessively in the Thai market.

The USTR published its annual National Trade Estimates report in 1996. The comment on Thailand included: "*the [new patent] law did not provide protection for products patented in other countries that had not yet been marketed in Thailand ("pipeline protection"), and it contained extremely broad authority to issue compulsory licenses in cases where patented goods are not yet produced in Thailand. The legislation also created a pharmaceutical patent review board with unique and extraordinary powers to require sensitive cost and pricing information. These provisions are a significant disincentive to obtain product patent protection for pharmaceuticals in Thailand and seriously reduce the benefits of the patent protection provided in the 1992 law.*" (USTR 1996). Again, to avoid trade sanctions, Thai patent law was revised again in 1999. The major changes were the dismantling of the Committee on Pharmaceutical Patent, and amendments to allow for a six year protection of petty patents which are simple inventions with industrial applicability, but which are not necessarily of a ground-breaking nature. It is said that the intuition behind these amendments in 1992 and 1999 was that it would offer a key incentive to promote foreign investment needed for technology and knowledge transfers (Markandya 2001).

Figure 6.3 shows the inward and outward FDI of the chemical industry, which includes the pharmaceutical industry. The pattern of FDI flows in and out of the chemical industry is similar to the movement of FDI in every industry. The FDI inflows in the chemical industry started to accelerate in 1985 to reach US$ 370 million in 1990. In 1993 and 1998 the inflows nearly reached US$ 400 million, and peaked at US$ 650million in 2000, and then levelled off to an average US$ 600 million per annum. It is interesting to see that the value of FDI inflow has never reached US$700 million, which is the level often suggested to represent the research and development cost for one medicine (DiMasi, Hansen et al. 2003). Outward FDI has increased but its absolute value is, on average, three times less than inward FDI. However, in 2007 there was more outward than inward FDI, when outward FDI reached a peak of approximately US$700million. After the revisions to patent law in 1992 and 1999, the value of both inward and outward FDI rose considerably.

Figure 6.3 Inflation adjusted value of FDI inflow, FDI outflow, net FDI and FDI inflows as a percentage of GDP of chemical industry from 1970-2008 (million USD at 2005 price)



Source: Bank of Thailand

From Figures 6.2 and 6.3, it can be seen that FDI inflows have been increasing steadily. Strengthening the patent law in 1992 may have contributed, but the dramatic changes in the Thai political and economic climate during the 1980s are perhaps themost important factorsincreasing the attractiveness of Thailand for countries to invest.

It is important however to know more preciseley whether the strengthening of patent protection benefitted FDI, operated as a channel of technology transfer, or not, in order to understand the converse – whether weakening patent protection, such as using CL, discourages foreign investment. This information is increasingly important, given that the era of bilateral trade agreements (TRIPS-Plus) is upon us. Having this information can help build evidence to support decision making in terms of these negotiations.

In conclusion, the review here poses four main questions:

-Did the amendment to the patent law in 1992, to comply with the TRIPS Agreement, lead to a change in FDI, both overall and for chemicals specifically?

-To what extent does patent protection determine FDI when compared to other factors?

-To what extent does CL implementation affect FDI?

-In Thailand, has patent protection met its objective in terms of innovation and R&D stimulation?

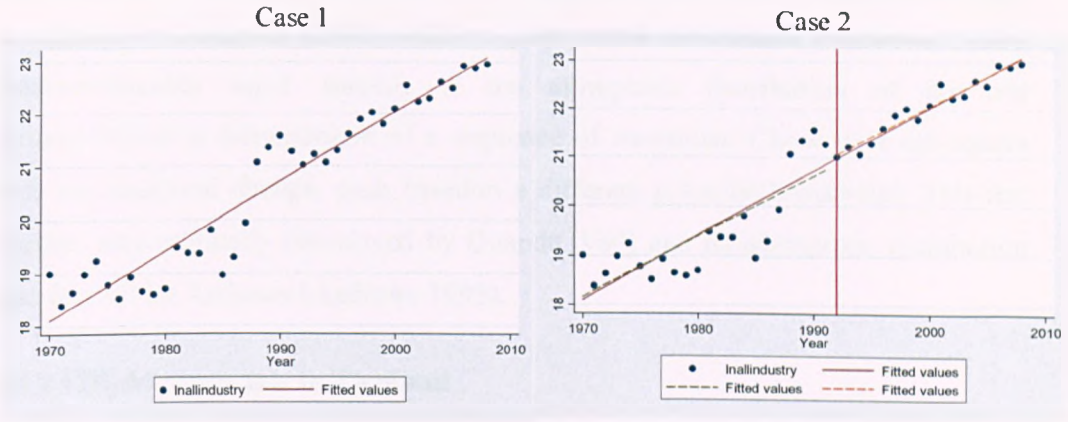
This chapter examines aspects of the effects of either strengthening and weakening patent protection in the areas of FDI and technology diffusion. The study is conducted four partsto directly address each of these four questions. The next section describes the methods.

6.4. Methodology

6.4.1 Testing the impact of the structural change of patent policy in 1992

To test if there is a structural break as a result of the patent law change in 1992, the Chow test was used to determine whether a single regression of a series of FDI inflows from 1970-2008, case 1 in Figure 6.4, is more efficient than two separate regressions involving splitting the data into two sub-samples as presented in case 2 as shown in Figure 6.4. This is illustrated in Figure 6.4, where in the first case it has only a single regression line to fit the data points from 1970-2008. In the second case, where there is a structural break in 1992, two separate models are developed for the periods 1970 to 1991 and 1992 to 2008.

Figure 6.4 Illustration of the Chow test applied for testing the structural break in 1992



The test statistic is calculated from three sum square of residuals from each regression equation, expressed as:

$$F = \frac{RSS_c - (RSS_1 + RSS_2)/k}{RSS_1 + RSS_2 / n - 2k} \qquad (1)$$

Where:

RSS_c is the sum square of residuals regressed by using all the data, before and after the structural break

RSS_1 and RSS_2 are sum square of residuals from two separate regressions on the data before and after the structural break

n is the number of observations

k is the total number of coefficients including the constant.

The Chow test tests whether the single regression line or the two separate regression lines fit the data best. However, it is possible that the breakdate might happen before or after the policy implementation. Therefore, the Chow test can be misleading, as the candidate breakdate is endogenous. This requires testing for structural change of unknown timing. The sequence of Chow statistics as a function of candidate breakdates, 1972 to 2007, was therefore constructed. If there is a structural break, then the subsample estimates will vary systematically across candidate breakdates.

To test whether the structural break happened in 1992, the Chow test value will be compared with the critical values with F-test statistics. In order to test for parameter instability and the structural change with unknown change point, the critical values developed by Andrews (1993) will be used as the benchmark (Andrews 1993). Andrews-Quandt sup-F statistic is the asymptotic distribution of the test statisticswhich is themaximum of a sequence of traditional Chow-style chi-square tests for structural change, each basedon a different potential breakpoint. This test statistic was originally introduced by Quandt(1960) and its asymptotic distribution was derived by Andrews (Andrews 1993).

6.4.2 FDI determinants in Thailand

There is considerable literature focusing on the determinants of investment, variables capturing the influence of macroeconomic factors, operational risk, wage costs, trade barriers, industrial structures, taxes, infrastructure, and other incentives or disincentives to investment (Kindlegerger 1969; Caves 1971; Hymer 1976). This part of the study will incorporate IPRs into this empirical work to examine whether Thailand's implementation of stronger patent protection played a significant role in stimulating FDI, while controlling for related (political or economic) factors. This section will provide a framework of study and outline the model and the hypotheses to be tested.

6.4.2.1 Framework

The connection between the investment promotion policy of a host country and a firm's decision to undertake FDI is highlighted by Dunning in a paradigm known as Ownership, Localization and Internalization (OLI) (Dunning 2001). Multinational companies hold ownership advantages over domestic firms in a given area, which can be a superior technology or improved marketing systems. With sufficient vocational advantages from quality and cost of material, lower transportation costs, and host government policies, foreign investors would establish production locally rather than choose to export. The last advantage, internalization, is the advantage for foreign firms to retain full control over the production process instead of licensing its intangible assets to local firms. A host country's government can influence the

presence of location-specific advantages directly, especially the liberalization of policies and business facilitation measures.

Based on Dining's OLI paradigm, this section outlines reasons for a firm to invest abroad: the search for resources, for markets, for efficiency, and for new strategic assets. Host country governments can influence location-specific advantages directly, including through trade liberalization policy and business facilitation measures. Table 6.4 shows the set of host country determinants of FDI developed by UNCTAD (1998) (UNCTAD 1998).

Table 6.4 The UNCTAD's classification of FDI determinants

Determining variables	Examples
Policy framework for FDI	-Economic and political stability
	-Rules regarding entry and operations
	-Privatization, trade and tax policy
Economic determinants	-Market size and capital income
	-Market growth
	-Cost of doing business i.e. materials, transportation and labour cost, labour productivity
Business facilitation	-Investment promotion (image building or investment-generation activities)
	-Social amenities (bilingual schools, quality of life, etc.)
	-after investment services

Source: UNCTAD (1998)

6.4.2.2 Selected variables and data sources

Typically, there are many host country factors involved in deciding where an FDI project should be located and it is often difficult to pinpoint the most decisive factor. This section describes specific variables representing each classification of the

UNCTAD framework and explains the rationale and sources of the variables selected, as shown in Table 6.5. For the value of FDI inflows, the dependent variable, data were retrieved from the Bank of Thailand (BOT) for the period available of 1970-2008.

❖ **Policy framework**

Governments typically can improve FDI potential through policies dealing with the rules and regulations governing the entry and operation of foreign investors, the standards of treatment accorded to them, and the functioning of the markets within which they operate (UNCTAD 1996). These policies vary from outright prohibition or restrictive policy of FDI entry to open policy, FDI liberalization, and non-discrimination in the treatment of foreign and domestic firms or preferential management of foreign firms.

Exchange-rate policy (EXC) is related to stability and may influence FDI decisions by affecting the prices of host country assets, the value of transferred profits, and the competitiveness of foreign affiliate exports. It can also be seen as affecting profitability, as fluctuation in the exchange rate can turn a business from profit to loss. There is a widely held view that countries can attract FDI by devaluing their currency (Calderon-Rossell 1985). However, the devaluation could decrease the net remittances of profits and dividends back to the parent company which actually discourages the foreign investor (de Mello 1997).The average annual exchange rate with the US dollar obtained from the Bank of Thailand (BOT) was used in the model.

Political stability is also one of the key factors attracting foreign investors. Numerous studies demonstrate that MNEs are less likely to invest in countries with risks of expropriation, ineffective legal systems, and terrorism and violence (Schneider and Frey 1985; Loree and Guisinger 1995; Fernandez-Arias and Hausmann 2000; Asiedu 2002). This study selected a situation of coup d'état and political unrest to represent **political instability** (POL). The binary variable will be identified as 0 if there are no coups d'état and no political unrest in that year, and as 1 when there is. The data for POL is taken from Teerevakin (2010), a Thai political history book (Teeravekin 2010).

Patent protection policy (PATENT) is the key independent variable representing protection of ownership, and is based on the changing of the patent law in 1992. In this study, dummy variable is created with 0 for 1970-1991 and 1 for the years after 1992.

❖ **Economic determinants**

Market attractiveness can be represented by the size of population or **Gross Domestic Product** (GDP) (Schneider and Frey 1985; Loree and Guisinger 1995; Fernandez-Arias and Hausmann 2000; Asiedu 2002; Ramirez 2006). Foreign investment is positively influenced by the size of the host economy, as a large market generates a large volume of business and, hence, influences market-seeking FDI. For this study, GDP is selected as an explanatory variable since the size of the Thai population has been relatively constant during the study period. The value of GDP is from the World Development Indicator (WDI).

High wages in the manufacturing industry would negatively affect resource-seeking FDI (Schneider and Frey 1985). The relative **US to Thai wage** (USTWAGE) in manufacturing industry will be employed. Average wage in manufacturing was obtained from the International Labour Organization (ILO) from 1989-2008. The monthly wage before 1989 is based on information reported by Attayuth (2010) which provides the minimum labour wage in Thailand from 1973 (Leeyawanich 2010).

❖ **Business facilitation**

Multinational firms engaged in export-oriented investments may prefer to locate in countries more open to international trade (Asiedu 2002). Since there is no systematic numerical value of image building, investment-generation activities and trade restrictions, the volume of international trade is always used to symbolize business facilitation. Countries that are open to international trade, less trade restrictive and provide a good platform for global business operations, are found to have more capital inflows. A higher level of **export value** (EXP) could represent a lower transaction cost associated with exporting that occurs from trade restriction or the **openness ratio** (OPEN), total value of imports and exports to total GDP, could represent the openness of an economy (Edwards 1990).

Although many studies have employed an openness ratio in their models (Edwards 1990; Gastanaga V, Nugent J et al. 1998; Fernandez-Arias and Hausmann 2000; Fedderke and A.T. 2006), this part of study will use export value to represent business facilitation. This is because, as mentioned previously in section 6.3, covering the FDI history and policy in Thailand, a policy of export promotion took place in the 1980s and this policy was implemented to attract export-oriented foreign investors. Moreover, investing in Thailand as a location to export was one of the main reasons for the surge of foreign investment in Thailand in 1987 (Eur 2003). It is also the case that the high correlation between EXP and OPEN variables (r=0.955) means that these two variables would produce virtually the same result. As a result, the volume of exports represents business facilitation, with the WDI databases providing the source data.

6.4.2.3 Model Specification and hypotheses tests

This section outlines the variables and model used to empirically test the level of influence of the aforementioned variables on FDI. The FDI inward data was obtained from the Bank of Thailand (BOT).

Dependent variable

This study developed two models to analyse the FDI determinants of overall foreign investment inflows to all industry and the pharmaceutical industry specifically. For the first model, the dependent variable is the aggregate value of FDI inflows in all industries, accounting for 53% of FDI inflow to Thailand (Decharuk, Leelapornchai et al. 2009). Although this study intends to study the role of patents in pharmaceutical industry FDI, since the data concerning the flow of inward FDI to the pharmaceutical sector is not available, the flow of inward FDI to the chemical industry was chosen to be the dependent variable for the second model (as the pharmaceutical industry is a subset of the chemical industry this is the closest proxy). Table 6.5 shows the trend of FDI inward to Thailand by sector.

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Table 6.5 Net FDI inward to Thailand classified by sector (average % share to total)

Sector	1980-1986	1987-1996	1997-1998	1999-2007
Industry	31.4	39.4	46.5	53
of which: Electrical appliances	9.7	13.4	10.9	13.5
Machinery and Transport equipment	2.4	3.3	11.9	16.7
Chemicals	5.1	6.4	4.5	5.3
Financial institutions	-2	6.3	9.7	7.1
Trade	19.1	17.1	24.5	12.3
Construction	18.8	8.7	4.1	0
Services	8.5	4.1	6.7	10.1
Real estate	4.3	21.5	1.8	2.8
Others	20	2.9	6.6	14.8
Total	100	100	100	100

Sources: Bank of Thailand

Independent variables

As shown in Table 6.6, the model includes standard arguments such as GDP, exports (EXP), exchange rate (EXC), and the monthly wage in Thailand (WAGE). All variables were adjusted with the consumer price index to be at 2005 price levels. Dummy variables to explain variations in political stability (POL) and to capture the patent law change effect (PATENT) were used. ε_t is a normally distributed error term.

Table 6.6 Summary variable description

Variable	Definition
Dependent variable	
LnFDI	Natural log of inflation adjusted FDI inflows in all industry (USD: at 2005 price)
LnFDIC	Natural log of inflation adjusted FDI inflows in chemical industry (USD: at 2005 price)
Independent variable	
LnGDP	Natural log of GDP (USD: at 2005 price)
LnEXP	Natural log of real export value (USD: at 2005 price)
LnEXC	Natural log of real exchange rate (Thai Baht: at 2005 price)
LnWAGE	Natural log of wage (USD: at 2005 price)
PATENT	Changing patent law (from 1992 =1, before 1992 = 0)
POL	Year that had coup d'état or political turmoil (1 if happened, 0 =no coup d'état)

GDP, EXP, WAGE and PATENT are expected to have a positive effect on FDI while POL is expected to have a negative effect. For the exchange rate variable (EXC), the important link between economic policy and international competitiveness, as explained in the section above, means that the relationship cannot be predicted, as depreciation may induce FDI because it can decrease costs and increase profits, but it could also reduce the value of currency transferred as remittances and thus could decrease FDI. This study therefore estimated an FDI function of the following general form:

$$LnFDI_t = \alpha + \beta_1 GDP_t + \beta_2 EXP_t + \beta_3 EXC_t + \beta_4 LnWAGE_t + \beta_5 PATENT_t + \beta_6 POL_t + \varepsilon_t \quad (2)$$

The specification in Equation (2) will be analysed with the Error Correction Model (ECM). Empirical studies have shown that the ECM is best suited for model estimation when economic variables that are individually non-stationary are

cointegrated, i.e. when there is a meaningful long-run relationship between them (Fedderke and A.T. 2006; Ramirez 2006). Moreover, the ECM is able to induce flexibility by combining the short-run dynamic and long-run equilibrium models in a unified system, allowing us to describe the long run relationships and the short run relationships of non-stationary variables (Johansen 1995; Lütkepohl 2005). Ramirez (2006) also employed the ECM to understand the role of economics and policy on inward FDI into Chile during 1960-2001 (Ramirez 2006)

The ECM model was incorporated using the Engle and Granger framework (Engle and Granger 1987). All variables were tested for the existence of unit root to comply with the condition, required to employ ECM, that series are non-stationary. The first stage in the Engle-Granger framework is to test whether the variables are cointegrated. This is accomplished by testing the residuals of the equation for a unit root or stationarity. The economic interpretation of cointegration is that if two or more series are linked to form an equilibrium relationship spanning the long run, then even though the series themselves may be non-stationary, they will move closely together over time and their *difference* will therefore be stationary. The unit root was tested using the Augmented Dickey Fuller tests on the residuals (as advocated by Engle and Granger).

The second stage requires estimating the short run ECM itself from the residuals of the regression of the first stage. That is, obtaining $ECT_{t-1}, = Y_{t-1} - b\hat{Y}_{t-1}$, as shown inequation (3), to determine the dynamic structure of the system. This equation is to test for a long-run relationship between FDI and policy, economic and business facilitation represented by the variables shown in table 2.

$$\Delta LnFDI_t = \alpha + \beta_1 \Delta GDP_t + \beta_2 \Delta EXP_t + \beta_3 \Delta EXC_t + \beta_4 \Delta LnWAGE_t + \beta_5 \Delta PATENT_t + \beta_6 \Delta POL_t + \delta ECT_{t-1} + \varepsilon_t \quad (3)$$

The same model will be re-estimated using the FDI inflows in the chemical industry (LnFDIC) more specifically as a dependent variable.

$$\Delta LnFDIC_t = \alpha + \beta_1 \Delta GDP_t + \beta_2 \Delta EXP_t + \beta_3 \Delta EXC_t + \beta_4 \Delta LnWAGE_t + \beta_5 \Delta PATENT_t + \beta_6 \Delta POL_t +$$

$$\delta ECT_{t-1} + \varepsilon_t \quad (4)$$

6.4.3 Testing of weakening patent protection by compulsory licensing

Since Thailand implemented CL during 2006-2008, the available data to analyse any impact after this policy implementation is too small; only two data points. It was therefore decided to extend this analysis to include other countries that had implemented CL for pharmaceuticals during the period 2000-2008. Those countries that initiated a CL but ended up with voluntary license or discounting, such as South Africa or Taiwan, are excluded.

6.4.3.1 Selected samples

A group of nine countries was selected from the Beall and Kuhn (2012), study which assembled a database of all incidents in which a CL was publically initiated or implemented (Beall and Kuhn 2012). Most countries that had implemented CL had done so for HIV/AIDS. Thailand began with HIV/AIDS medicines, but is the only country to then issue CLs for heart disease and cancer medicines. Egypt issued a CL on the male erectile dysfunction medicine sildenafil (Viagra). The details are presented in table 6.7.

Table 6.7 CL series by country and year

No.	Year	Country	Diseases	National Income group
1	2001	Brazil	HIV/AIDS	Upper-middle-income country
2	2002	Egypt	Erectile dysfunction	Lower-middle-income country
3	2003-2004	Malaysia	HIV/AIDS	Upper-middle-income country
4	2003	Zimbabwe	HIV/AIDS	Low-income country

5	2004	Mozambique	HIV/AIDS	Low-income country
6	2004	Zambia	HIV/AIDS	Lower-middle-income country
7	2005	Ghana	HIV/AIDS	Lower-middle-income country
8	2005	Indonesia	HIV/AIDS	Lower-middle-income country
9	2006- 2008	Thailand	HIV/AIDS, Heart disease, Anti-cancer	Upper-middle-income country

Source: Beall R. and Korbel J. (2012)

6.4.3.2 Variables and data sources

Variables were selected to represent the set of host country determinants of FDI developed by UNCTAD(1998) (UNCTAD 1998). FDI data were obtained from the WDI database. The data on FDI inflows were the net inflows of the amount of investment by foreign investors into affiliates where they own at least 10% of paid up capital. This is the sum of equity capital, reinvestment of earnings, other long-term capital, and short-term capital as shown in the balance of payments. The selected variables representing the policy framework are **Political Stability and Absence of Violence** (PV), **exchange rate** and **lending interest rate** (LEND). **Gross Domestic Product** (GDP) and **number of population** (POP) were selected to explain economic determinants. With respect to business facilitation, the degree of country **openness** to trade (OPEN), the proportion of import and export value of national GDP, is represented.

These data come from three databases. First, the World Development Indicator (WDI), the primary World Bank database compiled from officially-recognized international sources, presents global development data available including social, economic, financial, natural resources and environmental indicators covering the

period from 1960 onwards. The second source is the WGI, the source for the aggregate indicators drawn from a diverse variety of survey institutes, non-governmental organizations, and international organizations. PV is selected from the WGI database to measure the likelihood that the government will be destabilized or overthrown by unconstitutional or violent means, including domestic violence and terrorism. It is combined from the views of a large number of enterprises, citizens and expert survey respondents in developed and developing countries. Third, IMF International Financial Statistics is the source of time series of all aspects of international and domestic finance. The series of exchange rate, lending interest rate, and the total value of exports are retrieved from this source.

CL is a dummy variable, taking the value one for a period after policy implementation.FDI and other variables, as shown in the Table 6.8 were collected from 1995 to 2009 and adjusted to 2005 price.

Table 6.8 Summary variable description

Variable name	Variable description	Source
LnGDP	Natural log of GDP	WDI
LnEXP	Natural log of value of exports	IMF
LnPOP	Natural log of number of population	WDI
PV	Political stability and violence index	WGI
CL	Dummy variable of compulsory licensing	Beall R. and Kuhn R. (2012)
EXC	Exchange index (2005=100)	IMF
OPEN	Openness of country measured by the proportion of import and export value and total GDP	WDI
LEND	Lending interest rate, Lending interest rate is the rate charged by banks on loans to prime customers.	IMF

6.4.3.2 Model specification

The econometric analysis is based on a panel data set of ten countries from 1995-2009. The equation estimated is specified as follows:

$$LnFDI_{it} = \beta_0 + \beta_1 LnGDP_{it} + \beta_2 LnEXP_{it} + \beta_3 LnPOP_{it} + \beta_4 PV_{it} + \beta_5 CL_{it} + \beta_6 EXC_{it} + \beta_7 OPEN_{it} + \beta_8 INF_{it} + \beta_9 ILEND_{it} + \beta_{10} TIME_{it} + \mu_i + \varepsilon_{ij} \quad (5)$$

where, i signifies a country in year t; β_0 is the constant term; β_is are the coefficients to be estimated; μ_i represents the country-specific effect which is assumed to be time invariant, and ε_{it} is the error component. In addition to the variables explained earlier, the time variable (Time) is included to capture any relationship between time trend and FDI. Since country specific effects are included in the regressions, a decision was required concerning whether they are treated as random or fixed. The Hausman test was applied to check whether the fixed effects model is more efficient than the random effects model. This will be true if the null hypothesis of no correlation between the individual effects and the regressors is rejected.

6.4.4 Impact on innovation

This analysis is to assess the impact that strengthening patent protection has on innovation activities resulting from local inventors who benefit from technology transfer or spillover effects from foreign patents filed in Thailand, as well as their role in stimulating the R&D or innovation atmosphere. The descriptive statistics of patent applications filed in Thailand, as well as R&D expenditure, are analysed to see the trend of innovation activities is related to the patent protection atmosphere.

The number of patent applications made was obtained from the Department of Intellectual Property website (www.ipthailand.go.th). All types of patent application were obtained, and those specifically in the A61K industrial class referred to pharmaceutical compositions in the IPC (International Patent Classification) was isolated as a sub-group, over the period 1970-2008. Data on R&D expenditure was obtained from the Office of the National Research Council of Thailand, Ministry of Science and Technology.

The results from all four analyses outlined above were consolidated to build a holistic picture of the likely implications of the patent amendment in 1992 on Thai FDI and innovation.

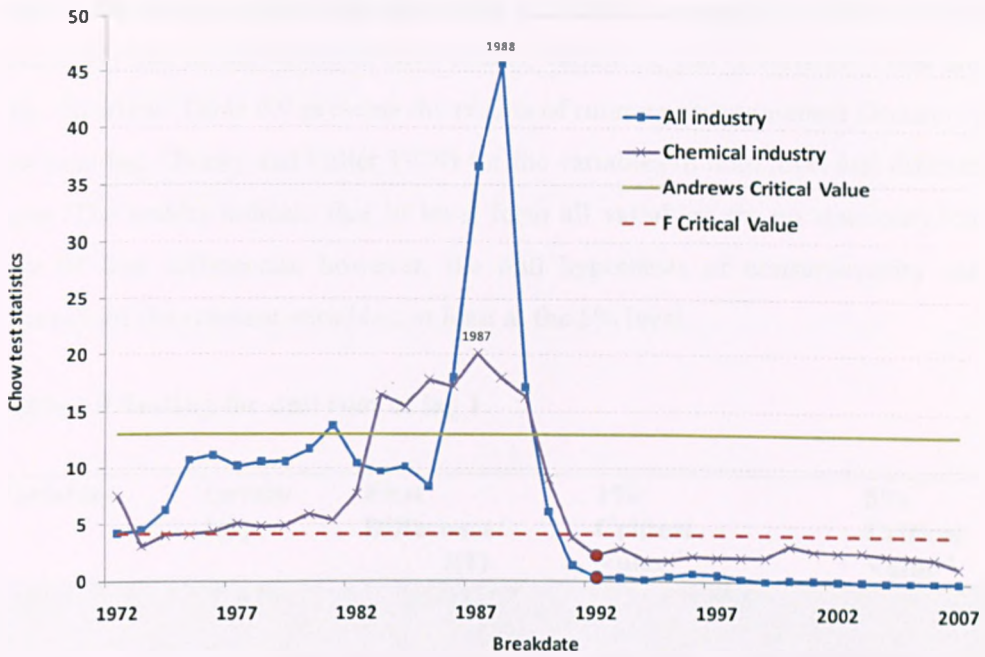
6.5. Results

6.5.1 Testing the structural change of patent policy in 1992

From a yearly time series of FDI inflows to all industries from 1970 to 2008 (yielding 39 observations), a Chow statistic, using 1992 as the breakdate, of 0.40 was obtained. The five percent critical value of F-test is 4.17, so there is no evidence of a structural break. A similar result is found from the structural test in the chemical industry only (Chow statistic of 2.28).

Figure 6.5 presents the results of treating the breakdate as unknown, plotting the sequence of Chow statistics as a function of candidate breakdates. The candidate breakdates are along the x-axis; the value of the Chow statistics on the y-axis. It can be seen that there is considerable variation in the Chow test sequence before the policy implementation but it is relatively stable after 1992. The Chow statistic reaches a peak at 45.7 in 1988 for all industries and at 20.14 in 1987 for chemical industry only. Testing for an unknown breakdate, the Andrews 5 percent critical value is 12.9, just over three times the F-test critical value. The Andrews critical value is sketched in Figure 6.5 as well.

Figure 6.5 Testing for structural change of unknown timing of FDI inflows in all industry and chemical industry



There is therefore no evidence of structural changes in the trend of FDI inflows into all industries in Thailand, or in to the chemical industry particularly, after the patent law change in 1992. However, there are significant structural breaks in 1987 and 1988, the shifting point of FDI inflows as the point of growing political and economic stability. The issue of inadequate patent protection for pharmaceuticals had been raised in the US Chamber of Commerce in 1986. The PhRMA filed a petition with the US Government to withdraw benefits under the GSP to Thailand and a series of meetings between the US and Thai governments took place in 1987 (Markandya 2001). As a result, it could be possible that the situation around 1987 was the more critical in affecting foreign investors (especially from the US) to feel more confident about investing in Thailand, and thus the 1992 policy change impact was effectively foreshadowed five years earlier and, perhaps peculiarly, thus had a 'retrospective' effect and the law itself was a formality to the action that had occurred a few years before. Thus, more qualitatively, it is perhaps likely that the 'process' leading to strengthening of patent law in 1992 did generate a significant structural break. This demonstrates the importance of looking for impact in the years around an event, rather than just at the event itself.

6.5.2 The determinants of FDI in Thailand

Unit root tests were undertaken for the variables in question given that it is well known that macro time-series data tend to exhibit a trend that renders them no stationary; that is, the variables have means, variances, and covariance's that are not time invariant. Table 6.9 presents the results of running an augmented Dickey-Fuller test (one lag; Dickey and Fuller 1979) for the variables in both level and differenced form. The results indicate that in level form all variables are no stationary. In the case of first differences, however, the null hypothesis of nonstationarity can be rejected for the relevant variables, at least at the 5% level.

Table 6.9 Testing for unit root at lag 1

Variables	Levels/ I(0)	First Difference/ I(1)	1% Critical Value [a]	5% Critical Value [a]
LnFDI	-0.679	-5.062**	-3.668	-2.966
LnFDIC	-1.061	-7.180**	-3.668	-2.966
LnGDP	-1.518	-3.818*	-3.668	-2.966
LnEXP	-1.151	-3.341*	-3.668	-2.966
LnEXC	-0.440	-4.526**[b]	-3.668	-2.966
LnWAGE	-1.792	-4.016**[b]	-3.668	-2.966

a Mackinnon critical values for rejection of null hypothesis of a unit root
b at second difference/ I(2)
*Denotes significance at the 5% level
**Denotes significance at the 1% level

In view of this, it is necessary to determine whether there is at least one linear combination of these nonstationary variables (in level form). The Johansen and Juselius (1990) method was used to determine whether there is a stable long-run relationship among the relevant variables in logarithmic form. Testing for a cointegrated relationship among the interested variables, using the Engel and Granger (1987) test, shows, in Table 6.10, that the null hypothesis of no cointegrating relationship can be rejected at both the 5% and 1% levels, thereby

suggesting that there is more than one linear combination of these non-stationary variables (in level form) that is stationary.

Table 6.10 Cointegration Tests

No	Residuals of equations	ADF statistics	5% Critical Value[a]	1% Critical Value[a]
1	$lnFDI_t$, $lnGDP_t$, $lnEXC_t$, $lnWAGE_t$, PATENT, POL	-3.247*	-2.964	-3.662
2	$lnFDI_t$, $lnEXP_t$, $lnEXC_t$, $lnWAGE_t$, PATENT, POL	-4.924**	-2.964	-3.662
3	$lnFDIC_t$, $lnGDP_t$, $lnEXC_t$, $lnWAGE_t$, PATENT, POL	-5.125**	-2.964	-3.662
4	$lnFDIC_t$, $lnEXP_t$, $lnEXC_t$, $lnWAGE_t$, PATENT, POL	-6.757**	-2.964	-3.662

a Mackinnon critical values for rejection of null hypothesis of a unit root
*Denotes significance at the 5% level
**Denotes significance at the 1% level

Table 6.11 shows the results of the ECM models. The coefficients of the variables represent short-run growth rates, whereas the coefficient of the lagged ECT term obtained from the cointegrating equation in level form denotes the speed of adjustment back to the long-run situation in which the variables grow at the same constant rate. Two ECM specifications of overall industry FDI are reported in models 1 and 2, while models 3 and 4 are FDI specifically in the chemical industry. Overall, the ECM estimation on FDI inflows to the chemical industry is identical to the estimation of FDI inflows to all industries.

The ECM estimators suggest that a percentage change in real GDP and export value have a positive and statistically significant effect on FDI inflows. For example, the estimates in models 1 and 2 suggest that a 1% increase in the percentage growth rate of real GDP and export growth generates a 1.8% and 1.1% growth in FDI inflows to all industries respectively. For the chemical industry results are similar; a 1%

increase in the percentage growth rates of real GDP and export growth generates a 2.4% and 1.6% growth in FDI inflows respectively. As anticipated, the real wage has a negative and statistically significant effect on FDI inflows. A 1% increase in wage generates around 1.6%-1.9% decrease in FDI flows to all industries, and a 2.5%-3.3% decrease in FDI flows to the chemical industry.

The exchange rate has an insignificant impact on FDI, both overall and for the chemical industry. In addition, all models show that political turmoil has a negative but not statistically significant effect on FDI inflows, except model 3 which shows political instability reducing FDI growth in the chemical industry by 0.4%. The dummy variable controlling for patent law change is also not significant, although direction suggests that after patent law amendment FDI inflows decreased by 0.07% overall and 0.15% in the chemical industry. The relative fit and efficiency of the ECM is acceptable, and as the theory predicts the lagged residual terms in all equations are negative and statistically significant; for example, the lagged error correction term in model 1 of FDI inflows to all industry suggests that a 1 percent deviation during the current year from long run FDI flows to all industry is corrected by approximately 0.35% in the next year on average. The relative fit and efficiency of the model is acceptable, but not as good a fit as the first model. As theory predicts, the lagged residual terms are negative and statistically significant.

Table 6.11 Error Correction and OLS regression models of FDI determinants in all industries (dependent variable = ΔLnFDI) and in the chemical industry (dependent variable=ΔLnFDIC)

Model	ΔLnFDI		ΔLnFDIC	
	(1)	(2)	(3)	(4)
ΔLnGDP	1.821**	-	2.427**	-
	(0.823)		(1.103)	
ΔLnEXP	-	1.111**	-	1.652**
		(0.426)		(0.631)
ΔLnEXC	-0.004	-0.005	-0.039	0.021
	(0.105)	(0.077)	(1.342)	(0.111)
ΔLnWAGE	-1.870**	-1.567***	-3.315***	-2.517***
	(0.808)	(0.504)	(1.084)	(0.741)
PATENT	-0.076	-0.070	-0.159	-0.068
	(0.131)	(0.100)	(0.173)	(0.148)
POL	-0.186	-0.164	-0.392*	-0.291
	(0.157)	(0.121)	(0.214)	(0.183)
ECT_{t-1}	-0.352***	-0.852***	-0.839***	-1.137***
	(0.134)	(0.167)	(0.173)	(0.16)
Constant	-0.152	0.118	0.215	0.096
	(0.104)	(0.087)	(0.139)	(0.129)
F-stat	2.15*	7.20***	5.90***	10.14***
R^2	0.294	0.582	0.533	0.663
Adjusted R^2	0.157	0.501	0.443	0.597

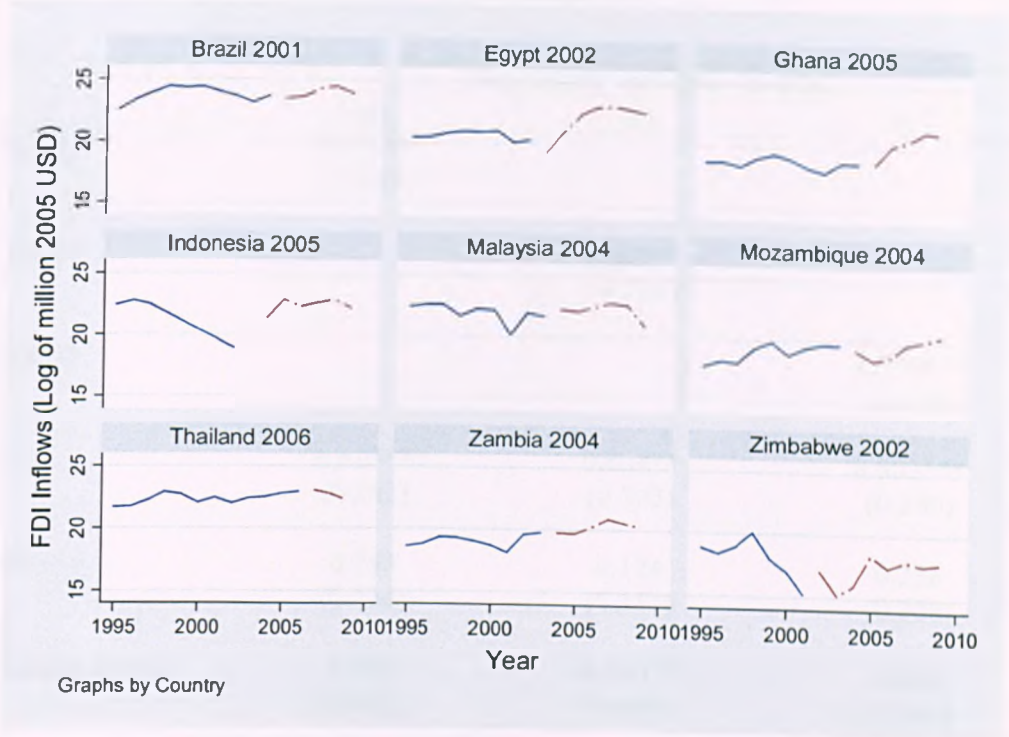
Notes: Terms in parentheses are standard errors, *Denotes significance at the 10% level, **Denotes significance at the 5% level, ***Denotes significance at the 1% level

6.5.3 The impact of compulsory licensing on FDI

Figure 6.6 illustrates the trend in FDI before and after the implementation of CL in nine countries. It can be seen that the FDI value for Brazil, Malaysia, Mozambique

and Zambia is stable, while Egypt, Ghana, Indonesia and Zimbabwe show an increasing trend. Only Thailand shows a decreasing trend.

Figure 6.6 FDI inflows in log of million USD at 2005 prices



The time effect was tested and was found to be insignificant; there is no time effect needed on this sample (see appendix 10 for the results). Since there is a high correlation within three variables, GDP, export value and number of population, they are subject to three separate specifications. The first model, Model A, tests for GDP impact and lending interest rate and inflation rate. The second model, Model B, removes GDP and tests for export variable, and the number of population was tested in Model C.

Table 6.12 shows that the control variables are of the expected sign. GDP, exports and the number of population have a positive and significant effect on FDI. The most highly significant and robust variable is political stability. The higher the score of political stability the higher the FDI inflows. CL policy shows a positive but not statistically significant impact on FDI. The most unstable coefficient is the exchange rate. It shows that depreciating the currency by 1% would increase FDI by 0.5% in model A but shows a different sign in the other models. Openness of the economy

conforms to theoretical priors that increased international trade raises FDI. The implied elasticity is around 2%. Lending interest rate shows a negative impact on FDI by 0.5-0.6%, which is significant in model C.

Table 6.12 Determinants of FDI in nine countries

	Dependent variable= ln FDI		
	(A)	(B)	(C)
lnGDP	0.933***		
	(0.137)		
lnEXP		0.822**	
		(0.394)	
lnPOP			1.776***
			(0.334)
PV	0.623**	0.668**	0.802***
	(0.262)	(0.303)	(0.280)
CL	0.253	0.124	0.236
	(0.224)	(0.271)	(0.228)
Exchange rate	0.005	-0.013**	-0.005
	(0.005)	(0.006)	(0.006)
OPEN	0.006	0.028***	0.017***
	(0.004)	(0.008)	(0.005)
Lending interest rate	-0.005	-0.005	-0.006*
	(0.003)	(0.004)	(0.003)
_cons	-2.625	0.764	-10.814*
	(3.400)	(8.982)	(5.879)
N	77	76	77
R^2(within)	0.271	0.369	0.261
u	0.663	2.153	0.897
e	0.793	0.467	0.823
Hausman-test	8.99	37.86	4.76
	(P=0.174)	(P=0.000)	(P=0.575)
Model Type	REM	FEM	REM

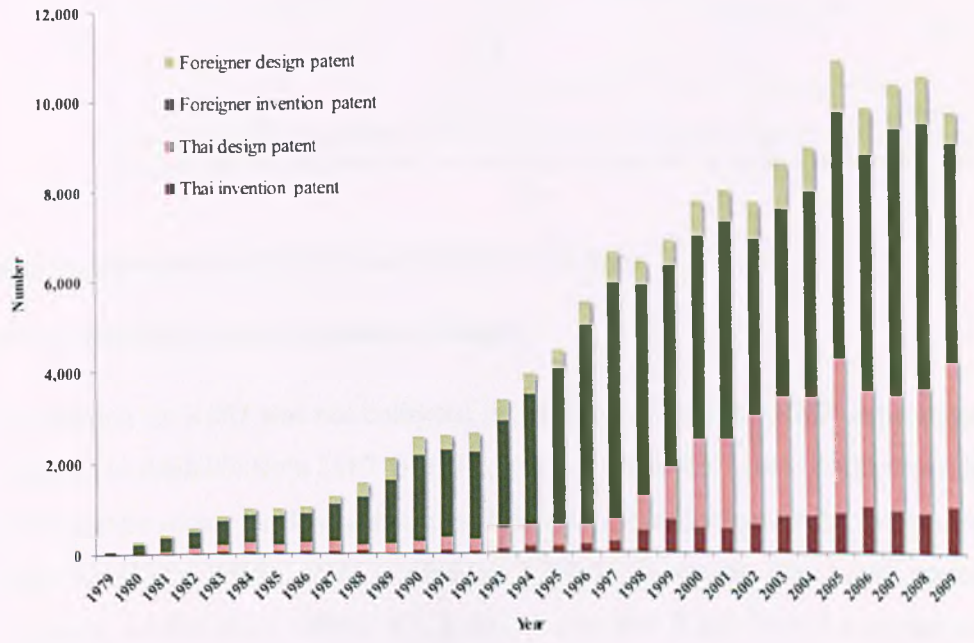
Notes: ***, **, and * represent statistical significance at the 1%, 5% and 10% levels, respectively
Figures in parentheses indicate standard deviation.
FEM: Fixed effect model
REM: Random effect model

6.5.4 The role of patent in stimulating local innovation and R&D investment

6.5.4.1 Innovative activities in general

Figure 6.7 shows the number of patent applications classified by type and nation. This figure illustrates the number of patents filed has been increasing steadily from 47 applications in 1979 to 9,730 applications in 2009 and reached a peak in 2005 at 10,885 applications. Approximately 60% of patents filed in Thailand are from foreigners. After patent law amendment in 1992, although the Thai patent rate has increased at an accelerating rate, the invention patent application rate, which reflects innovative activity, has levelled off at around 800-1000 applications per year since 1999. Approximately 70% of Thai patent applications are design patents, a patent that protects only the ornamental appearance of an invention, not its utilitarian features.

Figure 6.7 Number of patent applications by type and country in Thailand from 1979-2009

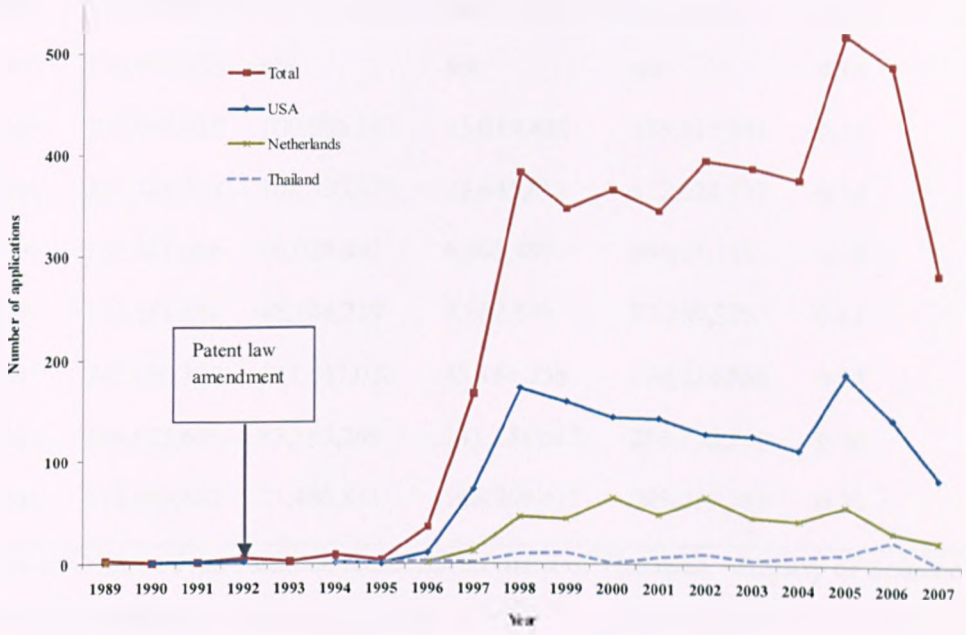


Source: Department of Intellectual Property, Thailand

6.5.4.2 Innovative activities in pharmaceutical industry

Specifically focusing on pharmaceutical patents, Figure 6.8 shows that US pharmaceutical firms are the largest patent owners, totalling 1,504 applications, while Dutch pharmaceutical firms are the second, totalling 489 applications. During 1989-2007 Thai firms filed patents for just 96 applications.

Figure 6.8 Number of patent filing in classification category A61K, pharmaceutical patent, by patent owner country



Source: Department of Intellectual Property, Thailand

6.5.4.3 Research and development budget

Information on R&D was not collected in Thailand until 1995. R&D expenditure in Thailand is available from 1987 to 2007, in non-consecutive years. R&D expenditure by the public sector has fluctuated from US$ 48-100 million annually. Private sector R&D has been steady, with a drop in 1997-1999 during the Asian economic recession. As shown in Table 6.13, it can be seen that R&D from the private sector began to increase in 2001, becoming higher than public sector R&D investment in 2003 and by 2005 private sector R&D was twice that of the public sector. Though the overall trend of R&D expenditure has increased over time, as a proportion of GDP it has stabilized since 2001 at around 2.5%.

Table 6.13 Value (USD) and source of R&D expenditure and percentage of GDP

Year	Total R&D expenditure (USD)	R&D Sources			R&D expenditure/ GDP (%)
		Public	Private	Education and not for profit organization	
1987	103,511,606	n/a	n/a	n/a	
1989	113,012,750	n/a	n/a	n/a	0.15
1991	153,920,546	n/a	n/a	n/a	0.16
1993	176,675,035	n/a	n/a	n/a	0.14
1995	206,969,428	100,986,607	15,019,403	105,817,841	0.13
1996	221,125,378	108,320,371	23,843,811	112,624,177	0.12
1997	155,201,086	86,025,037	6,465,499	69,027,118	0.10
1999	132,151,684	48,244,229	9,882,849	83,789,325	0.11
2001	245,888,857	111,547,030	85,161,258	134,229,864	0.22
2003	369,028,600	83,163,249	141,131,513	285,726,795	0.26
2005	416,669,492	71,480,831	166,969,417	345,015,751	0.23

Source: Office of the National Research Council of Thailand, Ministry of Science and Technology

6.6. Conclusion and discussion

This study analysed patent policy reform issues that arise with the global strengthening of protection for intellectual property. Thailand is an interesting case study given its role as a major developing country, which has the two extreme policies of strengthening and weakening patent law: complying with the TRIPS Agreement 13 years before it was required to and then implementing CL in seven medicines within two years. This chapter examined the contribution of strengthening and weakening patent protection to Thailand's inward flow of FDI and technology transfer. This chapter has generated four sets of results.

First, using a series of FDI inflows from 1970 to 2008, the empirical estimation suggests that there is no significant change in FDI inflows after the patent law

amendment in 1992.That is, patent law does not appear to have increased FDI; although the process leading up to, and culminating in this law, may have done.

Second, GDP, exchange rate and export growth have a positive and significant effect in attracting FDI. Amendment to the patent law in 1992 has a negative impact on FDI inflows to Thailand, but this is not significant and thus not robust.

Third, weakening pharmaceutical patent protection using CL does not necessarily keep away foreign investors. Market attractiveness, both size and quality in terms of GDP, population number, and international trade are significant factors in attracting foreign investors. In addition, political stability is an important factor affecting foreign investment.

Fourth, strengthening patent protection does not appear to lead to a positive jump in innovation activities as estimated by the number of inventive patent filed. Though the number of patent applications from local firms has increased, it is far smaller than those being filed from aboard.

Overall then, the results suggest that strengthening patent protection may have had an impact on increasing FDI in Thailand, but that there is a very weak level of evidence for this, and none for patent protection increasing innovation. Similarly, there is little evidence that weakening protection through CL has led to significant decreases in FDI. Though the Chow test revealed structural change in 1988, this coincided with when the Thai economy changed dramatically. Thus, although pressure on patent law amendment from trade negotiation with the US was initiated in 1988, and thus could have affected FDI, the country's economy was also opening rapidly to international trade. After correcting for time trend, neither amendment 1988 or 1992 have a significant effect on FDI inflows. This contrasts with the study of Kawai (2006). This may be because that study employed the number of patent applications as an IPR index. Since the trend is for patent application numbers to also increase over time, this could lead to a positive relationship. The study presented in this chapter instead used a dummy variable that shows the difference between the two periods, before and after the policy.

This study has limitations. First, although this study tried to identify the channel of technology transfer or knowledge diffusion which is claimed as the aim of setting up the patent system, there are some channels that knowledge transfer could gain through imports of high-technology products, adoption of foreign technology and acquisition of human capital, licensing, and personnel movements, or from informal means through imitation, reverse engineering, and spillover (Maskus 2004). Choosing activities to reveal patent impact on technology transfer is always difficult since it is hard to identify and measure. This study focuses on FDI as a main channel of knowledge transfer since it has been claimed as the most important channel for technology transfer (Wang and Blomström 1992; Borensztein, De Gregorio et al. 1998).

The second limitation regarding FDI inflow employed in this study is that every industry was considered to be equally influenced by patent protection. Although around 70% of FDI inward to industry sector was accounted for by electrical appliances, machinery and transport equipment and chemicals which could be considered as IPR sensitive, the limitation of this study is that the importance of IPR protection varies between industries (Mansfield 1994; Javorcik 2004). IPR protection may play a more prominent role in capital- or skill-intensive investment, such as R&D facilities, than labour-intensive facilities. Therefore, this suggests future work to assess the patent impact on technology transfer through other means or to develop a model that allows for different IPR coefficients between sectors.

Third, this study failed to investigate the quality of FDI since data at firm level cannot be obtained. There will be a range of influences on a foreign investor's decision between setting up manufacturing facilities and establishing facilities that are solely based on marketing and distribution of imported products. Javorick (2004) and An et al. (2008) found that stronger IPR protection is associated with the decision to set up production facilities rather than setting up distribution facilities (Javorcik 2004; An, Maskus et al. 2008). An analysis using a firm-level data set would allow for examination in future if data are available.

(Mansfield 1994; Javorcik 2004)Therefore, this suggests future work to assess the patent impact on technology transfer through other means

Fourth, since there is no data on FDI inflows specific to the pharmaceutical industry, the analysis in this study used the chemical industry instead, since the pharmaceutical industry is categorised in this industry. It is also not known how significant the pharmaceutical industry is, as a proportion of the chemical industry. In spite of patent protection not correlating with FDI inflows, it might have an effect on FDI inflows to the pharmaceutical industry if separately analysed. This limitation also exists with analysis of FDI inflows to developing countries that have implemented CL.

With respect to the pharmaceutical industry, it was anticipated that CL could 'destroy' FDI (Bird and Cahoy 2008). However, this analysis does not support this conclusion. This result is also supported by Correa (2000), who suggests that a weak system of patent protection on pharmaceuticals was the main factor in making a country a manufacturing base for these pharmaceutical companies (Correa 2000). Another study found that there was no uniform decline in the rate of medicine patenting and other measures of inventive activity by companies affected by CL (Colleen 2003). Interestingly, Weiburst and Scherer (1995) concluded that that the exclusion of pharmaceuticals from patent protection was a significant factor leading Italy to become a base for export-oriented production of generic medicines (Weisburst and Scherer 1995).

The potential for domestic product improvement or innovation is problematic, as local firms appear to be more interested in design patents. Qian (2010) pointed out that some developing countries have always had patent protection, yet, domestically, they do not have innovative potential and rely heavily on imports (Qian 2010). In the case of Thailand, the R&D budget is very small compared with neighbouring countries, i.e. Malaysia and Singapore. This may be the reason for the small application rate for invention patents by Thais compared with foreign firms. For the pharmaceutical industry specifically, there is little competence to produce complex medicines by local pharmaceutical companies in Thailand. Local drug companies invested less than 1% of total costs into R&D, and most active ingredients have to be imported from manufacturers overseas (Thailand Board of Investment 2011). Although some Thai researchers are capable of undertaking research and development (Vanichkorn 2012), the lack of the recognition of the scientific

community and clear potential career path, means that scientists are likely to work aboard rather than in Thailand leading to a shortage of scientists (Kuanpoth 2007). To create a positive impact of inward pharmaceutical R&D requires improvements in both the scientific community and R&D facilities.

The fundamental message from this chapter is that the role of stronger patent protection on stimulating innovation and knowledge transfer through FDI has not been met. Conversely, evidence from the experience of low- and middle-income countries suggests also that CL does not negatively impact FDI.

CHAPTER 7 CONCLUSION AND RECOMMENDATIONS

Before 1995, countries were able to set the level of patent protection for the pharmaceutical industry that suited their level of development. However, the initiation of the WTO-TRIPS Agreement set a minimum standard of patent protection for countries that are Members of the WTO. The main implication of this Agreement for health is that the monopoly rights from patents can make medicines more expensive, preventing the majority of people who are poor from affording them. Thailand, as a Member of the WTO, was not able to avoid this requirement. However, Thailand amended its patent law to comply with the TRIPS Agreement eight years ahead of the deadline for developing countries, with the justification that stricter patent protection would provide confidence to foreign investors, especially pharmaceutical companies, to invest in R&D or to produce medicines in Thailand. Therefore, Thailand would benefit from technology transfers and the restricted patent law would enhance local innovative activities.

It has been almost two decades since the Thai patent law changed. A number of articles and reports have been published suggesting the likely impact stricter patent legislation might have on limiting access to medicines. Surprisingly, empirical evidence is rare. The justification of changing the Thai patent law, to enhance technology transfers, has also not been yet been proven. Another issue is the effect of implementing measures under TRIPS flexibilities, such as CL. This measure provides the opportunity to purchase the generic equivalent version at a fraction of the price of the patented medicine. However, adverse reactions from pharmaceutical companies and the governments of patent owners are significant. The issuance of CL by the Thai government during 2006-2008 on seven medicines lead to controversy over whether Thailand was better off with the licenses or not.

This final chapter responds to the overall research question "What are the implications of pharmaceutical patent policy in Thailand?" through drawing together the findings related to the four research sub-questions which were, (i) how much does patent determine price?; (ii) do prices impede access to medicines?; (iii) do patent policy and price affect the entry of new medicines into the Thai market?; and

(iv) does stricter patenting meet the objective of stimulating technology transfers and innovation activities?

The thesis has aimed to help guide pharmaceutical patent policy in Thailand, using econometric tools as a common methodology. Together the four sub-studies contribute to a more holistic recommendation than would normally be provided, balancing various aspects of the effect of patent strengthening and weakening. It therefore provides a more comprehensive set of recommendations for pursuing optimal pharmaceutical patent policy strategy in Thailand. Lessons here are also useful to other countries in similar situations.

Following this introduction, the next section summarises the results related to each research question. It then follows with the limitations of this thesis and recommendations for future work. The recommendations for policy makers are provided subsequently. The last section discusses the overall conclusion and current issues of patent protection in other developing countries.

7.1 Summary of findings to address the research questions

The overall conclusion relating to each of these aspects is shown in Table 7.1. In conclusion, this study found that patent increases price which ultimately impedes access. However, strengthening patent protection increases the opportunity of being able to access newly developed medicines in the future. Implementing CL can bring down the price and increase access to current medicines. However, patients in the future would have, as a consequence, less access to new medicines. With regard to FDI, in Thailand the patent protection level has no relationship with foreign investor decisions and local R&D activities. Although CL is not correlated with FDI, the effects on the local innovation rate and on R&D activities are unknown. More details on each dimension are then provided below.

Table 7.1 Conclusion

Dimension	Aspects	Patent protection		Note
		Strengthening	Weakening	
Health	Price	↕	↓	Only oncology medicines
	Current access		↑	
	Future access	↑	↓	
Economic	FDI	≠	≠	Overall and chemical industry
	Local innovation rate	≠	N/A	Overall and pharmaceutical industry
	Local R&D investment	≠	N/A	No data on R&D in pharmaceutical industry

Note:
↑ Positive relationship; ↓ Negative relationship,≠: not significant change from patent policy
N/A: Not enough information

7.1.1 Patent information system

In estimating the impact of patent legislation on price and access, the most fundamental information is the patent status of the medicines concerned. It is somewhat surprising, therefore, that there is no updated patent information system linking patents with each active ingredient in Thailand, and that the patent search processes are complex and resource consuming. Chapter 2 outlined the processes by which patent status may be found in Thailand, following WHO guidelines.

This is not, however, just a practical issue for this chapter. The inaccessible or unavailable nature of patent information affects two crucial decision-making processes. First, cheaper procurements can only be made if the patent status of each medicine is known (World Health Organization 2004). This chapter shows that 13 monopoly medicines, accounting for 260 million Baht (US$7.9 million) in 2008, could have been procured from international providers without breaching patent legislation, potentially saving the Thai health system money. As stated in WHO's Medicines Strategy: Framework for Action in Essential Drugs and Medicines Policy 2000-2003, the average price of generic medicines can fall by as much as 30% of the

original price, suggesting that approximately 78 million Baht (US$2.4 million) could have been saved.

Second, patent information is required to ensure that domestic generic medicine manufacturers are able to make use of patent information for reverse engineering or bio-equivalent preparation of medicines to prepare for registration once the original version's patent is expired (Milani and Oh 2011). Therefore the first recommendation is for the Thai authorities to strengthen systems for gathering, validating and disseminating patent information for pharmaceuticals.

7.1.2 The role of patent on price

It is important to note that access to medicines is not only determined by price: as the World Health Organization (WHO) indicates, there are five main determinants and affordable pricing is only one of these. However, price is usually the focus of attention in debates concerning access to medicines. Patents are seen as a cause of high prices, and thus as a barrier to access.

Chapter 3 confirmed that patents play a substantial role in determining the price of pharmaceuticals. This effect is relatively high compared to other studies, which could be because there is no direct price control policy in Thailand, allowing the product owner to set the price. Of course this should not be a surprise, and indeed is expected, as the purpose of patenting is to ensure that the price is higher than the marginal cost of production in order to recoup and incentivise R&D; the questions relate more to whether that price is set to do this, or set at a higher level in order to generate 'super-normal profits'.

This study investigates the effect of patents, along with other market characteristics and medicine characteristics, on the retail prices of oncology medicines available in Thailand in the year 2008. Although market characteristics, i.e. a larger sales volume and a more competitive market also affect price, their effect on price is minimal, i.e. around 3-30%, and much less than the effect of patents, which is around 200%. Therefore, patent policy could be an effective option to bring down the price. Incorporating TRIPS-flexibilities such as CL, parallel importation or other exceptions to patentability into the Thai patent policy may help to achieve the desired price decreases.

7.1.3 The role of patented price on access

Clearly, the impact of patent on price is only a proxy for eventual impact on access, with the argument that patent increases price (by design) and that price is a key barrier to access, and hence that patents reduce access. By using the status of a medicine as being on the NLEM as a proxy of full access to Thai patients (or rather, zero price), Chapter 4 found that higher prices decrease the probability of a medicine being on thence, but that this was not statistically significant. That is, price is important, but not the most important factor driving the listing of the medicine on the NLEM. It is somewhat more surprising that a medicine being patented itself decreases the probability of being on the list significantly. It is likely, in this case, that patented medicines are new to the market, and the NLEM committee are perhaps less sure of their safety or the benefits gained from them, when compared with the cost incurred.

This is important, as whether a medicine listed on the NLEM is also influenced by cost-effectiveness analysis. The benchmark to be included on the NLEM has been set at 100,000 Thai baht (approximately US$ 3,300) per QALY gained (Kingkaew, Maleewong et al. 2012). Given this threshold, new medicines are likely to be seen as cost-ineffective in the Thai setting since they will have greater risk but also, of course, a greater cost, and leading most to be rejected. Also, as QALYs gained from oncology medicines are often very small, and again this biases against their being listed in the NLEM. These are possible confounding factors that may be being proxied for the patent variable in analysis.

Nonetheless, it appears that being patented will mean that a medicine is less accessible to the Thai population, but that, ironically, this is not the case with a higher price. With respect to non-NLEM medicines that are patented, they are clearly unaffordable for Thai workers based on the level of the daily wage required to buy them. Although price does limit access, the size of this effect might not be as high as expected, as the price elasticity is -0.4. Therefore, NLEM medicine selection should be considered regardless of patent status. Special measures such as financial support from the government or pharmaceutical companies, or using TRIPS-flexibilities, if needed, should be implemented to help poor patients get access to non-NLEM

medicines. However, the size of the effect should be considered seriously since it determines the appropriate measures to be implemented.

7.1.4 The role of patents on the speed of the product launch

Following from the above discussion, there are two critical factors determining access: affordability and availability. While affordability has been the main concern in many national and international debates, less attention has been paid to the availability of the medicine, and how patent legislation may impact on market entry strategies. In Chapter 5, it was found that policy variables, as well as market-driven factors, have a strong and significant impact on rapid entry. Stringent patent protection, by changing the patent law to protect product patents affects the launch lag significantly. In contrast, product-driven factors are weakly significant and have a minimal impact on the rapidity of launches.

Chapter 5 concluded that patent protection did indeed have a positive and significant relationship with how soon a medicine is launched; stronger patent protection facilitates more rapid entry. Conversely of course, weakening the patent system through measures such as CL discourages companies from launching new products, or launching them so soon, and thus reduces accessibility and hence 'future access'.

Most importantly from the perspective of this thesis, CL implementation could delay access for patients to new medicines available in other countries. Public health and social welfare would be affected, since removing patenting to gain increased access now would result in patients foregoing the opportunity to get new medicine in the future, as it would be less likely to be launched.This is a significant 'cost' of CL that does not get discussed, but clearly it is critical for policy makers to consider when looking at overall strategies to provide access. It is therefore vital for future research to establish in comparable metrics (e.g., in monetary or QALY terms) the gain from a CL medicine for a period of time versus the benefits forgone from delayed introduction of another new medicine.

7.1.5 The role of patents on the diffusion of technology

The main objective of patent law is to stimulate technology and knowledge transfers. Investment carried out by multinational corporations (MNCs) is believed to be one

of the most important vehicles for the international diffusion of technology. Unfortunately, as shown in Chapter 6, there is not enough evidence to conclude that strengthened patent law in Thailand has promoted FDI in the overall economy or in the chemical industry. Moreover, it has not been found that innovation activities in the chemical industry changed significantly as a result of changes in the patent law. In addition, this study found that although patent law has been weakened by CL, FDI appears, in aggregate, to not be significantly affected by this patent policy.

Empirical evidence from this study concerning the implications of patent law for the diffusion of knowledge contradicts the claim of TRIPS advocates that the adverse effect of TRIPS on the price of patented medicines would be adequately compensated for by the benefits gained from increased technology transfer and domestic R&D (Abrol 2004). This is confirmed by the study of Grainville and Leonado (2003) which pointed out that neither trade liberalisation nor TRIPS are likely to suppress the spread of research and innovation and of generics production (Grainville and C.S 2003).

Recent national and international changes in patent legislative frameworks are likely to have profound effects on the ways in which health and pharmaceutical innovations reach the poor and on how public and private research and development institutions pursue their work. Whereas patent rights are sometimes viewed as creating barriers to access to innovations in health, it is not intellectual property, per se, that raises barriers, but rather how intellectual property is used and managed, particularly by public sector institutions. Intellectual property is only one of a number of important components of innovation such as the availability of skilled labour or education and training (Mahoney and Krattiger 2007).

7.2 Limitations to the current study and recommendations for future research

Limitations of this thesis can be categorised into three groups: study scope, data availability, and estimator bias.

7.2.1 Study scope

The estimations presented here looked at price, access, market entry and knowledge transferred. Thus, given time limitations, a number of areas have been neglected that may be of relevance.

First, although the strength of the study is that it is in-depth and more comprehensive than previous studies, the weakness of this study is that, since it is focused on the Thai experience, especially the implications of patent on price and access, the analysis may need to be repeated for other countries due to differences in their health systems and market regulations . However, the most obvious lesson is the need for balance between current and future access which may be quite generalisable.

Second, this study did not cover the impact of patent on future access, in terms of new medicine development. Since the fundamental reason for patent protection is to provide an incentive for firms to invent new chemical entities, it is interesting to see how and to what extent patent influences the discovery of new medicine. Future research can potentially address this issue by observing the dynamic of patented medicines in the market before and after strengthened patent law. The level of therapeutic advancement should also be accounted for since some new patented medicines do not have higher efficacy than medicines already on the market.

Third, this study has focused on only one disease area, cancer, as a result of data limitations. This has compromised the generalizability of the conclusions drawn since each disease has different characteristics of price setting and access patterns. Future research can be done to strengthen this study by extending this scope to include other areas of treatment for major health problems in Thailand. The same models of the implications of patents on both price and access undertaken in this thesis could be replicated. Using the current patent information system it is difficult to identify patented medicines; this study suggests that US patent information could be used as a proxy of patent status in Thailand as a starting point. Then model development could follow that used in this thesis. These models should be validated or reanalyzed when the Thai pharmaceutical patent database is available.

Finally, there are limits related to the estimation of knowledge transferred from foreign investment. This study employed the value of FDI inflows as a proxy of knowledge transferred, which in reality might not be an accurate measure since technology transfers can be obtained either through formal means, through the import of high-technology products, adoption of foreign technology and acquisition of human capital, licensing, and personnel movements, or through informal means through imitation, reverse engineering, and spillover (Maskus 2004). However, previous studies suggested that choosing activity to reveal the impact of patents on technology transfers is always difficult; therefore, inward FDI has been identified as the most important channel for technology transfer (Wang and Blomström 1992; Borensztein, De Gregorio et al. 1998). Future work should try using other proxies of FDI, since FDI inflow as employed in this study was that every industry was considered to be equally influenced by patent protection

Since the sensitivity to IPR protection differs between industries, a weakness of this study is that it assumes that IPR protection equally affects every industry, and then only focuses on the chemical industry. IPR protection may play a more prominent role in capital- or skill-intensive investment, such as R&D facilities, than labour-intensive facilities. This suggests that future work to assess patent implications on technology transfer through other means, or to develop a model that allows for different IPR coefficient between sectors, would be useful.

Another limitation is that FDI is measured in absolute monetary terms, it also includes the capital invested in low-technology industries, to access low cost raw-materials and unskilled labour. Further study should be done, not only using gross FDI as representative of technology diffusion, but also of the quality of FDI inflows, setting manufacturing facilities or distribution facilities.

7.2.2 Data limitations

There are three key methodological limitations to this study. First, the sample size is relatively small, for both health and trade implications analysis, since this thesis focused only on one disease and one country. For instance, there were only 88 active ingredients with QALY data available for only 24 active ingredients. The FDI inflow data has information for around 40 years, leading to only 40 observations. some

models haveless than 30 observations for analysis , suggesting that it will be difficult to find significant relationships from the data and the model is not robust. As statistical tests normally require a larger sample size to ensure a representative distribution of the population, and to be considered representative of the groups of people to whom results will be generalized or transferred, the number of units of analysis used is dictated by the type of research problem investigated. Unless more QALY data becomes available in the future, future studies should investigate how different QALYs gained may determine the price of medicine, since it is a measure of the benefit of that treatment.

Second, there is lack of clarity in some items of data. With respect to the study of patents as determinants of price, within a country the same medicine may have different prices, depending on whether it is sold in its originator brand or generic form, in public charitable agencies or private pharmacies, or in urban or rural areas, and so it is hard to determine what the definitive 'price' is. This study employed price data from IMS, which reflect the price that companies aim to sell to hospitals, wholesaler's price. Yet, companies always offer promotions, so even the estimated price in hospitals is likely to be inaccurate, leading to the results of this study being possibly overestimated.

In terms of the role of patents on access, since the number of patients who ought to be treated by a patented medicine is unknown, this study cannot estimate the number of cancer patients affected by patent protection. Two areas of future work should be continued in order to extend this study, and to get clearer results of the impact of patents on access. First, future work should take the physician's decision into account. This is because, in general, cancer patients get medicines in a hospital, and the choice of which treatment they receive depends on the policies of the hospital and preferences of the doctor. Patients may also be unaware of medicine prices because they are paid for by the government, as NLEM medicines are, but physicians are becoming more aware of relative medicine prices, especially if they operate under a fixed budget system (Hellerstein JK. 1998). Future work could estimate the change in treatment selection from a non-patent regime to a patent regime. Second, this study assumes that the medicine will be available if listed on the NLEM which might not be true in rural hospitals. Not only is the focus on

affordability, but future studies should account for supply chain variables to extend the determinants on the availability area.

7.2.3 Estimation bias

The limitations here have been discussed in each empirical chapter, which this section summarises. Estimated models in this study could have undesirable properties, including biasness, inefficiency and inconsistency. Some models were constructed from very small sample sizes, with consequence inefficient coefficients, i.e. the estimators have high standard errors and the expected value is not the true value of the parameter. In addition, to avoid omitted variable bias, data employed in the econometric approaches in this thesis were selected to represent the theory which raises the possibility of bias in the data selection leading to inclusion of redundant variables. Therefore, regression analyses that are restricted to proxy variables is likely to return coefficient estimates that are inconsistent with their true population values.

A final limitation is from the interaction between variables. Although perfect multicollinearity has not been observed, it is expected that there are some interactions among explanatory variables. Thus, some variables may appear to be statistically insignificant while they should besignificant. The results therefore need to be interpreted with some caution.

7.3 Policy recommendations

This section offers some practical recommendations to improve policies related to access to medicines in Thailand. Seven recommendations are proposed to help guide policy makers, government authorities and related stakeholders towards the most effective use of the patent system whilst safeguarding public health.

1. A national database related to pharmaceutical patents should be established. This information is fundamental knowledge necessary to monitor the effect of patenting. Data would be useful for research and development, technology transfers, and price-negotiation. This would also open the door to researchers being able to provide even more empirical evidence to support policy makers. As presented in Chapter 2, it reveals that under Thai FDA authorities, the new medicine registration division and

the NLEM committee are able to identify patent information of each medicine, although it is a cooperation basis rather than command by law basis. In the short run, data submitted to the NLEM committee and market registration should be actively monitored and checked with the patent office for completeness and correction. For the long run, regulation to mandate patent information submission should be developed.

2. A permanent and authorized organization to monitor the price of patented medicines should be established. The experience in Canada has shown the benefit of the Patented Medicines Prices Review Board (PMPRB). The PMPRB uses the term 'excessive' to characterize either a high introductory price of a new medication, or a substantial increase in the price of an existing medication (Anis and Wen 1998). When it was established, Canadian prices for patented drugs were 23% above the median of foreign prices; today, they are 10% lower than that median. Relative to foreign prices, there has been a 30% decline in Canadian prices for patented medicines since 1987 (Gray C. 1998). Given that patent is the most significant determinant on price, policies affecting patent status such as parallel import, voluntary licensing and compulsory licensing are still useful measures to negotiate with pharmaceutical companies when the problem of access is mainly due to price. In addition, the mechanism of reference pricing that compares the price of patented medicine at national and international level should be freely available for local hospitals in order to improve procurement efficiently.

3. While the debate over patents and access is on-going and unavoidable, this study shows that most patented medicines are unaffordable by the majority of the Thai population. Although CL has shown itself to be an effective policy to increase access to medicines, it takes considerable time to implement and also creates strong reactions and likely impedements to access to medicines in the future. Thus, alternative health financing should be implemented through co-payment. An example would be tiered pricing, where different prices are charged determined by income level, rather than all medicines being free to all people on the NLEM.

4. Trade agreements between Thailand and developed countries tend now towards a higher patent protection system, TRIPS-Plus. It is necessary to establish an infrastructure providing economic evaluation to support decision making in order to

have a list of essential medicines that are freely accessible by the Thai population. Cost-effectiveness is widely used to provide economic appraisal to inform health policies in developed countries. Compared with developed countries, capacity to conduct cost-effectiveness analysis of health interventions in developing countries is limited. In Thailand, the Health Economics Working Group was established in 2007 by the Subcommittee for the Development of NLEM (Subcommittee for National List of Essential Medicine Development 2008).

Economic evaluation to support this working group is mainly carried out by Health Intervention and Technology Assessment Program (HITAP) (Tantivess, Teerawattananon et al. 2009). For capacity building, HITAP developed economic evaluation guidelines and conducts economic evaluation training to academics, government officers and pharmaceutical companies (Panpiemras, Suriyawongpaisal et al. 2009). HTA is now expanding to be used for informing coverage decisions of health technology in the development of the Thai Universal Coverage health benefit package (Mohara, Youngkong et al. 2012). A system to support the environment of evidence based policy should be established. Health professionals and government officers at the regulatory level should be able to conduct or understand the importance of CEA of health products.

5. Stronger patents will encourage new medicines to be made available in the Thai market more quickly, but will reduce the ability of the Thai government to place them on the NLEM and thus provide them at zero cost to the Thai population, and weaker patents, such as through the use of CL, will do the opposite. This is a straightforward conclusion, but with profound implications for temporal equity. It is therefore vital that work is conducted to ensure that the benefits from increased current access from CL and long-term benefits from products being launched in a market more quickly are measured in commensurate terms – monetary and/or QALYs or DALYS for instance – in order that a thorough cost: benefit analysis can be undertaken which incorporates the most relevant information.

6. There is no rationale for accepting stronger patent protection than the TRIPS Agreement requires (i.e. TRIPS-Plus should be rejected). As shown in this study, Thailand has not experienced notable changes in FDI since its patent law amendment

in 1992. Although there are specific instances of retaliation, these are minor when seen at the national macro-economic level.

7. Since Thailand has had a product patent system for two decades, the knowledge from those patents needs to be transferred to local inventors. Patents are not intended to protect new knowledge, but rather its embodiment in new products or industrial processes. Stimulating invention patents is important to the technology development in the future. As a result, pharmaceutical patents filed in the Thai patent database should be explored and knowledge of how to develop the active ingredient extracted. This can be initiated by GPO and eventually disseminated to the local pharmaceutical industry.

7.4 Overall conclusion

Many low – and middle-income countries are in the midst of negotiating bilateral trade and investment agreements with the EU or the USA, such as the Trans-Pacific Partnership Agreement (TPPA) (Saunders 2012). TPPA is currently being negotiated between the US and several countries on the Pacific Rim- Australia, Brunei, Chile, Malaysia, New Zealand, Peru, Singapore and Vietnam. It is expected that these market-opening negotiations could vastly expand trade between these countries in goods, services, and investments. However, a proposed requirement of the agreement is tighter IPR regimes that could bind countries to stronger protections than the WTO's TRIPS Agreement requires (TRIPS-plus) (Morin 2009). Therefore, these trade negotiations could have profound impacts on crucial public policy issues, especially access to essential medicines.

Among developing and least-developed countries that are negotiating bilateral trade agreements, India is an interesting case. The implications of this case are not just relevant for India itself, but will significantly impact access to medicines across the developing world, since Indian generic manufacturers are the main supplier of inexpensive medicines globally (Waning, Diedrichsen et al. 2010). As in other bilateral trade agreements, the Indian government has been requested to institute TRIPS-Plus provisions, including patent term extensions, data exclusivity laws and stronger enforcement measures (Chatterjee 2011). Greater restrictive measures are also the subject of negotiations. First, border measures, in which international trade

in generic medicines can be blocked by allowing customs authorities to seize any medicines suspected of infringing patents in the countries through which they transit (Seuba 2010). Second, the EU wants India to agree to include IPR within the definition of 'investment'. If it did so MNCs would be able to file cases against the use of TRIPS-flexibilities (such as CL) since they affect the investment. India would then have to pay compensation to these companies, or refrain from adopting measures to protect public health (Third World Network 2012).

Governments of developing countries are subjected to pressure by the US government to accept TRIPS-Plus proposals (COHEN-KOHLER, FORMAN et al. 2008). Empirical evidence of the benefits and costs of strengthening and weakening patent law is needed to support decision making. The results of this thesis, specific to the Thai experience, could support the negotiations process. While whether Thailand is better off strengthening or weakening its patent laws seems to be a simple question, there is a complex spectrum of answers depending on how one interprets the question. This thesis has laid out the evidence concerning strengthening and weakening that has been gathered in this study.

For Thailand, evidence from this thesis suggests that stronger patent legislation increases the price of medicines and plays an important role in reducing access to medicines through reducing the probability of their being listed on the NLEM. However, stronger patent legislation does mean that new products are launched several years earlier. Weakening patent laws through CL reduces the price of medicine and increases the number of patented medicines on the NLEM, but will delay new medicine entry. Although it is said that the adverse effect on price and access from stronger patent protection would be compensated for by the benefits of technology transfers and domestic R&D, the experience in Thailand can reveal that the benefits in term of local innovation and technology transference has not been seen. Moreover, strengthening and weakening patent law cause only insignificant changes in the level of FDI.

Whether patent protection can make a country a better place is still subject to debate since estimating future effects is complex and requires many assumptions. The patent system is a public policy tool: patents are contracts between their owners and society. The trade-off between patent protection and access to medicines is still

subject to debate, since empirical studies are relatively scarce, especially in developing countries. This underlines the urgent need to prioritise health research resources to assess the implications of patent protection and create other mechanisms to mitigate the adverse impact on access to medicines.

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Appendix 1: The list of companies which sell patented medicines (from Orange Book) or monopoly medicines in Thailand

1. **American Taiwan Biopharm Co.,Ltd.**

Active Ingredient	Proprietary Name	Strength
1. **Altretamine**	Hexalen®[cap]	50 mg x 100's
2. **Arsenic trioxide**	Asadin® (The Thai Working Group on Burden of Disease and Injuries)	1 mg/1 mL x 10 mL
3. **Doxorubicin**	Lipo-Dox® [vial]	40 mg/2 mL x 1's, 100 mg/5 mL x 1's
4. **Irinotecan**	Irino® [vial]	40 mg/2 mL x 1's 100 mg/5 mL x 1's
5. **Oxaliplatin**	Oxalip® [vial]	50 mg x 1's 100 mg x 1's
6. **Rituximab**	UFUR® [cap]	7 x 10's
7. **Calcium folinate**	Folina® (Vaughan)	15 mg x 10 x 10's

2. **Astellas Pharma (Thailand) Co., Ltd.**

Active Ingredient	Proprietary Name	Strength
1. **Ramosetron hydrochloride**	Nasea® [amp]	0.3mg x 2mL x 5's
	Nasea® (Vaughan)	0.1 mg x 10's

3. **AstraZeneca (Thailand) Ltd.**

Active Ingredient	Proprietary Name	Strength
1. **Anastrozole**	Arimidex® (Vaughan)	1mg x 28's
2. **Bicalutamide**	Casodex® [150film-coated tab]	50mg x 28's
3. **Gefitinib**	Iressa® [film-coated tab]	250 mg x 3x 10's
4. **Mitomycin**	Mitoxantrone Asta medica® [vial]	10mg/ 5mL x 1's 20mg/ 10mL x 1's
5. **Goserelin Acetate**	Zoladex® [SafeSystem depot inj]	3.6 mg x 1's
6. **Tamoxifen**	Nolvadex® (Vaughan)	10 mg x 30's, 20 mg x 30's

4. **B L Hua Co.,Ltd.**

Active Ingredient	Proprietary Name	Strength
1. **Dacarbazine**	Dacarbazine Medac® [vial]	100mg x 1's 200 mg x 1's

5. **Baxter Healthcare (Thailand) Co.,Ltd**

Active Ingredient	Proprietary Name	Strength
1. **Cyclophosphamide**	Endoxan® [coated tab]	50mg x 200's 50mg x 500's 50mg x 314's
	Endoxan® [vial]	500mg x 1's 1000mg x 1's
2. **Idarubicin**	Holoxan® [vial]	500mg x 1's 1000mg x 1's
3. **Mitomycin**	Mitoxantrone Baxter® [vial]	10mg/ 5mL x 1's 20mg/ 10mL x 1's
4. **vinorelbine tartrate**	Navelbine® [vial]	10 mg/1 mL x 1's

6. **Bayer Thai Co., Ltd. (Bayer Schering Pharma)**

Active Ingredient	Proprietary Name	Strength
1 **Cyproterone**	Androcur® (Vaughan)	50mg x 50's
2 **Ibritumomab tiuxetan**	Zevalin® (Wignaraja, Olfindo et al.)	1.6 mg/1 mL x 2 mL x 1's
3 **Rituximab**	Nexavar® [film-coated tab]	200 mg x 6 x 10's
4 **Tamoxifen**	Tuosomin® (Vaughan)	10 g x 100's 20 g x 100's
5 **Alemtuzumab**	MabCampath® [vial]	30 mg/1 mL x 1 x 3's
6 **fludarabine phosphate**	Fludara® [film-coated tab]	10 mg x 20's
	Fludara® [vial]	50 mg x 5's

7. **Berli Jucker Public Co., Ltd.**

Active Ingredient	Proprietary Name	Strength
1. **Interferon alfa-2b**	Bioferon® [vial]	3 MIU x 1's 5 MIU x 1's
2. **Epoetin alfa**	Hemax® [vial]	1000 iu/1 mL x 1's 2000 iu/2 mL x 1's 3000 iu/2 mL x 1's 4000 iu/2 mL x 1's 10000 iu/1 mL x 1's

3. **Carmustine**	Gliadel® [wafer]	7.7 mg x 8's
4. **Histrelin acetate**	Vantas® [implant]	50 mg x 1's

8. Bristol-Myers Squibb Pharma (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Carboplatin**	Paraplatin® [vial]	50 mg/5 mL x 1's 150 mg/15 mL x 1's 450 mg/45 mL x 1's
2. **Carmustine**	Bicnu® [vial]	100 mg x 1's
3. **Cisplatin**	Platinol® [vial]	10 mg/20 mL x 1's 50 mg/100 mL x 1's
4. **Dasatinib**	Sprycel® [film-coated tab]	20 mg x 60's
5. **Etoposide**	Vepesid® [cap]	50mg x 20's 100mg/ 5mL x 1's
6. **Hydroxycarbamide**	Hydrea® [cap]	500 mg x 100's
7. **Lomustine**	Ceenu® [cap]	40 mg x 1's
8. **Megestrol**	Megace® [susp]	40 mg/1 mL x 240 mL
9. **Megestrol**	Megace® (Vaughan)	160 mg x 100's 160 mg x 100's 40 mg x 100's
10. **Paclitaxel**	Taxol® [multidose vial]	30 mg/5 mL x 1's 100 mg/16.7 mL x 1's 300 mg/50 mL x 1's

9. Eli Lilly Asia Inc.-Thailand Branch

Active Ingredient	Proprietary Name	Strength
1. **Gemcitabine**	Gemzar® [vial]	200 mg x 1's 1 g x 1's
2. **Pemetrexed**	Alimta® [vial]	500mg x 1's

10. GlaxoSmithKline (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Busulfan**	Myleran® (Vaughan)	2 mg x 100's
2. **Chlorambucil**	Leukeran® (Vaughan)	2 mg x 25's
3. **Lapatinib**	Tykerb® [film-coated tab]	250 mg x 70's
4. **Lomustine**	Puri-Nethol® (Vaughan)	50 mg x 25's
5. **Melphalan**	Alkeran Injection® [vial]	50 mg x 1's
	Alkeran® (Vaughan)	2 mg x 25's
6. **Ondansetron**	Zofran® (Vaughan)	4 mg x 10's
	Zofran® [amp]	4 mg/2 mL x 5's
	Zofran® [Zydis tab]	4 mg x 10's
7. **Thioguanine**	Lanvis® (Vaughan)	40 mg x 25's
8. **Topotecan**	Hycamtin® [vial]	4 mg x 1's

11. Great Eastern Drug Co.,Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Epoetin alpha**	Renogen® [vial]	1 mL x 1's

12. IDS Marketing (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Epoetin alpha**	Hemapo® [pre-filled syringe]	30 g/1 mL x 1 x 3's

13. Janssen-Cilag Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Bortezomib**	Velcade® [IV vial]	3.5 mg x 1's 1.0 mg x 1's
2. **Cladribine**	Leustatin® [vial]	10 mg/10 mL x 1's
3. **Decitabine**	Dacogen® [vial]	50 mg x 20 mL x 1's
4. **Epoetin alpha**	Eprex® [pre-filled syringe]	1000 iu/0.5 mL x 1's 2000 iu/0.5 mL x 1's 3000 iu/0.3 mL x 1's 4000 iu/0.4 mL x 1's 5000 iu/0.5 mL x 1's 6000 iu/0.6 mL x 1's 8000 iu/0.8 mL x 1's 10000 iu/1.0 mL x 1's 20000 iu/0.5 mL x 1's 40000 iu/1.0 mL x 1's

14. Kyowa Hakko (Thailand) Co Ltd.

Active Ingredient	Proprietary Name	Strength
1. **L-ASPARAGINASE**	Leunase® [vial]	10,000 KU x 1's
2. **Mitomycin**	Mitomycin-C Kyowa® [vial]	2 mg x 1's 10 mg x 1's 20 mg x 1's
	Mitomycin-C Kyowa® (Vaughan)	1 mg x 1's

15. MSD (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Aprepitant**	Emend® [cap]	80 mg x 1's, 125 x 1's

16. Merck Ltd., Thailand

Active Ingredient	Proprietary Name	Strength
1. **Cetuximab**	Erbitux® [vial]	2 mg/1 mL x 50 mL
2. **Tegafur + Uraci**	UFT® [cap]	6 x 10's

17. Schering-Plough Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Amifostine**	Ethyol® [vial]	500 mg x 10 mL x 1's
2. **Doxorubicin**	Caelyx® [vial]	2 mg/1 mL x 10 mL x 1's
3. **Interferon alfa-2b**	Intron-A® [Multi-Dose pen]	Pen 18 MIU/1.2 ml x 1's
4. **Letrozole**	Fugerel® (Vaughan)	250 mg x 100's
5. **Metenolone**	Primobolan® (Vaughan)	5 mg x 500's
6. **Temozolomide**	Temodal® [cap]	20 mg x 5's 100 mg x 5's 250 mg x 5's
7. **Toremifene**	Fareston® (Vaughan)	60 mg x 30's

18. Novartis (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Imatinib**	Glivec® [film-coated tab]	100 mg x 60's 100 mg x 120's 400 mg x 30's
2. **Letrozole**	Femara® [film-coated tab]	2.5 mg x 30's
3. **Nilotinib**	Tasigna® [Hard cap]	200 mg x 28's
4. **Tropisetron**	Navoban® (Vaughan)	5 mg x 5's
	Navoban® [amp]	5 mg/5 mL x 1's
5. **Gemcitabine**	Gramagen® [vial]	200 mg x 1's 1 g x 1's
6. **Irinotecan**	Irenax® [infusion]	40 mg/2 mL x 1's 100 mg/5 mL x 1's
7. **Tamoxifen**	Tamoxifen Sandoz® [film-coated tab]	20 mg x 30's

19. Pfizer (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Carboplatin**	Carboplatin injection® [vial]	50 mg/5 mL x 1's 150 mg/15 mL x 1's 450 mg/45 mL x 1's
2. **Cisplatin**	Cisplatin injection® [vial]	1 mg/1 mL x 10 ml 1 mg/1 mL x 50 ml
3. **Cytarabine**	Cytosar CS® [vial]	100 mg/5 mL x 1's 500 mg/25 mL x 1's 2,000 mg/20 mL x 1's

Active Ingredient	Proprietary Name	Strength
		100 mg x 1's 500 mg x 1's
4. **Doxorubicin**	Adriblastina R.D.® [vial]	10 mg x 1's 50 mg x 1's
	Doxorubin Hydrochloride® [vial]	*2 mg/1 mL x 5 mL x 1's* 2 mg/1 mL x 25 mL x 1's
5. **Epirubicin**	Pharmorubicin CS® [vial]	10 mg/5 mL x 1's 50 mg/25 mL x 1's 200 mg/100 mL x 1's
	Farmorubicin® [vial]	10 mg x 1's 50 mg x 1's
6. **Exemestane**	Aromasin® [sugar-coated tab]	25 mg x 30's
7. **Idarubicin**	Zavedos® [cap]	5 mg x 1's 10 mg x 1's
	Zavedos® [vial]	5 mg x 1's 10 mg x 1's
8. **Irinotecan**	Campto® [infusion]	40 mg/2 mL x 1's 100 mg/5 mL x 1's
9. **Medroxyprogesterone**	Farlutal® (Vaughan)	500 mg x 30's
10. **Methotrexate**	Methotrexate® [vial]	50 mg/2 mL x 1's
11. **Sunitinib malate**	Sutent® [cap]	12.5 mg x 28's
12. **Vincristine sulfate**	*Vincristine sulfate inj® [vial]*	*2 mg/2 mL x 1's*

20. Siam Pharmaceutical Co Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Azacitidine**	Vidaza® [vial]	100 mg x 1's
2. **Lenograstim**	Granocyte® [vial]	100 mcg x 10's
3. **Thalidomide**	Thalidomide Pharmion® [cap]	50 mg x 2 x 14's

21. Pacific Healthcare (Thailand) Co., Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Triptorelin**	Decapeptyl® (The Thai Working Group on Burden of Disease and Injuries)	3.75 mg x 1's
	Diphereline P.R.® [vial]	3.75 mg x 1's
		11.25 mg x 1's

22. PL Asia Pacific (Thailand) Ltd.[19]

Active Ingredient	Proprietary Name	Strength
1. **Busulfan**	Busulfex® [vial]	6 mg/1 mL x 10 mL x 8's
2. **Dactinomycin**	Lyovac Cosmegen® [vial]	0.5 mg x 1's
3. **Filgrastim**	Gran® [Pre-filled syringe]	300 mcg/0.5 mL x 1's
4. **Pegfilgrastim**	Peglasta® [pre-filled syringe]	5mg x 0.6 mL x 1's

23. Roche Thailand Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Bevacizumab**	Avastin® [vial]	100 mg/4 mL x 1's 200 mg/ 16 mL x 1's
2. **Capecitabine**	Xeloda® [film-coated tab]	150 mg x 60's 500 mg x 120's
3. **Epoetin beta**	Recormon® [pre-filled syringe]	500 iu/0.3 mL x 1's
	Recormon® [vial]	2000 iu/1 mL x 1's
	Mircera® [pre-filled syringe]	50 mcg/0.3 mL x 1's 75 mcg/0.3 mL x 1's 100 mcg/0.3 mL x 1's 150 mcg/0.3 mL x 1's 200 mcg/0.3 mL x 1's
4. **Granisetron HCL**	Kytril® [amp]	3 mg/3 mL x 5's 1 mg/1 mL x 5's
	Kytril® [film-coated tab]	1 mg x 10's
5. **Erlotinib HCl**	Tarceva® [film-coated tab]	100 mg x 30's 150 mg x 30's
6. **Filgrastim**	Neupogen® [pre-filled syringe]	30 MU/0.5 mL x 1's 48 MU/0.5 mL x 1's
7. **Fluorouracil**	Fluoro-uracil® [vial]	500 mg/10 mL x 1's
8. **Ibandronic acid**	Bondronat® [vial]	1 mg/1 mL x 1's
	Bondronat® (Vaughan)	50 mg x 28's
9. **Pegfilgrastim**	Neulastim® [type I glass pre-filled syringe]	6 mg/0.6 mL x 1's
10. **Procarbazine**	Natulan® [cap]	50 mg x 1's
11. **Rituximab**	MabThera® [vial]	100 mg/10 mL x 2's 500 mg/50 mL x 1's

[19] Not found from PReMA member company list (http://www.prema.or.th/member_profile.php?menu=2&key=p)

Active Ingredient	Proprietary Name	Strength
12. **Trastuzumab**	Herceptin® [vial]	150 mg x 1's 440 mg x 1's
13. **Tretinoin**	Vesanoid® [cap]	10 mg x 100's

24. Sanofi-aventis (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Bacillus Calmette-Guerin**	Immucyst® [vial]	81 mg (dry wt) x 1's
2. **Buserelin**	Suprefact® [Depot inj]	6.6 mg x 1 implant 1.575 mg/gm x 10 gm x 2's 1 mg/1 mL x 5.5 ml x 1's
	Suprefact nasal spray® [bot]	0.1 mg/1 spray x 10 g (84 spray) x 4's
3. **Docetaxel**	Taxotere® [single-dose vial]	20 mg/0.5 mL x 1's 80 mg/2 mL x 1's
4. **Oxaliplatin**	Eloxatin® [conc]	50 mg x 1's 100 mg x 1's 50 mg/10 mL x 1's 200 mg/40 mL x 1's
5. **Rasburicase**	Fasturtec® [vial]	1 mg x 1's

25. Takeda (Thailand) Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Leuprorelin acetate**	Enantone L.P.® [vial]	1.88 mg x 1's 3.75 mg x 1's 11.25 g x 1's

26. Thai Meiji Pharmaceutical Co., Ltd.

Active Ingredient	Proprietary Name	Strength
1. **Pirarubicin**	Therarubicin® [vial]	10 mg x 1's 20 mg x 1's

27. Wyeth (Thailand) Ltd. (Consumer Healthcare)

Active Ingredient	Proprietary Name	Strength
1. **Methotrexate**	Methotrexate® (Vaughan)	2.5 mg x 100's
2. **Mitomycin**	Novantrone® [vial]	10 mg/5 mL x 1's 20 mg/10 mL x 1's

Appendix 2: Patent survey to PReMA translated from Thai version

Brief proposal: Survey on cancer drug patents in Thailand

1. Introduction

Survey on cancer drug patents is a part of a research project entitled " Implications of patent on access and foreign direct investment in Thailand: a case study of anticancer medicines". This part of the project will develop a model to study the medicine price sensitivity of the patent compared to the supply and demand variables with a hypothesis that patenting has no effect on the price of medicine. Anti-cancer medicines are selected as a case study due to the fact that cancer is the highest cause of death of the Thai people and these medicines are subject to numerous patents and are expensive. Moreover, the implementation of government use licenses for four anti-cancer medicines in 2008 leads to the wider debate. The suitable measure is therefore important to develop to promote sustainable access to patented medicines rather than the implementation of government use of patents.

Despite long-standing concerns over the implications of patent protection on access to medicines, there is still considerable uncertainty regarding the existence of patents on particular medicines. Patent information on pharmaceutical products is often not easily accessible in an easily understood or transparent format. Most patent databases always indicate that the information is not developed directly from the pharmaceutical companies. They tend to suggest contacting patent owners to verify the patent status again.

Patent information is necessary for the proposed research project that aims to increase access to anti-cancer medicines. However, patent information often has problems about accuracy and completeness. Most patent databases always indicate that the information may not be complete. They suggest contacting patent owners to verify the patent status again. Patent information of each anti-cancer medicine has been searched for in the Department of Intellectual Property database (http://patentsearch.moc.go.th). By using the generic name as a keyword in the searching strategy, there are only four medicines, out of 47, which appear to have

patents. This may be because the database does not collect the generic form of the name, but collect the name of the chemical instead.

For the reasons mentioned above, a survey of patent information from patent owners would be a directly effective way to get correct information. Health and procurement authorities now incorporate issues of intellectual property protection of medicines in their decision-making process. The question of whether or not a medicine is under patent protection is a crucial factor in decisions about medicine procurement (or local production), and will determine the options available to national authorities. This project aims to identify a pragmatic and cost-effective means of investigating and analyzing the extent to which specified essential medicines are protected by patents, and how long patent coverage will last in Thailand.

Action plan

1. Listing the name of companies selling suspected patented medicine (from Orange Book and or from the monopoly medicine status) (see Appendix 1).

2. Developing a patent survey questionnaire (example shown in appendix 2). The survey of medicine patent information includes the following.

- Application number
- Types of patents (Product, Process, or Petty patent)
- Date of the application
- Patent status (Filing, examination, advertisement or granted)
- Patent expiry date

3. Contacting the Association of Pharmaceutical Research & Manufacturers (PReMA) for cooperation and instructions on how to distribute questionnaires effectively and efficiently.

4. Meeting with members of the PReMA in the second week of January 2011.

Timeline

This project timeline is 14 weeks (The first week is the week of October 18-22 2010 and the 14th week is the week of January 17-21 2011). The activities of this project and time to finish are shown in the table.

Activities/Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1.Contact PReMA	✓	✓												
2.Questionnaire distribution			✓	✓										
evissergorP.3 gnirotinom				✓			✓		✓		✓			
4. Meeting (To be confirmed, 13-17 January 2010)													✓	
5. Conclusion														✓

Research contribution

A vital aspect of this decision-making process is the availability of accurate and up-to-date information about the patent status of essential medicines. The empirical evidence of the magnitude of patents as a component of pharmaceutical prices while controlling for other related factors is needed to support decision. Such information will help the government determine their options for procurement of medicines; including the option of procuring generic medicines.

Correspondence persons

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Patent medicine survey: anti-cancer medicines

Objectives

To know the patented anti-cancer medicines. This information will be a main input to study the relationship between patent and price of medicine. The result of model will be presented in May 2011

Instruction

Please fill in the form of the questionnaire. The questionnaire consists of three parts.

Part I survey of the completeness of anti-cancer medicines sold in Thailand by your company. **Only the medicines registered with the Thai FDA from 1983 to 2008**
Part II survey of patents under a particular medicine
Part III survey of patent information i.e. patent application number, type of patent and expiry date

Contact person
Name.....Title.....
Email.....
Tel.....
Fax .....

For more information

If you have any additional thoughts, questions, or comments, please feel free to contact

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Ministry of Public Health, Tiwanon Rd. Nonthaburi 11000
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Returning

Please return this survey by **January 10th** via email at inthira.y@hitap.net or by fax on 02 590 4369

Part1: Survey of the completeness of anti-cancer medicines sold in Thailand by your company. Only the medicines registered with the Thai FDA from 1983 to December 2008

1. Data from Monthly Index of Medical Specialties (MIMS) and the Thai FDA show that **Astellas Pharma (Thailand) Co., Ltd.** has **one** product selling in anti-cancer therapeutic group as shown in table below. Please check the completeness of the list in the table and put
√in ❑ of your company

Active Ingredient	Proprietary Name	Strength
1. Ramosetron hydrochloride	Nasea® [amp]	0.3mg x 2mL x 5's
	Nasea® (Vaughan)	0.1 mg x 10's

From verifying

❑ 1. Our company is selling medicines as shown in above table

❑ 2. We have other anti-cancer medicines as shown in the table below Please contact researcher to send part II and III or it can be copied as appropriate.

Active Ingredient	Proprietary Name	Strength
1.		
2.		
3.		
4.		
5.		

Part 2: Patent

Active Ingredient.	Proprietary Name
Ramosetron hydrochloride	Nasea® [amp]

Is anti-cancer medicine identified above a patented medicine? If yes, how many patents under this medicine?

☐ 2.1 Yes, there are patents under this medicine → Please answer part 3

☐2.2 No → Finish survey, please return the questionnaire back follows by instruction on cover page

Part 3: Patent information

Please fill the information of each patent in the table below respectively. The table can be if appropriate.

No.1	
1. Application number	
2. Patent type	☐Product patent ☐Process patent ☐Petty patent
3. Date of apply	
4. Patent status	☐Examination ☐Advertisement ☐Patent granted No..... ☐ Other (Please specify).....
5. Patent expiry date	
No.2	
1. Application number	
2. Patent type	☐Product patent ☐Process patent ☐Petty patent
3. Date of apply	
4. Patent status	☐Examination ☐Advertisement ☐Patent granted No..... ☐ Other (Please specify).....
5. Patent expiry date	

No.3	
1. Application number	
2. Patent type	☐Product patent ☐Process patent ☐Petty patent
3. Date of apply	
4. Patent status	☐Examination ☐Advertisement ☐Patent granted No..... ☐ Other (Please specify).....
5. Patent expiry date	
No.4	
1. Application number	
2. Patent type	☐Product patent ☐Process patent ☐Petty patent
3. Date of apply	
4. Patent status	☐Examination ☐Advertisement ☐Patent granted No..... ☐ Other (Please specify).....
5. Patent expiry date	
No.5	
1. Application number	
2. Patent type	☐Product patent ☐Process patent ☐Petty patent
3. Date of apply	
4. Patent status	☐Examination ☐Advertisement ☐Patent granted No..... ☐ Other (Please specify).....
5. Patent expiry date	

Thank you for your cooperation

Appendix 3: List of unknown patent status and non-patented medicines

Table 1 List of Drugs found to have patents in US or Canadian drug patent database but not enough information to conclude

No.	Active ingredient	No.	Active ingredient
1	Alemtuzumab	5	Megestrol*
2	bacillus Calmette-Guerin	6	pemetrexed
3	Cyproterone	7	sunitinib malate
4	leuprorelin acetate	8	thalidomide

* Likely to have no patent since registered before 1992 and is not a monopoly medicine

Table 2 List of non-patented medicines

No.	Active ingredient	No.	Active ingredient
1	Altretamine	28	hydroxycarbamide
2	amifostine*	29	idarubicin
3	Anagrelide	30	ifosfamide
4	Anastrozole*	31	interferon alfa-2b*
5	arsenic trioxide*	32	lenograstim
6	Asparaginase	33	medroxyprogesterone
7	Azacitidine	34	melphalan
8	Bicalutamide	35	mercaptopurine
9	Bleomycin	36	mesna
10	Buserelin	37	methotrexate
11	Busulfan	38	mitomycin
12	calcium folinate	39	mitoxantrone
13	Carboplatin	40	ondansetron
14	Carmustine	41	paclitaxel
15	Chlorambucil	42	Pegfilgrastim*
16	Cisplatin	43	ramosetron hydrochloride
17	Cladribine	44	tamoxifen
18	cyclophosphamide	45	tegafur + uracil
19	Cytarabine	46	Temozolomide*
20	Dacarbazine	47	tetrachlorodecaoxide
21	Dactinomycin	48	thioguanine
22	Epirubicin	49	Topotecan*
23	epoetin alfa	50	Toremifene*
24	exemestane*	51	Triptorelin*
25	filgrastim*	52	Vinblastine sulfate
26	fluorouracil*	53	vincristine sulfate
27	Flutamide	54	vinorelbine tartrate

* patent data from pharmaceutical companies

Appendix 4: Search terms and strategy of Chapter 3

No.	Searches	Results
1	(('intellectual property rights' or patent) and TRIPS).af.	507
2	(intellectual property rights, patent, TRIPS or patent or TRIPS).af.	97,705
3	(health or pharmaceutical or medicine or drug).af.	18,050,431
4	2 and 3	36,592
5	(price or affordability).af.	162,722
6	8 and 9	632
7	limit 10 to english language [Limit not valid in Econlit; records were retained]	605
8	limit 11 to yr="1990 -Current"	581
9	remove duplicates from 12	417

Appendix 5: List of medicines that are on NLEM and not on NLEM

NLEM medicines		Not on NLEM medicines	
No	Generic name	no	Generic name
1	alemtuzumab	1	asparaginase
2	altretamine	2	bacillus calmette-guerin
3	amifostine	3	bleomycin
4	anagrelide	4	busulfan
5	anastrozole	5	calcium folinate
6	aprepitant	6	capecitabine
7	arsenic trioxide	7	carboplatin
8	azacitidine	8	chlorambucil
9	bevacizumab	9	cisplatin
10	bicalutamide	10	cyclophosphamide
11	bortezomib	11	cytarabine
12	buserelin	12	dactinomycin
13	carmustine	13	docetaxel
14	cetuximab	14	doxorubicin
15	cyproterone	15	epoetin alfa
16	dasatinib	16	epoetin beta
17	epirubicin	17	etoposide
18	erlotinib hcl	18	filgrastim
19	exemestane	19	fluorouracil
20	fludarabine phosphate	20	flutamide
21	gefitinib	21	gemcitabine
22	goserelin	22	hydroxycarbamide hydroxyeurea
23	granisetron	23	idarubicin
24	ibandronic acid	24	ifosfamide
25	ibritumomab tiuxetan	25	imatinib
26	interferon alfa-2b	26	lenograstim
27	irinotecan	27	letrozole
28	lapatinib	28	medroxyprogesterone
29	leuprorelide acetate	29	megestrol
30	nilotinib	30	melphalan
31	oxaliplatin	31	mercaptopurine
32	pegfilgrastim	32	mesna
33	pemetrexed	33	methotrexate
34	ramosetron hydrochloride	34	mitoxantrone
35	rituximab	35	Ondansetron

NLEM medicines		Not on NLEM medicines	
No	**Generic name**	**No**	**Generic name**
36	sorafenib	36	sorafenib
37	sunitinib malate	37	sunitinib malate
38	tetrachlorodecaoxide	38	tetrachlorodecaoxide
39	thalidomide	39	thalidomide
40	topotecan	40	topotecan
41	toremifene	41	toremifene
42	trastuzumab	42	trastuzumab
43	tretinoin	43	tretinoin
44	triptorelin	44	triptorelin
45	vinorelbine tartrate	45	vinorelbine tartrate

Appendix 6: Search term and strategy of Chapter 4

No.	Searches	Results
1	(patent or TRIPS or price).af	218,127
2	(medicine or drug or pharmaceutical).af	8,556,851
3	(access or afford or utilization).af	877,218
4	1 and 2 and 3	3,147
5	limit 4 to english language	1,410
6	limit 5 to human	975
7	limit 6 to yr="1990 -Current"	959
8	remove duplicates from 7	744

Appendix 7: Estimates by logit model

Variable	Model (1)		Model (2)		Model (3)		Model (4)	
	Coefficient	Marginal effect	Coefficient	Marginal effect	Coefficient	Marginal effect	Coefficient	Marginal effect
Patent	-1.469*	-0.351*			-6.598	-0.811***		
	(0.836)	(0.182)			(4.107)	(0.276)		
Cost of treatment	-0.250	-0.062	-0.227	-0.057	-1.673	-0.162	-1.767**	-0.274**
	(0.217)	(0.053)	(0.189)	(0.047)	(1.213)	(0.149)	(0.900)	(0.122)
Log of No. of patients	0.096	0.024	0.254	0.063	-1.968*	-0.191	-1.021	-0.158
	(0.192)	(0.047)	(0.174)	(0.043)	(1.145)	(0.170)	(0.637)	(0.101)
Log of sales value	0.950***	0.234***	0.720***	0.180***	3.605	0.349	1.634*	0.253**
	(0.274)	(0.069)	(0.230)	(0.057)	(2.201)	(0.267)	(0.934)	(0.114)
Product age	0.312***	0.077***	0.322***	0.081***				
	(0.082)	(0.020)	(0.074)	(0.018)				
QALYs gained					0.157	0.015	-0.049	-0.008
					(0.191)	(0.017)	(0.095)	(0.015)
					-6.598	-0.811***	-1.767**	-0.274**
N	85	85	93	93	22	22	24	24
pseudo R^2	0.546	0.546	0.507	0.507	0.686	0.686	0.479	0.479
Log likelihood	-26.621	-26.621	-31.754	-31.754	-4.534	-4.534	-7.966	-7.966
Chi-squared	64.015	64.015	65.320	65.320	19.772	19.772	14.620	14.620

Notes: Standard errors in parentheses. Significant at (*) 10%, (**) 5% or (***) 1%

Appendix 8: Search term and strategy of Chapter 5

No.	Search terms	Results
1	(patent* or intellectual property).af.	112,050
2	(Public health or health or drug or drugs or Pharmaceutical* or Medicine).af.	18,332,912
3	#1 and #2	43,534
4	(availabilit* or entry or launch).af.	510,590
5	#3 and #4	1,346
6	Limit #5 to english language, human	1,124
7	limit #6 to year="1990 - 2011"	938
8	remove duplicates	689

Appendix 9: Correlation table

	law92	alaw99	uc2002	CL	Drug import	Lpatient no	prior	total	Log expected profit	patent
law92	1									
alaw99	0.69	1								
uc2002	0.58	0.84	1							
CL	0.00	-0.01	0.06	1						
Drug import	0.86	0.86	0.81	0.09	1					
Log patient no	0.89	0.85	0.79	0.07	0.98	1				
prior	0.10	0.21	0.19	0.11	0.21	0.19	1			
Total	-0.09	-0.05	-0.02	0.09	-0.03	-0.09	0.23	1		
Log expected profit	0.18	0.14	0.09	0.02	0.18	0.21	-0.1	-0.19	1	
patent	0.23	0.15	0.13	0.00	0.21	0.2	-0.1	-0.11	0.19	1

Appendix 10: Search term and strategy of Chapter 5

No.	Search terms	Results
1	(patent* or intellectual property).af.	112,050
2	(Public health or health or drug or drugs or Pharmaceutical* or Medicine).af.	18,332,912
3	#1 and #2	43,534
4	(foreign direct investment or FDI or technology transfer or technology diffusion).af. or compulsory licens* or government use licens*	19432
5	#3 and #4	516
6	Limit #5 to english language, human	344
7	limit #6 to year="1990 - 2011"	333
8	remove duplicates	261

Appendix 11: Testing for time variable

To see if time fixed effects are needed when running a FE model use the command testparm. It is a joint test to see if the dummies for all years are equal to 0, if they are then no time fixed effects are needed.

```
. xi:xtreg lnfdi2005 i.Year, fe
i.Year            _IYear_1995-2009    (naturally coded; _IYear_1995 omitted)

Fixed-effects (within) regression               Number of obs      =       125
Group variable: cid                             Number of groups   =         9

R-sq:  within  = 0.1849                         Obs per group: min =        10
       between = 0.3154                                        avg =      13.9
       overall = 0.0544                                        max =        15

                                                F(14,102)          =      1.65
corr(u_i, Xb)  = 0.0411                         Prob > F           =    0.0777

------------------------------------------------------------------------------
    lnfdi2005 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
   _IYear_1996 |   .2573916   .5616603     0.46   0.648    -.8566589    1.371442
   _IYear_1997 |   .3565334   .5616603     0.63   0.527    -.7575171    1.470584
   _IYear_1998 |    .928647   .5800603     1.60   0.112    -.2218998    2.079194
   _IYear_1999 |   .5389198   .5800603     0.93   0.355    -.6116271    1.689467
   _IYear_2000 |   .1681035   .5800603     0.29   0.773    -.9824433    1.31865
   _IYear_2001 |  -.5275636   .5800603    -0.91   0.365     -1.67811    .6229832
   _IYear_2002 |   -.286696   .5616603    -0.51   0.611    -1.400746    .8273545
   _IYear_2003 |  -.0021531   .5800603    -0.00   0.997      -1.1527    1.148394
   _IYear_2004 |   .0523008   .5762315     0.09   0.928    -1.090652    1.195253
   _IYear_2005 |   .4413089   .5762315     0.77   0.446    -.7016435    1.584261
   _IYear_2006 |   .2151768   .5616603     0.38   0.702    -.8988737    1.329227
   _IYear_2007 |   1.285322   .5762315     2.23   0.028     .1423698    2.428275
   _IYear_2008 |   1.345679   .5762315     2.34   0.021     .2027267    2.488631
   _IYear_2009 |   .2611469   .5616603     0.46   0.643    -.8529036    1.375197
         _cons |   19.08979   .4089335    46.68   0.000     18.27867     19.9009
--------------+---------------------------------------------------------------
       sigma_u |  2.4088066
       sigma_e |  1.1524629
           rho |  .81373437   (fraction of variance due to u_i)
------------------------------------------------------------------------------
F test that all u_i=0:     F(8, 102) =    57.48                 Prob > F = 0.0000

. testparm _IYear*
 ( 1)  _IYear_1996 = 0
 ( 2)  _IYear_1997 = 0
 ( 3)  _IYear_1998 = 0
 ( 4)  _IYear_1999 = 0
 ( 5)  _IYear_2000 = 0
 ( 6)  _IYear_2001 = 0
 ( 7)  _IYear_2002 = 0
 ( 8)  _IYear_2003 = 0
 ( 9)  _IYear_2004 = 0
 (10)  _IYear_2005 = 0
 (11)  _IYear_2006 = 0
 (12)  _IYear_2007 = 0
 (13)  _IYear_2008 = 0
 (14)  _IYear_2009 = 0

       F( 14,   102) =    1.65
            Prob > F =    0.0777
```

This shows that it is failed to reject the null that all years' coefficients are jointly equal to zero therefore no time fixed-effects are needed.