EVALUATING PHARMACEUTICAL POLICY IN SOUTH KOREA

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Thesis Abstract

Background

To find an effective strategy for regulating pharmaceuticals, it is essential to learn lessons from foreign experience; to consider salient contextual specific factors; and to establish good scientific evidence that can be used in decision-making. During the last ten years, South Korea has experienced an unprecedented transformation in the pharmaceutical market. So far, few researchers have questioned whether the Korean strategy is an appropriate and efficient measure for regulating pharmaceuticals.

Objectives

- To explore the impact of policy interventions in the global pharmaceutical market
- To investigate the impact of pharmaceutical policies in the Korean market
- To study contextual factors contributing to gaps between evidence and practice, and contextual challenges in evidence-based policy-making in the Korean market

Methods

1. Systematic reviews were conducted of existing rigorous studies that evaluated the impact of pharmaceutical policies internationally.
2. Korean pharmaceutical claims were examined using an interrupted time series design to explore two recent Korean pharmaceutical policies.
3. Semi-structured in-depth interviews were conducted with eight core personnel, who are either policy-makers or those who influence policy-making to discuss contextual challenges in the Korean pharmaceutical arena.

Results

Despite the usefulness of international experience, reviews highlight the lack of validity, generalisability and transferability of specific research findings in the pharmaceutical arena. Strikingly, 78% of included studies came from five countries – Canada, Spain, Sweden, the UK and the US, which are more affluent. Little evidence was found that provides direct pragmatic lessons for South Korea, but there were still some worthwhile implications. Some of these were clarified by the following empirical studies. The empirical investigation suggested that the present Korean policy interventions might achieve only marginal success in containing pharmaceutical costs, but could potentially

increase social inequity and reduce market competition. Even participants, who are closely involved in the process of the Korean pharmaceutical policy cycle, recognise the major weaknesses of the current system, but face considerable resistance to moving towards strategies that may be more effective. In South Korea, regulating pharmaceuticals is challenged by lack of available information, widespread distrust, resource constraints, and strong professionals.

Conclusion

It is important to remember that drug policies are often derived from a complex mix of constrained evidence, sometimes irrational judgments and wishful thinking, perhaps focusing on benefits and ignoring the potential negative consequences. At the same time, it is necessary to develop policy-making capacity in the face of an immature evidence base. Efforts that build research capacity and seek local evidence are essential to strengthen such capacity as well as to be an ultimate solution to the absence of a knowledge base.

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Author's Declaration

All the research presented in this thesis was initiated and conducted by the author. Dr. Karen Bloor, Professor Alan Maynard and Dr. Catherine Hewitt supervised the thesis. Karen Smith assisted in the systematic review. Dr. Joy Adamson and Dr. Vivien Hendry assisted in the qualitative study. Dr. Simon Crouch assisted in ARIMA analysis. However, the author is completely responsible for the research presented in this thesis.

Iynhyang Lee

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INTRODUCTION: SCOPE AND OUTLINE

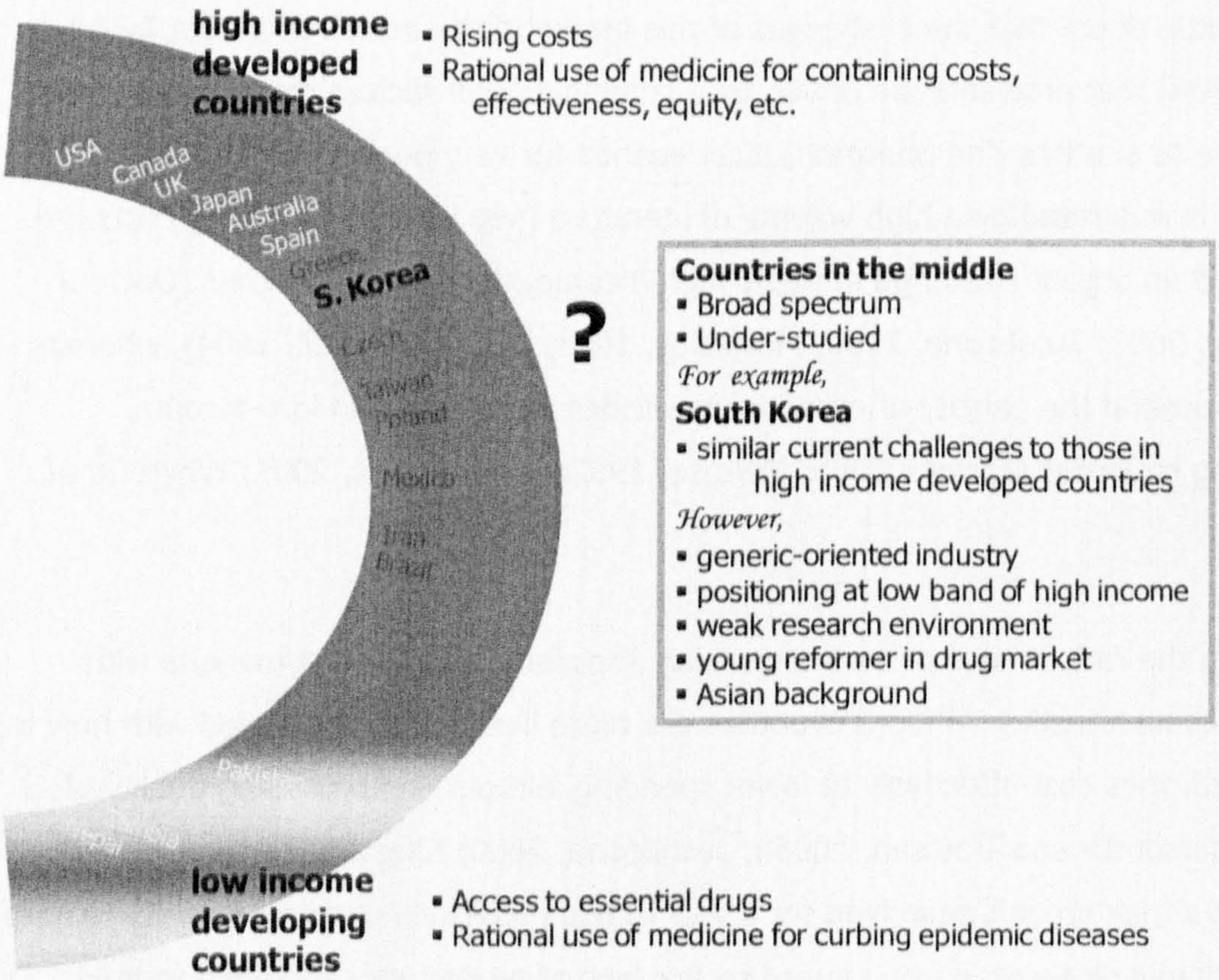
Over recent decades, funding and use of pharmaceuticals have become global concerns, giving rise to intense debates across many countries, both rich and poor. There is little doubt that the challenges of this market differ across countries, which is natural given that problems are driven by a combination of factors that can differ from one nation to another. The pharmaceutical agenda for very poor and very rich countries is illustrated by a high volume of literature (see Figure i-1). Rising costs are considered an urgent challenge in many high-income, developed countries (Docteur and Oxley, 2003; Jacobzone, 2000; Mossialos, 1998; Mossialos *et al.*, 2004), whereas concerns around the paucity of essential medicines are debated in low–income, developing countries (Farmer, 2005; Melrose, 1982c; Smith *et al.*, 2001; Whyte *et al.*, 2007).

Enhancing the rational use of medicines is an important issue across markets with different characteristics. Affluent countries are more likely to be concerned with how to utilise medicines cost-effectively to lower spending without compromising quality of care (Almarsdottir and Traulsen, 2005b; Jacobzone, 2000; King and Kanavos, 2002). Poorer countries are still searching for a way to use medicines properly in order to curb basic epidemic diseases, partly caused by the lack of proper education and trained health workers (Melrose, 1982a, 1982d), but also inevitably associated with the shortage of essential drugs under the current market system (Lichtenberg, 2005b; Pecoul *et al.*, 1999). Pharmaceutical access in low income developing countries is potentially viewed as a 'human right' and is increasingly found on the agenda of international organisations, including the World Health Organization and several Non-governmental Organizations (Ford *et al.*, 2009; Medecins Sans Frontieres, 2006a; Sachs *et al.*, 2001; Smith *et al.*, 2001). This is an important issue for pharmaceutical regulations and fuels immense debates, but falls outside the scope of this thesis.

Relative to rich and poor countries, there is a lack of attention to pharmaceutical market challenges in the middle range of countries. Most studies evaluating pharmaceutical policies have emerged from a handful of limited environments in the world's most developed societies in North America and Western Europe. Not surprisingly, nations located geographically closer to developed countries such as the Czech Republic, South Korea and Taiwan, may share common challenges with the

developed nations. This, however, does not imply that what is observed in their neighbourhood settings must also be the case in these nations.

Figure i-1: Challenges in pharmaceutical markets by national wealth



* Countries within the figure were lined up by GNI per capita 2008 (PPP int. $) statistics released by World Bank (World Bank, 2009). A comparable figure for Taiwan came from Taiwanese governement website (available at: http://eng.stat.gov.tw/point.asp?index=1).

Traulsen and Almarsdottir (2005) stated that policy analysis is comprised of two elements; "predicting the impacts of possible policies" and "evaluating past policies". Nowadays in the public policy arena, it occurs ubiquitously that policy-makers watch and learn from foreign policies (Guillen and Cabiedes, 2003; Klein, 1997; Rose, 2005; Stone, 1999). In the policy process, there are many nation-specific factors influencing policy formation and outputs (Dolowitz *et al.*, 2000). Thus, 'predicting the impacts of possible policies' is often conducted by combining foreign experience with some degree of contextual consideration. Contextual factors, however, cannot be fully captured in simulation, and there is no way of knowing whether the outcome of a certain policy will be in line with its anticipated effects in advance. In this regard, it is becoming clear that 'evaluating past policies' is essential in a sound policy system.

There are at least three reasons why making the study of policy impact in individual nations is essential. This is particularly the case in countries where many pharmaceutical regulations have been emulated, but rarely evaluated after their introduction, as in South Korea.

First, experience in analysing policies allows governments to seek an effective strategy for their own arrangements. Bloor and Maynard (2004; p61) argue that in regulating pharmaceutical markets "there is no 'best' regulatory system", "but all [policy objectives] involve trade-offs". Their claim implies that an individual government should find an effective strategy in trading off competing objectives in their own society. A good strategy can hardly be specified until an in-depth insight into its success or failure is reached by widening the pool of analytic knowledge. For example, the effect of policies encouraging generic use on drug expenditure may be smaller in a nation maintaining a premium price for generics than in another nation keeping prices low. Faced with smaller policy impacts, how is a nation able to confirm its own problem (e.g. high price of generics), if it lacks infrastructures such as databases that capture reality, but just follows the global trend of encouraging cost-effective utilisation? Even though it is capable of recognising its own problems, it may be hard nowadays to match the complex requirements of stakeholders without rigorous evidence. Such infrastructures, for example a database taking prescribing claims or national measures distinguishing generics from brand-named drugs, are unable to be established quickly. Even when there is a database, it is quite a different matter to just hold data rather than making it available and useful (Garrison *et al.*, 2007; Majeed *et al.*, 1997; Wong and Hellinger, 2001). There are frequent calls for changes in the variables in existing databases in many developed countries, where there has been a relatively rich experience in policy analysis (Majeed *et al.*, 1997; St Leger *et al.*, 1992).

Second, and more importantly, as Maynard (2005) indicates, policy can damage population health, as would the use of new and untested pharmaceuticals. Prescription capping in US Medicaid is an example of this. As shown in Chapter 4, it reduced the state of health in the elderly poor as well as pharmaceutical costs incurred by Medicaid on their behalf (Soumerai *et al.*, 1991). Additionally, making the wrong choice could carry unwanted consequences not only in population health, but also in resource utilisation. Making a choice among several policy options always creates opportunity costs, depending on what must be given up (e.g. the next best alternative) as a result

of the decision (Morris *et al.*, 2007b). For instance, taxes spent on supplying hospital beds could alternatively be spent on building schools or houses. In this case, wasting resources by a wrong decision in the healthcare arena loses an opportunity for better educational or living environments in a society.

Third, existing evidence is not sufficient either in quantity or quality, regardless of setting. The accelerated increase in pharmaceutical expenditure has prompted many industrialised nations to establish various cost-containment policies since the 1970s. Consequently, efforts have been made to evaluate the impact of newly introduced regulations. However, such efforts are far from satisfying all demands (Kanavos *et al.*, 2004). Soumerai *et al.* (1993; p219) remark that "policy makers have often implemented cost-containment policies with little empirical evidence about their true impact". This comment was made nearly two decades ago and still holds true (see Part 2).

Unfortunately, 'evaluating past policies' has been overlooked in South Korea, one of the countries positioned in the upper band of the middle arena. This argument is supported by the fact that there are few available empirical studies in Korea. In part, this is due to the country's short history of pharmaceutical policy and evaluation. It has been just a decade since Korean policy-makers paid attention to evaluating the performance of policies in the pharmaceutical field (see Chapter 2).

South Korea is a country that has already established a basic system for controlling epidemic diseases, and has begun to encounter problems similar to those in the developed countries. For example, Korea is currently experiencing a sharp increase in chronic conditions among its ageing population (NHIC and HIRA, 2007). The aged population has increased sharply by 50 per cent from 1994 to 2004 (see Table 2-6 in Chapter 2). Alongside this, health expenditure (public plus private) has inflated from 5,000 billion to 22,500 billion Korean Won (2.5 billion to 11.25 billion in pound sterling at 2008 exchange rates) in the corresponding 10 year period (NHIC and HIRA, 2007).

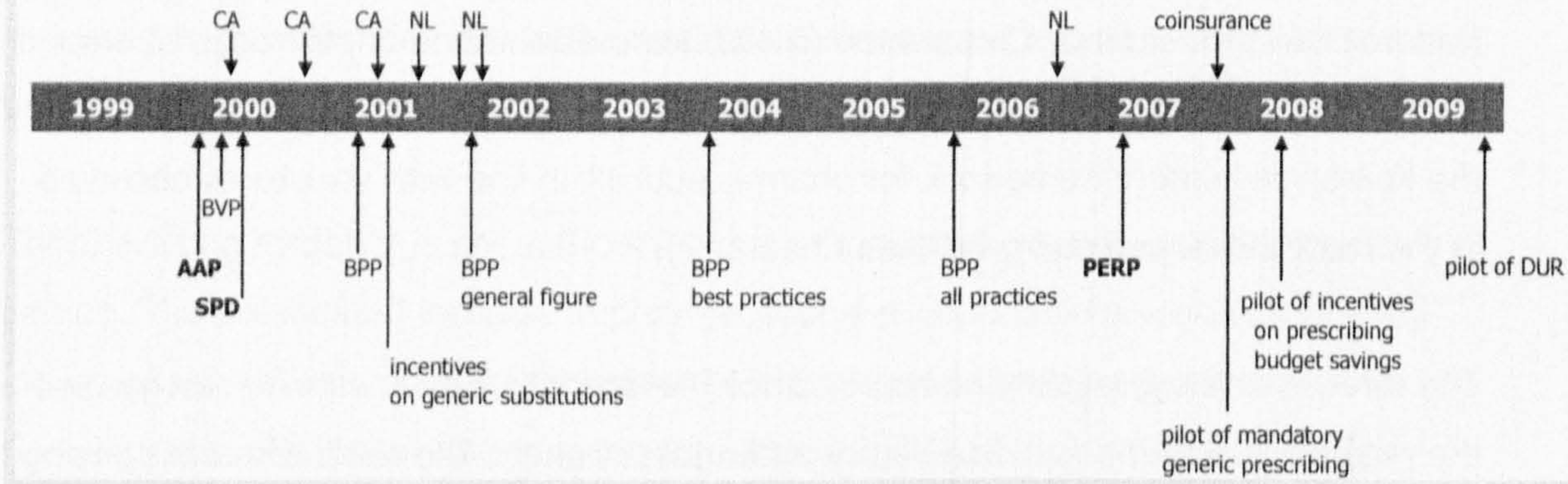
In its healthcare system, especially relating to pharmaceuticals, South Korea has experienced an unprecedented transformation in the span of just ten years. It started with the unification of insurance funds, and reached a pinnacle with the separation of prescribing and dispensing of drugs (SPD) initiated in 2000 (Hwang, 2006b; Kwon and

Reich, 2005). In parallel, vital government bodies such as the Korea Food & Drug Administration (KFDA), Health Insurance Review & Assessment Service (HIRA) and National Health Insurance Corporation (NHIC) were established or restructured around the same time. Largely, a series of reforms initiated from 2000 onwards modernised the Korean regulatory framework for pharmaceuticals in line with structures observed in the most developed countries (see Chapter 2).

The reforms and subsequent measures since the late 1990s have entirely reorganised the pharmaceutical market. Regulatory authorities changed the reimbursement pricing mechanism, so that the reimbursed price is the same as the real acquisition cost, eliminating potential profit from dispensing pharmaceuticals in medical institutions. This was implemented to remove the extra income derived from dispensing drugs, so as to introduce the separation policy smoothly a year later. A reduction of around thirty per cent cut of the drug reimbursement price was carried out in November 1999. In return, the government rearranged a remuneration system for professionals, introducing an annual payment contract between the government and each professional group. This, along with a substantial increase in patient visits after the separation policy, put a great financial burden on national insurance funds, almost to the point of bankruptcy (DailyPharm, 2001b, 2001c). In the pharmaceutical arena, after the separation policy, pharmaceutical expenditure surged, partly because of cost shifting from the private to the public sector. The substantial increase in patient visits resulted in a similar increase in publicly reimbursed prescriptions (Cho *et al.*, 2003; Cho *et al.*, 2002; Kim, 2002b; NHIC and HIRA, 2007). Evidence also suggests that rising expenditure has been associated with changing prescribing patterns in favour of more expensive drugs (Cho *et al.*, 2003; Cho *et al.*, 2001; Jang *et al.*, 2001; Kim, 2005; Lee and Malone, 2003).

It may be surmised, from the brief history above, that the issue of pharmaceutical costs has come to the forefront of policy debate. The government has made various efforts to contain costs, and many subsequent policies following the SPD were devised to handle the financial crisis. Figure I-2 demonstrates major pharmaceutical policies implemented in South Korea during the current decade in chronological order. This will be discussed in more detail in Chapter 2.

Figure i-2: Major pharmaceutical policies in Korea from 1999 and onward



* **AAP**; Actual Acquisition Price system, **BPP**; Better Prescribing Project, **BVP**; Bio-equivalence Validation Programme, **CA**; Copayments Adjustment, **DUR**; Drug Utilisation Review, **NL**; Negative list, **PERP**; Pharmaceutical Expenditure Rationalisation Plan, **SPD**; Separation of Prescribing and Dispensing of drugs

In the process of policy development, Korean policy-makers often benchmark interventions in the world's most developed countries. Learning from abroad is certainly valuable in determining potential policy options and finding out how to institutionalise them in order for their effects to result. Equally importantly, it provides opportunities to observe the considerable contextual variations within and between policy programmes. A similar policy may generate divergent effects across countries, or each national government might respond differently to a common problem, taking internal conditions into account. The transferability of a certain policy and the generalisability of its results are limited to a great degree between countries (Kanavos *et al.*, 2004).

Pawson and Tilley (1997; p57) describe this situation, arguing that "programs work (have successful 'outcomes') only in so far as they introduce the appropriate ideas and opportunities ('mechanisms') to groups in the appropriate social and cultural conditions ('contexts')." This implies the importance of understanding foreign policies (mechanisms) and specific surroundings (original contexts) in observing the effects of policies. At the same time, it is necessary to consider 'environments in a target setting (own contexts)' for successful policy outcomes. They expressed the idea as the following conceptual formula: *"outcome = mechanism + context".*

South Korea has quite a different background from the most developed countries, especially in political, industrial and cultural environments, and even in an economic capacity, although it is now often considered an industrialised country in many aspects.

Many factors, such as shortages of political will, social consensus, money, personnel, and administrative capability, could be obstacles not only in introducing policy, but also in enacting it successfully (Chapter 2). All such factors must interplay with interventions and bring about somewhat different outcomes (Pawson and Tilley, 1997).

Thus far, few researchers have questioned whether the Korean strategy is appropriate for regulating pharmaceuticals within local conditions. There is a pressing need to examine the actual impact of interventions within Korean-specific environments in parallel with learning from foreign experience to speed progress in this area. However, evaluating pharmaceutical policies has lagged far behind in South Korea, compared with some developed countries.

Therefore, the purposes of this thesis are:

- To explore the impact of policy interventions in the global pharmaceutical market
- To investigate the impact of pharmaceutical policies in the Korean market
- To study contextual factors contributing to gaps between evidence and practice, and contextual challenges in evidence-based policy-making in the Korean market

Given the lack of high quality studies from a global perspective, South Korea provides an excellent setting to study the impact of several pharmaceutical policies, in the context of a regulated pharmaceutical market during this decade. This is even more interesting, given that South Korea has a dissimilar economic status and industrial structure to nations in North America and Western Europe, and a considerably different political, historical, and societal background from those settings.

Outline of thesis

The thesis comprises four parts; *background, systematic review, empirical research* and *prospects for the future*. The background study consists of two chapters, which are dedicated to shaping the theoretical framework of the thesis from two angles – mechanism and context according to the ideas of Pawson and Tilley (1997). Chapter 1 will address, firstly, evidence and causes of market failure for pharmaceuticals from a welfare economics perspective and, secondly, various policy devices currently in place and how they would function in the pharmaceutical market against factors causing the market to fail. This will give a brief general background of the policy mechanisms.

The initial chapters are followed, in Chapter 2, by depicting several salient environments seen in South Korea, largely from four perspectives – health status, economic stance, political environment and cultural background. In this chapter pharmaceutical policies implemented in South Korea during recent decades are also outlined. This helps to explain the two policies explored in the empirical research (Part 3) in the broader context. Thirdly, there is a discussion of the significance of good grounds for policy-making, tools of policy evaluation and the weaknesses of existing Korean studies, and the shaping of a methodological framework for the whole thesis.

The second part of the thesis reviews the most rigorous evidence currently available in a global context concerning the impact of pharmaceutical policies. Measures regulating pharmaceuticals and their impact or consequences are explored through systematic review (Chapter 3 through 7). Chapter 3 illustrates the methods of systematic review in the thesis and the following three chapters present findings from systematic reviews categorised by policies influencing patients, providers and industry. The final chapter on the systematic review discusses issues emerging from the methods and lessons for the empirical investigation in Part 3. It also summarises key findings from the systematic review.

The third part of the thesis investigates empirical data in the Korean pharmaceutical arena, beginning with a description of time series methods in general (Chapter 8). Chapter 9 provides detailed backgrounds of policies of interest and investigates their impact on overall pharmaceutical expenditure, utilisation and prices. Chapter 10 examines their impact on essential drug utilisation and the generic market with two

therapeutic drug classes, to gain a better understanding of how policies work in the market. Chapter 11 discusses the meanings of the findings from the empirical investigation.

Finally, there is a qualitative examination of the views of local experts, either policy-makers or those who influence policy-making. The primary aim of the qualitative study is to explore contextual difficulties in evidence-based policy-making from the local policy-makers' perspective, using in-depth interviews (Chapter 12). This enables specification of the current stances, challenges and uncertainties in local pharmaceutical policy-making, which illuminates the subjects of future drug policy in South Korea.

Lastly, in Chapter 13 all the major themes found within this thesis are drawn together. Key findings are summarised, shaping local challenges in pharmaceutical regulations. Study limitations are discussed along with contributions to the existing literature. Based on lessons from systematic reviews and empirical research, recommendations for future pharmaceutical policies in South Korea are addressed. The thesis closes by highlighting other research opportunities.

PART 1 BACKGROUND

CHAPTER 1: PHARMACEUTICALS AND MARKETS

1.1 Introduction

Regulating pharmaceuticals in relation to safety and clinical efficacy has been accepted as a vital role of the state after an iatrogenic tragedy caused by thalidomide in the 1960s (Annas and Elias, 1999; Britten, 2008). Since the 1970s, interest in pharmaceutical policies has been augmented beyond safety and efficacy internationally, as concerns grow over rising pharmaceutical expenditure. Efforts to regulate pharmaceuticals have diversified in the span of less than three decades. Most industrialised countries in North America or Western Europe are ahead in this movement (Ess *et al.*, 2003; Guillen and Cabiedes, 2003; Jacobzone, 2000; Kozma *et al.*, 1993; Mossialos and Le Grand, 1999; Mossialos *et al.*, 2004; Reeder *et al.*, 1993).

The subject of public regulation itself is, however, still controversial. At one extreme, Stigler (1971) is concerned that public regulation does not serve the purpose of "the protection and benefit of the public" because it is 'captured' in a strongly capitalist society by industry, so over time regulation tends to be designed and operated primarily for industry's benefit. The same is asserted by Navarro (1986b).

At the other end of the scale, some writers worry that public regulation could do more harm than good in curtailing economic freedom and market competition. Danzon and colleagues demonstrated empirical evidence in their investigation of international commercial sales data that price control may be adversely associated with innovation and price competition among generics (Danzon and Chao, 2000; Danzon and Furukawa, 2003). Industry and its advocates continue to insist that excessive efforts to reduce profit may result in shrinking industry's R&D activity (Grabowski *et al.*, 1978; Vernon, 2005; Vogel, 2007d), which would have a negative influence on public welfare such as health and choice in the long term (Reekie, 1996). Some writers warn of over-regulation by listing all known consequences of reimbursement policies with little proper assessment (Levy and Cocks, 1999).

From a broader perspective, the pharmaceutical industry is an important employer, investor, and a source of wealth. In the UK, for example, 73,000 people were directly

engaged in the pharmaceutical industry in 2004. Those were more than 0.2 million in Japan and the US in 2000 (Department of Health, 2006a). In this sense, although regulating industry could contain healthcare expenditure, there is some loss of benefits from reducing employment and potentially decreasing the development of profitable patent drugs in return (Schweitzer, 2007e).

The issues surrounding pharmaceuticals may be approached from several different perspectives, including economic, social, political and philosophical views. This thesis approaches the subject mainly from a welfare economics perspective. Welfare economics aims to achieving more efficient use of available resources by "making judgments about the relative desirability of alternative ways of delivering health and health care" and seeking potential Pareto improvements in terms of their effects on the well-being of society (Morris *et al.*, 2007e).

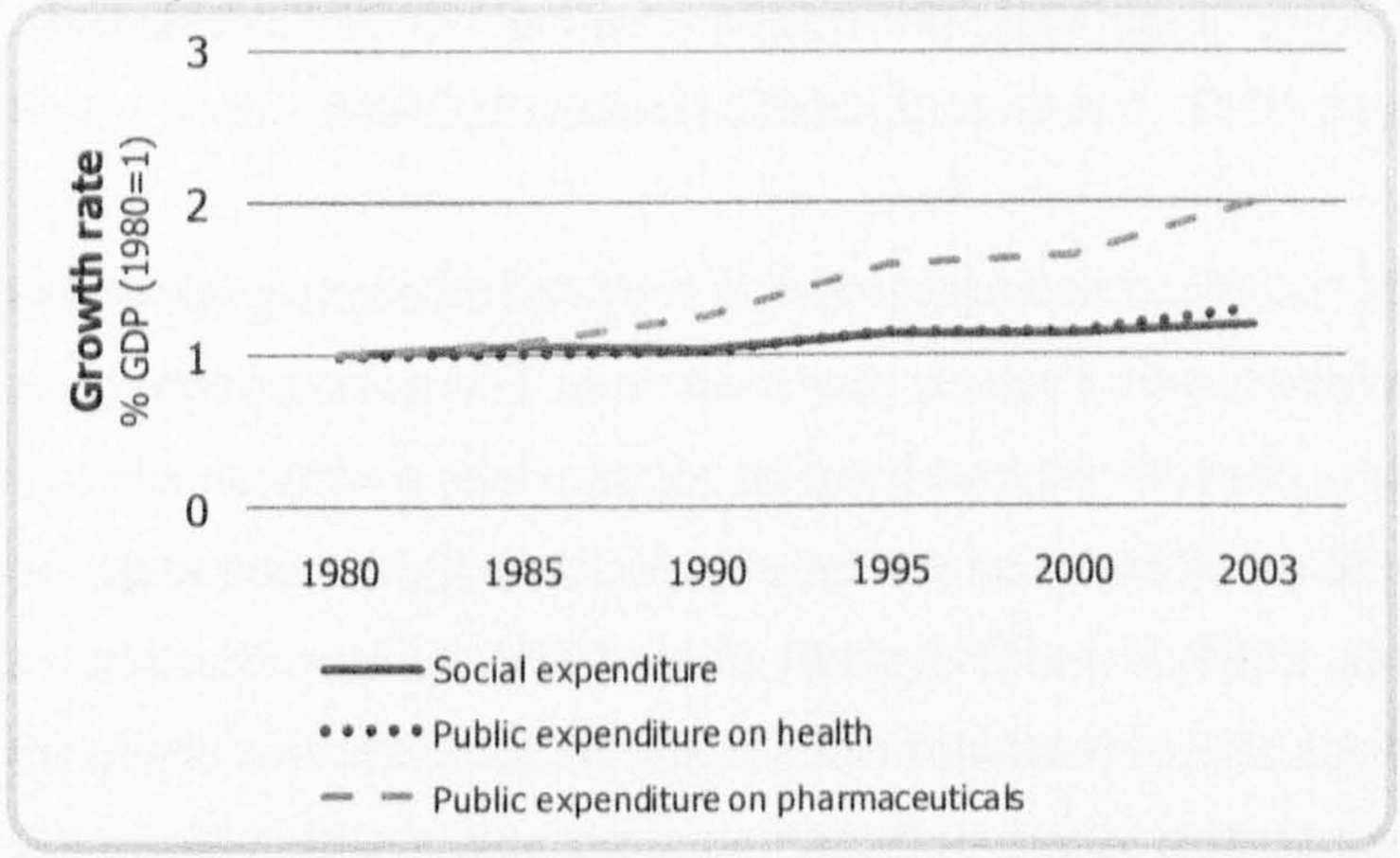
The first purpose of this chapter is to consider why government interventions are widely accepted in pharmaceutical markets despite considerable debate. This develops a better understanding of the theoretical mechanisms underpinning policy interventions in this arena. The present chapter, then, explores pharmaceutical policy, including the objectives of regulation and measures that are in place.

1.2 Markets and health care

1.2.1 Scarcity of resources

Mooney (2003b; p1) writes that "in the beginning, middle and end was, is and will be scarcity of resources", expressing the supreme economic challenge that every society confronts. Resources available for health care, including pharmaceuticals, are certainly limited all over the world. Despite finite resources, demand in health care continues to grow and "the more health care we choose, the more of something else must be sacrificed" (Morris *et al.*, 2007b; p3). In 2005, OECD countries spent around 6~15% of their national wealth on health (OECD, 2008). Pharmaceuticals, the central subject of this study, occupy a significant proportion of health expenditure, representing around 8~30% of the total health budget in OECD countries (OECD, 2008). In particular, the recent growth rate of public pharmaceutical expenditure is evident and outpaces other public expenditure as shown in Figure 1-1.

Figure 1-1: Public expenditure on overall social protection, health, and pharmaceuticals in OECD countries (OECD average)



(Data source: OECD, 2008; see Annex 1 for the raw data)

1.2.2 Markets in theory

Deficit necessitates choice. Society faces choices between competing demands – whose needs come first, who makes prioritisation decisions, and how such decisions are made in the pharmaceutical market. A real difficulty in this regard is that answers to these questions are likely to be as many as there are individuals. Since interests are too diverse to make a single choice, society needs a set of criteria justifying decisions in order to attain legitimacy. These days, criteria appearing most commonly are efficiency and equity (Gray, 1993; Le Grand *et al.*, 2008b; Stevens, 1993a).

Efficiency can be defined as maximising benefits (for instance health) to society, from a given resource constraint (Stevens, 1993a). The pursuit of technical efficiency does not determine who gets what and how much of it. It only relates to the total amount of benefits produced from a given amount of inputs (Palmer and Torgerson, 1999). Hence, a system can be technically efficient without implying fairness, and without guaranteeing society maximum welfare from a broader perspective. Allocative efficiency takes account of the distribution of these outcomes, with discussion of opportunity costs and patients' utility (Mooney, 2003a).

The distribution of resources is often skewed towards a small proportion of the population in the real world. Another criterion for choice, equity, puts distributional justice at the centre of discussion. Equity is a more debatable concept, as definitions

vary according to the definer (Mooney, 1994c). The term 'equity' tends to be used interchangeably with fairness or justice. Equity in health can be defined horizontally, equal treatment for equal need, or vertically, preferential treatment for disadvantaged groups (Culyer and Wagstaff, 1993; James *et al.*, 2005; Mooney, 1994c).

Pursuing equity often costs society some degree of efficiency and vice versa, which has been one of the greatest dilemmas that society has to address. There is no clear-cut solution to harmonising two criteria to achieve the best result. Thus, society should always make a choice in a trade-off between equity and efficiency (Brinsmead and Williams, 2004; James *et al.*, 2005; Rice, 2002; Sassi *et al.*, 2001). To make choices, societies have devised various sets of mechanisms including religion, tradition, military power, markets, experts, consensus, voting, representative systems and so forth (Stevens, 1993b). Of these, a combination of market provision with government intervention is currently employed for pharmaceuticals in most leading societies.

1.2.2.1 Markets and efficiency

Markets consist of the interaction of demand and supply. In a free market place, the price mechanism ensures that the market reaches an equilibrium point between demand and supply. If there is a change in the quantity of demand or supply, price changes until a new equilibrium is reached. Equilibrium equates the marginal benefit to consumers with the marginal cost to producers. From the economic perspective, the most efficient level of output is that which maximises the sum of consumers' surplus and producers' surplus, i.e. maximises the *net economic value* (Johansson, 1991b; Le Grand *et al.*, 2008b; Stevens, 1993a).

This theoretical mechanism is achieved in a real market if the following conditions are satisfied (Barr, 2004c; Johansson, 1991a; Stevens, 1993c):

- consumers are sovereign with perfect information;
- markets are competitive;
- all elements are certain;
- goods or services are private goods.

Economists call this a perfect market. In a perfect market, all actors, goods and factors are able to self-adjust to allocate resources in the most efficient way as follows. Prices

of goods or services are determined at the level that consumers are willing to pay for them. Informed consumers are able to make a choice to maximise utility. Rational consumers must not pay for any goods that use more resources and give less benefits; hence, inefficient goods will be eliminated from the market soon after being introduced.

At the point of equilibrium, the marginal benefit of any activity is just equal to the marginal cost of resources necessary to produce the activity. No unpaid costs are imposed on others. Competition keeps producers efficient and drives high cost producers out of business. Under perfectly competitive conditions, no one producer can influence the market over another. Extra profits would induce other participants into the market and drive profits back to an acceptable level. As a result, perfect markets achieve an optimum distribution of goods, services and resources in the process of production as well as in use, which maximises benefits for society.

1.2.2.2 Markets and equity

In modern welfare states, an equally important debate is about equity. This concept is broadly integrated across the whole of the healthcare establishment, including the pharmaceutical arena. Inequalities in health among social groups exist everywhere, but some variations are avoidable. Avoidable inequalities are created by unfair opportunities to use health care resources, and this is considered inequitable.

Mooney (1994c) defined the concept of equity with three concepts: *equal health; equal use;* and *equal access*. *Equal health* refers to the equal distribution of health, implying vertical equity that supports greater benefits given to the vulnerable. *Equal use for equal need* denotes treatment given according to illness, irrespective of personal characteristics such as ability to pay. This indicates horizontal equity and justifies the subsidy of fees for the poor. *Equal access* denotes equal opportunity for the utilisation of health services, which can guarantee neither equal health, nor equal use in consequence. The definition of equity in health and health care is however unsettled and includes several conflict concepts and arguments (Culyer and Wagstaff, 1993). In general, most healthcare systems currently aim for equal access, rather than equal health (Gulliford, 2003; Mooney, 1994c; Wagstaff, 1991).

Since a market, a widely accepted trade-off tool, works primarily for efficiency, debates

over equity have been raised among different ideological schools. Libertarianism advocates Individual freedom, the ideology of *laissez-faire*, competition, so implying preference for the absence of coercion in the market (Barr, 2004b; Friedman, 1962). The concern of libertarians is that the pursuit of equity would reduce or destroy liberty. Hence, they assert that markets with less restraint are the most effective in resource allocation. Not surprisingly, efficiency weighs more heavily than equity in a libertarian society such as the US or the UK under the Thatcher government (Ham, 2004a; Walker, 1986).

In contrast, collectivism advocates social solidarity and mutual aid (Barr, 2004b; Mooney, 2009b). Collectivists are sceptical that equity could be achieved within a 'free' market (Nafstad *et al.*, 2009; Navarro, 1986a). They argue that pervasive globalisation, consumerism and individualism have increased social inequality during the regime of neo-liberalism in past decades, which is associated with reducing overall standards of health (Coburn, 2000; Mooney, 2009c). Collectivism supports government action to correct unfair allocation in the market to achieve social equity or justice even though it costs some efficiency (Barr, 2004b; Mooney, 2009a). This ideology is dominant in European welfare states such as the Scandinavian countries (Blank and Burau, 2010b).

Their contrasting views over government interventions are described by Barr :

> Libertarians argue that there is too much planning in the welfare state, Marxists that there is not enough ... (Barr, 2004b; p55).

Barr (2004b) explains that these conflicts originate from the different concept of freedom; libertarians define it as "the absence of coercion"; but collectivists define it as "some guarantee of economic security" implying government redistribution of wealth to secure purchasing power. In this way, two views draw different conclusions with respect to the concept of equity. This is linked tightly to the degree to which government action is advocated to attain social equity at the cost of efficiency. The former asserts the attainment of minimum standards; the latter proclaims the fundamental concept of horizontal equity: equal treatment for equal need (Hauck *et al.*, 2004).

1.3 Market failure

1.3.1 Markets in reality

In the real world, there is no perfect market. The role of the market is increasingly met by considerable scepticism, particularly as a way of allocating health care resources. Writers argue that the market severely discriminates against the poor.

> The relative absence of *coercion*, the ability to make free and independent decision, is central to any distinction between markets and government. ... [however], markets also coerce people in very real ways. The rich and the poor aren't equally free to make economic decisions. (Stevens, 1993c; p55-56)

This indicates that resources may be highly biased towards the rich rather than being allocated efficiently across society.

In some sense, the market may already be flawed because, as Swedberg (2003; p57) remarked, "[markets] alone can lead to capitalism; [because] production in a capitalist economy is driven not only by the need for consumption but also by the desire for profit". This argument was also asserted by Navarro who sought the causes of explosive growth in healthcare demands in two aspects; the nature of capitalism and infinite demand for 'health'.

> Growth and ineffectiveness thus seem to be the two main characteristics of our Western system of medicine. ... ... [These] result from the needs created by the process of capital accumulation on the one hand and the demands expressed by the working population on the other. (Navarro, 1986a; p25)

It has been recognised for many years that any of the four assumptions of a perfect market (i.e. perfect information, perfect competition, certainty and private goods) seem to occur rarely in the health care market. In the market for pharmaceutical products, for example, consumers are usually subject to medical and industry suppliers' professional knowledge, and information asymmetry can affect patients' demands to favour medical professionals. Competition is limited due to barriers to entry and differentiated products, facilitated by the international legal system. Uncertainty is

particularly high in this market; demand for medicines is likely to occur unexpectedly; benefits to consumers are often implicit; prices in the pharmaceutical market are often affected by various factors not always measurable. In some conditions, pharmaceuticals qualify as public goods whose benefits the members of society share. These issues will be revisited in more detail.

1.3.2 Evidence of failure in pharmaceutical market

1.3.2.1 Has a market been efficient with pharmaceuticals?

Increasing expenditure on pharmaceuticals may not be good news for the payer – the government in most welfare states. From a broader perspective, however, it should not necessarily be regarded as evidence of inefficiency. For example, with inflated expenditure ascribed to increasing coverage for essential consumption, with a resulting increase in the overall level of societal health, one may not consider such costs inefficient.

Two situations, however, give clear indication that the pharmaceutical market is currently inefficient. First, preventable demands appear to represent a substantial share of cost inflation. Second, an increase in resource input is not necessarily associated with a corresponding increase in health output.

To address the first argument, it may be necessary to look at what constitutes drug expenditure growth. Common causes often shown in the literature include:

- aging populations, in other words, transferring social morbidity towards chronic and degenerative illnesses;
- new demands induced by technological and social changes (e.g. breakthrough treatments for many cancers previously untreatable, and lifestyle drugs);
- expensive new drugs;
- increases in people's expectations.

(Almarsdottir and Traulsen, 2005a; Blank and Burau, 2010a; Mays, 1993; Mossialos and Oliver, 2005; Salter, 2004d)

Of these, the greatest controversy generally concerns new demands and expensive new drugs. Life-style drugs are likely to bring about an intensive debate over "quasi-

drug products" and sustainability (Walley, 2004). Some writers introduce new vocabulary, "medicalisation" or "pharmaceuticalisation", to express concerns about over-medication by encouraging consumers to use pharmaceuticals even in unnecessary conditions (Abraham, 2009; Blech, 2006a; Illich, 1975; Illich, 2003; Moynihan and Cassels, 2005).

Breakthrough medicines have been few (Angell, 2004; Grabowski and Wang, 2006; Guell and Fischbaum, 1995). Newly developed drugs are often blamed for being not truly innovative, merely expensive with a minor incremental clinical value; hence, they are pushing pharmaceutical bills up sharply, but improving health only marginally (Morgan *et al.*, 2005; Young and Surrusco, 2001). In the analysis of drug expenditure, studies conventionally separate the two components: price and volume (Enos and Sultan, 1977c; Huber, 2006; Strunk and Ginsburg, 2004). Some researchers have argued that these two existing components may not be enough to capture the change in overall price per unit dose (e.g. defined daily dose), that it is not due to drug price inflation. They have named this "product shift" (Mullins *et al.*, 2001) or "a residual" (Gerdtham *et al.*, 1998a, 1998b). This third element comprises treatment shift from less-expensive therapies toward new and more-expensive ones. Critics believe that the industry primarily leads the trend by spending sizable sums of money on marketing activities, which society would prefer to see spent on R&D activity (Braithwaite, 1984a; Pecoul *et al.*, 1999; Trouiller *et al.*, 2002).

Moving on to the second argument, it is well-known that the US currently has the greatest expenditure on pharmaceuticals and is the only one among industrialised countries where there is no systematic national health system (Navarro, 1992). Does higher spending result in an improved overall level of health? This would seem unlikely, given the example of the US. International health indicators, such as life expectancy, show that high spending does not achieve greater health gains (Schmitt and Zipperer, 2007). Relevant data are presented in Chapter 2 (see Table 2-5 to 2-7 in Chapter 2).

1.3.2.2 Has a market created fairness in access to or use of pharmaceuticals?

It is well known that the pharmaceutical industry is one of the top businesses worldwide (see Table 2.5 at p38 in Vogel, 2007c). While the industry enjoys

unprecedented success, pursuing profitability is likely to bring an imbalance of resource allocation invested in R&D relative to marketing, and it generates a 'neglected diseases' market (Angell, 2000; Pauly, 2005; Smith *et al.*, 2001). Trouiller *et al.* (2002) who examined new chemical entities (NCEs) between 1975 and 1999 reported that there were at least three times the number of NCEs for the main diseases in high-income countries than those of the poor. These are ascribed to the characteristic of profit-seeking firms that are likely to respond to market demand rather than health needs when they determine research priorities (Mays, 1993; Pecoul *et al.*, 1999). Without doubt, developing products that will be sold in a lucrative market is a rational business strategy to the drug industry. However, it is not necessarily justified from a societal point of view.

1.3.3 Causes of failure in the pharmaceutical market

Evidence briefly described here illustrates that so far the market has not created efficiency or equity in use of pharmaceuticals. This section explores the theoretical aspects of underlying causes of unsatisfactory outcomes in the pharmaceutical market, mainly from a welfare economics perspective.

1.3.3.1 Monopolistic Industry

At a glance, the pharmaceutical market does not appear to be highly monopolised. There are many manufacturers and medical providers in the marketplace and they appear to be aggressive competitors, none of them seeming to overwhelm another by occupying an excess share of the market. Nonetheless, many writers have raised concerns regarding competition in the pharmaceutical market (Bodenheimer, 1985; Braithwaite, 1984a; Melrose, 1982c). Why is this so?

The monopoly or oligopoly status of this industry is hardly avoidable owing to three aspects. First, new entry is suppressed in the pharmaceutical market due to rigorous demands for safety in handling and high costs of R&D processes to meet legislative requirements to demonstrate safety, efficacy and manufacturing quality standards, which raise circulation and production costs (Grabowski *et al.*, 1978) and reduce the number of firms competing on the basis of price (Morris *et al.*, 2007d).

Second, among hundreds of thousands of pharmaceuticals, comparability is limited to relatively small therapeutic categories (Reekie, 1996; Schweitzer, 2007d). Substituting one drug with another is clearly restricted according to the purpose of use; hence, competition among medicines exists quite differently from that of sale of fruit in a marketplace. As all kinds of fruits are substitutable, one can buy oranges, berries, or whatever affordable according to one's preference. However, one cannot consume digestives or antibiotics instead of antihypertensives for controlling high blood pressure. In other words, a drug manufacturer who produces antihypertensive products would not compete with those who produced digestives or antibiotics. Therefore, the concentration of manufacturers in the pharmaceutical industry needs to be regarded not as an overall market, but by each sub-market comprising products within a therapeutic category. In light of this, the structure of the pharmaceutical industry appears to be a near-monopoly market (Braithwaite, 1984a).

Third, and most fundamentally, there is a legal system, supporting about 20 years of exclusive rights for new medicine patentees (Schweitzer, 2007c). Of course the rationale for patents is to provide an incentive for investment in innovation because pharmaceutical R&D, as is well-known, is one of the most time-consuming and resource-demanding fields (Reekie and Weber, 1979; Weissman, 1996). This has, however, been greatly contentious since its establishment (Barton and Emanuel, 2005). There are severe ethical arguments that patent monopoly reduces patients' access, particularly to essential medicines in poor countries (Medecins Sans Frontieres, 2006b).

There has also been wide disagreement as to how much incentive is justifiable (Braithwaite, 1984a; DiMasi and Grabowski, 2007b; Smith *et al.*, 2001; Young and Surrusco, 2001). Many writers argue that existing incentives may be too high for several reasons. First, R&D spending may be exaggerated (Smith *et al.*, 2001). Second, profits from a patent right may not lead to increased R&D spending (Canadian Generic Pharmaceutical Association, 2008). Third, the industry benefits considerably from publicly funded basic research, which is often ignored in the calculation (Angell, 2000; Young and Surrusco, 2001). Fourth, the industry enjoys a patent right beyond the designated period (Hudson, 2000; Kesselheim, 2007), or extra incentives from the popularity of a 'brand name' built during such a long period of exclusivity (Schweitzer, 2007c).

Opponents claim there should be more incentives for the industry (such as strengthening a patent right) in order to foster further innovation (DiMasi and Grabowski, 2007a; Grabowski and Moe, 2008), but this seems less persuasive given the continuous success and greater, occasionally unethical, spending on the marketing activities of 'big pharma' over several decades (Healy, 2006; Lovell, 2006).

The oligopolistic structure of the industry in the real world has brought major success to pharmaceutical manufacturers in the recent past, and several unwanted consequences to society. As already mentioned, profit-seeking firms are more likely to respond to demand from lucrative markets rather than from health needs when deciding research priorities. This generates an orphan drug market in which the least privileged are the most victimised (Smith *et al.*, 2001). Even within a lucrative market, resources have been spent on 'me-too' products rather than on truly breakthrough medicines (Angell, 2004). Subsequently, producers of me-too products tend to compete with each other not by innovation, but by commercial promotion (Chetley, 1990b; Melrose, 1982b, 1982c). While pharmaceutical companies spent 5~7 per cent of sales on research and development in the first half of the 1980s, they paid out about three times more on promotion in the same period (Chetley, 1990a). This gap was not narrowed in the late 1990s (National Economic Research Associates, 1998) or this decade (Schweitzer, 2007b; Vogel, 2007a). Unfortunately, there is substantial evidence of scandals between manufacturers and medical professionals (Blech, 2006b; Blumenthal, 2004; Braithwaite, 1984b; Moynihan, 2003; Schweitzer, 2007b; Weiss, 1997).

1.3.3.2 Overwhelming agency

Sovereign (Oxford English Dictionary, 2009)

1. a king or queen who is the supreme ruler of a country
2. possessing supreme or ultimate power
3. (of a nation or its affairs) acting or done independently and without outside interference

In the market, what brings sovereign power to consumers may be knowledge and money (Le Grand *et al.*, 2008a). Consumers can enjoy sovereign status in the market as they are capable of making decisions by themselves over what they need based on 'reasonable' knowledge and how they can afford their decisions (Morris *et al.*, 2007c).

Pharmaceuticals, however, are different. The body of knowledge concerning medication is abstruse as well as enormous; hence, consumers may find it difficult to exploit it in an effective and proper manner. This being so, decisions over drug use are normally made by qualified personnel on behalf of a patient in practice (the agency relationship). Information asymmetry between providers and consumers is the norm in the pharmaceutical market (Morris *et al.*, 2007a). The role of consumers has been very limited in the decision-making process. Specialised knowledge creates a prestige position for medical providers, which is amplified by licensing and specialising (Enos and Sultan, 1977d; Turner and Samson, 1995).

Society wishes every doctor to make a decision based upon his or her patients' best interest, also upon society's, not upon one's own. Mooney (1994a; p94) viewed a perfect agency to be constituted by two aspects:

> ... first, agency which is perfect from the standpoint of the doctor's patients; and second, agency which is perfect from the standpoint of society as a whole.

Leaving aside 'perfect' agency, making a choice as an 'impartial' agent is rarely realised. One's own interests are likely to be reflected. Ample evidence suggests that fee-for-service (FFS) payment, in which providers are reimbursed for each item of care supplied, often motivates providers to offer more services, prescriptions and tests than would rationally be used, some of which appear unnecessary (Basky, 1999; Etter and Perneger, 1998; Gosden *et al.*, 2000; Greenfield *et al.*, 1992; Maynard and Bloor, 2003b; Steiner and Robinson, 1998; Yip and Eggleston, 2004). Namely, these incentive structures may create a false demand, a so-called "supplier-induced demand" (Mooney, 1994b; William, 1999).

1.3.3.3 Externalities and uncertainty

From outward appearances, pharmaceuticals seem close to being purely private goods like shoes, clothes and fruit. They can be consumed only by one specific person at one time, sold one unit at a time, and withheld from the market by producers at any time (Johansson, 1991a; Stevens, 1993c). Pharmaceuticals, however, also present features similar to public goods such as roads, clean air and fine views. This becomes

particularly obvious in cases of medication for communicable diseases. Suppose, for example, that one patient takes medicine to treat tuberculosis. Medicines carry, firstly, private benefits to the patient by counteracting symptoms and treating one's disease. Simultaneously, they convey secondary 'extra benefits' (positive externalities) to others who are potentially exposed to the risk of contagion. These external benefits from preventing communicable diseases from spreading are shared by many people who are at risk of infection and are unable to be withheld from a potential beneficiary, which are features of public goods.

In the presence of externalities coming from the features of public goods, the total social benefits or costs can be viewed as follows:

> private benefits + external benefits = social benefits
> private costs + external costs = social costs (Le Grand *et al.*, 2008a; p36)

The greater the size of the externality, the greater the divergence between social and private costs or benefits. Suppose that there is one case in which private costs outweigh private benefits, but benefits to the whole society outweigh costs. In this case, being treated would be efficient for the society as a whole. Nevertheless, a 'rational' consumer is likely to abandon a chance to be treated under the market system because an individual is usually concerned solely about private costs and benefits. Thus, public subsidy has been justified for some pharmaceuticals to maximise benefits to the society. In this sense, externalities create a situation where some benefits or costs to society are not reflected in market prices (Johansson, 1991a), indicating that externalities may increase the uncertainty in drug pricing.

Besides externalities, there are many factors increasing the ambiguity of pricing for pharmaceuticals. New pharmaceuticals require an inordinate amount of research and development, in other words, money and time (Vogel, 2007b). In addition, pharmaceuticals are subject to high standards of safety requirements throughout the whole process, including research, development, manufacturing and distribution. They require expertise in handling, prescribing and dispensing. All these properties not only incur additional costs, but also, and more importantly, augment uncertainty in pricing. Uncertain features are also derived from unpredictable demand, a gap between expected and observed behaviour of the physician, uncertain product quality, and

uncertain effects of treatment (Arrow, 1963).

1.3.3.4 Moral Hazard

Moral hazard exists when an individual or institution does not take full responsibility for the consequences of its actions, creating a tendency to act less carefully than it would otherwise. In the pharmaceutical market, various pharmaceutical benefit schemes ease the financial burden of individuals at the time of drug use and could cause actors to commit moral hazard.

People search for pharmaceuticals when they have an uncomfortable condition. Illnesses are likely to occur unexpectedly and result in unpredictable expenses for people. Unexpected expenses for pharmaceuticals are sometimes negligible, but sometimes large insofar as they inhibit people from seeking treatment. This creates a mechanism for pooling risk – insurance – to relieve money worries in times of illness (Barr, 2004a). Public funds are raised differentially across nations (Blank and Burau, 2010c). For example, in the UK National Health System (NHS), funding comprises mostly general taxation, whereas in countries like Germany and South Korea patients contributions are prepaid in a national health insurance system. In the US, a variety of bodies exist ranging from federal and state subsidised programmes (Medicare and Medicaid) to commercial health insurance organisations. Regardless of country, services provided by professionals are generally remunerated by funds from a third-party payment financing structure.

Insurance or third-party payment is tightly linked to moral hazard, a clear source of market failure (Arrow, 1963; Barr, 2004a; Enos and Sultan, 1977c). A third-party payment financing structure can mislead patients. A body of evidence supports the hypothesis that patients' demand for medicines may become relatively price-inelastic because they are free of charge at the time of use (Gianfrancesco *et al.*, 1994; Newhouse, 1993; Rudholm, 2005). Insensitivity to prices may encourage patients and providers to make unnecessary use of drugs. This is well described in the following remarks by Guillén and Cabledes (2003; p23):

> In particular, in the prescription-drug market financed through public funds, "who consumes neither chooses nor pays, who pays neither consumes nor chooses, and

who chooses, neither pays nor consumes." In such a context, it is obvious that doctors' decisions are not sensitive to prices, unless their public employers use specific measures to counteract such insensitivity.

1.4 Public regulations in the pharmaceutical market

So far, it has been argued that without regulation the pharmaceutical market may allocate resources neither efficiently nor equitably. Existing evidence clarifies the speculation that the pharmaceutical market is rarely governed by solely economic principles. In parallel, potential causes were discussed to explore why the pharmaceutical market does not satisfy the conditions for a perfect market. Regulatory policies have been developed to correct flaws seen in markets and, by doing so, to increase efficiency and equity in the pharmaceutical arena. There are considerable cross-national variations in pharmaceutical policies. In the US, pharmaceutical policies are more concerned with safety and clinical efficacy (Wiktorowicz, 2003) with broader regulation of the industry left largely to the market and regulation of professionals or patients performed in a fragmented fashion at state level or private institution level (Kozma *et al.*, 1993; Reeder *et al.*, 1993). In contrast, the regulation of all stakeholders has been exercised in European countries where they are governed by the ideology of the welfare state (Guillen and Cabiedes, 2003; Mossialos *et al.*, 2004).

1.4.1 Policy objectives

Maynard (2005; p280) remarks that regulations in the healthcare arena attempt "to influence the price, volume and quality of the goods and services that are produced and traded and ensure that the performance of markets is more consistent with social goals". Currently, the core objectives of pharmaceutical policies are *cost containment*, *efficiency*, *equity* and *safety or quality*.

1.4.1.1 Cost containment

Cost-containment itself is not an ultimate goal of society, so thus far I have focused on efficiency and equity. However, the issue of costs has been an important force in real world pharmaceutical policy-making. "It is evident that without successful initiatives to constrain costs, healthcare systems face severe funding crises, and perhaps breakdown,

in the not too distant future" (Blank and Burau, 2010d; p118). Statistics tell us that most developed countries and many developing countries have experienced a considerable increase in pharmaceutical expenditure during recent decades. According to OECD Health Data, between 1990 and 2005, total spending on pharmaceuticals as a percentage of GDP increased by more than 70 per cent in Canada, Czech Republic, Finland and the US and around 50 per cent in Portugal, Spain, Sweden and Switzerland. In the UK, the growth rate was about 40 per cent in the 7-year period between 1990 and 1997 (OECD, 2007b). In response to budget deficits, governments have not only sought methods of curbing demand, but also have sought a way to utilise resources more efficiently.

1.4.1.2 Efficiency

To increase efficiency in the utilisation of health resources, policy interventions aim to produce maximum health at minimum cost. Over recent decades two concepts have created intense debates: rationing (or priority setting) and the use of cost-effectiveness information in pharmaceutical reimbursement decisions (Bowling, 1996; Holm, 1998; Klein, 1993; Kleinert, 1998; Maynard, 1993; Maynard and Bloor, 2003a). Rationing denotes "withholding potentially beneficial treatment" because of limited resources, making it necessary for policy-makers to determine whose needs get priority (New, 1996).

Cost-effectiveness information is increasingly used in making rationing decision (Donaldson and Mooney, 1991; Klein, 1993; Mason and Drummond, 1993). Over a relatively short span, the term 'cost-effectiveness' became initially a contentious subject in this arena, but has since become more widely accepted. Since the Australian government formally applied this criterion to its reimbursement decisions in 1993, it has quickly spread across governments who sought to improve both technical and allocative efficiency (Dickson *et al.*, 2003; Yang, 2009). The use of economic evaluation to determine the relative cost-effectiveness of treatment options also strengthens a trend toward evidence-based medicine and evidence-based policy-making (Banta, 2003; Mooney, 2003c). Some writers described the new policy objective of using cost-effectiveness information in reimbursement decisions as a 'fourth hurdle' alongside existing objectives, i.e. safety, efficiency and equity (Maynard and Bloor, 2003a; Taylor *et al.*, 2004). It is argued to be unethical if decisions relating to healthcare expenditure

are made without consideration of cost-effectiveness.

> ... to be ethical we must examine our healthcare expenditures in light of how they affect other societal needs. To fail to do so is unethical in any society with finite resources. (Harrison, 1992; p148)

1.4.1.3 Equity of Access

Policy interventions must also pay attention to the concept of social equity. Many modern healthcare systems were principally brought about by the increased awareness of human rights (Webster, 1988). This was well described in the core principles of the UK NHS (NHS, 2009), which elucidate that the NHS is "free at the point of delivery" and delivered "based on clinical need, not ability to pay".

As briefly stated in an earlier section, most healthcare systems aim for equal access to health care for equal need (see 1.2.2.2). Often, pursuit of cost containment and efficiency goals leads policy-makers away from equity, which could undermine the health and welfare of some parts of the population. Linked to this, Mooney (1994c) argued for the importance of regular monitoring of the effect of any public interventions on access to health services. Access to pharmaceuticals may be affected by the content of lists of reimbursed drugs, or the level of cost-sharing of drugs.

1.4.1.4 Safety and Quality

In the early years of regulation, the key objective of regulating pharmaceuticals was clinical safety and effectiveness, and these are still clearly of great importance. The current safety and effectiveness regulation systems (e.g. US FDA) cover pre-market testing to post-market advertising and manufacturing.

Pharmaceuticals accompany professional services such as prescribing and dispensing. The recent UK NHS report expanded a conventional safety concept to a whole concept denoting 'quality care' (NHS, 2008). The basis of quality is certainly patient safety:

> The first dimension of quality must be that we do no harm to patients. This means ensuring the environment is safe and clean, reducing avoidable harm such as excessive drug errors or rates of healthcare associated infections.

Added to safety, it proposed that quality should include "quality of caring" the patients experienced and "effectiveness of care" concerning people's well-being as well as clinical effectiveness. The proposed elements are linked closely with ensuring access to the most effective therapy and measuring outcomes reflecting patient satisfaction in relation to pharmaceuticals.

1.4.2 Policy Interventions

As markets are networks of buyers (demand) and sellers (supply), previous studies tended to discuss regulations from demand-side and supply-side (Busse *et al.*, 2005; Mossialos and Le Grand, 1999; Mossialos and Oliver, 2005; Mrazek, 2002). The pharmaceutical market, however, seems more complex and cannot be described purely in terms of demand and supply. Professionals are linked with consumers as their agents, and under this relationship most decisions over drugs are made by professionals on behalf of a consumer. In this sense, healthcare providers have features not only as a service supplier, but also a consumer in the market (Monday, 2002). Hence, some differences in approach are to be expected, for example, mechanisms and effects of policy interventions differ between those influencing patient demand and those affecting provider demand. In addition, the quality of services that providers supply for their patients should be considered separately. Therefore, it is appropriate for the pharmaceutical market to be explored with one more vital player, i.e. 'a service provider' comprising a variety of professionals, and bridging the consumer and a product supplier. With a similar rationale, some preceding research explored pharmaceutical policy interventions by targeted stakeholders (Bloor and Freemantle, 1996; Bloor *et al.*, 1996; Freemantle and Bloor, 1996), which will also be followed in this thesis.

Irrespective of whether policies target demand or supply, each intervention can be viewed as a response to the problems of the current market. In this regard, pharmaceutical policies largely affect market players in three ways. Firstly, regulations try to reduce extravagant utilisation, which mostly falls on patients. Secondly, regulations try to amend prescribing (or dispensing) behaviours toward efficient use, which falls on providers. Thirdly, regulations try to correct the monopoly status and excessive entrepreneurial activity of manufacturers with the least cost of R&D activity,

which falls on industry. Whichever categorisation is employed, however, there is inevitably a blurred aspect because a single policy, in reality, may act upon the demand-side and supply-side simultaneously, as seen in the example of a reference-pricing programme below.

1.4.2.1 Policies influencing patients

As already discussed in the preceding section, the subjects of externalities and equity have justified public subsidy for pharmaceuticals. Accordingly, patient demand for medicines may become relatively price-inelastic (Gianfrancesco *et al.*, 1994; Newhouse, 1993; Rudholm, 2005). Hence, the most common measure to curb patients' excessive demands is to increase cost-sharing. The rationale of cost-sharing is that prices help to convey information and enable individuals to economise in their resource consumption (Hayek, 1945). If patients are subject to some charges at the time of consumption, they are more likely to value the money spent in purchasing some medicines against other alternatives. Cost-sharing has been developed into many different features (Jacobzone, 2000).

Other ways of limiting demand include medication caps, where demands can be limited directly and allowed only to a pre-determined degree, for instance, five items per prescription. Another method of limiting patients' access to medicines is an amending their categorisation. Most nations group pharmaceuticals into two or three sub-sets such as prescription-only medications (POM), over-the-counter (OTC) drugs and/or general sales list (GSL). The original underpinning reason for this was safety. POMs are restricted from use without professional authorisation and are more likely to be subsidised publicly, while medications designated OTCs are considered safe, and are usually used in temporary, symptomatic illnesses under patients' own responsibility and at their own cost. Drugs on GSL are between the two categories and are usually sold under the supervision of pharmacists. Recently, categorising drugs as OTCs, a so-called OTC switch, is often exploited as a way of saving money for reimbursement agencies, through excluding some pharmaceuticals from public coverage, but it is also a way of companies retaining brand loyalty of consumers following the end of a patent protection period.

1.4.2.2 Policies influencing providers

Because of information asymmetry, medical providers may occupy a dominant position over their patients in terms of pharmaceutical decision making (1.3.3.2). Thus, the authorities in this area are likely to pay more attention to defending the patient's vulnerable stance to avoid moral hazard potentially nurtured by professionals.

A relatively soft approach to influencing providers may be to provide guidance on practice and to encourage providers to be involved in a programme on a voluntary basis. Examples include many kinds of educational interventions, such as guidelines, protocols, or prescribing feedback, and some voluntary based incentive programmes such as UK fund-holding.

A harder option could be to place some legal limitations on prescribing (or dispensing). This includes a lot of reimbursement restricting regulations. Some countries impose responsibility on providers, for example, if they fail to satisfy their duties, providers incur some penalties. Examples may include the German prescribing budget with mandatory financial disadvantages, although negative penalties have seldom been exercised (Chapman *et al.*, 2004; Walley and Mossialos, 2004).

Capitation and Diagnosis-Related Groups, although not solely related to drugs but more to overall healthcare services, were developed as one of various ways of remuneration, moving away from a conventional FFS system in order to avoid supplier-induced demand (Schweitzer, 2007a). Global budgets have been argued to be a more effective policy option "because [price or volume controls alone] cannot be avoided by raising volume when prices are fixed or raising prices when volume is fixed" (Blank and Burau, 2010d; p109).

During recent years, electronic decision support systems allow one to convey a variety of real-time information – ranging from drug-specific to patient-specific – to physicians' desks. Examples include drug utilisation review programmes at various levels from a single institute to the whole nation, and computerised decision supporting devices with a variety of purposes.

1.4.2.3 Policies regulating industry

Pharmaceutical policies regulating industry are often related to controlling oligopolistic market conditions to restore market competition. Over a long time period, governments have set price limits, profit limits, and mark-up limits to restrain producers from exploiting their monopolistic position in pricing. Some governments negotiate pharmaceutical prices with industry through mutual agreements such as a price-volume agreement (Mrazek and Mossialos, 2004).

Price control alone has been considered not as successful as expected in containing costs (Jacobzone, 2000). Guillen and Cabiedes (2003; p9) argued:

> That the introduction of stricter price-control mechanisms is usually accompanied by greater levels of pharmaceutical spending leads some authors to conclude that the industry is able to create 'escape valves' by increasing the volume of sales of already commercialised products and/or obtaining more favourable prices via product differentiation through new trademarks.

In line with this perception, a reference-pricing system has been developed for avoiding the artificial substitution of more expensive products. Reference-pricing schemes originated from Germany in 1989 (Ioannides-Demos *et al.*, 2002). These have been increasingly exercised with multifaceted aims, firstly functioning to influence patients, throughcopayments, but largely expected to be less likely to obstruct patient access because patients would opt for fully-reimbursed drugs rather than just giving up access. It also influences providers, through creating a reimbursement restricting formulary and lastly, it motivates manufacturers to lower prices to the reference line or below.

In the UK, the regulatory authority sets a limit on marketing resources to suppress excessive inefficient competition in marketing (Department of Health, 1996, 2006b). In recent years, reimbursement decisions increasingly require cost-effective evidence, through which the government wishes to curb expensive but marginally innovative new drugs by refusing public subsidy (Dickson *et al.*, 2003).

Global efforts to encourage R&D investment have been made through the enforcement

of Intellectual Property Rights by the World Trade Organisation since 1986 (Schweitzer, 2007c). Coupled with intellectual property, a growing trans-national industry blurs the distinction of national borders, which sets clear limits on a range of actions taken by a national government. On this issue, international collaboration of counter-industry actors has recently been called for in this area (Buse *et al.*, 2002). Linked to this, new measures such as compulsory licensing have been issued to ameliorate drug accessibility in developing countries after the establishment of powerful intellectual property rights on patent drugs (Ackiron, 1991; Braithwaite, 1984a; Oriola, 2008).

1.5 Summary

This chapter outlined the working of the pharmaceutical market in terms of theory and practice, largely from a welfare economics perspective. It has been argued that symptoms indicating inefficient and unfair allocation of resources have been observed in the pharmaceutical market, and these have become a spur to government action. The salient characteristics of the pharmaceutical market that make a market system hardly able to achieve efficient resource allocation have been discussed. Next, four key objectives of pharmaceutical policy – cost containment, efficiency, equity and safety or quality – were addressed. This chapter ends with tackling current policies and their expected mechanisms. These are grouped by three market actors – patients, providers and industry - and this structure will be repeated throughout this study. The next chapter explores realistic issues in pharmaceutical policy studies, which are contextual factors and methodological considerations.

CHAPTER 2: PHARMACEUTICAL POLICY AND LOCAL CONTEXT

2.1 Introduction

In order to achieve a proper understanding of the lessons from policy evaluation, it is necessary to recognise a set of general policy mechanisms and the context in which a programme is activated (Pawson and Tilley, 1997). With this in mind, the preceding chapter discussed a basic mechanism of drug policy. This chapter will discuss the second issue, which is 'context'.

The objectives of this chapter are, firstly, to discuss the importance of contextual considerations in policy studies, and secondly, to describe Korean pharmaceutical policies and explore contexts surrounding the pharmaceutical policy-making process. Arguments over context develop a further subject of policy evaluation. Thus, the third aim of the chapter is to address evidence-based policy-making from theoretical aspects to practical issues. Lastly, methods employed overall in the thesis are outlined.

2.2 Policy and context

As is well-known, the overall shape of policy, especially in the healthcare arena including pharmaceuticals, is formed by the interplay of political, social, economic and historical determinants (Blank and Burau, 2010b; Enos and Sultan, 1977a, 1977b; Navarro, 1992). For instance, it is certainly difficult to think of the British NHS without thinking of the political context of Britain during the 20th century (Ham, 2004a, 2004b). Thus, Salter (2004c; pxiii) remarked that "the British NHS is part of the basic fabric of British political life".

Even a single intervention often shows great diversity across settings. For example, co-payment of prescription drugs is a policy used to curb patient demand across many countries (Chapter 1). Within the simple idea of curbing consumption by charging, each nation has developed various co-payment structures with different types of exemptions, copayment limits, amount of payment and so forth (Jacobzone, 2000). This may be due to the "adaptation" of co-payment programmes to local circumstances (Klein, 1997).

Context-bound factors affect not only policy interventions but also, more importantly, influence policy outcomes. Recently, Dolowitz *et al.* (2000) analysed four British policies: the Child Support Agency; an internal market in the NHS; post-compulsory education; and the electronic monitoring of offenders. These policies were imported from the US, by a framework of policy transfer. They suggested several factors that made these programmes unsuccessful in Britain. Factors they specified, of course, included some procedural difficulties, such as insufficient information or problems with importing. However, it seems that contextual issues occupy a more central part among such factors. Contextual factors include:

- insufficient attention paid to the differences between the social, political and ideological contexts
- differences in organisational/institutional circumstances
- lack of demand for the introduced policy in the applied setting
- absence of active support from the local elite pressure groups
- hostility of the progressive local press
- opposition from the public and the medical profession
- differences in social attitudes and medical practice (ideology and culture)

Pawson and Tilley (1997; p70) argued:

> Programs are always introduced into pre-existing social contexts and, as we shall see, these prevailing social conditions are of crucial importance when it comes to explaining the successes and failures of social programs. ... It is futile for researchers to ignore and anonymize the contexts of their programs as in experimental evaluation. ...

Taken together, two things are becoming clear. First, it is necessary to understand contextual conditions before discussing policy outcomes. Contexts might be regarded as one of two forms – those in which a programme has already worked or failed and those to which a programme has been newly applied. The former can be achieved by studying overseas experience, deriving lessons that can help policy-makers seek effective measures for their existing social arrangements, construct appropriate conditions for a new intervention, or avoid repeating mistakes made in other countries.

As to the latter, the upcoming subsection will discuss core issues about Korean contexts.

Second, policy evaluation studies need to be constructed in each national context in order to determine the real impact of programmes after being influenced and amended by such factors. As seen from the British examples above, even though a programme works in one place, there is no guarantee that it will in another. Situations can be improved by a close inspection of the contextual conditions both abroad and at home. Nevertheless, it may be impossible to remove all uncertainty constituting the policy environment and outcomes. Faced with such uncertainty, assessing the policy may be the best strategy to know its the true impact. This stresses the significance of policy evaluation. Moreover, expertise from rigorous evaluation can contribute to a better understanding of policy options leading to future improvements. In line with this, more issues concerning evidence-based policy-making and methods studying policy are discussed in section 2.6.

2.3 Overview of the Korean health care system

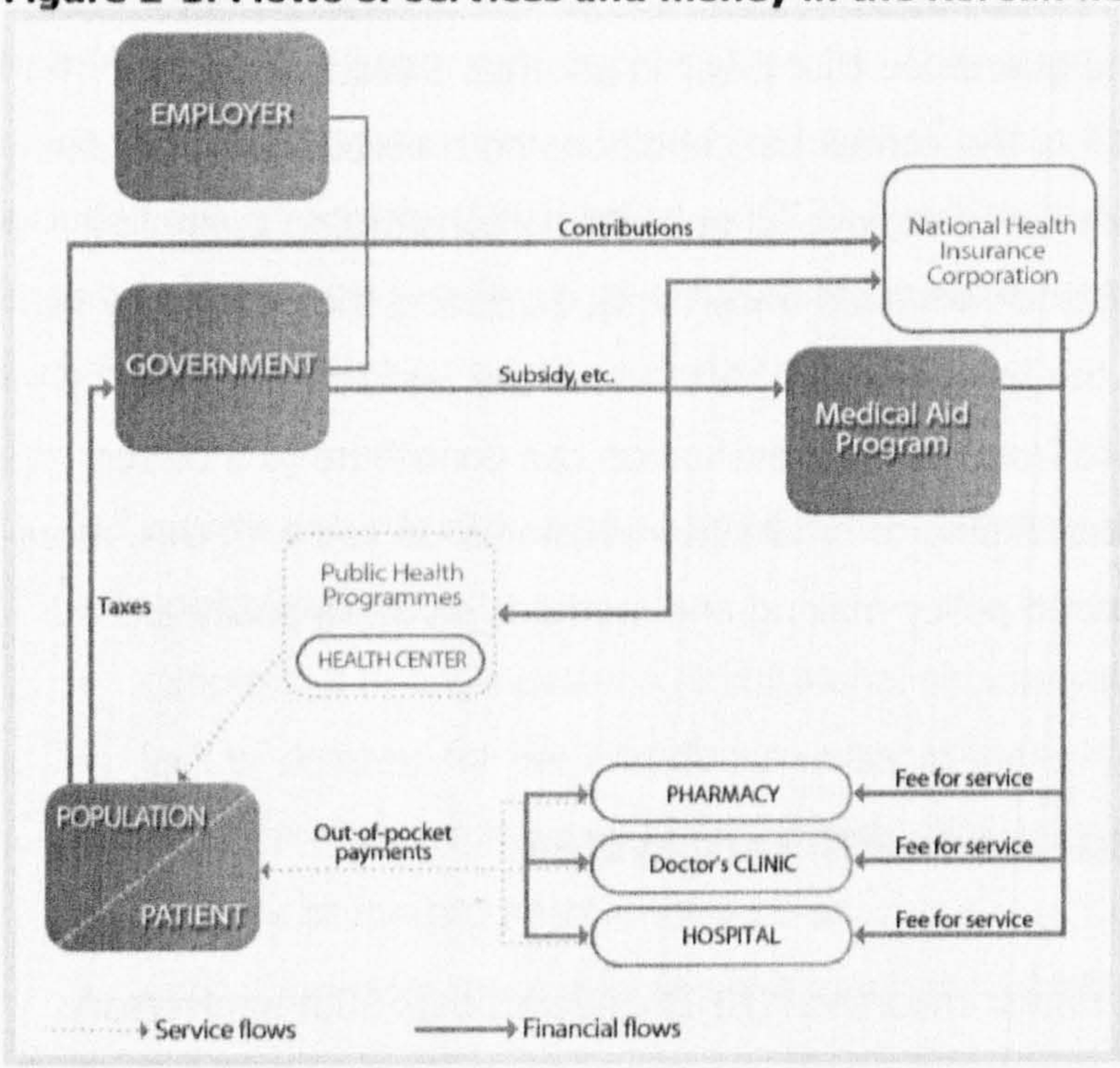
In 2007, the Korean National Health Insurance (NHI) celebrated its 30th anniversary. After its inception in 1977 as a patchy social health insurance benefiting employees only in sizable workplaces[1], the Korean NHI has expanded rapidly in a government-oriented manner (Hwang, 2006b). From 1989, only 12 years later, it provided universal coverage for Korean residents, and its benefits reached 98 per cent of the population by 2006 (NHIC and HIRA, 2007). The Medical Aid Programme (MAP) has complemented the NHI in order to provide a more comprehensive coverage to low income households.

The Korean NHI has been financed by beneficiaries' contributions with a substantial out-of-pocket payment at the point of use. It is in part funded from public money, but only to a very limited extent – around 17 per cent of all revenue in 2006, while beneficiaries' contributions were 80 per cent in the corresponding year (NHIC and HIRA, 2007). Beneficiaries' contributions are determined based on their income (employee) or income & property (self-employed). Employers and employees share

[1] The first wave of compulsory medical insurance programme was initiated to involve limited companies whose employees were more than five hundred.

equally the employees' contribution, while beneficiaries in the self-employed group pay individually. Figure 2-1 illustrates the flows of services and finance in the Korean health care system.

Figure 2-1: Flows of services and money in the Korean health care system



(Source: National Health Insurance Corporation, 2008)

Conventionally, the Korean health care delivery system consists of three level of care; primary (clinics), secondary (hospitals) and tertiary (teaching hospitals) care. However, with the exception of co-payment differences restrictions did not exist until January 2002. Patients generally enjoyed substantial freedom of choice among health care providers as long as they were willing to pay a premium fee. In January 2002, a compulsory two-tier system was instituted by law. The new Medical Act required patients to see physicians in primary care first, and then if necessary be referred to hospitals (*The Medical Act, provision 3*). Primary care physicians have rarely undertaken the expected role as a gatekeeper to specialist services until recently (Lee, 2005a; Lee, 2005b; Yang, 1997).

Currently most Korean healthcare providers are engaged in private practice and paid on a fee-for-service basis. There are no public community pharmacies and few public hospitals. According to a recent report released by the Ministry of Health & Welfare (MOHW), only 8.5 per cent of hospitals and 20.6 per cent of acute beds were managed

on a public basis in 2005 (Ministry of Health & Welfare, 2006b).

2.4 Outline of Korean pharmaceutical policies

Until the 1990s, copayments and direct price control were two major pharmaceutical policies existing in addition to safety regulations in South Korea. Since the late 1990s, South Korea has experienced an unprecedented transformation in the pharmaceutical arena, ranging from the organisational structure to the policy agenda. Table 2-1 shows key government bodies involved in regulating pharmaceuticals in Korea. It shows the Korean stance assimilated with global trends around 2000, with a great development in institutions engaging in audit and evaluation. At the same time, several significant changes took place in pharmaceutical policies. Amongst others, the separation of prescribing and dispensing of drugs (SPD), the Better Prescribing Project (BPP) and the Pharmaceutical Expenditure Rationalisation Plan (PERP) brought about the biggest changes.

Table 2-1: Government bodies over pharmaceuticals in South Korea

Role	Name	Note
Establishing national pharmaceutical policies	Ministry of Health & Welfare (MOHW)	since 1948
Core decision advisory committee over pharmaceuticals	Central Phramceutical Affairs Council (CPAC)	since 1963
Safety control	Korea Food & Drug Administration (KFDA)	independent from the ministry since 1998
Administrating the national health insucance system	Naiotnal Health Insurance Corporation (NHIC)	established in 1998 to merge patchy source of funds; full integration was completed in July 2003
Reviewing and assessing insurance claims	Health Insucance Review & Assessment Service (HIRA)	restructed from the National Federation of Medical Insurance in 2000
Searching/disseminating cost-effectiveness evidence	National Evidence-based Healthcare Collaborating Agency (NECA)	since 2009

2.4.1 Separation of prescribing and dispensing of drugs (SPD)

Before the SPD, there existed a combined system of drug prescribing and dispensing. Patients' pharmaceutical products were generally prescribed and dispensed by medical doctors at clinics. For slight ailments, they often dropped into community pharmacies and could access medications without authorised prescriptions. The roles of prescribers and dispensers were separated only at medical institutions greater than a certain size.

The unseparated system was subject to criticism if it could foster large and inappropriate drug consumption. For instance, the pervasive appearance of antibiotic resistance in microorganisms – more than 70% of the incidence of penicillin-resistant pneumococcus strains in the late 1990s – may have been caused by the inappropriate use of antibiotics in the community (Kim *et al.*, 2004; Korea Health Industry Development Institute, 2006).

The primary aims of the SPD were 1) to prevent misuse and overuse of medicines, and 2) to facilitate the judicious use of pharmaceuticals by double-checking all prescriptions and by banning pharmacists from prescribing. The SPD was expected to result in encouraging professional collaborations and reducing inappropriate drug use. In addition, the authorities hoped that it would have some favourable effects on containing pharmaceutical spending (Ministry of Health & Welfare, 1999b).

With similar aims, the SPD is a measure increasingly adopted in Asian settings such as South Korea, Taiwan and Japan. In Taiwan, doctors are still able to dispense drugs at their premises by hiring pharmacists, even after the implementation of the SPD. In Japan separation has been recommended and professionals can freely choose to practice it. The establishment of the SPD in South Korea was, however, different from that in Taiwan or Japan. The Korean government rolled it out nationwide in July 2000. No on-site pharmacies were allowed at clinics. In hospitals, in-house pharmacies were to be devoted to inpatient services. Outpatient dispensing services were allowed for only a small number of exempted cases such as emergency episodes, patients with severe disability or with specific groups of disease (including Alzheimer's disease, AIDS, haemophilia, rare types of leukaemia or cancer and so forth) (*Korean Pharmaceutical Affairs Law, provision 23*). Additionally, there are regional exceptions resulting from the scarcity of institutions in some remote districts.

The SPD certainly affords substantial changes in the environment of pharmaceutical provision. It has initiated a 'cultural revolution' in every aspect of the Korean pharmaceutical market. Technically, it verified the function of health professionals such as prescribers or dispensers, but it has revealed that the reality might be much more than just separation. On the one hand, many of the preliminary changes such as the

MAC-AAP[2] and the BVP[3] were introduced to build an environment supporting the SPD (Chung and Kim, 2005). On the other hand, many subsequent changes such as the BPP and the PERP were established to cope with the consequences of the SPD, since it was followed by an unexpected increase in pharmaceutical expenditure. Most of all, severe debates lasting over several years concerning the introduction of the SPD roused public awareness of problems in current pharmaceutical spending and physicians' routine practices over pharmaceuticals.

2.4.2 Better Prescribing Project (BPP)

Public awareness has been increased by information produced by a continuous audit of prescribing activity. The BPP, a national prescribing monitoring and feedback programme, has generated a variety of information concerning prescribing practices nationwide since 2001 and communicated to the public since 2002. Outcome variables include the rate of antibiotics prescribed, the rate of injections prescribed, the number of items per prescription and costs per prescription, followed by the rate of pre-defined drugs prescribed by diagnosis. For instance, the rate of antibiotics prescribed for J00 ~ J06 (the national diagnostic codes for acute upper respiratory infection and acute nasal infection, namely the common cold) has been investigated. Gradually, evaluations have been expanded to cover expensive drugs[4] (rate since 2003, value since 2008), steroids (2004), NSAIDs[5] (2005), polypharmacy[6] (2006) and gastrointestinal drugs (2007) although details still remain the simple comparison of aggregate prescribing rates rather than the quality of prescribing.

It is noteworthy that the BPP has provided an opportunity for insight into prescribers' behaviour. It suggests that a rapid increase in pharmaceutical spending might account for poor prescribing practices. It also uncovers large and often puzzling variations in drug spending and utilisation. For example, the highest prescriber spent thirty times

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[2] Maximum Allowable Cost – Actual Acquisition Price system

[3] Bio-equivalence Validation Programme

[4] defined the most expensive drug among each unique chemical ingredient group which has at least three products available in the reimbursement list. Categories in which the most expensive drug is priced less than 50 KRW are excluded.

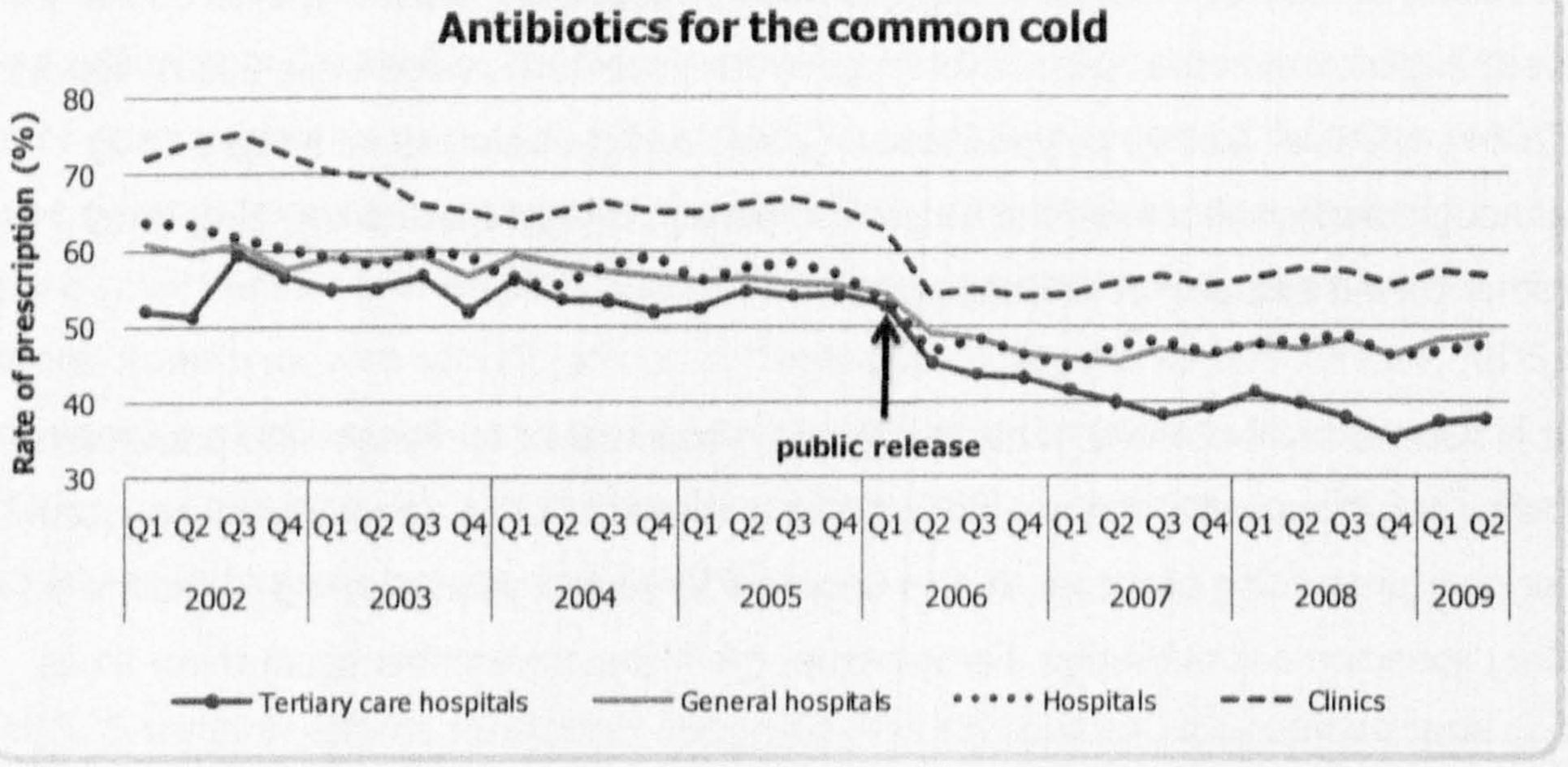
[5] non-steroidal anti-inflammatory drugs

[6] defined as daily intake of six or more drug items per prescription

more than the lowest in average costs per prescription for the common cold in the fourth quarter of 2003 (DailyPharm, 2003b). Figures for use of antibiotics for the common cold, usually not recommended by scientific evidence, seems to be much worse; the prescribing rate per patient visit varied from 0 to 99% across clinics in 2006 (DailyPharm, 2006).

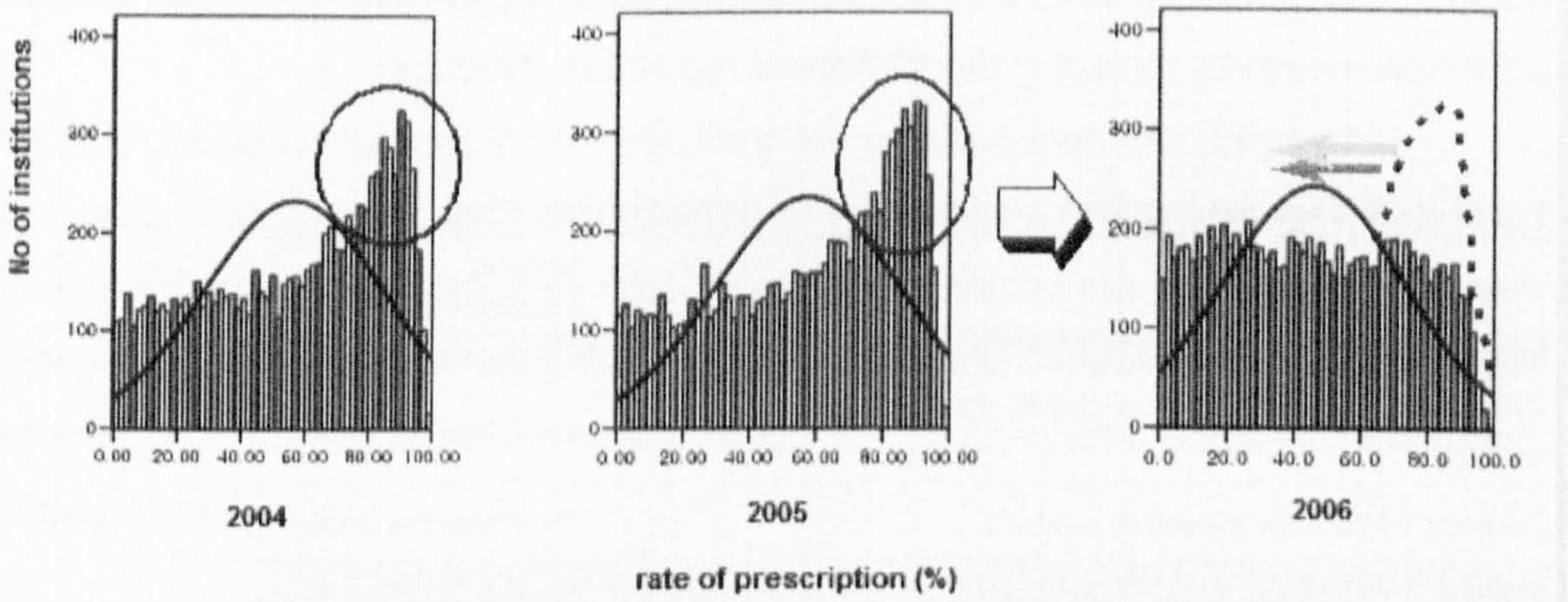
After the BPP, aggregated claims data show a steady decrease in the problematic utilisation of antibiotics and injections over time. However, it became clear that the prescribing audit had merely a temporary effect often ignored by doctors (DailyPharm, 2004b). To improve the adherence to recommendations, information on the performance of hospitals and clinics has been made public since 2006. The disclosure brought about immediate changes in prescribing behaviour, particularly for the rate of antibiotics as shown in Figure 2-2. The biggest changes occurred in medical institutions where doctors prescribed antibiotics for more than seven in every ten visits with the common cold (Figure 2-3). With the exception of antibiotics and injections it remains unclear if the audit activity influences the physicians' prescribing behaviour.

Figure 2-2: Changes in antibiotics prescribing in patients with the common cold by type of institution from 2002 to 2009



(Data sources: Health Insurance Review & Assessment Service, 2003, 2004, 2005, 2006a, 2006b, 2007a, 2007b, 2007c, 2007d, 2007e, 2008a, 2008b, 2008c, 2009a, 2009b, 2009c, 2009d, 2009e)

Figure 2-3: Number of institutions against the rate of prescriptions for antibiotics in patients with the common cold after the public disclosure of the BPP results



(Source: Ministry of Health & Welfare, 2006a)

Although the overall impact does not seem substantial, the new system clearly set a milestone in the history of pharmaceuticals. Information described above never existed before the SPD and the BPP. It was previously impossible to capture an outline of pharmaceutical consumption in the whole territory. Insurance claims provided only a partial figure because most medicines sold in community pharmacies were omitted. Transaction data might be an alternative way of measuring pharmaceutical use, yet, it was not recommended for two reasons: firstly, the Korean pharmaceutical market was too complex to be defined only with transaction data; secondly, transaction data itself is often produced spuriously.

2.4.3 Pharmaceutical Expenditure Rationalisation Plan (PERP)

Before the PERP, regulations often tended to be inconsistent and so offset potential influences one against another, seemingly due to implementation with the absence of systematic planning. In this respect, there was a great need for comprehensive measures making policies work in harmony. With this objective, the PERP was enacted on 29 December 2006, about 8 months after it was initiated in May 2006. It was launched with the dual goals of minimising unnecessary drug expenses by modifying prescribing behaviour and promoting transparency in the market.

The PERP is a comprehensive package of pharmaceutical regulations and consists of four sub-domains, which are *price control, volume control, quality control* and *the restructure of the pharmaceutical market* (Table 2-2). Many of the measures in the

PERP are little more than existing regulations drawn together which previously were fragmented. However, some, such as the positive list and price-volume agreement, were new measures replacing the traditional regulation structure.

Table 2-2: Pharmaceutical Expenditure Rationalisation Plan

Contents	Date of implementation
Price control	
Price-volume agreements (new bodies, the CERM & the CRRM, established)[1)]	29, December 2006
Price cut by 20% for off-patent products	29, December 2006
Volume control	
Positive list	29, December 2006
Formal requirements for cost-effective evidence in the reimbursement decision	29, December 2006
Strengthen prescribing review	continuous activity
Quality control	
Strengthen the bioequivalence validation programme	continuous activity
Upgrade of standards for re-evaluation system	continuous activity
Strengthen recall and adverse event reporting system	continuous activity
Restructure of the pharmaceutical market	
Establishment of a central drug information centre (pharmacy-information network)	July 2007
Strengthen drug identification system[2)]	continuous activity

1) CERM; Committee on Evaluation of the Reimbursement of medicines, CRRM; Committee on reconciliation of the reimbursement of medicines

2) carried out in the mid of 2006, update of a barcode system, a pilot test of the introduction of radio frequency identification (RFID), introducing a smart card system in a pharmaceutical purchasing procedure

2.4.3.1 New pricing system

Before 2006, a cross-national price comparison (hereafter, A7 average price system) was employed when prices for new chemical entities (NCEs) were determined. The average wholesale prices in seven industrialised countries[7] were considered as the international comparator. This was criticised as potentially inflationary as it compared drug prices with countries with much stronger economies than South Korea (Bae and Kim, 2001; Lee, 2006). Moreover, the prices of generics after patent expiry might also be higher because of the linkage price system[8] in Korea. Some recent evidence

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[7] France, Germany, Italy, Japan, Switzerland, the UK and the US

[8] The first to fifth generic drug is set at less than 80% of cost for its off-patent alternative. The

indicates that direct price control might damage generic competition, maintaining relatively high generic prices in Korea (Huh *et al.*, 2006; Shin and Choi, 2008).

The PERP included changes in the determination of reimbursement prices of pharmaceuticals. Average price systems were replaced by a price agreement between the authorities and manufacturers. The initial price is reassessed in the second year according to sales volume during the first year. PERP also included a price cut for out-of-patent products, and consequently, their generic counterparts. Details for the new system follow.

Before 1997, ***patent drugs*** were priced according to the total amount of the ex-factory price, value-added tax and distribution mark-up. When prices were determined, market prices of existing drugs with a similar therapeutic range were the most important reference. From 1997, the A7 average price system was employed to set an initial price for innovative patent drugs. The term 'innovative' has never been precisely defined and innovative patent drugs were likely to remain at premium prices in South Korea, sometimes even more expensive than in more affluent countries (DailyPharm, 2001a). Mounting opinion was in favour of reducing pharmaceutical prices to an affordable level for Korean patients (DailyPharm, 2004c; Kim, 2002a; Korean Pharmacists for Democratic Society, 2006; Lee, 2006; People's Solidarity for Participatory Democracy, 1998).

The PERP employed price-volume agreements for the pricing of all patent drugs, with the authorities publicising statements that evidence of cost-effectiveness would be the first and most important parameter of pricing. However, owing to the scarcity of economic studies (Choi, 2008), a cross-national price comparison seems likely to play a role in pricing for some time to come. Taiwan and Singapore, with similar economic environments to Korea, have recently been added to the group of reference countries, when economic evidence is lacking (*Pharmaceutical Price Agreement Guideline, National Health Insurance Corporation Official Instruction 2006-122; provision 11).*

One year after the first decision, the volume of each product consumed in the

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sixth and later product is set at the 90% price of the least expensive alternative (*MOHW Official Instructions 2005-14; provision 8*).

healthcare sector is studied based on data from pharmaceutical claims. If a product's consumption is 30% higher than predicted, then the price of the product should be lowered in proportion to the increasing volume[9]. From the second year, products with consumption of 60% or greater than the preceding year will be the target of re-pricing[10] (*MOHW Official Instruction 2006-165, Pharmaceutical Price Agreement Guideline; provision 12*).

Off-patent drugs are reduced in price by 20% when the first generic counterpart is submitted for listing. This was applied to all existing off-patent drugs when the new system was implemented, reflected in the Maximum Allowable Costs (MAC) edition of January 2007.

The pricing system for ***generics*** maintained the same rules as before PERP. Prices for generics are linked to those of pre-existing drugs with the same active molecules. Since November 2001 from the first to the fifth generic there must be at least a 20% price cut relative to the original equivalent (*MOHW Official Instruction 2001-59*). The sixth generic should offer an additional 10% price cut relative to the least expensive corresponding drug at the time of listing. In actuality, the new system cuts the price of the off-patent original drugs by 20% making the price of generic products equal to 64% of the price of the original counterpart in the previous system. Other related regulations such as the MAC and the Actual acquisition price (AAP) are maintained as before.

2.4.3.2 New listing system

The reimbursement listing system replaced a negative list with a positive one. Listing and reimbursement decisions are determined based on cost-effectiveness. Under the positive list system, the authorities are able to refuse a listing when they consider the candidate drug less cost-effective than existing alternatives (*HIRA Guidelines for economic evaluations of pharmaceuticals)*. To avoid exclusion from benefit coverage, manufacturers must prove that their drugs are cost-effective compared with the most

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[9] New price = 0.9x (current price) + (1-0.9) x {current price x (predicted volume/actual volume)}.

[10] New price = 0.85x (current price) + (1-0.85) x {current price x (volume in a year before previous year /volume in the previous year)}.

frequently used drug(s) or technique(s).

After implementing the new list system, more than 16,000 items remained on the reimbursement list. The authorities stated that they kept every drug previously on the benefit list, excluding ghost products that were listed but not actually produced, to avoid chaos at the beginning of the new list, but would continue to downsize according to the progress of economic evaluation. From the second half of 2007, a comprehensive review of the cost-effectiveness of each product has been undertaken and will continue until 2011 (Ministry of Health & Welfare, 2007b). The authorities predict that the number of items on the benefit list will be reduced to around 5,000 after completing the evaluation. In reality, however, few changes have been seen in the total number of pharmaceuticals in the list. The first step of economic evaluation (including antihyperlipidemics, antimigraine preparations) was delayed by almost six months, completed in May 2008 (Health Insurance Review & Assessment Service, 2008d).

The initial effects of the PERP are investigated in Chapter 9 on overall drug expenditure, utilisation and market prices and Chapter 10 on essential drug utilisation and generic utilisation.

2.4.4 Detailed anatomy of pharmaceutical policy

Table 2-3 exhibits Korean pharmaceutical policies since the inception of NHI, categorised into interventions influencing patients, providers, and industry.

2.4.4.1 Policies influencing patients

Since its establishment, the Korean NHI system has included a cost-sharing scheme to curb patient demand. Recently, the structure of cost-sharing was changed as detailed in the following section. The impact of this will be explored in Chapter 9 and 10 along with the PERP. On the demand side, other measures such as consumer education have seldom been used. The OTC or self-medication market has not been well-defined. Most potential OTC drugs must be sold under the supervision of pharmacists. Up to date, direct-to-consumer (DTC) advertising has been allowed only for drugs on the general sales list (GSL) (*KPAL Regulation, provision 84)*.

Table 2-3: Current pharmaceutical policies in South Korea

Pharmaceutical policies	Notes	1977	1987	1990	1995	2000	2001	2005	2006	2007	2008	2009
Mandatory separation between prescribing and dispensing of drugs	establish two drug categories of POM and GSL[1)]					■	■	■	■	■	■	■
Policies influencing patients												
Cost-sharing	fixed copayments, coinsurance	■	■	■	■	■	■	■	■	■	■	■
Consumer education	occasionally											
Public advertisement of prescription medicines	banned											
Policies influencing providers												
Guidelines in prescribing practices	advisory, for some therapy											
Reimbursement criteria	for some therapies	■	■	■	■	■	■	■	■	■	■	■
Monitoring prescribing and feedback	for some subjects							■	■	■	■	■
Drug utilisation review	piloted										■	■
Benefit drug listing	negative list							■	■	■		
	positive list									■	■	■
Generic substitution	Yes					■	■	■	■	■	■	■
	incentives on pharmacists					■	■	■	■	■	■	■
Generic prescribing	piloted									■		
Incentives on saving in pharmacy budget	piloted										■	■
Policies influencing industry												
Direct price control	maximum allowable cost	■	■	■	■	■	■	■	■	■	■	■
	price-cut on original drugs after patent expiry									■	■	■
Price agreement	Yes									■	■	■
Patent regulation	Yes					■	■	■	■	■	■	■
formal request of economic evidence in reimbursement decisions	Yes, for some products									■	■	■

1) POM stands for prescription-only-medicines; GSL stands for general-sales-list

Structure of cost-sharing before the change: The Korean NHI system has had a cost-sharing scheme since its inception in 1977. Medical institutions could dispense medicines until the implementation of the separation policy in 2000; copayments for prescription drugs were combined with those for general medical services.

For the first decade after the establishment, there was only a coinsurance scheme; beneficiaries paid 30-40 per cent (20 per cent since July 1979) of total costs for inpatient service and 30-50 per cent for outpatient services at the point of consumption. In 1986, a fixed co-payment was imposed upon patients who dropped into clinics. Since then a dual-system of copayment and coinsurance has existed. Patients pay slightly more out-of-pocket to use services provided by dentists or herbal doctors than at the usual clinics. Drug consumption through community pharmacies began to be subsidised from 1989, the share of total healthcare spending being negligible until the introduction of the separation policy. Table 2-4 demonstrates the structure of cost-sharing of pharmaceuticals at outpatient services from 1997 to 2007.

Table 2-4: Cost-sharing on pharmaceuticals at outpatient services

Cost-sharing		Institution	Sept 1997-Jun 2000	Jul 2000-Dec 2000	Jan 2001-Jun 2001	Jul 2001-Jul 2007	From Aug 2007
copayment (in KRW[1])							
	upper limit	clinics	up to 12,000[2]	Separation of Prescribing and Dispensing for drugs (SPD)			
		pharmacy	up to 3,000[3]	up to 8,000	up to 10,000	up to 10,000	up to 10,000
	seniors[4]	clinics	2,200	SPD			
		pharmacy	900	1,000	1,000	1,200	1,200
	general	clinics	3,200	SPD			
		pharmacy	900	1,000	1,000	1,500	***30%*** *(changed to coinsurance)*
coinsurance			30% of total spending (when total expenses is over the upper limit)				

1) 2000 KRW = £1 in June 2008
2) total expenses including physician consulting fee and costs for prescription drugs
3) total expenses including dispensing fee and costs for prescription drugs
4) seniors; 70 or more from December 1995 to June 2000, 65 or more from July 2000
Source; Park 2002, *National Health Insurance Act Regulation, provision 22-1, Appendix 2*

From 2001 to July 2007, for every prescription dispensed at a community pharmacy patients paid a fixed copayment of 1,500 KRW (£0.75), unless the total drugs cost per single prescription (including a dispensing fee) exceeded 10,000 KRW (£5). In this regard, there had been considerable concern that a fixed copayment would disproportionately benefit patients with temporary, symptomatic illnesses, because a

prescription for chronic medications was more likely to go over the upper limit. In 2006, nearly 60% of prescriptions were priced lower than the upper limit (10,000 KRW), the average costs of which was about 7,500 KRW. Hence, patients prescribed medications costing less than 10,000 KRW per slip paid only around 20% of total expenses (Ministry of Health & Welfare, 2007a).

There are some exemptions to in the cost-sharing scheme. In December 1995, seniors started to pay lower costs for the same services. Beneficiaries aged 70 (65 since 2000) or older paid slightly less. When total expenses exceed the limit, the amount of co-payment was determined proportionally regardless of age. There were no generous benefit schemes for children until August 2007 (*NHIA Regulation; provision 22-1, Appendix 2*). If patients see doctors in public health centres, then they pay less. Some patients with severe diseases such as cancers, rare and incurable diseases, or those covered by the Medical Aid Programme also incurred lower charges (*National Health Insurance Act Regulation; provision 10-2*). Since July 1979, institutionalised patients have paid 20% of costs for services including pharmaceuticals.

A stop-loss (copayment ceiling) was implemented in July 2004, with the NHI subsidizing all extra costs exceeding a certain limit. If a patient pays more than 3 million KRW (£1500) out-of-pocket within the period of six consecutive months (later lowered to 2 million KRW in July 2007) he/she is exempt from any further copayments (*National Health Insurance Act Regulation; provision 22-1).* In this case, out-of-pocket includes the whole spending on medical services including pharmaceuticals by statutory cost-sharing, but excludes voluntary uninsured out-of-pocket.

Copayment increase for prescription drugs: In April 2007, the authorities announced the removal of a fixed copayment for patients aged between 6 and 64 and, instead, applied a 30% coinsurance scheme (Table 2-4). In other words, non-elderly patients have to pay 30% of total drug costs per prescription even when the total amount of expenses is under the previous 'upper limit'. For instance, for a prescription costing 7,500 KRW in total expenses, payment is 2,250 KRW, where previously the payment was only two thirds (1,500 KRW) because total expenses were less than 10,000 KRW. Because of the new cost-sharing schedule, the actual increase in the out-of-pocket rate was around 50% from 20% to 30% in prescriptions previously under the fixed-copayment scheme. The elderly population continue to pay a fixed copayment as

before. A slightly lower cost-sharing rate began to apply to children under six, which since August 2007 has been 70% of the adults charge.

2.4.4.2 Policies influencing providers

Reimbursement criteria were first developed by the National Federation of Medical Insurance (NFMI) and later by the Health Insurance Review & Assessment Service (HIRA). They have been used to screen beneficiaries' prescriptions to identify deviations from pre-specified refundable services in terms of quantity (including overdose, under-dose, or days of supply) and quality (including drug-drug interactions, drug-disease contraindications, or therapeutic duplications). In cases of inappropriate services (prescriptions), refunds would be refused or curtailed. To date, however, it has hardly influenced medical providers because such disadvantages have been negligible in practices, around 1~3 per cent between 2000 and 2001 (Jo and Lee, 2002). The HIRA, a successor of the NFMI, currently strives not only to expand evaluation criteria, but also to convey the information concerning prescribing practices through the BPP, as discussed earlier. Most recently, a national drug utilisation review programme (DUR) was piloted in limited local regions with the purpose of guiding the rational use of drugs (Ministry of Health & Welfare, 2009).

Before the initiation of the positive list, pharmaceutical manufacturers (importers) have to apply for listing within 30 days after market approval in order to have their new products reimbursed. Applications were generally accepted until the first negative list was implemented in 2001 (*National Insurance Benefit Regulation, provision 9*). Over five years, the government excluded more than two thousand items from public subsidy for reasons either that they treated only minor symptoms or had inferior clinical effectiveness. In 2002, nonetheless, almost two thirds of pharmaceuticals on the market (about 18,000 products) were reimbursed (Ministry of Health & Welfare, 2003). There was mounting concern that a long list of insured drugs may not only increase administrational expenses, but also restrain take up of cost-effective pharmaceuticals, which appeared to increase pharmaceutical expenditure more than necessary (Bae and Kim, 2001; Korean Pharmacists for Democratic Society, 2006). This stimulated the launch of a positive list at the end of 2006 in the PERP. Thereafter, the authorities could refuse listing when they considered the candidate drug inferior, for instance less cost-effective, to existing alternatives (*HIRA Guidelines for economic*

evaluations of pharmaceuticals).

From the beginning of the SPD, pharmacists were allowed to substitute a prescribed medication for an equivalent product unless doctors explicitly stated 'no substitution allowed' on the prescription pad. Originally, the primary purpose of a substitution policy was not to encourage the use of less costly drugs, but to ease consumers' inconvenience and the burden of stockpiling in community pharmacies. The policy aim, however, soon reverted to the former as a couple of studies continuously suggested that an increasing use of expensive drugs might be the cause of increasing pharmaceutical expenditure after the SPD (Cho *et al.*, 2002; Cho *et al.*, 2001; Jang *et al.*, 2001; Lee and Malone, 2003). The authorities introduced incentives for generic substitution for pharmacists in July 2001. Thereafter, pharmacists have been allowed to keep one-third of the savings made via the use of less costly generic alternatives (*MOHW Official Instruction 2001-32*). It soon revealed that incentives for substitution are unlikely to contain pharmaceutical spending. According to the MOHW the rate of substitution has been negligible, less than 0.03 per cent in 2005 and 2006 (Ministry of Health & Welfare, 2006b).

2.4.4.3 Policies Influencing Industry

In the Korean market, pharmaceutical manufacturers are free to set drug prices. Retailers, i.e. pharmacists, have also set their own prices for each drug since 1999 when open prices were introduced aimed at price competition (Lee, 1999) (*Korean Pharmaceutical Affairs Law; provision 78*). Inevitably, there have been some differences between the market price and the reimbursement price for the same product. After the SPD, POMs are no longer allowed to be sold without authorised prescriptions, implying that POMs are unlikely to be consumed at suppliers' market prices. Instead, the Maximum Allowable Cost (MAC) seems to govern the market price for POMs in most cases.

The MAC is, as its name implies, a form of price cap that sets an upper limit of remunerative payment for each pharmaceutical product, and has been in force since the beginning of NHI. It is decided at ministerial level via a process involving several government bodies. Different rules apply to in-patent drugs, off-patent drugs (newly introduced by the PERP) and generics (see 2.4.3 for details). The MAC list is revised

regularly via a price survey to catch up with the market dynamics and three major changes have taken place in the survey guideline: Investigating price system; Reporting price system; and Actual Acquisition Price (AAP) system.

During the era employing the investigating or reporting price system, the differences between the reimbursement price and the actual acquisition cost were a source of income for providers (People's Solidarity for Participatory Democracy, 1998, 1999); this was sizeable, over 40 per cent of the total revenue of physicians' clinics (Ministry of Health & Welfare, 2000 cited by Kwon, 2003). To remove such an unmerited profit, the authorities adopted the AAP in 1999 just prior to the SPD. At the onset of the AAP, the authorities undertook a major inspection of pharmaceutical prices on the market, and consequently imposed a mandatory cut in drug prices by 30 per cent on average (DailyPharm, 1999c).

2.4.5 Summary: Korean pharmaceutical policies

During the last decade, South Korea has experienced a sharp increase in pharmaceutical expenditure. To cope with the cost inflation, the Korean government has introduced several new strategies. Nevertheless, Korean policies still seem to be focused on measures influencing patients or pricing, showing little ability to control prescribers.

Notably, there had been no diverse measures in the pharmaceutical market until the SPD, as shown in Table 2-3. Before 2000, cost-sharing, reimbursement criteria and price control were the only measures regulating the pharmaceutical arena, except for safety controls. Most of all, this shows that interventions focused on providers had been totally neglected until 2000s. After the SPD, a body of empirical evidence from the BPP has invariably caused alarm that curbing inappropriate prescribing behaviour is essential to lower the growth of pharmaceutical spending. Hence, some measures such as generic prescribing, incentives on the prescribing budget savings have recently been piloted to influence prescribing practice. There is also animated discussion over potential policies such as a reference-pricing scheme (Lee and Lee, 2007).

Overall, it is clear that the policy agenda is moving from regulating prices and patient demand toward regulating prescribing behaviour. While, outwardly, it has followed

global trends, Korean pharmaceutical policies in reality still seem to rely more on measures limiting patient demand or pricing. Interventions influencing prescribing behaviour are rarely developed further after initial piloting attempts. The underpinning difficulties of this reality are explored in Chapter 12 by conducting in-depth interviews with Korean policy-makers.

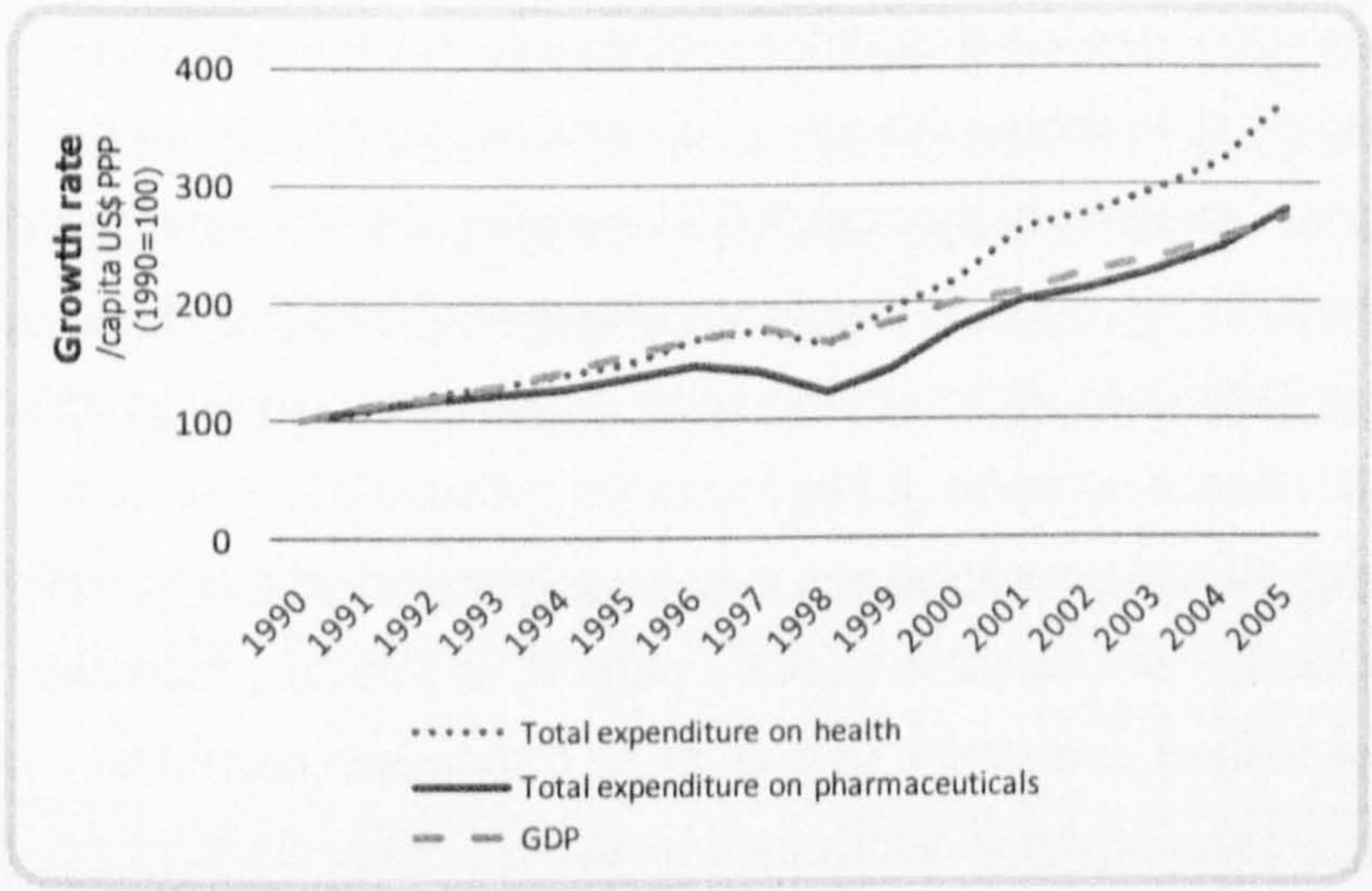
2.5 Overview of the Korean context

The next sections explore the Korean context in five respects: pharmaceutical expenditure; health status; economic and resource capacity; political; and cultural and societal context. To highlight the similarities and differences of these issues between nations, some brief comparisons are made between South Korea and eight other nations on certain limited topics. These countries are Australia, France, Germany, Japan, Sweden, the UK, and the US. These countries were chosen because they are included frequently in systematic reviews (see Part 2) or in comparisons by Korean policy-makers (Annex 26d).

2.5.1 Pharmaceutical expenditure

Korea spends a relatively large sum of money on pharmaceuticals. Until 1995, its share of total health expenditure was in excess of 30 per cent. Although this figure has declined steadily to around 25 per cent in recent years, this decline is mainly ascribed to a rapid expansion of spending on overall healthcare rather than a specific decrease in pharmaceutical spending. As seen in Figure 2-4, spending on pharmaceuticals has increased sharply since 1998, and the growth rate outpaces that of the general economy from 2004.

Figure 2-4: Trends of pharmaceutical expenditure in parity comparison with total healthcare expenditure and general economics, at the basis of the value of 1990



(Data source: OECD, 2007b)

Table 2-5: Pharmaceutical spending and growth rate between 1995 and 2005 in the selected countries

	Pharmaceutical expenditure per capita, US$ PPP[1)]			Pharmaceutical expenditure, % of TEH[2)]		
	1995	2005	Growth %	1995	2005	Growth %
Australia	195	426	118.5	12.1	14.3	18.2
Canada	284	595	109.5	13.8	17.2	24.6
France	314	553	76.1	15.0	16.7	11.3
Germany	292	506	73.3	12.9	15.1	17.1
Japan	346	489	41.3	22.3	19.8	-11.2
South Korea	137	332	142.3	26.1	25.7	-1.5
Sweden	215	406	88.8	12.3	13.7	11.4
UK[3)]	206	n/a	n/a	15.3	n/a	n/a
US	324	790	143.8	8.7	12.0	37.9

1) purchasing power parity
2) total expenditure on health
3) n/a refer to not available

(Data source: OECD, 2009)

Spending on drugs was US$ 332 PPP[11] per capita in 2005, still less than other selected countries; however, the growth rate between 1995 and 2005 was more rapid than other nations in the comparison, and similar to the US, the biggest drug consumer in the world (Table 2-5).

[11] Values adjusted by purchasing power parity (PPP) was used to eliminate price level differences in inter-country comparisons, conversions using purchasing power parities equalise currencies to allow the purchase of the same basket of goods and services in different countries.

2.5.2 Health status

In recent decades, Korean society has faced common problems found in the most industrialised countries, especially in those with aging populations and an increased burden of chronic conditions. According to the recent OECD profile, the life expectancy of the Korean population was 78.5 in 2005. It caught up with that of the US and reached that of the UK (see Table 2-6). Although the aging population (over 60 years) is still smaller than other developed societies, it has increased substantially – at least twofold – compared with Japan or Germany, where they have experienced the highest expansion of an aging population among these selected nations. In addition, mortality caused by major chronic conditions was similar to that in the comparison countries. Mortality from diabetes was rather higher in Korea; and mortality from acute myocardial infarction increased between 1995 and 2005 while it decreased in other places in the same period. Not surprisingly, this changing health status brought about similar challenges to those seen in industrialised societies, such as expenditure inflation in the pharmaceutical arena, as illustrated in the preceding sector.

Table 2-6: Aged population and chronic conditions in the selected countries
(Data sources: OECD, 2009; WHO, 2006)

	Population aged 60+ years[1], %			Life expectancy[2]	AMI[3],[4]		Cancer[4]		Diabetes[4]	
	1994	2004	Growth %	2005	1995	2005	1995	2005	1995	2005
Australia	15.4	17.0	10.4	80.9	88.7	44.7[5]	173.8	154.3[5]	13.4	13.4[5]
Canada	16.0	17.5	9.4	80.4	66.5	41.5[5]	180.7	169.0[5]	16.4	18.4[5]
France	20.3	20.9	3.0	80.2	32.2	21.4	181.1	165.6	6.9	10.9
Germany	20.6	24.8	20.4	79.4	73.8	46.3	185.9	159.3	18.6	16.2
Japan	19.9	25.6	28.6	82.0	30.6	18.7	158.9	142.3	8.4	5.7
South Korea	8.9	13.3	49.4	78.5	17.3	26.6	166.7	158.3	28.8	30.2
Sweden	22.1	23.0	4.1	80.6	96.1	54.5	154.1	148.5	10.6	11.3
UK	20.9	21.0	0.5	79.1	100.2	45.3	197.3	173.3	7.8	6.7
US	16.3	16.5	1.2	77.8	68.5	37.9	183.1	157.9	19.5	20.3

1) The World Health Report 2006
2) at birth, Total population (in years)
3) Acute myocardial infarction
4) deaths per 100,000 population
5) in 2004

2.5.3 Economic stance

South Korea is in an economically weak position compared to the other selected countries. Its GDP is about half of that of the US; and two thirds of the other European countries or Japan (Table 2-7). A weak economic position is associated with lower

spending on health. In 2005, South Korea spent 6 per cent of its GDP on health and was still below international levels. As can be surmised, when costly programmes are involved, such as expensive drugs or medical treatment for all citizens, financial constraints are, to date, one of the most important obstacles in South Korea. Sometimes, the authorities intentionally excluded medical technologies such as positron emission tomography (PET), or new expensive medicines, from the list of benefits owing to the economic burden on public funds (*MOHW Regulation 266*).

Table 2-7: Spending on health and growth rate between 1995 and 2005 in the selected countries (Data sources: OECD, 2008; OECD, 2009)

	GDP/capita, US$ PPP[1)]	Total expenditure on health, % GDP			Public expenditure on health, % of TEH[2)]		
	2005	1995	2005	Growth %	1995	2005	Growth %
Australia	34259	7.4	8.7	17.6	65.8	67.4	2.4
Canada	35079	9.0	9.9	10.0	71.4	70.3	-1.5
France	29644	10.4	11.1	6.7	79.7	79.3	-0.5
Germany	30495	10.1	10.7	5.9	81.6	77.0	-5.6
Japan	30312	6.9	8.2	18.8	83.0	82.7	-0.4
South Korea	21342	4.1	6.1	48.8	36.3	52.1	43.5
Sweden	32770	8.0	9.2	15.0	86.6	81.6	-5.8
UK	31585	6.8	8.2	20.6	83.9	81.9	-2.4
US	41740	13.6	15.7	15.4	44.9	44.4	-1.1

1) purchasing power parity (OECD 2008)
2) total expenditure on health

Linked to the lack of resources, high private expenditure has been subject to strong criticism in South Korea (Choi *et al.*, 2005b; Lee, 2005b; OECD, 2005, 2006, 2007a). The Korean health system has kept a relatively high legal copayment level, almost a quarter of total expenditure on health until recently. In practice, figures are even higher. Patients are required to pay nearly half of total expenses out-of-pocket at the point of care, which consists of legal copayments plus out-of-pocket derived from uninsured services (Kim and Jung, 2005; Kim and Lee, 2006). Over time, people became used to copayments and to inequity among the social groups by ability to pay. A philosophy of victimisation has been present throughout Korean society.

There has been extensive anecdotal evidence concerning the increase in social inequality. The growth rate of household expenditure on health was 25 per cent in the first quarter of 2003, which was the highest growth rate in the top 10 household expenses (DailyPharm, 2003a). One in four leukaemia patients and their families reported declining from middle class to a low-income class after illness occurred in the

household (Kim, 2003). A third of the beneficiaries in the lowest contribution group have had experience in giving up access to healthcare services owing to the financial burden entailed (DailyPharm, 2005a).

On the other hand, the industrial context may confirm South Korea in a different position from the selected countries. Globally, the pharmaceutical industry is regarded as promising and profitable (Fortune, 2008; Reekie and Weber, 1979), whereas the Korean pharmaceutical industry still has little influence on the national economy. The share of the national GDP made up by the pharmaceutical industry has reduced slightly since 1998, and was lower than 1.5 per cent in 2005 (Korea Health Industry Development Institute, 2007). In the same year, 546 manufacturers produced pharmaceuticals. Among them, 20 producers recorded more than 100 billion KRW (£50 million) of annual sales, and these sales represented 70 per cent of the whole (Korea Health Industry Development Institute, 2007), indicating that most producers are still small businesses in South Korea.

Table 2-8: Pharmaceutical industry

	top 100 drug company[1),2)]	top 20 drug company[1),2)]	Generic share, %				
			volume	value	ratio[3)]	year	references
Australia	1	0	15.5	10.2	0.7	1998/9	Lofgren 2002
Canada	5	0	43.5	17.4	0.4	2006	Canadian Generic Pharmaceutical Association, 2007
France	4	1	12.0	6.4	0.5	2004	European Generic Medicines Association, 2004
Germany	6	2	41.1	22.7	0.6	2004	European Generic Medicines Association, 2004
Japan	18	2	18.7	6.4	0.3	2007	Pharma Marketletter 2008
South Korea	0	0	42.8	39	0.9	2004	Huh 2006
Sweden	1	1	39.4	12.3	0.3	2004	European Generic Medicines Association, 2004
UK	6	2	49.3	20.6	0.4	2004	European Generic Medicines Association, 2004
USA	37	10	69.0	16.0	0.2	2008	Generic Pharmaceutical Association, 2009

1) Where the headquarter being situated is considered a host nation of each company. The global top 100 of pharmaceutical compaies are listed by Scrip 2007.

2) AstraZeneca is included both in Sweden and the UK because it establishes the headquarter in both nations.

3) ratio = value/volume

The numerical figures in Table 2-8 confirm Korean the industrial environment. In 2006, Korea had no pharmaceutical companies in the world's top 100 companies (even

including important generics manufacturers).

Linked to this issue, most Korean manufacturers have largely neglected any research and development activity. No new chemical entity was developed by a local manufacturer until 1999 (Korea Health Industry Development Institute, 2006). Average R&D investment remained less than 5 per cent of annual sales in 2006 (Korea Health Industry Development Institute, 2007), which was far behind the 15 per cent in international patent holders in the late 1990s (National Economic Research Associates, 1998). Korean companies conventionally make more efforts in selling generics and, as a result, the volume share of generics in the pharmaceutical market was quite high, over 40 per cent in early 2000s (Table 2-8). This figure is comparable with Sweden or the UK, who greatly encourage the use of generics (Andersson *et al.*, 2007; Simoens and De Coster, 2006). However, it should be noted that the share of value may be as high as of volume, unlike Sweden and the UK, indicating the low possibility of saving by using generics. It implies that generic policies, which are advocated as useful measures easing cost crises in other settings, might not be as effective in South Korea if this situation persists. Issues relating to this are explored further with the empirical data in Chapter 10.

2.5.4 Political environment

Since Independence, modern Korean society has been influenced considerably by American traditions in every respect. Additionally, South Korea has developed through state-led industrialisation programmes (Hasan, 1976). Until recently, the Korean government has been more likely to prioritise economic development than welfare (Hwang, 2006a). A weak inherent ideology of welfare coupled with limited national wealth made past governments construct a minimum benefit package at the expense of quality of care, and the structure was retained for more than two decades until the end of 1990s. Hwang (2006b) provides a good description of how political imperatives were exercised above economic principles or welfare concerns in the decision-making process of healthcare provision in that same period. Equity issues were paid less attention until the late 1990s, as the function of social insurance was health security for limited beneficiaries (the relatively better-off), not wealth redistribution (Hwang, 2006b).

Recently, Korean society has experienced a change in this inherent tradition. During the last decade, the growth rate of public expenditure on health rose from 39 per cent in 1996 to 53 per cent in 2005 (OECD, 2007b) The preceding two governments (1997-2002; 2003-2007) emphasised social solidarity (Hwang, 2006c; Kwon and Reich, 2005), moving "informal, familial, community-based mutual support" towards more state-provision of welfare systems (Hwang, 2006a). As a result, debates over equity appear more often in the public arena these days, even though social consensus in the whole society has not yet been reached (Lee, 2009).

At the micro-level, details are more likely to reflect the power of relationships between stakeholders. Pharmaceutical policy-making involves a multiplicity of stakeholders whose interests often compete. In practice, politicians, healthcare providers, manufacturers, payers and experts are ultimately concerned with their own influence, reputation, and research funds. It is, thus, far from surprising that a power game among Korean stakeholders is serious and highly complex (Kwon, 2003). Herbal medicines also form a considerable portion of the healthcare system and this multiplies the complexity of this market (Cho, 2000).

Since the beginning of the 1990s, South Korea has seen conflict among professionals over pharmaceuticals, for example between pharmacists and practitioners of traditional medicine. This created a new professional, the 'herbal pharmacist' in 2000 (The Association of Korea Oriental Pharmacy, 2004). Severe tensions were also evident at the inception of the Korean SPD. There were five nation-wide physicians' strikes[12] during the year that the SPD was introduced, which influenced greatly the details of its regulation and payment rate (Choi, 2000; Kwon, 2003). For instance, the classification of prescription-only-medicines (POMs) kept changing for up to a year after the implementation. More recently, troubles between domestic wholesalers and Zuellig Pharma, an international wholesaler in the Asia Pacific region, saw the entire country struggling with a situation where certain trans-national corporations' (TNCs') products were 'out of stock' for almost a month in 2007 (Medical Today, 2007a, 2007b).

Among stakeholders, evidence suggests that medical professionals may play a substantial role in policy outcomes. One survey undertaken by an online press in the

[12] February, April, June, August and October 2000

year preceding the SPD showed that seven physicians out of ten practicing in Seoul, the capital city of South Korea, responded that they would prescribe original drugs when the SPD was implemented (DailyPharm, 1999a). Doctors expressed concern for their reputations if their prescriptions were disclosed to the public, as the SPD lets patients take prescriptions away to be dispensed in their catchment pharmacies. Although the survey did not provide the number of original drugs prescribed at the time of the survey (before the SPD) by the doctors surveyed, it showed clearly that physicians had an unfavourable opinion towards generics and foretold a future trend of market dynamics. About two years after the survey, the Health Insurance Review & Assessment Service (HIRA) reported to the National Assembly that spending on expensive drugs (mostly original drugs and some expensive branded generics) doubled from 1,466 KRW (£ 0.75) per day in the two months before the SPD to 3,130 KRW (£1.5) per day in the three months after the SPD (DailyPharm, 2001d). This was not surprising because the demand for prescription drugs is determined largely by prescribers' preferences (Chapter 1).

Contrary to this, civil society has been in a weak position until very recently. Its voice has steadily increased, generating a social consensus over the SPD against the power dynamics between the government and professionals at the end of the 1990s (Choi, 2000; Kwon and Reich, 2005). Albeit augmenting the role of civil movements, there is still scepticism about whether the official process of pharmaceutical decisions pays due regard to consumers' welfare, given that formal committees have been largely dominated by professionals to date (Choi, 2005; Hwang, 2004).

2.5.5 Cultural background

It should not be overlooked that drug consumption is determined to a substantial extent by cultural factors (Bradley *et al.*, 2004; Crawford, 1984). As depicted in the preceding section, Korea spends relatively large amounts of money on pharmaceuticals. Low spending on healthcare with a high proportion of pharmaceutical spending is certainly typical in Korea. Presumably, this is partly caused by a drug-oriented custom that had been established during poor economic periods in Korea. People were used to community pharmacies for relieving their health problems and considered medical institutions more expensive, time-consuming and authoritative. It might also be explained by the tradition of Chinese medicines, within which there has been no

separation between prescribers and dispensers. This culture was expanded to encompass the system of western medicines. No legal barriers existed to dispensing pharmaceuticals until 2000, when the separation policy required authorised prescriptions for POMs.

As already mentioned, the separation policy has recently been adopted in several Asian nations with the expectation of reducing drug expenditure and achieving clinically desirable drug consumption. This is in sharp contrast with the situation in many Western countries where independent roles of prescribers and dispensers have been steadily developed over time with little mandatory power (Savage, 1994). This is also a different trend from the US where dispensing doctors have recently emerged (Schweitzer, 2007a), or the UK attempting an alternative role with nurse practitioners and pharmacists allowed to prescribe from a limited formulary, with the purpose of saving salaries and time of medical professionals (Department of Health, 2009).

2.5.6 Summary: Korean context

This section has probed the Korean contextual factors that may influence pharmaceutical policy interventions. Health parameters indicate that the health status of the Korean population is aging rapidly, resulting in a sharp increase in health spending, similar to most industrial countries. At the same time, there are several points making South Korea different from such settings, including economic, political, and cultural internal contexts.

Firstly, the Korean economy is in a relatively weak position, resulting in less available healthcare resources than other countries, including in the pharmaceutical field. The private share of health costs is currently higher than other welfare states. Under such conditions, social inequity caused by income differences seems considerable. Secondly, the Korean drug industry is uncompetitive in the global market. At home, there is concern over too much reliance on generic business by the pharmaceutical manufacturers. Thirdly, political imperatives seem to be more influential in policy decisions. Economic development has been of great importance to Korean politicians in the period since independence. Considerations over social equity and social security have only a decade of history and are limited. Fourthly, tensions are high and complex among actors in the health arena. Whilst professionals' influences are considerable in

the establishment of pharmaceutical policies, the strength of civil society is still weak compared with that of other actors. Fifthly, Korean consumers have a high level of dependence on pharmaceuticals.

2.6 Evaluating pharmaceutical policy outcomes

In this section, increasing demands for a sound basis in policy making is addressed briefly, followed by the framework of research methods frequently used in policy evaluation, to allow discussion of practical difficulties of policy analysis in certain areas. Finally, discussion returns to the local context from a perspective of the quality of evidence currently available in South Korea, to help to understand the research questions and methods for this study.

2.6.1 Evidence base for policy-making

While government intervention is needed to correct the failures in the drug market, there seems to be no particular reason to assume government intervention will necessarily be either efficient or equitable on its own. Some writers are concerned that public policies could potentially be ineffective (Dolowitz *et al.*, 2000), could increase inequity (Mastilica and Bozikov, 1999), or could cause more harm than good in some conditions (Soumerai *et al.*, 1991).

Over the past 15 years, voices proclaiming the link between science and policy have become apparent, as the belief that scientific evidence can improve the rigour of decision-making has spread. Over a relatively short time period the concept of 'evidence-based' policy-making (EBP) has succeeded in permeating governments as a principle (Department of Health, 2008; van Kammen *et al.*, 2006; Wilson *et al.*, 2007). This trend has been partly facilitated by the social environment increasingly calling for transparent, accountable as well as efficient policy-making (Daniels and Sabin, 1998). As the population's expectations and costs of health care continue to grow, problems with finite resources worsen. Electorates ever more ask politicians to justify their decisions, forcing them to seek evidence.

The idea of an 'evidence-base' or 'knowledge-base' was firstly used in medicine as 'evidence-based medicine (EBM)' which requires "the conscientious, explicit and

judicious use of current best evidence in making decisions about the care of individual patients" in clinical care (Sackett *et al.*, 1996; p71), in which effectiveness or efficiency is the first and best cause for a decision (Gray, 2001b). EBP is the concept expanded from EBM in shaping decisions for individual patients to policy decisions for groups of people. The key element of EBM and EBP is the importance of evidence in decision-making. Cookson (2005; p118) defined the term EBP "as a set of rules and institutional arrangements designed to encourage the transparent and balanced use of evidence in public policy-making". In healthcare, it was firstly interested in "doing things cheaper" then moved onto "doing the right things right" by incorporating quality concerns (Gray, 2001a).

Although this new agenda has been widely accepted in recent years as a concept, translating this concept into practice has proved challenging. Several causes may underlie this. First, as discussed earlier, policy-making can be influenced by many other factors, such as political interests. For example, Kay (2002) demonstrated how efforts seeking evidence for policy decisions were neglected in the UK fundholding scheme from its introduction to abolition, as political thinking dominated. Second, scientifically good research may not necessarily be ready for use in policy-making. For example, research conducted in developed countries may not provide a proper solution to context-specific problems in developing nations (Behague *et al.*, 2009). Moreover, conclusions from each study are usually single-faceted and frequently remain ambiguous or uncertain. Wilson *et al.* (2007; p248) argued that "good research on [policy] issues is necessary but not sufficient to underpin [policy decisions]" Linked to this, writers indicated that the concept of evidence might differ between the producers and users (Choi *et al.*, 2005a; Innvaer *et al.*, 2002; Sharpe, 2004). Third, evaluating policies is still a weak area and generally proves more difficult to conduct compared with clinical research. Often, a robust design such as a randomised trial is impractical or unethical, so policy impact is confounded by uncontrolled external and internal factors. As a result, good quality, available evidence is often lacking.

Impact assessment of concomitant policies is a growing field of research in the provision of pharmaceuticals, in line with illustrating the significance of EBP. Despite efforts over the past two decades, robust studies are still scarce in this field (Kanavos *et al.*, 2004; Soumerai *et al.*, 1993). Existing evidence is fragmented and concentrated, limited to a small number of regions, as shown in both the body of existing literature

and the three systematic reviews in this thesis (see Chapter 3 to Chapter 7).

A number of suggestions have been made to cope with such obstacles. They can be broadly categorised into two types: firstly, researchers and policy-makers working together; and, secondly, encouraging the establishment of a good knowledge base sensitive to policy demand (Behague *et al.*, 2009; Elliott and Popay, 2000; Sharpe, 2004; Soumerai *et al.*, 1997; van Kammen *et al.*, 2006; Wilson *et al.*, 2007). The purpose of this thesis is related closely to the latter.

2.6.2 Tools for studying pharmaceutical policy

Studying policy is a complicated task, which has its base in social science and is by nature multidisciplinary, ranging from political science and economics to sociology. Moreover, policy analysis within the pharmaceutical arena requires sound knowledge concerning epidemiology and natural sciences in order to utilise secondary information because pharmaceutical provision is rooted in natural science.

In clinical science, randomised designs are generally employed, typical examples of which are drug trials measuring the safety and efficacy of a new chemical entity (NCE). In randomised experiments, subjects are allocated randomly either to an intervention group or to a control group (Shadish *et al.*, 2002d). For high quality studies, it is necessary to maintain 'randomised' allocation throughout the study period by adhering to allocation concealment and intention-to-treat analysis (Tilling *et al.*, 2005). Any break in randomisation introduces bias that may produce false conclusions. Among several designs, randomised controlled trials (RCT) are considered a 'gold standard' study design with the least bias and increasingly required in all research fields. In research addressing pharmaceutical policy issues, the famous RAND health insurance experiments were performed using a randomised experimental design (Newhouse, 1993).

However, true experiments are challenging in policy studies. Firstly, it may be simply not feasible in the context of social policies. Let us assume there is a researcher who plans to evaluate public policy introduced at the national level, but is unable to find a proper control group because the policy affects the whole population. One may select a comparable population from outside of the country but it is clear that subjects have not

been allocated randomly. Secondly, randomisation often entails ethical considerations (Edwards *et al.*, 1999; Mahler *et al.*, 1982; Resnik, 2008). For example, it is unethical to assign persons at random into an intervention that may cause significant harm, such as heavy copayments on essential drugs.

When these events occur, researchers resort to quasi-experiments. Among others, two relatively well-designed tools are interrupted time series (ITS) and controlled before and after (CBA) designs. Time series designs are valued for their power in ruling out many threats to internal validity and are highly feasible (Shadish *et al.*, 2002c). A time series is a sequence of observations made on a single variable at successive time intervals. ITS refers to a particular form of time series that is *interrupted* by an external intervention, for instance, a copayment change. This design will be explored in greater detail in Chapter 8.

CBA designs are quasi-experiments in which the allocation of intervention and control groups is determined not by a random process, but in some other manner (Shadish *et al.*, 2002a). Data is collected before the intervention and then further data collected after the intervention is introduced, and outcomes are usually discussed in terms of group differences in pretest-posttest changes (Cook and Campbell, 1979b). In this case, an evaluator seeks a comparable population outside of the intervention state as a control, which is an example of CBA. The most likely threat to internal validity in this design is selection bias, because there may be unidentified differences between the intervention and control groups that could confound the results.

There are also several designs scientifically less advocated but frequently employed, such as one-group posttest-only design, one-group pretest-posttest design, or posttest-only design with non-equivalent groups (Shadish *et al.*, 2002b). These designs have value in suggesting new ideas, yet they are normally thought insufficient in demonstrating a clear relationship between cause and effect. They often exaggerate policy outcomes (Soumerai *et al.*, 1989). However, they are still used frequently in policy studies. According to the recent article by Kanavos *et al.* (2004), these kinds of studies occupied more than 80 per cent of 18 studies examining the cost-containment policy they reviewed.

Quantitative approaches described so far tend to be limited to areas where the

collected data can provide explanation. Faced with such limitations, qualitative approaches can be useful. Not only can qualitative research illuminate the research question in ways that a quantitative approach cannot, but also it has advantages in disclosing hidden issues or underlying meanings, or to help with better understanding of quantitative findings (Pope and Mays, 2006). Recently, studies employing 'mixed' methods combining qualitative and quantitative designs have emerged. These types of study are expected to answer a wider range of questions and increase the reliability of study (Denscombe, 2007b; O'Cathain and Thomas, 2006).

A single study may produce a false conclusion and is often in contrast with another. Generalisation of results from one study beyond a certain condition is often limited. In this respect, reviews are a useful tool to draw together sometimes inharmonious evidence. Nowadays, researchers, practitioners and policy-makers are overwhelmed with unmanageable amounts of evidence. Thus, easily accessible, up-to-date evidence is as essential for further evidence-based studies. Moreover, reviews can highlight fields that are neglected in research. However, conventional narrative reviews often suffer from poor quality and are often regarded as another unreliable source of information (Egger *et al.*, 2001). By contrast, a systematic review has a predefined, explicit, reproducible protocol involving several steps. A protocol contributes to the minimisation of bias and reduces uncertainty in comparison with a narrative review, allowing a more transparent appraisal (Egger *et al.*, 2001).

2.6.3 Evaluating pharmaceutical policy in South Korea

Before moving onto the framework of methods for the thesis, it is useful to tackle the common weaknesses of the preceding research of Korean pharmaceutical policies to highlight the contributions of this thesis to the existing literature.

First, pharmaceutical policy evaluation has been made on limited subjects in South Korea. Little is known about the impact of the most of policies on pharmaceutical spending and utilisation, although many policies have been introduced. Any existing studies have been dedicated primarily to investigating the separation policy (SPD).

Second, the impact of the policies on medication for chronic diseases is largely under-studied. Although the HIRA has assessed prescribing practices since 2001, it is likely to

be limited to certain particular parameters, mostly assessing medication for acute conditions – including antibiotics, NSAIDs and gastro-intestinal preparations.

Third, robust methods have rarely been employed. Lack of proper statistical analysis is a widespread problem across studies. Most evaluations for pharmaceutical policies in Korea have used the intuitive pre-post comparison approach so far (Cho *et al.*, 2003; Cho *et al.*, 2002; Cho *et al.*, 2001; Jang *et al.*, 2001; Lee *et al.*, 2001). Some used a time series design, but without a proper statistical analysis or only over a short time period (Kim, 2002b; Kim, 2005; Lee and Malone, 2003).

A pre-post design with small data points can be subject to numerous possible threats to validity such as maturation, history, testing, and attrition (Shadish *et al.*, 2002b). Given that many confounders probably exist in a rapidly changing environment like South Korea, researchers should have considered employing a more robust design to avoid biased conclusions. For example, in 1999 a year before the SPD, there were two important changes which might have promoted the use of brand-named drugs– the deregulation of the market approval process for new entities (DailyPharm, 1999b) and the expansion of benefit coverage for expensive brand-named drugs (Ministry of Health & Welfare, 1999a). Nevertheless, few researchers took this into consideration when they examined changes in the utilisation of expensive drugs before and after the SPD.

A short period of data collection seriously damages the credibility of studies. In the existing evidence on Korean pharmaceutical policy, authors often used a single month or an even shorter period of claims data before and after the intervention (Cho *et al.*, 2003; Cho *et al.*, 2002; Cho *et al.*, 2001; Jang *et al.*, 2002; Jang *et al.*, 2001), or a single month every year over one or two years (Kim, 2005).

Fourth, there was no reliable dataset before the SPD. One of the greatest challenges for Korean researchers in policy pharmaceutical studies is the lack of a comparable national database relating to the consumption of pharmaceuticals before the year 2000. Hence, many researchers depended on data collected using a cross-sectional survey with small study population in order to fill the gap between the national claims database and real consumption (Cho *et al.*, 2003; Cho *et al.*, 2002; Cho *et al.*, 2001; Jang *et al.*, 2001). Results were varied across sample groups even within a single study

although participants were randomly selected.

To summarise, although many studies were conducted to examine the impact of Korean pharmaceutical policies on drug spending and prescribing behaviour, evidence from empirical research still seems fragmented, spurious and in short supply. Certainly, there is a great need to evaluate the impact of the SPD and other subsequent changes on the pharmaceutical market over a longer-term period with well-designed methods in Korea.

This study, therefore, was carried out in order to extend empirical evidence of the impact of Korean pharmaceutical policies and to explore what have been the barriers to evidence-based policy-making. Table 2-9 illustrates designs and research methods employed in this thesis to study and evaluate pharmaceutical policy. In the table, four studies are displayed including either the research or evaluation questions posed as well as a specific chapter in which the results of each study are presented.

Table 2-9: Methodological framework for the thesis

Study	Research/evaluation questions posed	Design	Methods used
Evaluation of current drug policy evidence across nations	1) What was the impact of pharmaceutical policies on drug costs, utilisation, other resource use and health? 2) What was the methodological strength and weakness of studies evaluating pharmaceutical policies?	Systematic review (Ch 3)	Systematic reviews: 1) policies influencing patients (Ch 4) 2) policies influencing providers (Ch 5) 3) policies influencing industry (Ch 6)
Evaluation of the impact of local drug policies in Korean market	What was the impact of the policy changes on drug costs, utilisation and prices?	Quasi-experimantal study (Ch 8)	Interrupted time series analysis of drug costs, utilisation and prices data (Ch 9)
Evaluation of the impact of drug policies in essential drugs market	1) What was the impact of the policy changes on patients' access to essential drugs? 2) What was the impacts of the changes on generic utilisation?	Quasi-experimantal study (Ch 8)	Interrupted time series analysis of cost and drug utilisation data of two therapeutic categories grouped into brand-named and generic drugs (Ch 10)
Investigation of Korean policy-making stance	What makes it difficult to formulate evidence-based policy-making in South Korea?	Qualitative study (Ch 12)	Semi-structured questionnaire and telephone interviews with key policy-makers, and framework analysis (Ch 12)

To draw appropriate lessons, it is essential to explore how programmes work elsewhere. Thus, firstly, systematic reviews are conducted to investigate existing evidence internationally. These provide the opportunity to learn general policy lessons from

foreign experience and to gain understanding of the contextual surroundings that may make a policy succeed or fail. Careful evaluation of International experience could also suggest ideas for future Korean policies in seeking the best strategy, with consequent benefits to society. Another equally important purpose of reviewing preceding studies is to widen the knowledge of methodological designs. With such goals, only the three most rigorous designs, RCT, ITS and CBA are included in the systematic reviews of this thesis.

Following the systematic reviews, empirical research is performed both quantitatively and qualitatively. For quantitative investigation, ITS designs are employed to examine the impact of two Korean pharmaceutical policies using prescription claims data. Two quantitative studies are conducted; one deals with general outcomes, the other investigates the consequences of the policy interventions by analysing subgroup data.

Quantitative studies illustrate that there are considerable limitations in research. Primarily, quantitative approaches have proven particularly challenging for exploring certain subjects because of the low availability of valid data. Faced with such limitations, a qualitative study is performed to address the stance and the challenges of evidence-based policy-making in Korea from the standpoint of Korean policy-makers and those who influence policy. Interviewing local policy-makers and influencers also offers a valuable opportunity for understanding policy environments in a local context. Details of the three different study techniques will be presented at the beginning of each part in Chapters 3, 8 and 12.

2.6.4 Summary: Evaluating pharmaceutical policy outcomes

Globally, the significance of evidence-based policy-making increased in importance in the area of public policy. Accordingly, the demand for good evidence is growing, but the supply of available evidence is still limited in relation to pharmaceutical policies. Studying pharmaceutical policies is challenging because the presence of unknown factors potentially influences the policy impact. Good study design may reduce external confounding and increase the reliability of research.

In a Korean context, previous studies often demonstrated common shortcomings such as poor study designs, short-time frames, or the lack of reliable data. Although new

strategies continue to be introduced, evaluation activity still seems weak. Little is known either about the impact of current strategy, or about how contextual factors affect policy decisions and policy effects. This thesis will undertake a quantitative investigation of how current strategies are working in the Korean context. Issues relating to contextual factors are also addressed in a qualitative investigation.

2.7 Summary

This chapter explores realistic issues in studying pharmaceutical policies focusing on two aspects: contextual-specific influential factors; and methodological factors. At the beginning, the Korean health care system and pharmaceutical policies were outlined to describe this particular local arrangement, showing that pharmaceutical policy-making in South Korea is at a crossroads in this decade. The traditional structure has been removed, but a new one has not yet been firmly established. In the following sections, the salient characteristics seen in the Korean pharmaceutical arena were explored from five perspectives: pharmaceutical expenditure; health status; economic and resource capacity; political; and cultural context, which support the argument that the pharmaceutical strategy requires a different set of tools and knowledge to cope with fundamental differences within each context. The second part of this chapter addressed the global trend of evidence-based policy-making and several methods frequently employed in policy evaluation. Finally, the chapter returned to the Korean context to highlight the weaknesses of pharmaceutical policy studies previously conducted in Korea. This emphasises the contribution of the thesis to the existing literature and the strength of study designs that were presented at the end of the chapter.

PART 2 SYSTEMATIC REVIEW:

EVIDENCE ACROSS NATIONS

CHAPTER 3: DESIGN OF SYSTEMATIC REVIEWS

3.1 Introduction

The first two chapters examined some underpinning rationales and intended mechanisms of pharmaceutical policy. Chapters three to seven explore existing experimental and quasi-experimental evidence about policy impact in the pharmaceutical arena from three angles: pharmaceutical policies influencing patients, providers, and industry. Three systematic reviews identify rigorous evaluative studies and examine them to assess the impact of pharmaceutical policies.

International experience plays a principal role in constructing a store of knowledge in this field. Lessons from foreign experience are evaluated for several pragmatic reasons. Some countries share common problems such as demographic changes, technological advances, expenditure inflation, finite resources and the growth of global pharmaceutical companies, as the society is developed and economically globalised (Blank and Burau, 2010a). The distinction between national and international problems is blurred in certain quarters. Hence, if policy-makers can learn a proper lesson from foreign experience, it may be a shrewd way of saving effort. In addition, there is inevitably a considerable time-lag between implementation and evaluation of policy. Thus, lessons from overseas experience may help policy-makers to avoid repeating foreign mistakes in their own arrangements before proper evaluation.

In relation to this project, studying the experience of the international community provides a chance to learn the general mechanisms of interventions and to understand the original environment which makes them work or fail. This may offer an opportunity to learn the strengths and weaknesses of policy programmes, providing insights for the Korean pharmaceutical policy, and this effort is also essential to draw lessons from empirical studies in Part 3.

Already, there are several reviews of particular pharmaceutical policies, such as 'cost-sharing and prescription limits' (Soumerai *et al.*, 1993), 'educational approaches to providers' (Soumerai *et al.*, 1989), 'prior authorisation' (MacKinnon and Kumar, 2001), 'reference-pricing' (Danzon and Ketcham, 2003; Ioannides-Demos *et al.*, 2002; Lopez-Casasnovas and Puig-Junoy, 2000) and 'restricted formulary' (Levy and Cocks, 1999;

Lipsy, 1992; Pearce and Begg, 1992). More broadly, some studies reviewed various pharmaceutical regulations in European arrangements (Ess *et al.*, 2003; Guillen and Cabiedes, 2003), in the US context (Kozma *et al.*, 1993; Reeder *et al.*, 1993), or in the global context (Bloor and Freemantle, 1996; Bloor *et al.*, 1996; Freemantle and Bloor, 1996). None of these studies were conducted systematically and many of them focused primarily on policy review, not on actual impact.

Some reviews were conducted systematically, but the information becomes out of date. One study reviewed pricing mechanisms, focusing on regulation rather than impact (Mrazek, 2002). Gosden and Torgerson (1997) reviewed evidence relating to the effects of UK fundholding on prescribing and referral costs. One study reviewed drug policies in developing countries between 1966 and 1999, and found no studies conducted by robust research designs such as a randomised controlled trial (RCT), a controlled before and after (CBA) or an interrupted time series (ITS) design (Ratanawijitrasin *et al.*, 2001).

There are some existing recent systematic reviews. Goldman *et al.* (2007) carried out a systematic review of primary studies of cost-sharing programmes, defined comprehensively, including copayments, tiering, coinsurance, benefit caps, reference-pricing, prior-authorisation and formulary restrictions without any limitations in study designs. Puig-Junoy and Moreno-Torres (2007) conducted a systematic review on prior-authorisation. Three reviews were carried out by the Cochrane collaboration; two focused respectively on 'pricing policies' (Aaserud *et al.*, 2006a) and 'financial incentives' (Sturm *et al.*, 2007) prior to the current review and one addressed 'cap and copayments' (Austvoll-Dahlgren *et al.*, 2008) concurrently with this review. Most reviews focus on a limited set of interventions and do not provide a comprehensive overview about the effect of the wide range of policy interventions used internationally.

The present review has three aims:

1) To compile the evidence of the impact of pharmaceutical policies applied internationally, which will be useful for researchers and policy-makers in general;
2) To analyse the evidence available for South Korea; and
3) To identify and analyse the methodological weaknesses in studies that employed a robust study designs, which will help improve the quality of evidence in future studies.

This chapter details the search strategy, inclusion criteria, quality assessment, data extraction, and data analysis. The chapter closes with an overview of identified studies. The next three chapters (Chapters 4,5 and 6) will present the results of each review on outcome variables of interest; that is separately for patients, providers and industry. Methodological issues and overall findings from the three reviews will be addressed in Chapter 7.

3.2 Methods

3.2.1 Search strategy for identification of studies

Published studies were identified with an electronic search using two major databases (MEDLINE and EMBASE from 1980 to 2007). This search was conducted in the middle of April 2008. Search strategies were developed from strategies used in the Cochrane reviews exploring pharmaceutical policies (Aaserud *et al.*, 2006a; Aaserud *et al.*, 2006b; Sturm *et al.*, 2007).

For identifying pharmaceutical policies influencing patients, the strategy included such terms as 'cost-sharing', 'out-of-pocket', 'copay (or copayment)', 'coinsurance', 'deductible', 'charge', 'fee', 'direct-to-consumer', 'over-the-counter', 'benefit limit', 'caps', 'tiered benefit', 'drug information service', and 'patient education' alongside several terms indicating pharmaceuticals (Annex 2).

In order to identify pharmaceutical policies influencing providers, the strategy included the terms 'reimbursement restriction (or policy)', 'formulary', 'positive (or negative) list', 'benefit plan', 'step-therapy', 'prior-authorisation', 'drug (or global/local) budget', 'fundholding', 'capitation', 'salary', 'incentive', 'quality framework or payment', 'drug information', 'drug feedback (or monitoring)', 'academic detailing', 'outreach visit', 'guideline', 'protocol', 'generic policy (or substitution/prescribing)', and 'quality payment' combined with terms indicating pharmaceuticals (Annex 3).

To identify pharmaceutical policies regulating industry, the strategy included terms 'market authorisation', 'licensing', 'price (or pricing)', 'patent regulation', 'profit control (or return)', 'advertising', 'generic market', 'labelling', and 'competition' with pharmaceutical policy terms (Annex 4).

No language restriction was applied. Additionally, the reference lists of all potentially relevant reviews were scrutinised to ensure that all potentially relevant studies were identified (Gray, 2001c; McDonald *et al.*, 1996). In particular, this review expanded the information from the previous Cochrane studies by including studies in the lists for awaiting assessment in the Cochrane studies if they were satisfying the inclusion criteria in relevant policy interventions.

3.2.2 Study selection criteria

3.2.2.1 Types of intervention

A study was included in the reviews if the article explored the effect of at least one pharmaceutical policy. Pharmaceutical policies defined and implemented by government, non-government organisations or private insurers that were intended to directly affect the use or cost of drugs were included.

3.2.2.2 Types of studies

The reviews included studies with true experiments and strong quasi-experiments. A study design was clarified according to the Cochrane Effectiveness Practice and Organisation of Care collaborative review group (EPOC) definitions as follows (Cochrane Effective Practice and Organisation of Care Review Group, 2002):

- Randomised controlled trial (RCT): a study in which the participants (or other units) were assigned prospectively to one or two (or more) alternative forms of health care using a process of random allocation
- Interrupted time-series design (ITS): a study in which there is a clearly defined period of intervention and at least three data points before and three data points after the intervention
- Controlled Before and After study (CBA): Involvement of intervention and control groups other than by random process, and inclusion of baseline period of assessment of main outcomes

3.2.2.3 Types of participants

Participants were healthcare consumers and providers within a large jurisdiction or system of care. Jurisdictions could be organisational, regional, national or international.

3.2.2.4 Types of outcome measures

A study was included in the reviews if the article investigated at least one of the following outcome categories:

- Pharmaceutical expenditure
- Pharmaceutical prices
- Pharmaceutical utilisation
- Other resource utilisation/ relevant costs relating to pharmaceuticals
- Health outcomes relating to pharmaceuticals
- Patients' or providers' behaviour changes concerning pharmaceuticals

3.2.2.5 Exclusion criteria

Studies were excluded from the reviews if they met any of the following criteria:

- Interventions conducted within a single hospital or clinical practice were excluded to reduce potential confounding by the characteristics of a study institution. It was thought that the way in which the intervention affected participants within a single institution would differ considerably from that in multi-centre study.
- Pharmaceutical care services or disease-managed care were excluded. Pharmaceutical care services were excluded because they comprised of another wide-ranging field of research, focusing on the new roles of clinical pharmacists and collaboration among stakeholders rather than just pharmaceutical regulations (Guillen and Cabiedes, 2003). Disease-managed care studies were excluded because they were more likely to focus on the improvement of patient compliance to a course of medical prescription including diet, exercise, life style as well as medications to 'manage' their illness (e.g. Eccles *et al.*, 2002). Hence, these would be out of the scope of this review.
- Studies with less than a 6-month follow-up were excluded in order to avoid biases from any transition phase and to focus on longer term effects of

interventions.

- ITS studies with less than 12 months study period (overall) were excluded to avoid bias from secular trends.
- CBA studies were excluded if data were not collected contemporaneously or the author(s) failed to demonstrate rationales for the choice of control site or activity.
- Studies were excluded if they did not provide relevant and interpretable data because it would be hard to appraise the quality of the study.

3.2.3 Study quality assessment

The quality assessment criteria for each study design were developed based on the standard criteria recommended by the EPOC and Centre for Reviews and Dissemination to assess the methodological limitations of studies (Centre for Reviews and Dissemination, 2001; Higgins and Green, 2008). On each criterion, the reviewer scored **CLEAR** when a paper satisfied the criterion, **UNCLEAR** when a paper did not provide enough information to judge, **NONE** when a paper provided no information on the criterion, or when it was clear that the study did not meet the criterion. All figures and tables were closely investigated to confirm whether their practices were in line with their statements. Details of quality criteria are presented in Annex 5.

The quality criteria for an RCT study were:

1) concealment of allocation;
2) blinded assessment of primary outcome(s);
3) baseline measurement;
4) reliable primary outcome measure(s);
5) employment of an intention-to-treat analysis;
6) attrition rate; and
7) reasons for drop-out of participants explained.

The quality criteria for an ITS study were;

1) protection against secular changes;
2) data were analysed properly;
3) reasons for the number of points pre and post intervention given;
4) shape of the intervention effect was specified;

5) use the same methods of data collection before and after the intervention;
6) blinded assessment of primary outcome(s);
7) completeness of data set; and
8) reliable primary outcome measure(s).

A conservative standard was set on the criterion 'protection against secular changes'. Authors suggest considerably different ideas on the number of data points able to control secular trends from more than 100 (Shadish *et al.*, 2002c) to 12 before and after the intervention (Wagner *et al.*, 2002) (see Chapter 8 for more details). In the present review, it was scored '**HIGH**' if the number of data collection points were 1) more than 50 before and after the intervention in studies using ARIMA models, or 2) more than 12 before and after the intervention (i.e. included four seasons in each period) in studies using segmented regression; scored '**MEDIUM**' if the number of data collection points were 1) between 49 and 20 before and after the intervention in studies using ARIMA models, or 2) between 11 and 4 before and after in studies using segmented regression and the study period included four seasons in each period (for example, 4 quarterly data points before and after); and scored '**LOW**' if studies did not meet the above criteria.

The quality criteria for a CBA study were:

1) baseline measurement;
2) characteristics for control group(s);
3) reliable primary outcome measure(s);
4) attrition rate;
5) reasons for drop-out of participants explained;
6) blinded assessment; and
7) protection against contamination.

3.2.4 Data extraction, analysis and presentation

The following additional information was extracted from included studies using a data extraction form designed for the present reviews:

- characteristics of the participants;
- characteristics of the intervention(s);
- study setting;

- main outcome(s);
- study duration;
- the results for the main outcome measures;
- the sponsors of the study.

Crucial findings such as study design, intervention, population in the study and the control groups, study drugs, primary outcomes, conclusions, relative effect sizes, and settings were tabulated in summary tables by intervention. If there was more than one time point measuring outcomes, results from the longest point were taken in this review. But meaningful mid point outcomes were also discussed in the context. In cases where a study employed two or more study designs, the primary design was generally included. For example, Knowlton and Knapp (1994) compared intervention pharmacists with a control assigned by randomisation (RCT) as well as with another control group from a different geographic region (CBA). In this case, outcomes from the RCT were firstly taken into account; those from the CBA were also considered in context if necessary.

Regarding educational interventions targeting providers, many interventions were observed with just a slightly different form one to another. It was difficult to differentiate clearly between them because many of them employed a multifaceted strategy rather than a single intervention. They were often overlapping each other. In this review, educational interventions were categorised according to: firstly, the materials distributed such as guidelines, protocols, prescribing feedbacks or drug utilisation reviews; and, secondly, the methods of dissemination, such as passive contacts, group detailing, individual contacts, or computerised devises.

It is usual in policy evaluation studies, that baseline characteristics of the intervention group and those of the comparison group might differ (Cochrane Effective Practice and Organisation of Care Review Group, 2001). To adjust for the baseline imbalance, the effect size was presented as a relative percent change. In cases where both empirical numbers in the pre- and the post-intervention period were available, the proportion of relative change was computed as presented in Table 3-1.

Table 3-1: Calculation of relative changes

	baseline	post	differences	% changes
study group	a	b	b-a	e = {(b-a)/a}×100
control group	c	d	d-c	f = {(d-c)/c}×100
relative changes				e-f

(Cochrane Effective Practice and Organisation of Care Review Group, 2001)

In other cases, if primary authors provided a relative effect size and they did not present a complete set of pre and post scores, change scores provided by authors were extracted; if such scores were not reported, only primary authors' conclusions were presented. For studies with no comparison group, primary authors' conclusions were also quoted. Level and slope changes in studies using an ITS design were illustrated in cases of statistical significance. Absolute changes in real terms (e.g., $10 per capita expenditure differences between groups) were not considered highly significant because there seemed little value in comparing such effect sizes across countries with different currencies and economic conditions, or across time periods with almost a three-decade gap.

3.3 Overview of studies and interventions included

Overall, 176 studies were included across the three reviews. Six studies were reviewed multiple times because they explored different interventions within a single study. Thus, the number of studies included is 184 by intervention. Table 3-2 summarises the intervention studied for each review.

Table 3-2: Intervention and studies included

Intervention	Number of studies
policies influencing patients	*46*
Cost-sharing	30
Tiered formularies	9
Prescription caps	5
Educational approach	1
Over-the-counter switch	1
policies influencing providers	*119*
Educational approaches	63
Reimbursement restrictions	33
Incentives	17
Distribution of samples	3
Mandatory generic substitution	1
Repeat prescribing	1
Separation policy	1
policies regulating industry	*19*
Price control- reference-pricing	13
Price control- others	3
Market authorisation	1
Patent regulation	1
Profit control	1
Total	***184***

3.4 Summary

This chapter summarises the methods employed for the systematic review of pharmaceutical policies. In principle, the methods, criteria, definitions used by the Cochrane EPOC were adopted. Studies published from 1980 to 2007 were identified with an electronic search using two major databases in April 2008, each study was assessed against pre-defined inclusion and exclusion criteria, and 176 studies were finally included. Results from the reviews are presented in the following three chapters grouped into three sectors: pharmaceutical influencing patients, providers, and industry. Lessons learned from the reviews and implications will be discussed in Chapter 7.

CHAPTER 4: THE EFFECTS OF PHARMACEUTICAL REGULATIONS INFLUENCING PATIENTS

4.1 Introduction

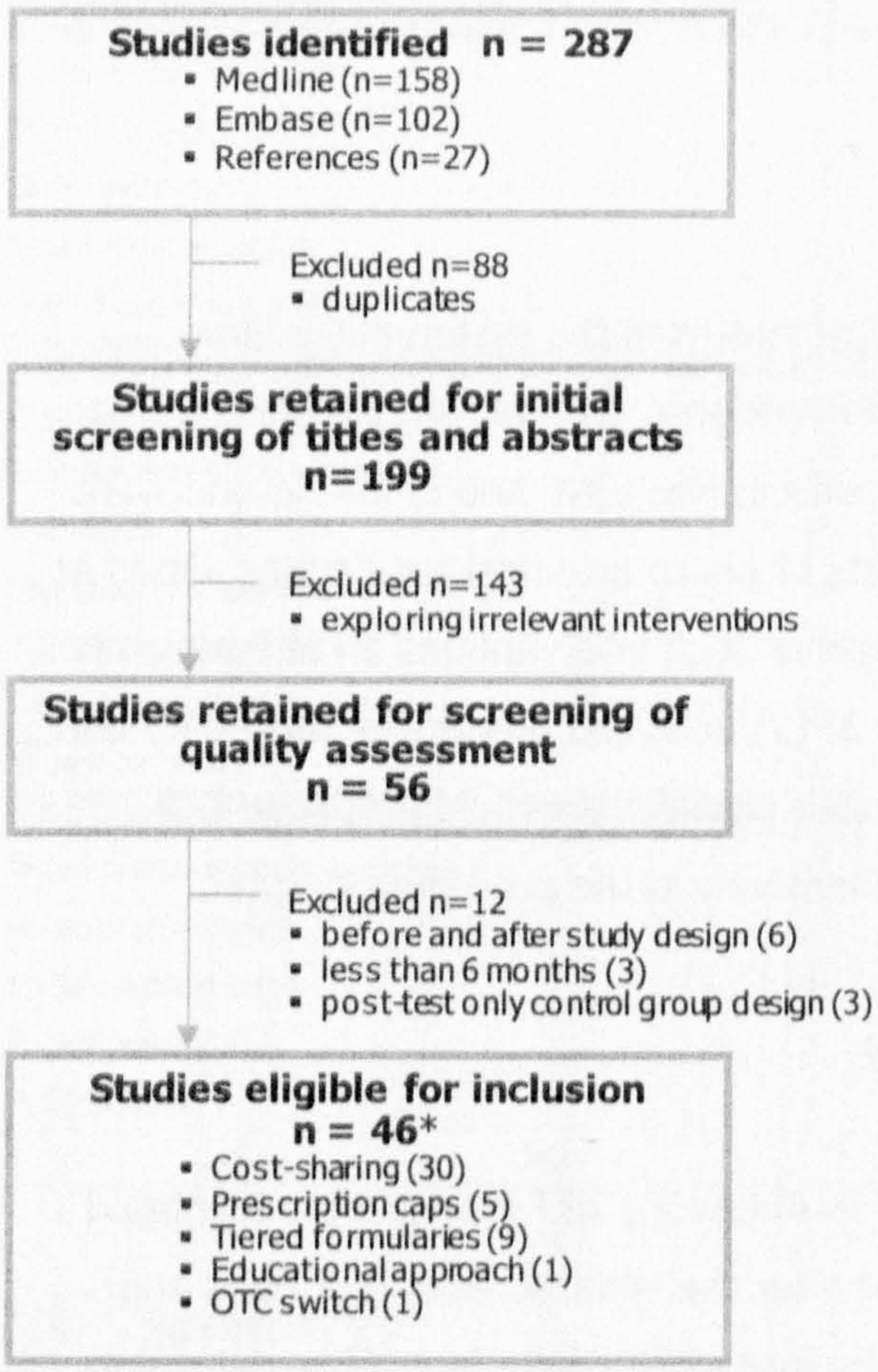
The objective of this chapter is to present findings from the systematic review examining pharmaceutical policies influencing patients. In brief, studies for the first review were identified from two major databases, MEDLINE and EMBASE, and were included if the article (1) explored the effects of pharmaceutical regulations aimed at influencing patients; (2) examined the effects of such interventions on at least one of the relevant outcomes depicted in Chapter 3; (3) analysed primary or secondary data; and (4) performed this with one of three most robust designs, RCT, ITS, or CBA. Details on method were presented comprehensively in the preceding chapter.

4.2 Overview of included studies

From the search (the strategy is illustrated in Annex 2), 287 studies were identified (Figure 4-1). Fifty-six studies were retained after the initial screening of titles and abstracts. From these 56 studies, 44 met the inclusion criteria (see Table 4-1). Two studies were included twice because they explored two different interventions – cost-sharing and prescription capping (Starmans *et al.*, 1994), or over-the-counter (OTC) switch (Gurwitz *et al.*, 1995).

The large majority of studies explored the effects of 3 interventions: cost-sharing (n=30), tiered formularies (n=9), prescription capping (n=5). Single studies explored the effects of an educational intervention, and OTC switch programme. No studies addressing direct-to-consumer (DTC) advertising satisfied the inclusion criteria. Reasons for exclusion are reported in Figure 4-1 and Annex 6.

Figure 4-1: Flow diagram of studies (patients)



* Two studies were included twice because they explored multi-interventions. (Gurwitz *et al.*, 1995; Starmans *et al.*, 1994)

Table 4-1: Studies included

Intervention		Studies
Cost-sharing	30	Almarsdottir *et al.* 2000, Andersson *et al.* 2006, Blais *et al.* 2001, Blais *et al.* 2003, Foxman *et al.* 1987, Gibson *et al.* 2006, Gurwitz *et al.* 1995, Harris *et al.* 1990, Holloway *et al.* 2001, Hughes and McGuire 1995, Johnson *et al.* 1997, Kephart *et al.* 2007, Klepser *et al.* 2007, Kozyrskyj *et al.* 2001, Lavers 1989, Lee *et al.* 2006, Leibowitz *et al.* 1985, Liu and Romeis 2004, Martikainen *et al.* 2007, McManus *et al.* 1996, Nelson *et al.* 1984, O'Brien 1989, Ong *et al.* 2003, Reeder and Nelson 1985, Roblin *et al.* 2005, Ryan and Birch 1991, Starmans *et al.* 1994, Sun and Lee 2007, Tamblyn *et al.* 2001, Winkelmann 2004
Tiered formularies	9	Fairman *et al.* 2003, Gibson *et al.* 2005, Huskamp *et al.* 2003a, Huskamp *et al.* 2005, Landon *et al.* 2007, Landsman *et al.* 2005, Motheral and Fairman 2001, Motheral and Henderson 1999b, Nair *et al.* 2003
Prescription caps	5	Martin and McMillan 1996, Soumerai *et al.* 1987, Soumerai *et al.* 1994, Soumerai *et al.* 1991, Starmans *et al.* 1994)
Educational approach	1	Valles *et al.* 2003
OTC switch	1	Gurwitz *et al.* 1995

4.3 Policies influencing patient demand

The interventions which appeared most frequently were a cost-sharing schemes across settings. These required patients to pay a fixed or a proportional charge of the cost of a prescribed drug. Cost-sharing structures have been changed over time from a simple flat rate copayment to a more complicated form, such as coinsurance or tiered copayments.

In some countries, the share of private pharmaceutical expenditures have increased over time (Jacobzone, 2000). As the proportion shared by patients has risen, concerns about inequity have increased. As a result, cost-sharing structures have become combined with safety net exemptions. Examples seen in the reviewed studies included an annual maximum ceiling that appeared universally across countries from the West to the East, pharmaceutical allowances for a disadvantaged group in Australia, or an income-based formulary in Canada to avoid excessive suppression in the demand for drugs. These may lessen net policy effects.

Many commercially managed health plans in the US employed complex interventions such as tiered formularies to reduce the use of expensive drugs. Tiered formularies in the retrieved studies have two kinds of structure according to the method of categorising medications into each tier; they have a generic/brand-named drugs structure, in which a lower copay tier is allocated to generics and an upper one for brand-named drugs (2-tier), more recently, for formulary and non-formulary brand-named drugs (3-tier).

Prescription capping places limits on reimbursable amounts per patient within certain time periods. Interventions included were 'a three-drug monthly payment limit' or 'a five-prescription limit' in American Medicaid programmes, or 'prescription regulation' which restricted prescribing for each prescription item to dosages for a 30-day maximum in the Netherlands. OTC switch is also used in attempts to reduce patient demand by shifting products from lists of reimbursable drugs to over-the-counter purchasing. In one Spanish study, an educational approach was employed to deliver information on use of generics. Basic characteristics of the included studies and outcomes from the review are discussed in the following sections according to intervention.

4.4 Cost-sharing schemes

4.4.1 Characteristics of included studies

The basic characteristics of included studies are presented in Annex 7. Evidence for cost-sharing programmes came from various settings, although 16 out of 30 (53%) studies were from North America. All but two RAND studies (Foxman *et al.*, 1987; Leibowitz *et al.*, 1985) employed a quasi-experimental design, CBA (n=8) or ITS (n=20). Among the eight CBA studies, six selected a comparison population in a comparable plan or place, or a comparable activity. The other two studies from Germany and Taiwan used the exempted population as a comparison group, and baseline differences between groups seemed to be more problematic (Liu and Romeis, 2004; Winkelmann, 2004). Most studies followed up in a short or intermediate time period; only four British studies tackled a long-term effect of more than 60 months. Most studies used aggregated claims data held at an organisational level, but six studies employed market sales data, constructed by commercial companies such as IMS Health, data constructed for the RAND experiments, carbon copy prescriptions, or a national annual survey.

4.4.2 Impact on drug utilisation

Twenty-six studies examined the effects of cost-sharing on the use of pharmaceuticals. Cost-sharing programmes have been shown to lower drug utilisation significantly in most settings (Table 4-2). Across studies, it was observed that copayments might lower not only discretionary drugs, but also essential drugs (including antihypertensives, asthma drugs, oral hypoglycemics, statins) to a considerable degree when priced moderately. Conversely, small copayments might fail to influence patient demand. However, we must be cautious in our interpretation as the studies were of mixed quality. There appeared to be little relationship between the study findings and quality.

Evidence is very limited regarding the association of cost-sharing with increases in the utilisation of generics. Among three studies addressing this issue, only one study suggested that beneficiaries exceeding the reimbursable limit tended to consume generics about 20% more than those below this limit (Sun and Lee, 2007). However, this was not supported by the other two studies, which used a more balanced control

population. (Klepser *et al.*, 2007; Leibowitz *et al.*, 1985).

Table 4-2: Impact of cost-sharing on drug utilisation

Study	Population	on overall utilisation	on specific drugs		Setting
			Essential	Less-essential	
Introduction of cost-sharing programme in Western Europe					
Starmans *et al.* 1994	General		no change~ higher (+6~ +14%) or lower (-4~ -9%)		Netherlands
Increased cost-sharing in Western Europe					
Andersson *et al.* 2006	General	no change (smaller policy changes) mixed[1] (larger policy changes)			Sweden
Ong *et al.* 2003			no change~ higher		
Hughes and McGuire 1995		lower			UK
Lavers 1989		lower			
O'Brien 1989		lower			
Ryan and Birch 1991		lower			
Decreased cost-sharing in Western Europe					
Martikainen *et al.* 2007	General		higher (+21~ +109%)		Finland
Introduction of cost-sharing programme in North America					
Foxman *et al.* 1987	General			lower (-46%)	USA
Harris *et al.* 1990		lower (-8~ -10%)	no change~ lower (-13%)	lower (-11~ -16%)	
Leibowitz *et al.* 1985		lower (-22~ -39%)			
Blais *et al.* 2003	Vulnerable		no change~ lower (-37%)		Canada
Kephart *et al.* 2007			no change~ lower (smaller)	no change~ lower (-5~ -15%)	
Nelson *et al.* 1984		lower (-3~ -11%)			USA
Increased cost-sharing in North America					
Gibson *et al.* 2006	General		lower		USA
Gurwitz *et al.* 1995				no change	
Klepser *et al.* 2007		no change	lower (-4~ -6%)		
Roblin *et al.* 2005			no change~ lower (-19%)		
Blais *et al.* 2001	Vulnerable		no change	no change	Canada
Kozyrskyj *et al.* 2001			lower (-15%)		
Tamblyn *et al.* 2001		lower (-9~ -16%)	lower (-9~ -14%)	lower (-15~ -22%)	
Johnson *et al.* 1997		no change~ lower (-6~ -8%)			USA
Sun and Lee 2007		lower (-18%)			
Introduction of cost-sharing programme in other settings					
Liu and Romeis 2004	Vulnerable	lower (-9%)	lower (-26%)	lower (-38%)	Taiwan
McManus *et al.* 1996 (1)			lower (smaller)	lower	Australia
Increased cost-sharing in other settings					
Holloway *et al.* 2001	General	no change~ lower (-21~ -31%)			Nepal
McManus *et al.* 1996 (2)			lower (-18%)	lower (-25%)	Australia

1) no change~ lower (levels), lower or higher (slopes)

Based on evidence from included studies, this review found a number of factors influencing the size of the impact of cost-sharing on drug utilisation:

First, the size of effect varied across *drugs* as displayed in Annex 8. In spite of this, one very general figure from the reviewed studies was that use of discretionary drugs tended to decrease at a greater rate than essential drugs. In Sweden, the cost-share scheme did not change the market trend, such as the explosive use of psychiatric drugs (Ong *et al.*, 2003).

Second, *the level of cost-share or magnitude of change* resulted in various effects. The greater the cost-share or changes that occurred, the greater the effects. In the US, Harris *et al.* (1990) demonstrated that copayments smaller than a certain threshold ($3) could have a selective influence on non-essential drug utilisation. Roblin *et al.* (2005) found that a large increase in cost-sharing (>$10) reduced the utilisation of oral hypoglycaemic agents by 18.5%, which was at least twice the other two levels of cost-sharing – an increase of small ($1-6) and moderate ($7-10) amounts showing a non-significant decrease. In Sweden, smaller changes did not affect the upward trend of drug utilisation in the switch from copayment to coinsurance with a stepwise scale (Andersson *et al.*, 2006).

Third, the *patient's specific situation* could generate different results. Evidence from included studies supported the fact that patients who were newly diagnosed were more likely to give up their medication (Gibson *et al.*, 2006). The presence of annual payment limits could diminish the reduction effects of cost-sharing programmes because it influenced only those patients who were unlikely to reach the limit (Kephart *et al.*, 2007). But it is hard to discern from this review whether the vulnerable population is more likely to be affected by cost-sharing (Table 4-2).

Fourth, the *measurement units* used by the researcher could generate different results. This was often seen in utilisation outcomes because the level of drug utilisation could be presented in various ways, such as the number of prescriptions issued, the number of days prescribed per person(s) or prescription(s), and the number of drug doses prescribed per person(s) or prescription(s). One Dutch study suggested that prescribers reduced the number of prescriptions but increased the prescription size

when copayment per prescription was introduced; as a result, no significant change was actually made (a limitation on size brought reverse results in the same study, illustrated later in the section on prescription capping) (Starmans *et al.*, 1994). There is an implication that a single facet of drug utilisation may mislead the researcher into overestimating policy effects.

4.4.3 Impact on drug expenditure

Of the thirty studies, twelve explored the impact of cost-sharing on drug expenditure. As shown in Table 4-3, most studies examined drug spending from a payer's perspective and produced mixed outcomes.

Table 4-3: Impact of cost-sharing on drug expenditure

Study	Population	Drug expenditure			Setting
		Overall	Payer	Out-of-pocket	
Increased cost-sharing in Western Europe					
Almarsdottir *et al*. 2000	General		no change		Iceland
Andersson *et al*. 2006			no change (copay increase) lower (stepwise coinsurance)		Sweden
Introduction of cost-sharing programme in North America					
Harris *et al*. 1990	General		lower (-5~ -7%)		USA
Leibowitz *et al*. 1985			lower (-31 ~ -56%)		
Nelson *et al*. 1984	Vulnerable		lower (-12~ -14% until 2nd year, -1% in 3rd year)		
Reeder and Nelson 1985			no change~ lower		
Increased cost-sharing in North America					
Klepser *et al*. 2007	General	lower (-3%)	no change	no changes	USA
Johnson *et al*. 1997	Vulnerable		lower (-14~ -16%)		
Sun and Lee 2007			lower (-30%)	higher (+94%)	
Introduction of cost-sharing programme in other settings					
Lee *et al*. 2006	General		no change		Taiwan
Liu and Romeis 2004	Vulnerable		lower (-25%)		
Increased cost-sharing in other settings					
Holloway *et al*. 2001	General	lower (-25 ~ -46%)			Nepal

In Western Europe, evidence is very weak that copayments may lower drug expenditure, but it was inconclusive because only two studies from Nordic countries, with mixed methodological quality, were included. In the US, generally studies with higher quality rating indicated that cost-sharing schemes reduced payers' expenditure. In two studies with low quality from Taiwan, a greater reduction in drug expenditure was observed in a vulnerable population, compared to the general population. Among the reviewed studies, the greatest reduction was seen in a Nepal study with moderate quality. Evidence concerning private expenses was extremely limited. Only two of the studies investigated out-of-pocket expenses. Klepser *et al.* (2007) found no significant change in out-of-pocket among the general population. Conversely, elderly patients who were spending more than the permissible limit, paid 94% more out-of-pocket than those spending less than the limit (Sun and Lee, 2007).

In a similar way to utilisation, the impact of cost-sharing on budgets could differ *depending on conditions* such as the amount of copayment change and drug classifications. Reeder and Nelson (1985) showed, unexpectedly, that the imposition of copayment yielded a significant reduction in expenditure on essential medications such as cardiovascular, diuretic, cholinergic, and psychotherapeutic drugs, rather than those from discretionary medications in a Medicaid population.

4.4.4 Summary: Evidence about cost-sharing scheme

Cost-sharing schemes have been shown to lower drug expenditure by reducing utilisation across settings. Despite that the included studies were of very mixed quality, apparent differences were not found between the high and low quality studies in terms of the findings. The dilemma is that small changes may fail to affect the existing trend; however, moderate changes could see a substantial decrease in demand for essential drugs. It has been thought that savings were ascribed partly to budget shifting, but this was inconclusive because of the paucity of evidence in the present review. Generic substitution effects were not supported by studies with higher quality and it seems that evidence about this issue is still lacking. Factors influencing the effect size may be study drugs, patient charges, patient conditions, and measurement units.

4.5 Tiered formularies

4.5.1 Characteristics of included studies

Nine studies examined the association between tiered formularies and study outcome variables. Overall these studies were of moderate quality. The basic characteristics of included studies are presented in Annex 9. All studies were conducted in the US and all but one used a CBA design. Motheral and Fairman (2001) undertook an ITS analysis with a control group. Seven studies used aggregated claims data held by private health plans and two employed market sales data constructed by commercial companies such as IMS Health. All studies followed up the impact of intervention in a short or intermediate time period.

All authors compared enrollees who experienced changes in a tiered structure with those who stayed with the same benefit structure during the pre-post change period. Changes were increased or decreased copayments without alteration in the benefit structure, or a modification of the benefit structure from a 1- or 2-tier to a 2- or 3-tier. Huskamp *et al.* (2005) performed research with a child population. Nair *et al.* (2003) confined their investigation to participants who suffered from at least one of five pre-determined chronic diseases, while others explored the impact of interventions on general plan members.

4.5.2 Impact on drug utilisation

Table 4-4 illustrates the impact of policy changes on drug use grouped by the benefit structure and suggests that the modification of a tiered formulary could curb an increase in drug utilisation. A greater decline was achieved in demand for non-formulary brand-named drugs as a greater increase was made in copayments for those drugs; few changes were observed in the demand for generics. Only Gibson *et al.* (2005) reports an unexpectedly large decrease in the use of generics. The change looks sizable in a relative term, but the absolute change was actually negligible both in the study and control groups because the denominator (a previous generic share in each group) was so small.

The magnitude of change varies depending upon the change in structure. Greater

changes in benefit design generally yielded a greater decrease in use, (Huskamp *et al.*, 2003a; Landon *et al.*, 2007). The effects decrease over time (Fairman *et al.*, 2003; Gibson *et al.*, 2005). Across drug classes, the demand for symptom-relief medications might be more susceptible to copayment increase. Two studies found that essential drugs (including medication for heart conditions and depression) were also more likely to stop after a moderate benefit structure change (Huskamp *et al.*, 2003a; Landsman *et al.*, 2005). However, this was not observed in work by Motheral and colleagues that showed slightly higher quality, who found no adverse effects on the use of medication for chronic illnesses such as antihypertensives and antihyperlipidemics (Fairman *et al.*, 2003; Motheral and Fairman, 2001; Motheral and Henderson, 1999b).

Table 4-4: Impact of tiered formularies on drug utilisation

Study	Overall	Generics	Brand-named drugs	
			formulary	nonformulary
from 1-tier to 2-tier				
Gibson *et al.* 2005	lower (-22%)	lower (-21%)	single source; lower (-24%) multi sources; lower (-67%)	
from 1-tier to 3-tier				
Huskamp *et al.* 2003a (1)	lower (-24~ -34%)			
Huskamp *et al.* 2005	lower (-17%)			
Landon *et al.* 2007 (1)		higher (+1.9~+4% in 3/5) no change (in 2/5)	lower (-1% in 1/5) no change (in 4/5)	lower (-0.9~-4.6% in 3/5) no change (in 2/5)
from 2-tier to 2-tier copayment increase				
Motheral and Henderson 1999b	lower (-27%)	no change	lower (-27%)	
from 2-tier to 3-tier				
Fairman *et al.* 2003	no change	no change	no change	lower (-31%)
Huskamp *et al.* 2003a (2)	no change			
Landon *et al.* 2007 (2)		higher (+1~+3.6% in 2/4) no change (in 2/4)	lower (-2.5% in 1/4) higher (+2.8% in 1/4) no change (2/4)	lower (-1~-3.6%)
Landsman *et al.* 2005	lower			
Motheral and Fairman 2001	lower (-6%)	no change	lower (-4%)	lower (-24%)
Nair *et al.* 2003	unclear	unclear	unclear	unclear
from 3-tier to 3-tier copayment increase				
Landon *et al.* 2007 (3)		no change	no change	no change
from 3-tier to 3-tier copayment decrease				
Landon *et al.* 2007 (4)		no change	no change	no change

4.5.3 Impact on drug expenditure

Eight out of nine studies investigated the impact of tiered formularies on drug expenditure. As shown in Table 4-5, in the majority of cases, benefit changes function on payers' (decrease) and patients' expenses (increase). Whereas the size of the reduction was moderate in overall expenditure (about 3~22%) and slightly larger in payers' expenditure (about 2~58%), the increase was much greater in patients' expenses (around 5~205%), compared to the absence of change. Two studies suggested that less intensive changes failed to curb the upsurge in expenditure (Huskamp *et al.*, 2003a; Landon *et al.*, 2007). The effects diminished over time (Fairman *et al.*, 2003; Motheral and Fairman, 2001)

Table 4-5: Impact of tiered formularies on drug expenditure

Study	Drug expenditure		
	Overall	Payer	Out-of-pocket
from 1-tier to 2-tier			
Gibson *et al.* 2005		lower (-28%)	
from 1-tier to 3-tier			
Huskamp *et al.* 2003a (1)	no change~ lower (-3%)	lower (-14~-58%)	higher (+118~+148%)
Huskamp *et al.* 2005	no change	lower (-43%)	higher (+46%)
Landon *et al.* 2007 (1)	lower (-7~-13% in 4/5) no change (in 1/5)	lower (-15~-43%)	higher (+13~+205%)
from 2-tier to 2-tier copayment increase			
Motheral and Henderson 1999b	lower (-22%)	lower (-33%)	higher (+31%)
from 2-tier to 3-tier			
Fairman *et al.* 2003	no changes	lower (-27%)	higher (+47%)
Huskamp *et al.* 2003a (2)	no change ~ higher (+2~+3%)	no change ~ lower (-2~-6%)	no change ~ higher (+5~+8%)
Landon *et al.* 2007 (2)	lower (-4~-7% in 2/5) no change (in 2/5)	lower (-24~-27% in 3/5) no change (in 1/5)	higher (+21~+149%)
Motheral and Fairman 2001	lower (-7%)	lower (-33%)	higher (+34%)
Nair *et al.* 2003	unclear	unclear	unclear
from 3-tier to 3-tier copayment increase			
Landon *et al.* 2007 (3)	lower (-9~-10%)	lower (-22~-28%)	higher (+27~+43%)
from 3-tier to 3-tier copayment decrease			
Landon *et al.* 2007 (4)	higher (+7%)	higher (+29%)	lower (-29%)

4.5.4 Summary: Evidence about tiered formularies

Tiered formularies have been shown to lower public drug expenditure both by reducing the utilisation of non-formulary brand-named drugs and by budget shifting in the US. There was little evidence for generic substitution effects. Although a greater drop was seen in symptom-relief medications, the benefit structure changes accompanying the increase in copayments might see patients' access to essential drug constraint moderately. Overall, the quality of studies was generally moderate with little variation in findings across studies.

4.6 Prescription caps

4.6.1 Characteristics of included studies

Five studies examined the effects of prescription capping. The basic characteristics of included studies are displayed in Annex 10. All but one study examined policy effects on a vulnerable population in the US Medicaid arrangements, two of which involved the most vulnerable patients. All included studies employed an ITS design to analyse claims data maintained at state organisational level (Medicaid or Sickness funds). Starmans *et al.* (1994) collected data biannually and investigated the effects of an intervention more than 2 years (30 months) after the intervention, whilst others used monthly data and followed up policy effects for no longer than 12 months.

4.6.2 Impact on drug utilisation

Four studies involving a vulnerable population showed that prescription capping lowered drug utilisation significantly by 7~49% (Table 4-6). The magnitude of the reduction was greater in Soumeral and colleagues' studies, which were rated as high quality, and different across therapeutic classes that was less in essential drugs (1.8~28%) than in symptom-relief drugs (11~38%).

Conversely, a Dutch study found little change in the general population after capping prescribed drugs. A 24% increase in volume was offset by a 17% reduction in size, while the opposite was the case when the cap was replaced by a cost-sharing programme as mentioned in the previous section (Starmans *et al.*, 1994).

Table 4-6: Impact of prescription caps on drug utilisation and expenditure

Study	Population	Drug utilisation	Drug expenditure (payer)	Setting
Martin and McMillan 1996	Poor	lower (-7%)		USA
Soumerai *et al.* 1987	Poor	lower (-30%)	lower (-19%)	
Soumerai *et al.* 1994	Poor elderly	lower (-15~-49%)	lower (-23%)	
Soumerai *et al.* 1991	Poor elderly	lower (-35%)		
Starmans *et al.* 1994	General	various		Netherlands

4.6.3 Impact on drug expenditure

Two studies explored the impact of prescription capping on payers' drug expenditure. They found a 19~23% decline in payers' monthly spending after the cap (Table 4-6). Soumerai *et al.* (1994) suggested that savings through cutting expenditure on drugs in patients with schizophrenia might be overwhelmed by expenses incurred from the increased use of mental health services (see also Table 4-7). No studies made a formal investigation of out-of-pocket expenditure, but there was some evidence of a budget shift (Martin and McMillan, 1996; Soumerai *et al.*, 1987).

4.6.4 Summary: Evidence about prescription caps

Prescription capping has been shown to lower drug expenditure by reducing drug utilisation and possibly by budget shifting in the US good quality studies. Similar to other interventions that restrict patient demand, although a greater drop was seen in symptom-relief medication, prescription capping also considerably lowered the use of essential drugs in vulnerable populations. In the Netherlands, the effects of capping on prescription size were lessened by increasing prescription volume.

4.7 Educational approach

Valles *et al.* (2003) examined the association between an educational approach targeting patients and 1) generic drugs utilisation, and 2) drug expenditure using a clustered RCT design over a 12-month period which had been rated as being of moderate quality (Annex 11).

Patients were about 2.5 times more likely to be prescribed generics, compared to those in the control group. Generic substitution resulted in an 11% reduction of the drug expenses (those with available generic counterparts) in the eight study centres in comparison with the control centres. However, authors argued that generic substitution was very limited in Spain due to the low availability, thus reduction in expenditure was also limited.

4.8 OTC switch

Gurwitz *et al.* (1995) examined the association between OTC switch of vaginal antifungal products and drug utilisation using an ITS design over two 12-month periods which was rated as good quality. Participants were female, aged 11 and older at one health maintenance organisation in central Massachusetts, US (Annex 11).

The study found that prescription rates for drugs that were switched to OTC decreased to zero after six months. Drugs that remained only available by prescription also saw an abrupt reduction after the change, but there was little alteration in trend. Patients' behaviour after the OTC switch was not investigated, so it is unknown whether they shifted to non-study alternatives (such as oral antifungal products), or endured health complaints without treatment.

4.9 Impact of interventions discouraging patients' drug demand on other resource use

Nine of the included studies explored the association of interventions and other resource utilisation and was rated as being of high quality (see Table 4-7). Evidence from North America shows that interventions limiting demand for medication may lead to an increase in the use of other healthcare resources in vulnerable populations. In a Canadian cost-sharing scheme, Tamblyn *et al.* (2001) found that the reduction in essential drug use (including antihypertensives, antihyperlipidemics, antidepressants, etc.) was followed by a small but significant increase in ER visits. Prescription capping in the US saw elderly patients with chronic diseases about twice as likely to be institutionalised in a nursing home, compared to those who were not subject to a cap (Soumerai *et al.*, 1991). Patients with schizophrenia were 50% more likely to visit

mental hospitals, although it is hard to generalise due to small study samples (Soumerai *et al.*, 1994).

Two studies reported that suppressing patient demand was accompanied by a moderate decline in physician visits (Gurwitz *et al.*, 1995; Winkelmann, 2004), indicating an increase in self-medication or forgoing treatment altogether.

Table 4-7: Impact of interventions discouraging patients drug demand on other resource use

Study	Population	Study drugs	Variables	Effects	Setting	Follow-up[1)]
cost-sharing						
Gurwitz *et al.* 1995	General	Less-essential	physician visits	no change	USA	M
Johnson *et al.* 1997	Vulnerable	Overall	medical expenditure	no change		M
Tamblyn *et al.* 2001	Vulnerable	Overall/ Essential/ Less-essential	ER visits	no change~ increase (+2~ +5%)	Canada	M
			hospitalisations	no change		
Winkelmann 2004	General	Overall	physician visits	decrease (-7~ -13%)	Germany	M
tiered formularies						
Fairman *et al.* 2003	General	Overall	office visits			M
			ER visits	no change	USA	
Motheral and Fairman 2001	General	Overall	hospitalisations			S
prescription caps						
Soumerai *et al.* 1994	Vulnerable	Essential	health centre visits	increase (+50%)	USA	S
			hospitalisations	no change		
Soumerai *et al.* 1991	Vulnerable	Essential	hospitalisations	no change		S
			nursing home admissions	increase (RR=1.8)		
OTC switch						
Gurwitz *et al.* 1995	General	Less-essential	physician visits	decrease	USA	M

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

4.10 Discussion

From the search of two major electronic databases and relative references, 44 studies examining the effects of pharmaceutical regulations influencing patients demand were identified. The majority of studies investigated cost-sharing changes or tiered formularies. A few studies addressed the impact of prescription capping, educational intervention, or OTC switch. More than a half of the included studies were conducted under public or private insurance in North America.

Overall, this review found the following from included studies:

- Studies exploring the impact of copayment increases were of mixed methodological quality; those exploring the impact of tiered formularies were of generally moderate quality, with little variation in findings. Among studies exploring the impact of prescription caps, high quality studies suggested a greater change in drug utilisation and payer's expenditure. Studies exploring the association between the interventions and other resource utilisation were of mostly good quality and suggested the increase use of other medical services in the vulnerable population after the interventions that restricted patient demand.
- Copayment increases could decrease drug utilisation; the size of the decrease may vary by drug class, level of copayment, patient-specific situation, or measurement unit. The differential increase of copayments (generally greater increases in nonformulary brand-named drugs) could achieve a more significant decline in the use of nonformulary brand-named drugs. There was little evidence for substitution of decreases in drugs with lower priced alternatives such as generics.
- Copayment increases could lower payers' costs for pharmaceuticals; however, only limited evidence is available about overall and private costs. Existing evidence suggests that the copayment changes may increase a financial burden in a disadvantaged population. The differential increase of copayments could bring about a substantial decrease in payers' expenses, a marginal decrease in overall drug costs, a dramatic increase in private expenses, clearly indicating a budget shift.
- Prescription caps can lower drug utilisation and expenditure, but constrain essential as well as unessential drugs and many create unintended consequences. Evidence from included studies suggests that capping could increase the use of

some other medical services in the most vulnerable populations, such as poor and elderly with chronic conditions.

- Interventions discouraging patient demand may lead to a greater decrease in the use of less-essential drugs, but a moderate rise in the private financial burden could decrease essential drug use as well. Thus, there are some concerns about a decrease in overall health.
- In general, interventions showed only short-lived effects, as patients accommodated to the changes.
- There was a lack of rigorous evidence available to establish the effects of other interventions such as educational interventions, OTC switch (self-medication), or DTC advertisements.

Previous reviews were mostly concerned that drug spending might shift from the payer to the patient rather than an absolute decline by interventions discouraging patient demand. In this review, a budget shift was not studied in detail in cost-sharing programmes, but it was clearly seen in tiered formularies. In addition, given that most included studies used claims data, which most likely covers the utilisation of prescription drugs reimbursed by payers and gives scant attention to OTC consumption, the magnitude of out-of-pocket spending could be more than that of primary authors' observations.

Given the policy aims or underlying theory, it was unexpected that patients did not consume less costly alternatives. From the included studies, there are few favourable findings supporting the fact that imposing restrictions on patient drug use leads them to seek less pricy alternatives. Even under a tiered formulary scheme, in which patients may have more opportunity to be informed about generic alternatives, the reduction in the use of expensive brand-named drugs appeared not to translate into generic utilisation. Patients may just give up their medication or pay more out-of-pocket.

This might be due to decision making processes in clinicians' offices, where the right to choose prescription drugs is delegated to prescribers (Chapter 1). Patients still seem to rely on their physician's opinion when they select pharmaceuticals, despite the recent attention to consumer power and collaboration between professionals and patients (Bradley *et al.*, 2004; Salter, 2004b). In these circumstances, patients may have two options – to GO or NOT go. If they **GO** to see their doctors, they are most likely to be

subject to the doctors' decisions. But, doctors may have little concern about copayments, or be more likely to think of the satisfaction of patients sitting next to them rather than considering the complex aspects of healthcare resources. Closely linked to this, it was observed that prescribers tended to increase the average prescription size under a fixed copayment scheme, meaning that patients would receive more units for each item, or a longer duration of therapy in a single prescription, reducing the number of prescriptions for which they were charged (Holloway *et al.*, 2001; Starmans *et al.*, 1994). This would lessen the policy impact. In this regard, an educational approach informing patients about reimbursable (less-expensive), interchangeable products would be a useful measure to improve the policy impact. However, this has received little attention in the literature.

If patients do **NOT go** to visit their doctors, the result could be a drop in consumption and expenditure. It may also result in the deterioration in overall health by reducing essential utilisation. A number of North American studies suggested that an extra financial burden may function discriminately in a vulnerable population, which might result in increasing the use of other medical services, such as ER visits or institutionalisations in such populations. This needs further investigation in order to generalise over other settings or populations.

One Cochrane review exploring the effects of cap and copayment on drug use was issued published at a similar time to this study (Austvoll-Dahlgren *et al.*, 2008). Both drew similar conclusions in the impact of cap and copayment on drug expenditure, utilisation and other relevant outcome variables, but the current study includes additional studies that are awaiting assessment in the Cochrane review.

In this review, only two studies came from countries similar to South Korea in terms of economic position and Asian background, but they were rated as poor quality (Lee *et al.*, 2006; Liu and Romeis, 2004). Hence, it is difficult to generalise the results of this review directly to the Korean context. Despite such a limitation, this review suggests several implications for South Korean pharmaceutical policy-makers:

As discussed in Chapter 2, the level of cost-sharing is already high in Korea. This means that there might be little room for raising the copayment. So, first, the copayment increase may yield a minimal effect on drug consumption and spending in

South Korea, because empirical evidence in this review shows that only considerable and continuous changes achieve any success in practice. Linked to this, it may be surmised that, on one hand, most consumers in advantaged groups in Korea may be extremely inflexible regarding such a small increase because they have been used to high out-of-pocket expenditure.

Second, a copayment increase would appear to discriminate against the poor. This population may already bear a heavy financial burden due to high cost-sharing in Korea and will generally show a greater response to even a small increase in out-of-pocket than those better-off.

Third, it would seem necessary to follow-up closely after any increase in copayment, as to whether this increase is too great for patients to obtain essential medication.

4.11 Summary

Pharmaceutical policies influencing patient demand, especially cost-sharing programmes, are frequently exploited across various settings. They have been changed from a simple dichotomous (yes/no) form to something complex. This review found that cost-sharing and prescription capping reduced drug volume in both essential and non-essential drugs. Although the interventions yielded sizable decreases in payers' drug expenditure, the net effect in spending seemed small overall. Drug costs were not ultimately being reduced, but shifted from payer to consumer. Although a few high quality studies suggest that increasing the private financial burden may have a disproportionate influence on socially disadvantaged groups, the conclusion is debatable because of the relatively small number of studies identified. Given the pre-existing high level of cost-sharing, the copayment increase would achieve limited success in South Korea, while reducing access to pharmaceuticals. Further discussion over methodological aspects of the reviewed studies and implications for the present research are continued in Chapter 7.

CHAPTER 5: THE EFFECTS OF PHARMACEUTICAL REGULATIONS INFLUENCING PROVIDERS

5.1 Introduction

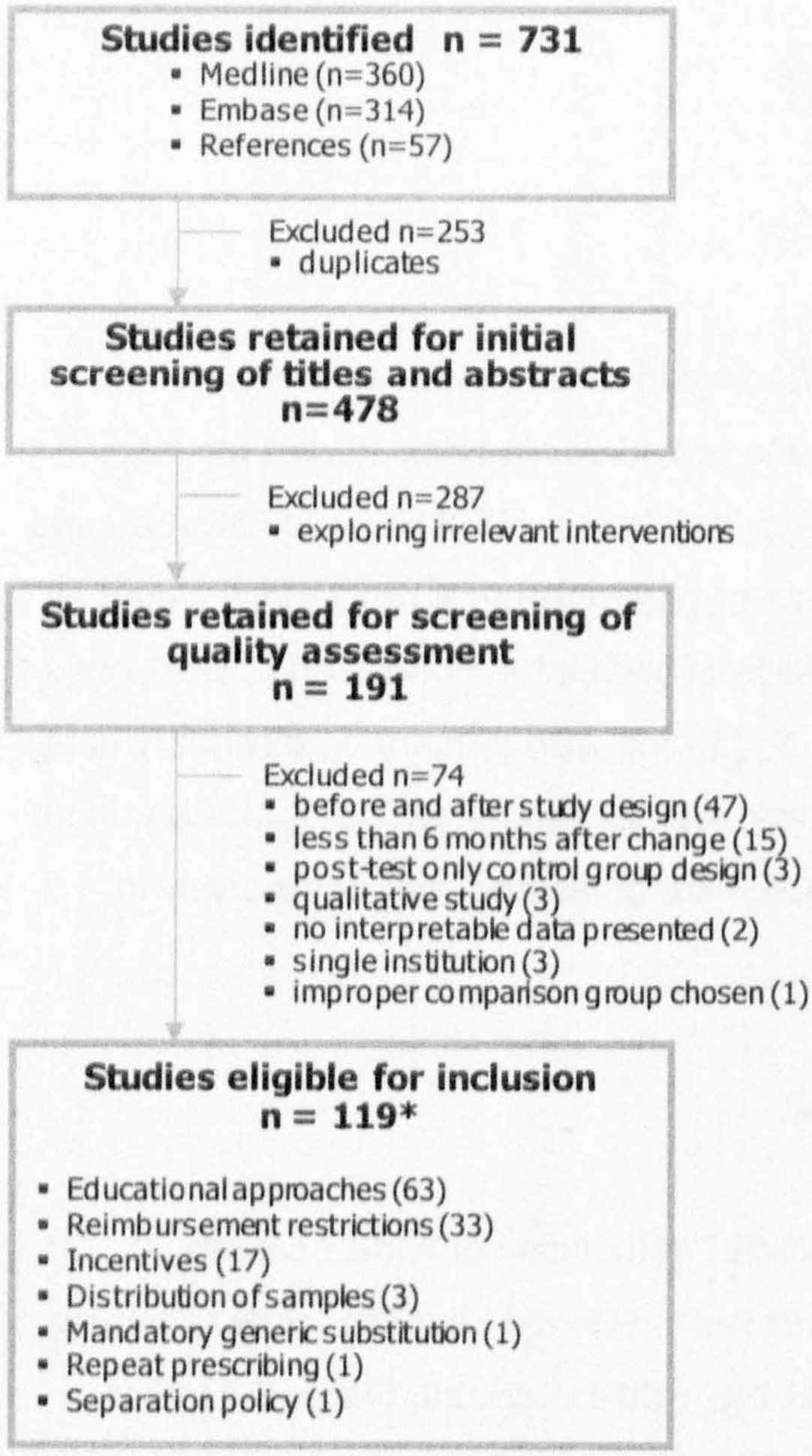
The objective of this chapter is to present findings from the systematic review concerning pharmaceutical policies influencing providers. In brief, studies for the second review were identified from two major databases, MEDLINE and EMBASE, and included if the article (1) explored the effects of pharmaceutical regulations aimed at influencing providers; (2) examined the effects of such interventions on at least one of the relevant outcomes depicted in Chapter 3; (3) analysed primary or secondary data; and (4) performed this with one of three most robust designs, RCT, ITS, or CBA. More detailed methods and the criteria of selection were presented comprehensively in Chapter 3.

5.2 Overview of included studies

In the second search for pharmaceutical policies influencing providers (Annex 3), 731 studies were retrieved, of which, 191 studies were retained after the initial screening of titles and abstracts. Finally, 117 studies met the inclusion criteria (Table 5-1). One study was included for three interventions (O'Malley *et al.*, 2006) – educational approach, incentives and distribution of free drug samples.

The large majority of studies explored the effects of 3 interventions: educational approaches (n=63), reimbursement policies (n=33), incentives (n=17). Three studies explored the impact of free drug samples. Single studies explored the effects of a generic substitution reform, repeat prescribing programme and separation of prescribing and dispensing drugs. Table 5-1 displays the reviewed studies by sub-intervention. Reasons of exclusion are reported in Figure 5-1 and Annex 6.

Figure 5-1: Flow diagram of studies (providers)



* One study was included three times because of addressing multi-interventions (O'Malley *et al.*, 2006).

5.3 Policies influencing providers

In recent years, educational initiatives have been introduced with the hope of improving physician prescribing behaviour across settings. Inappropriate prescribing decisions could not only waste resources through using inefficient therapies, but also cause deterioration of health through adverse drug reactions. Therefore, 'improving prescribing behaviour' generally involves both economic and clinical aspects (Soumerai *et al.*, 1989). The interventions include providing educational information, or informative data from prescribing analyses in terms of volume and cost. Owing to the variety of contents, the present review classified them into three groups: guideline-like information; prescribing feedback; and drug utilisation review (DUR).

Table 5-1: Studies included

Intervention		Studies
Educational approaches		
Guideline-like information	32	Jones *et al.* 1996, Martens *et al*. 2006, O'Malley *et al*. 2006, Sheldon *et al*. 2004, Tu *et al.* 2002
		Avorn and Soumerai 1983, Bernal-Delgado *et al.* 2002, Bexell *et al*. 1996, Chazan *et al.* 2007, Coen 1998, Diwan *et al*. 1995, Fessler *et al*. 2006, Hagen *et al.* 2005, Knowlton and Knapp 1994, Maclure *et al.* 1998, Midlov *et al.* 2006, Mohagheghi *et al.* 2005, Soumerai and Avorn, 1986; 1987
		Freemantle *et al*. 2002, Jackson *et al.* 2004, Mason *et al*. 2001, Pit *et al.* 2007, Shuval *et al.* 2007, Simon *et al.* 2005, Weatherby *et al.* 2001
		Filippi *et al.* 2003, Martens *et al.* 2007a, McMullin *et al*. 2004, Murray *et al.* 2004, Tamblyn *et al.* 2003, Vedsted *et al*. 1997
Prescribing feedback	21	Bradley *et al.* 2000, Braybrook and Walker 1996; 2000, Calvo-Alcantara and Inesta-Garcia 1999, Horn *et al.* 2007, Lassen and Kristensen 1992, Perez-Rodriguez *et al.* 1996, Sicras-Mainar and Pelaez-de-Lono 2005, Sicras-Mainar *et al*. 2007, Sicras-Mainar *et al*. 2004, von Ferber *et al.* 1999, Wilson *et al.* 2003, Witt *et al.* 2004
		Finkelstein *et al.* 2001, Hux *et al.* 1999, Madridejos-Mora *et al.* 2004, Nilsson *et al.* 2001, O'Connell *et al.* 1999, Pimlott *et al.* 2003, Raebel *et al*. 2007, Wensing *et al.* 2004
Drug utilisation review	10	Allard *et al.* 2001, Atthobari *et al.* 2004, Collins *et al.* 1997, Culbertson *et al.* 1999, Fretheim *et al*. 2006a; 2006b, Goldstein *et al.* 2005, Gregoire *et al.* 2006, Rascati *et al.* 1996, Samore *et al.* 2005
Reimbursement restrictions		
Delisting	4	Breen *et al*. 2004, Campbell *et al*. 2003, Soumerai *et al*. 1990, Zechnich *et al*. 1998
Formulary and Preferred Drug List	10	Abdelgawad and Egbuonu-Davis 2006, Christian-Herman *et al*. 2004, Huskamp *et al*. 2003b, Kephart *et al*. 2005, Lichtenberg 2005a, Motheral and Henderson 1999a, Murawski and Abdelgawad 2005, Ridley and Axelsen 2006, Virabhak and Shinogle 2005, Wang *et al*. 2003
Prior-authorisation	10	Carroll *et al*. 2006, Delate *et al*. 2005, Fischer *et al*. 2004, Hartung *et al*. 2004, Kotzan *et al*. 1993a, Kotzan *et al*. 1993b, Marshall *et al*. 2007, Roughead *et al*. 2006, Smalley *et al*. 1995, Yokoyama et al. 2007
Step-therapy and Limited use	9	Dunn *et al*. 2006, Fretheim *et al*. 2007, MacCara *et al*. 2001, Mamdani *et al*. 2007, Marshall *et al*. 2006, Motheral *et al*. 2004, Schneeweiss *et al*. 2004, Schneeweiss *et al*. 2006, Sun *et al*. 2007
Incentives		
UK fundholding	9	Baines *et al*. 1997, Bradlow and Coulter 1993, Corney and Kerrison 1997, Harris and Scrivener 1996, Rafferty *et al*. 1997, Whynes *et al*. 1995; 1997, Wilson *et al*. 1995, Wilson *et al*. 1999
Global budget	4	Etter and Perneger 1998, Granlund *et al*. 2006, Lee *et al*. 2006, Yip and Eggleston 2004
Others	4	Elhayany *et al*. 2001, Law and Wu 2003, Martens *et al*. 2007b, O'Malley *et al*. 2006
Miscellaneous		
Distribution of samples	3	Mukamal *et al*. 2002, O'Malley *et al*. 2006, Scott *et al*. 2007
Mandatory generic substitution	1	Andersson *et al*. 2007
Repeat prescribing	1	Bond *et al*. 2000
Separation of prescribing and dispensing of drugs	1	Chou *et al*. 2003

Guideline-like information includes standardised therapeutic guidelines such as NHS NICE guidance, hypertension guidelines, a variety of educational information with the

purpose of influencing prescribing practices such as a stepped-care prescribing protocol, campaigns encouraging generic use or discouraging antibiotic use, evidence-based prescribing algorithms, or cost comparison information. *Prescribing feedback* covers interventions providing prescribers' data generated from the analyses of prescribing data of prescribers' practices. *DUR* contains interventions informing patients' individual medication histories or prescribing recommendations to their medical care providers. DUR is relatively a recent device, with most trials in a North American context in identified studies.

Although some nation-wide cases were included, such as British programmes based on prescribing analysis and cost (PACT) or NICE guidelines, German prescribing feedback programmes known as 'Quality circle', or American campaigns encouraging the use of generics, most studies included in the review explored educational interventions at multi-institutional or regional level. Mostly, interventions were not enforced, but were conducted on a voluntary base.

Another voluntary-based intervention that frequently appeared was the imposition of incentives on healthcare providers to improve routine practices. Interventions included a global pharmacy budget or one-off bonus. Non-financial advantages were not specified in the current review. Budgetary control may have provided an incentive to constrain the costs of prescribing by allowing prescribers (or dispensers) to keep some of the savings. Among the included studies, a British fundholding programme was evaluated most often. Britain had introduced individual general practice budgets between 1991 and 1998. Recently, the UK NHS introduced another voluntary incentive scheme, named 'Quality and Outcomes Framework (QOF)' in 2004 (Lester, 2008). Studies evaluating the impact of the QOF on pharmaceuticals were not identified in this review.

Without enforcement drives, interventions may be easily ignored. Thus, most governments (or private insurers) often implement regulatory measures through reimbursement decisions. Reimbursement policies stipulate that payers prioritize publicly funded drugs, which are intended to make prescribers prescribe drugs fully-subsidised away from those limited. Under these regulations, some products are ruled out from reimbursement (delisting, negative or positive lists). Although most countries have a set of reimbursable list, the impact on prescribing practices has been evaluated

rarely except in North America.

In the US and Canada, to have access to restricted medications, patients must either pay an extra premium (formularies, preferred drug lists, etc.) or undergo pre-requisite procedures (prior-authorisation) or treatments (step-therapy). Prior-authorisation and step-therapies are often applied to expensive medications for minor illnesses, such as new non-steroidal anti-inflammatory drugs (NSAIDs).

Several interventions were also included, such as free drug samples, mandatory generic substitution, repeat prescribing and separation policy. However, these were all very limited, hence, this review principally evaluated the impact of the three interventions described above. The basic characteristics and outcomes of the included studies are discussed in turn by intervention.

5.4 Educational approaches

5.4.1 Characteristics of included studies

Of 63 studies, 32 addressed guideline-like information which were rated as more mixed and/or poor quality; 21 dealt with prescribing feedback with moderate quality in general; and 10 investigated DURs with moderate to high quality (Table 5-1). For the purpose of analysis, the first level category was sub-divided by the mode of dissemination: passive, such as mail or bulletin; group education; individual contact; computerised devices. Basic characteristics of included studies are displayed in Annex 12.

Educational measures have been tested in various settings: North America (n=25), Western Europe (n=29), Australia (n=5), Israel (n=2), Iran (n=1) and Zambia (n=1). Six studies employed ITS designs with moderate to low quality; 21 used CBA designs with moderate quality; 36 were conducted using RCT designs with moderate to high quality.

Nearly two-thirds of the studies followed up participants no longer than a year after the introduction of interventions. In only six studies was the period longer than 3 years (Bradley *et al.*, 2000; Fessler *et al.*, 2006; Horn *et al.*, 2007; Sicras-Mainar *et al.*, 2007;

Tu *et al.*, 2002; Weatherby *et al.*, 2001) and none was longer than 5 years.

Two thirds of the studies used aggregated claims data at organisational level. Most of the remainder employed data in medical records held at institution level. Other sources included commercial or academic databases. Two RCT studies analysed data collected from patients (Allard *et al.*, 2001; Pit *et al.*, 2007).

5.4.2 Impact on prescribing behaviour and drug utilisation

Evidence from the included studies suggested that educational approaches might have a limited improvement in prescribing behaviour (Table 5-2). In particular, studies with higher quality suggested smaller improvement of about 0~7% regardless of contents or contact method (Allard *et al.*, 2001; Bradley *et al.*, 2000; Freemantle *et al.*, 2002; Goldstein *et al.*, 2005; Hux *et al.*, 1999; Madridejos-Mora *et al.*, 2004; Tamblyn *et al.*, 2003). However, such improvements did not necessarily lead to changes in drug utilisation (see Table 5-3). In Britain, for instance, aggregated prescribing feedback increased prescribing appropriateness, but failed to make any difference to consumption (Bradley *et al.*, 2000). No association between quality and results was apparent for drug utilisation.

Individual prescribing feedback has not been shown to affect the trend of drug use in a well-designed randomised study in Australia (O'Connell *et al.*, 1999). The authors concluded that "unsolicited, centralised, government-sponsored feedback based on aggregate data had no impact on the prescribing levels of general practitioners" (p510). Likewise, as seen in Table 5-3, broadly-focused educational interventions were less likely to change the existing utilisation pattern.

Conversely, educational interventions with a clear purpose may be effective in improving prescribing profiles (Table 5-4 through 5-6). Regardless of setting or intervention, change was more likely when information was delivered supported by widely-agreed evidence (for instance, discouraging inappropriate prescribing in antibiotics or benzodiazepines, encouraging appropriate prescribing in antihypertensives or antihyperlipidemics). In contrast, interventions focusing on certain drug classes (including asthma medications, antiulcer medications, antipsychotics, or antidepressants) were less likely to influence prescribing practices.

Table 5-2: Impact of educational approaches on prescribing appropriateness

Study	Study drugs[1)]	Prescribing appropriateness[2)]	Setting
guideline-like information, group detailing			
Bexell *et al*. 1996	essential drugs	no change ~ higher (+12%)	Zambia
Coen 1998	overall	higher (+5%)	9 European countries
Diwan *et al*. 1995	lipid-lowering drugs	higher (+20%)	Sweden
Fessler *et al.*, 2006	lipid-lowering drugs, antidiabetics, cardiovascular drugs	(no change)	Germany
Maclure *et al.* 1998	antihypertensives in elderly	no change ~ higher	Canada
Simon *et al*. 2005 (group detailing)	diuretics, beta-blockers	higher (OR=1.4 at the 1st year)	USA
guideline-like information, individual detailing			
Freemantle *et al*. 2002	antiplatelets, ACE inhibitors, NSAIDs, antidepressants	higher (+5%)	UK
Pit *et al*. 2007	NSAIDs, low-dose thiazides, benzodiazepines in elderly	no change	Australia
Shuval *et al*. 2007	thiazides, statins	no change	Israel
Simon *et al*. 2005 (individual detailing)	diuretics, beta-blockers	no change	USA
Weatherby *et al*. 2001	cisapride	higher	
guideline-like information, computerised devices			
Martens *et al*. 2007a	antibiotics, asthma medications	little change	Netherlands
Murray *et al*. 2004	antihypertensives	no change	USA
Tamblyn *et al*. 2003	inappropriate prescribings	no change~ higher	Canada
group-level prescribing feedback, group detailing			
Bradley *et al*. 2000	gastrointestinal, cardiovascular, respiratory, central nervous, musculoskeletal medications, antibiotics	higher	UK
group-level prescribing feedback, individual detailing			
Perez-Rodriguez *et al*. 1996	overall	no change (p=0.08)	Spain
Sicras-Mainar *et al*. 2004	antiulcers, antidepressants, antihypertensives, antiasthmatics, antibacterials, NSAIDs	no change	
Sicras-Mainar and Pelaez de Lono 2005		higher (+2%)	
Sicras-Mainar *et al*. 2007		no change	
individual-level prescribing feedback, passive			
Hux *et al*. 1999	antibiotics	higher (+6%)	Canada
individual-level prescribing feedback, group detailing			
Madridejos-Mora *et al*. 2004	antibiotics, NSAIDs, antiulcerative agents	no change	Spain
drug utilisation review, passive			
Allard *et al*. 2001	inappropriate prescribings	no change (p=0.08)	Canada
Collins *et al*. 1997 (Physician only)	dipyridamole	no change	USA
Collins *et al*. 1997 (Pharmacist only)		no change~ higher (OR=2.22)	
Collins *et al*. 1997 (Both)		higher (OR=2.10~3.81)	
Rascati *et al*. 1996	antiulcer medications	higher (+17%)	
drug utilisation review, individual contacts			
Goldstein *et al*. 2005	antihypertensives	higher (+7%)	USA
Gregoire *et al*. 2006	cisapride	no change ~ higher	Canada

1) ACE; angiotensin-converting enzyme: NSAID; non steroidal anti-inflammatory drug
2) In cases no proper statistical evidence given but more than 10% differences reported, the results are in perantheses.

In spite of intended changes in the utilisation of targeted drugs, smaller changes were often seen in overall related utilisation (Table 5-4 through 5-6), possibly owing to the fact that the primary hope of educational interventions were in general not to reduce drug use, but to improve prescribing practices. As a result, a reduced utilisation was often compensated by substitutes; for example, the increasing use of recommended NSAIDs offset the reduction of those NSAIDs which were discouraged, hence, few differences were observed in overall prescription volume (Bernal-Delgado *et al.*, 2002).

Table 5-3: Impact of broadly-focused educational approaches on drug utilisation,

Study	Study drugs*	Drug utilisation			Setting
		overall related drugs	increase intended	decrease intended	
guideline-like information, group detailing					
Coen 1998	overall	no change (-16%, p=0.07)			9 European countries
Knowlton and Knapp 1994	overall	no change			USA
guideline-like information, computerised devices					
Vedsted *et al*. 1997	overall	no changes			Denmark
group-level prescribing feedback, group detailing					
Bradley *et al*. 2000	gastrointestinal, cardiovascular, respiratory, central nervous, musculoskeletal medications, antibiotics		no change	little change	UK
Lassen and Kristensen 1992	overall	no change			Denmark
group-level prescribing feedback, individual contacts					
Sicras-Mainar *et al*. 2004	antiulcers, antidepressants, antihypertensives, antiasthmatics, antibacterials, NSAIDs, analgesics	lower (-15%)			Spain
Sicras-Mainar and Pelaez de Lono 2005		lower (-9%)			
Sicras-Mainar *et al*. 2007		no change			
individual-level prescribing feedback, passive					
O'Connell *et al*. 1999	overall	no change		no change	Australia
individual-level prescribing feedback, group detailing					
Wensing *et al*. 2004	overall	no change	little change	little change	Germany

* NSAIDs; non steroidal anti-inflammatory drugs

In delivering guideline-like information, a few studies demonstrated that active dissemination by face-to-face outreach visits either at group- or individual-level was more likely to persuade physicians to comply with study intentions, compared to passive contacts (Table 5-4). For example, Avorn and Soumerai (1983) examining an educational measure discouraging the use of three undesirable drugs, demonstrated that face-to-face approaches lowered drug utilisation by about 14% in the drugs

targeted, while mailing produced no significant effects. This was supported by another American study (Simon *et al.*, 2005).

Table 5-4: Impact of *guideline-like information* on drug utilisation

Study	Study drugs*	Drug utilisation			Setting
		overall related drugs	increase intended	decrease intended	
guideline-like information, passive					
Avorn and Soumerai 1983 (mailing)	propoxyphene, vasodilators, cephalexin			no change	USA
Jones *et al*. 1996	NSAIDs	no change		lower (-31~ -35%)	
	antibiotics			no change	
Martens *et al*. 2006	asthma drugs		no change		Netherlands
	statins		higher (+23%)		
O'Malley *et al*. 2006	generics		little change		USA
	taxanes		higher		
Sheldon *et al*. 2004	Alzheimer drugs		no change		UK
	Orlistat		higher		
Tu *et al*. 2002	antihypertensives	no change	no change		Canada
guideline-like information, group detailing					
Avorn and Soumerai 1983 (group detailing)	propoxyphene, vasodilators, cephalexin			lower (-14%)	USA
Bernal-Delgado *et al*. 2002	NSAIDs	no change	no change (vs. conventional education)	no change (vs. conventional education)	Spain
			higher (+7~+10%) (vs. no intervention)	lower (-24~-37%) (vs. no intervention)	
Bexell *et al*. 1996	antibiotics			lower (-13%)	Zambia
Chazan *et al*. 2007	antibiotics	lower (-3%)		lower (-14%)	Israel
Hagen *et al*. 2005	psychotropic drugs	no change		no change	Canada
Horn *et al*. 2007	antihypertensives	higher (+6~ +8%)	higher (+8%)		Austalia
Midlov *et al*. 2006	antipsychotics			no change	Sweden
	benzodiazepines			lower (-26%)	
Mohagheghi *et al*. 2005	antibiotics, injections			lower (-9%)	Iran
guideline-like information, individual contacts					
Jackson *et al*. 2004	antithrombotic drugs		no change~ higher (+4%)		Australia
Pit *et al*. 2007	NSAIDs, low-dose thiazides, benzodiazepines	no change			
guideline-like information, computerised devices					
Filippi *et al*. 2003	antiplatelet drugs		higher (OR=1.99)		Italy
Martens *et al*. 2007a	antibiotics, asthma drugs			little change	Netherlands

* NSAIDs; non steroidal anti-inflammatory drugs

As opposed to general conclusions drawn in one previous review (Soumerai *et al.*, 1989), it is unclear that face-to-face deliveries are more effective in prescribing feedback (Table 5-5). Among the papers testing head-to-head comparisons in providing prescribing feedback between direct and indirect contacts, studies reported no

observed differences in Denmark (Witt *et al.*, 2004) and only marginal effects in the UK (Braybrook and Walker, 1996, 2000). Only one Australian study showed favourable outcomes for offering prescribing feedback through direct contact in contrast with mailing (Wilson *et al.*, 2003). Evidence for DURs on this issue was relatively limited (Table 5-6).

Table 5-5: Impact of *prescribing feedback* on drug utilisation

Study	Study drugs*	Drug utilisation: overall related drugs	Drug utilisation: increase intended	Drug utilisation: decrease intended	Setting
group-level prescribing feedback, group detailing					
Braybrook and Walker 1996	antibiotics		no change~ higher	no change~ lower	UK
Braybrook and Walker 2000	NSAIDs	no change	no change~ higher	no change~ lower	
Calvo-Alcantara and Inesta-Garcia 1999	generics		higher (+27%)		Spain
Diwan *et al*. 1995	antihyperlipidemics		no change (p=0.06)		Sweden
Wilson *et al*. 2003	antibiotics			lower (-15%)	Austalia
Witt *et al*. 2004	asthma drugs	no change			Denmark
individual-level prescribing feedback, passive					
Pimlott *et al*. 2003	benzodiazepines	no change		lower (-11%)	Canada
individual-level prescribing feedback, group detailing					
Finkelstein *et al*. 2001	antibiotics			lower (-12~ -16%)	USA
Madridejos-Mora *et al*. 2004	antibiotics	lower (-13%)			Spain
	NSAIDs	no change			
	atiulcer medications	no change			
Nilsson *et al*. 2001	antihypertensives		no change	no change~ lower (-31%)	Sweden
	atiulcer medications		no change	no change	
	antidepressants	no change			
individual-level prescribing feedback, individual contacts					
Raebel *et al*. 2007	inappropriate prescribings	lower (-16%)		lower (-26%)	USA

* NSAIDs; non steroidal anti-inflammatory drugs

Table 5-6: Impact of *DUR* on drug utilisation

Study	Study drugs	Drug utilisation: overall related drugs	Drug utilisation: increase intended	Drug utilisation: decrease intended	Setting
drug utilisation review, passive					
Allard *et al*. 2001	inappropriate prescribings			no change	Canada
Atthobari *et al*. 2004	antihypertensives, antihyperlipidemics		higher (+11~ +31%)		Netherlands
drug utilisation review feedback, group detailing					
Fretheim *et al*. 2006b	antihypertensives, antihyperlipidemics		higher (+9%)		Norway
drug utilisation review, individual contacts					
Culbertson *et al*. 1999	atiulcer medications			no change~ lower (-6%)	USA
Samore *et al*. 2005	antibiotics	lower (-12%)			

In the reviewed studies, individual-specific information on prescribing feedback and DURs resulted in better impact over group-level information (Madridejos-Mora *et al.*, 2004; Samore *et al.*, 2005). Prescribing feedback or DUR is preferable to guideline-like information in affecting drug use (Wilson *et al.*, 2003). Real time advice was more likely to affect prescribing routines than that given retrospectively (Gregoire *et al.*, 2006). However, extremely sophisticated information was shown to fail to influence prescribing practices even when it was provided by ongoing computerised systems in several settings, including Canada, Denmark, the Netherlands and the US. This would suggest that physicians found excessive and complex information "to be intrusive or time consuming" in clinical practice (Murray *et al.*, 2004). This was pointed out by the previous review as a problem of "information overload" (Soumerai *et al.*, 1989).

Greater effects have been shown in studies in which patients (Atthobari *et al.*, 2004; Chazan *et al.*, 2007; Finkelstein *et al.*, 2001; Samore *et al.*, 2005), their carers (Wilson *et al.*, 2003), or pharmacists (Collins *et al.*, 1997; Raebel *et al.*, 2007) participated in the drug use process along with physicians. Physicians were more likely to change prescribing practice when they were in agreement with the recommendations (Hux *et al.*, 1999; Jackson *et al.*, 2004; Rascati *et al.*, 1996; Soumerai and Avorn, 1987) or when they were actively participating (Midlov *et al.*, 2006; Samore *et al.*, 2005). High prescribers (Virabhak and Shinogle, 2005; von Ferber *et al.*, 1999), small practices (Freemantle *et al.*, 2002), or new prescriptions (Tamblyn *et al.*, 2003) were more susceptible to educational information. Simple-faceted voluntary educational efforts alone may be ineffective (Maclure *et al.*, 1998). The policy effects fade away over time (Sicras-Mainar *et al.*, 2007; Simon *et al.*, 2005). In this regard, evidence shows the importance of generating measures which reinforce the message or making the dissemination continuous (Chazan *et al.*, 2007; Soumeral and Avorn, 1987).

5.4.3 Impact on drug expenditure

Included studies showed smaller variations in the impact of interventions on drug expenditure than on utilisation (Table 5-7). The majority of the studies suggested that educational approaches could reduce drug expenditure from the payers' perspective. Prescribing feedback and DURs appeared to provide more consistent results than guideline-like information. It is unclear from those studies reviewed whether the method of dissemination was associated with the various effects on drug expenditure.

Table 5-7: Impact of educational approaches on drug expenditure

Study	Study drugs[1)]	Generic use rate	Drug expenditure[2)] (payer)	Setting
guideline-like information, passive				
Jones *et al*. 1996	NSAIDs		lower (-29~ -33%)	USA
Soumerai and Avorn 1986 (mailing)	propoxyphene, vasodilators, cephalexin		no change	
guideline-like information, group detailing				
Fessler *et al.*, 2006	antidiabetics lipid-lowering drugs, cardiovascular drugs		(-26%) (no change)	Germany
Knowlton and Knapp 1994	overall	higher (+6%)	lower (-8%)	USA
Soumerai and Avorn 1986 (group detailing)	propoxyphene, vasodilators, cephalexin		lower (-13%)	
guideline-like information, computerised devices				
McMullin *et al*. 2004	overall		lower (-11%)	USA
Vedsted *et al*. 1997	overall		no change	Denmark
group-level prescribing feedback, group detailing				
Braybrook and Walker 2000	NSAIDs	higher (+10~ +13%)	(higher)	UK
von Ferber *et al*. 1999	various		(-12%)	Germany
group-level prescribing feedback, individual detailing				
Perez-Rodriguez *et al*. 1996	overall		lower (-19%)	
Sicras-Mainar *et al*. 2004	antiulcers, antidepressants, antihypertensives, antiasthmatics, antibacterials, NSAIDs	higher (+15%)	lower (-15%)	Spain
Sicras-Mainar and Pelaez de Lono 2005		higher (+51%)	lower (-11%)	
Sicras-Mainar *et al*. 2007		higher (+41%)	lower (-2%)	
individual-level prescribing feedback, group detailing				
Madridejos-Mora *et al*. 2004	antibiotics, NSAIDs, antiulcerative agents		lower (-14%)	Spain
Wensing *et al*. 2004	overall	higher (+3%)	lower (-6%)	Germany
drug utilisation review, passive				
Collins *et al*. 1997 (Physician only)	dipyridamole		no change	USA
Collins *et al*. 1997 (Pharmacist only)	dipyridamole		lower (-5~ -11%)	
Collins *et al*. 1997 (Both)	dipyridamole		lower (-22~ -29%)	
drug utilisation review, individual contacts				
Culbertson *et al*. 1999	atiulcer medications		lower (-13~ -14%)	USA

1) NSAIDs; non steroidal anti-inflammatory drugs
2) In cases no proper statistical evidence given but more than 10% differences reported, the results are in perantheses.

There is some evidence that slight change in utilisation may not necessarily indicate little impact on costs. Several studies showed a modest saving, despite no difference in overall consumption (Culbertson *et al.*, 1999; Jones *et al.*, 1996; Madridejos-Mora *et al.*, 2004; Wensing *et al.*, 2004). Two studies from the US and Germany demonstrated the increasing use of generic alternatives (Knowlton and Knapp, 1994; Wensing *et al.*,

2004). Presumably this would imply improvement in prescribing practices in terms of cost-effectiveness.

In the US, a computerised tool providing information about the relative efficacy, safety, and costs of different therapeutic options was associated with decreasing costs (McMullin *et al.*, 2004), though this was different from a Danish study which provided drug cost information via a real-time computer programme, but failed to achieve any changes in either utilisation or expenditure (Vedsted *et al.*, 1997).

Other factors facilitating the reduction of drug expenditure were similar to those yielding a greater impact on utilisation. Face-to-face detailing rather than mailing (Soumerai and Avorn, 1986), involving more stakeholders (Collins *et al.*, 1997) or heavy prescribers (Madridejos-Mora *et al.*, 2004; Perez-Rodriguez *et al.*, 1996; von Ferber *et al.*, 1999), or continuous interventions (von Ferber *et al.*, 1999; Wensing *et al.*, 2004) seem to be more effective in reducing drug costs, with other conditions being equal.

Two studies conducted economic evaluations of the intervention programmes taking administrative expenses into account (Fretheim *et al.*, 2006a; Mason *et al.*, 2001). Mason *et al.* found a positive net effect in the outreach programme for the prescribing guideline of angiotensin-converting enzyme inhibitors in heart failure, but not for antidepressants (first-line use of tricyclic antidepressants and second-line use of selective serotonin reuptake inhibitors). Fretheim *et al.* concluded that their DUR programme, encouraging thiazides (first-line choice of antihypertensives) prescriptions, might be cost-effective if the intervention effect is sustained beyond the study period (one year) to at least 2 years.

5.4.4 Other outcomes

Studies, exploring the effect of educational interventions on other outcomes below, were rated as moderate to high quality. No studies reported any meaningful changes in quality of life, patient satisfaction, treatment goals, or other service use after implementing educational interventions in the short-term (Table 5-8).

Table 5-8: Impact of educational approaches on health or other service use

Study	Variables	Effects	Follow-up[1)]
guideline-like information, group detailing			
Knowlton and Knapp 1994	hospital admission rate	no change	S
guideline-like information, individual detailing			
Pit *et al*. 2007	quality of life	no change	S
Simon *et al*. 2005	outpatient visits	no change	S
	hospitalisations	no change	
	blood pressure control	no change	
guideline-like information, computerised devices			
Murray *et al*. 2004	emergency visits	no change	S
	hospitalisations	no change	
	medical expenditure	no change	
	blood pressure control	no change	
	patient satisfaction	no change	
drug utilisation review, group detailing			
Fretheim *et al*. 2006b	blood pressure control	no change	S
drug utilisation review, individual contacts			
Culbertson *et al*. 1999	other service use	no change	S
Goldstein *et al*. 2005	blood pressure control	no change	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

5.4.5 Summary: Evidence about educational interventions

Evidence from reviewed studies suggested that educational interventions could lower drug expenditure when the focus is on cost-effective information, even when little change was shown in utilisation. Drug utilisation profiles can also be improved if the information is well-focused on problematic medications, on improper behaviour proven by individual-specific data, or with professional support, or provided repeatedly. These findings are in line with statements by Sheldon *et al.* (2004; p1006) that "implementation is likely to be improved if the guidance is clear and based on an understanding of clinical practice, if the evidence is strong and relatively stable, if adequate funding is available, and if the guidance is supported and disseminated by professional bodies". In most cases, the impact was modest. Faced with marginal impact, a multi-faceted or collaborative approach is suggested across included studies to achieve better outcomes. There is no evidence that educational interventions affect use of other resources or quality of care. The quality of the included studies was generally moderate with few rated as poor or high quality. Thus, readers should bear this in mind in the interpretation of the findings. Greater caution might need to be given when interpreting the effects of guideline-like information because these studies were rated as being of poorer quality.

5.5 Reimbursement restrictions

5.5.1 Characteristics of included studies

Thirty-three studies explored the impact of reimbursement restrictions including delisting (n=4), formularies or Preferred Drug Lists (PDLs) (n=10), prior-authorisations (n=10), step-therapies or limited use edits on reimbursement criteria (n=9). Basic characteristics of included studies are shown in Annex 13. The included studies were of very mixed quality. Studies exploring the impact of formularies and PDLs or step-therapies or limited uses were rated as moderate to high quality, while those exploring the impact of prior authorisations were rated as moderate to low quality. In studies exploring the impact of delisting, half were rated good quality, but the remaining studies were rated as poor quality.

All except two studies – one from Australia, the other from Norway – were conducted in North America. Of the 23 studies from the US, 18 examined the impact of reimbursement restrictions on vulnerable groups such as the poor in Medicaid programmes, wounded veterans, and the elderly; five studies included general populations in commercial health plans. All eight studies from Canada involved an elderly population on the benefit programmes provided by provinces.

Twenty-one studies employed ITS analyses and 11 used CBA study designs. Slightly more than half of the studies from North America (including both ITS and CBA studies) employed control populations from comparable states or health plans. Two CBA studies compared a Medicaid population with non-Medicaid population, and raised some concerns about baseline differences between groups (Lichtenberg, 2005a; Murawski and Abdelgawad, 2005). All but four studies used claims databases maintained by national or organisational bodies. Four studies employed commercial databases or electronic medical records held at practices. All studies explored the policy effects over a short period, no longer than 2 years after the implementation with two exceptions that covered around 30 months (Lichtenberg, 2005a; Marshall *et al.*, 2007).

5.5.2 Impact on drug utilisation

Evidence from included studies showed that reimbursement policies could achieve a considerable decrease in the use of restricted drugs, which were offset by the increasing use of substitutable drugs, for instance, preferred drugs in PDLs, or first-line therapies in step-therapy restrictions (Table 5-9 through 5-12).

Table 5-9: Impact of delisting on drug utilisation

Study	Patient population	Study drugs	Drug utilisation		
			overall related drugs	dropped	potential substitutes
Breen *et al.* 2004	General	temazepam capsule	no change	lower (-73%)	higher
Campbell *et al.* 2003	Elderly	topical corticosteroid products	mixed[1)]		
Soumerai *et al.* 1990	Poor	nonscientific drugs	higher	lower	higher (~+282%)
Zechnich *et al.* 1998	Poor	OTC drugs	mixed[1)]	lower	higher[2)]

1) Policy impacts varied by drug classes.
2) only in hematinics among the nine therapeutic categories

Such a reduction was unlikely to lead to improved drug use in delisting. Soumerai *et al.* (1990) studying the effects of reimbursement cessation of 12 categories of drugs with questionable efficacy in a New Jersey Medicaid population found that a decline in the use of delisted drugs was often substituted by other questionable drugs, more costly but with uncertain efficacy. Australian authors assessing the effect of a restriction on temazepam (frequently misused benzodiazepine) suggest that complementary prescribing guidelines may be required to prevent mis-users from accessing the medications through prescription via "fake symptoms" (Breen *et al.*, 2004).

In other reimbursement restricting policies, the increase of substitution was smaller than the decline of restricted drugs, resulting in a modest drop in total volume (Table 5-10 through 5-12). The lower volume in target drugs was in part offset by the increasing utilisation of alternatives such as generics for brand-named drugs, non-narcotic analgesics for NSAIDs, or first-line drugs for upper level therapies.

Table 5-10: Impact of formularies and PDLs on drug utilisation

Study	Patient population	Study drugs	Drug utilisation		
			overall related drugs	restricted	preferred
Abdelgawad and Egbuonu-Davis 2006	Poor	statins	lower		
Christian-Herman *et al.* 2004	General	overall	lower (-4%)	lower (-19%)	higher (+7%)
Kephart *et al.* 2005	Elderly	respiratory drugs		lower (-47~ -65%)	
Motheral and Henderson 1999a	General	overall	lower (-41%)		
Virabhak and Shinogle 2005	Poor	cardiovascular medications		lower (-41~ -68%)	
Wang *et al.* 2003	Poor	proton-pump Inhibitors			higher (+77~ +78%)

Table 5-11: Impact of prior-authorisations on drug utilisation

Study	Patient population	Study drugs*	Drug utilisation		
			overall related drugs	PA drugs	potential substitutes
Carroll *et al.* 2006	Poor	Cox_2 Inhibitors		lower	higher
Delate *et al.* 2005	Poor	proton-pump Inhibitors		lower	higher
Fischer *et al.* 2004	Poor	Cox_2 Inhibitors		lower (-15%)	
Hartung *et al.* 2004	Poor	celecoxib		lower (-47%)	no change
Kotzan *et al.* 1993a	Poor	H_2RIs		no change	
Kotzan *et al.* 1993b	Poor	NSAIDs	no change	lower (-50%)	higher
Marshall *et al.* 2007	Elderly	Cox_2 Inhibitors	lower		
Roughead *et al.* 2006	Poor	Cox_2 Inhibitors	no change	lower (-42%)	
Smalley *et al.* 1995	Poor	NSAIDs, analgesics, psychotropics	lower (-19%)	lower	higher
Yokoyama *et al.* 2007	General	ARBs		lower	

* ARBs; angiotensin-receptor blockers, Cox_2 inhibitors; cyclooxygenase inhibitors, H_2RAs; histamine-2-receptor antagonists, NSAIDs; nonsteroidal anti-inflammatory drugs

The amount of reduction in utilisation varied, as seen in the tables. Larger reductions were observed when stricter rules were implemented, for instance, a closed formulary over an open formulary (Motheral and Henderson, 1999a), a prior-authorisation over limited use criteria or formulary (Marshall *et al.*, 2007), more restrictive criteria among prior-authorisations (Fischer *et al.*, 2004), a multi-faceted intervention over a single intervention, or a step-therapy over a formulary (Sun *et al.*, 2007). Medicaid

formularies might influence doctors further to prescribe formulary drugs in other populations as well as Medicaid populations (Virabhak and Shinogle, 2005; Wang *et al.*, 2003). According to Wang *et al.* (2003), the market share of preferred proton pump inhibitors (PPIs) was increased by 1~2% among cash or other third-party payer prescriptions in Maine for every 10% member patients' share of the practice after a restrictive Medicaid formulary.

Table 5-12: Impact of step-therapies or limited uses on drug utilisation

Study	Patient population	Study drugs*	Drug utilisation		
			overall related drugs	restricted	first-line or related drugs
Dunn *et al.*, 2006	General	antidepressants	no change		
Fretheim *et al.* 2007	General	antihypertensives			higher (+17%)
MacCara *et al.* 2001	Elderly	fluoroquinolones	lower (-3%)	lower (-80%)	higher (+11~ +56%)
Mamdani *et al.* 2007	Elderly	fluoroquinolones	no change	lower	higher
Marshall *et al.* 2006	Elderly	fluoroquinolones	lower	lower	higher
Schneeweiss *et al.* 2004	Elderly	ineffective asthma medications		lower (-5~ -14%)	
Schneeweiss *et al.* 2006	Elderly	PPIs	no change	lower (-75%)	higher
Sun *et al.* 2007	General	NSAs	lower (-28~ -36%)		

* NSAIDs; nonsteroidal anti-inflammatory drugs, NSAs; non-sedating antihistamines, PPIs; proton-pump inhibitors, SSRIs; selective serotonin reuptake inhibitors

However, reimbursement restricting policies may also yield unexpected and unwanted outcomes. It was shown that the implementation of generic-only benefits lowered the use of medications for chronic conditions, especially in statins prescriptions which decreased by nearly 30% in an American Medicare managed organisation (Christian-Herman *et al.*, 2004). As shown in Table 5-13, three US studies indicated that patients were more likely to discontinue their chronic medications (including sexual hormones, antidiabetics, antihypertensives and related heart medications, antipsychotics and anticonvulsants) by around 10% in the short-term, implying that it could reduce overall health in the longer-term if the trend persisted. These studies exploring the impact of reimbursement restrictions on drug discontinuation were rated as good quality.

One study concerned the possible increasing of social inequities by decreasing patient access to new medications, because they found Medicaid patients were more likely to

take older drugs after the application of Medicaid PDLs (Lichtenberg, 2005a). The largest impact was seen in pain management medication, which occurred between six months and 2 years. Much less delay (from less than a month to around a year) was seen in response to medication for chronic complaints (including antihypertensives, antidepressants, diabetic drugs, and cholesterol-lowering drugs).

Table 5-13: Impact of reimbursement restrictions on drug discontinuation

Study	Patient population	Intervention	Study drugs	Effects	Setting	Follow-up[1)]
Motheral and Henderson 1999a	General	closed formulary	chronic medications	higher (+12%)	USA	S
Ridley and Axelsen 2006	Poor	Preferred Drug List	statins	higher (+13%)	USA	S
Schneeweiss et al. 2006	Elderly	step-therapy	proton-pump inhibitors	no change	Canada	S
Yokoyama *et al.* 2007	General	prior-authorisation	angiotensin-receptor blockers	higher (+7%)	USA	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

5.5.3 Impact on drug expenditure

Reimbursement policies may have a substantial effect on lowering payers' drug expenditure on related drugs (Table 5-14). The interventions lowered drug expenditure between 7% and 53%, which might be achieved by reducing the claims for off-reimbursement drugs and increasing the use of less expensive alternatives. Potential substitutes were mostly less costly, except for the delisting programmes; thus, the changes in use were linked to savings in payers' expenditure for the relevant drug classes.

Among sub-interventions, step-therapies or limited use edits have shown more irregular effects. Four studies reported a 19~33% decrease, while 3 studies found no significant changes in public expenditure (Table 5-14). Differences may be partly explained by drug categories. Savings from step-therapies were observed in the medication classes of PPIs, NSAIDs, non-sedating antihistamines (NSAs), but were mixed in fluoroquinolones and did not appear in antidepressants or asthma drugs. Mixed results in two studies exploring the impact of reimbursement criteria on the costs of fluoroquinolones may be explained by contextual factors between Nova Scotia – showing a significant fall (MacCara *et al.*, 2001) and Ontario – showing little reduction (Marshall *et al.*, 2006) in Canada. Firstly, restrictions in Nova Scotia seem to

be stricter than in Ontario; for example, Nova Scotia requested an extra official form alongside the prescription for fluoroquinolones, including for norfloxacin which was on the general benefit list in Ontario. Secondly, a couple of fluoroquinolones were not available when the Nova Scotia study was conducted.

Table 5-14: Impact of reimbursement restrictions on drug expenditure

Study	Patient population	Study drugs*	Drug expenditure			Prices
			overall	payer	out-of-pocket	
delisting						
Campbell *et al*. 2003	Elderly	topical corticosteroid products	lower			
Soumerai *et al*. 1990	Poor	nonscientific drugs	no change			
Zechnich *et al*. 1998	Poor	OTC drugs	lower			
formularies or preferred drug lists						
Christian-Herman *et al*. 2004	General	overall	lower (-12%)	no change		
Huskamp *et al*. 2003b	Elderly, disabled	various	lower (-7~ -41%)			lower (-13~ -36%)
Motheral and Henderson 1999a	General	overall	lower (-44%)			no change
prior-authorisations						
Carroll *et al*. 2006	Poor	Cox_2 inhibitors	lower			
Delate *et al*. 2005	Poor	proton-pump inhibitors	lower (-50%)			
Fischer *et al*. 2004	Poor	Cox_2 inhibitors				lower (-18%)
Hartung *et al*. 2004	Poor	celecoxib	lower			
Kotzan *et al*. 1993a	Poor	H_2RIs	lower			
Kotzan *et al*. 1993b	Poor	NSAIDs	lower			
Smalley *et al*. 1995	Poor	NSAIDs, analgesics, psychotropics	lower (-53%)			
Yokoyama *et al*. 2007	General	ARBs	lower (-17%)			
step-therapies or limited uses						
Dunn *et al*., 2006	General	antidepressants	no change			no change
MacCara *et al*. 2001	Elderly	fluoroquinolones	lower (-22%)			
Marshall *et al*. 2006	Elderly	fluoroquinolones	no change			
Motheral *et al*. 2004	General	PPIs, SSRIs, NSAIDs	lower (-19%)			
Schneeweiss *et al*. 2004	Elderly	ineffective asthma medications	no change			
Schneeweiss *et al*. 2006	Elderly	PPIs	lower	lower	lower	
Sun *et al*. 2007	General	NSAs	lower (-28~ -38%)	lower (-27~ -33%)	lower (-31~ -43%)	

* ARBs; angiotensin-receptor blockers, Cox_2 inhibitors; cyclooxygenase inhibitors, H_2RAs; histamine-2-receptor antagonists, NSAIDs; nonsteroidal anti-inflammatory drugs, NSAs; non-sedating antihistamines, PPIs; proton-pump inhibitors, SSRIs; selective serotonin reuptake inhibitors

Sun *et al.* (2007), comparing three cohorts with slightly different interventions, suggest that step-therapy could be a more effective strategy to contain drug expenditure than formulary changes. The strongest effects were achieved by a multi-faceted intervention; spending on non-sedating antihistamines was reduced by 38%. Step-therapy alone produced a drop of 28%. Formulary changes alone did not achieve statistically significant changes.

Three included studies examined out-of-pocket payment. Two studies found a decrease in private expenses as well as public expenditure after the implementation of step-therapies or limited use criteria. However, claims data may not capture out-of-pocket expense in real terms. Sun *et al.* (2007) disclosed their concerns about cost shifting to substitutable OTC products that could not be investigated with claims data.

5.5.4 Impact on health

Among the 33 included studies, only one explored the impact of the policy on health. Fretheim *et al.* (2007), investigating a thiazide-first step-therapy in Norway, reported that there were no differences before and after the intervention in the proportion of patients who achieved optimal blood pressure.

5.5.5 Impact on other resource use

Table 5-15 presents ten studies investigating the association between the reimbursement restrictions and the utilisation of other services. Seven studies reported that the reimbursement policies did not bring any meaningful changes in relevant medical service except a temporary increase in the months immediately following the change (Murawski and Abdelgawad, 2005; Schneeweiss *et al.*, 2006). The quality of these studies was mixed as were either rated as being of high or low quality.

Evidence from the rest of the studies, rated as being of moderate quality, is mixed. In Canada, a rigorous quasi-experimental study found a modest increase in hospital admissions for urinary tract infections, the primary indication of fluoroquinolones, and a considerable decrease in those for gastrointestinal infections (Mamdani *et al.*, 2007).

In the US, Christian-Herman *et al.* (2004) showed that a generic-only formulary in a

California Medicare managed organisation increased overall hospital admissions by 17% in their controlled study. The authors concluded that higher admissions might be owing to the limitation of generic availability in some serious chronic diseases.

After the introduction of prior-authorisation for celecoxib in a Managed-Care Medicaid population, a quasi-experimental study by Hartung *et al.* (2004) found that there was a significant increase in the slope of emergency department encounters and a temporary increased trend in other service use in the overall analysis, which did not support sub-analyses with NSAIDs users. Thus, the inference between the intervention and these outcomes seems unclear.

Table 5-15: Impact of reimbursement restrictions on other resource use

Study	Patient population	Study drugs[1)]	Variables			Follow-up[2)]
			physician visits	hospitalisations	others	
formulary or preferred drug lists						
Christian-Herman *et al.* 2004	General	overall		higher (+17%)		S
Kephart *et al.* 2005	Elderly	respiratory drugs	lower	lower		M
Murawski and Abdelgawad 2005	Poor	antihypertensives	no change	no change	no change[3)]	S
prior-authorisation						
Hartung *et al.* 2004	Poor	celecoxib	no change	no change	higher[4)] lower[5)]	S
Kotzan *et al.* 1993a	Poor	H_2RIs	no change		no change[6)]	S
Kotzan *et al.* 1993b	Poor	NSAIDs	no change	no change		S
Smalley *et al.* 1995	Poor	NSAIDs, other analgesics, psychotropics	no change	no change		M
step-therapy or limited use						
Mamdani *et al.* 2007	Elderly	fluoroquinolones		no change	higher[7)](+8%) lower[8)](-32%)	S
Schneeweiss *et al.* 2004	Elderly	nebulised bronchodilators, steroids, cromoglycate	no change	no change	no change[3)]	S
Schneeweiss *et al.* 2006	Elderly	proton-pump inhibitors	no change	no change		S

1) H_2RAs; histamine-2-receptor antagonists, NSAIDs; nonsteroidal anti-inflammatory drugs
2) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months
3) other service expenditure
4) ER visits
5) gastrointestinal-related encounters
6) upper gastrointestinal endoscopy
7) utinary tract infaction-related hospitalisations
8) gastrointestinal infection-related hospitalisations

Concerns become greater when focusing on non-significant studies. There did not seem enough time to detect meaningful clinical changes in patients, particularly those with chronic illnesses. As shown in Table 5-15, all but two studies followed up policy consequences for no longer than a year. Episodes of admissions and emergency room visits might possibly be too rare to produce statistically meaningful changes over such a short period. Thus, it may be inappropriate to make any concluding remarks here, because retrieved studies might not be sufficient to generate meaningful information for policy consequences in terms of time-span and quantity.

5.5.6 Summary: Evidence about reimbursement restrictions

The included studies were of very mixed quality, with little apparent association between quality rating and direction or strength of results. Evidence from the retrieved studies suggests that reimbursement policies could lower spending on drugs considerably by a differential effect on preferred and restricted drugs. Largely, there was increasing consumption in fully-funded drugs such as generics or first-line medications and decreasing use in restricted drugs, indicating cost-effective prescribing in practice. However, worrisome aspects have been seen across studies. Simple withdrawal of payment not supported by other interventions such as prescribing guidelines could yield other undesirable prescribing. Mandatory reimbursement restrictions may increase the use of other resources, often more expensive, and discourage patients from adhering to medication schedules. Consequences may be exacerbated by inappropriate coverage decisions. It seems essential for policy-makers to bear in mind advice from Sun *et al.* (2007; p375-6) that "[plans] may need to examine the wide-ranging consequences of their medication coverage decisions". A systematic review by Cochrane reviewers, published in 2010 (Green *et al.*, 2010) , explored prior-authorisations and step-therapies reimbursement changes, included around 50% of the studies included in this review. That review included studies published after 2007 that this review could not include and excluded three studies that this study included. The two reviews are in accordance that reimbursement restrictions reduce payers' expenditure and drug utilisation selectively without explicit adverse effects on other resource utilisation. Both, however, also found that these conclusions are conditional on appropriate coverage decisions.

5.6 Incentives for professionals

5.6.1 Characteristics of Included studies

Among 17 studies, 9 examined UK fundholding by comparing fundholding and non-fundholding practices, which were rated as moderate to low quality. Four studies investigated the global budget in Sweden, Switzerland, China and Taiwan. Two studies from Europe were of moderate quality, while two from Chinese countries were rated as poor quality. One examined an itemised budget in Israel (rated as low quality); one tested the impact of one-off bonuses on Dutch physicians (rated as good quality); and two studies from North America addressed the introduction of financial incentives for less expensive therapies on physicians or pharmacists, rated as moderate quality. The basic characteristics of included studies are presented in Annex 14.

All but three studies employed CBA designs, the remaining three were analysed using ITS designs. All studies used a claims database maintained by a national or organisational body. Nine studies followed up the impact of interventions for no longer than a year after the implementation; eight studies addressed the intermediate-length of follow-up period after the policy interventions. Often, considerable baseline discrepancies were seen in CBA studies, especially those for UK fundholding, despite matching. Differences were particularly obvious between the first wave fundholders and others.

5.6.2 Impact on drug utilisation

Existing evidence shows that budgetary constraints may lower drug consumption only to a limited degree in the British fundholding programme (Table 5-16). The size of falls in utilisation was small – no greater than 5%, and inconsistent. The largest study including all fundholding practices from the first to the fifth wave in England showed that there were no significant differences between fundholders and non-fundholders in drug consumption (Harris and Scrivener, 1996). Some increases were found to be dependent on conditions such as comparators (Bradlow and Coulter, 1993; Wilson *et al.*, 1995).

As shown in Table 5-17, in the US, reward payments for generic prescribing did not

influence prescribing behaviour (O'Malley *et al.*, 2006). One-off bonuses to Dutch physicians in return for adhering to prescription guidelines brought only slight intended changes in gastric drugs among 10 recommendations (Martens *et al.*, 2007b).

Table 5-16: Impact of UK fundholding on drug utilisation and expenditure

Study	Wave	Drug utilisation	Drug expenditure (payer)	Generic prescribing rates	Prices (cost/item)
Baines *et al.* 1997	1st		lower (-12~ -13%)	higher in Devon (+21%) no change in Lincolnshire	
Bradlow and Coulter 1993	1st	higher (+1.4%)[1)]	lower (-6~ -9%)	higher (+5~ +13%)	lower (-7%)
Corney and Kerrison 1997	1st/2nd		no change		
Harris and Scrivener 1996	1st~5th	no change	(-6%)[2)]		
Rafferty *et al.* 1997	1st~3rd	no change	lower (-7~ -18%)	higher (+9~ +13%)	no change
Whynes *et al.* 1995	1st~3rd	lower	lower		no change
Whynes *et al.* 1997	4th	lower (-3%)	lower (-11%)	higher (+14%)	
Wilson *et al.* 1995	1st~3rd	lower in wave 1&3 (-4~ -5%) higher in wave 2 (+2%)	lower (-3~ -7%)	higher (+8~ +13%)	no change
Wilson *et al.* 1999	3rd/4th	lower	lower	no change	no change

1) non-dispensing fundholding practices, compared to non-fundholding practices
2) no statistical analsis given

Table 5-17: Impact of other incentives programmes on drug utilisation and expenditure

Study	Setting	Drug utilisation	Drug expenditure (payer)	Prices
global budget				
Etter and Perneger 1998	Switzerland		lower (-41~ -44%)	
Granlund *et al.* 2006	Sweden	no change ~ higher		no change
Lee *et al.* 2006	Taiwan		no change ~ higher	
Yip and Eggleston 2004	China		lower (-46%)	
others				
Elhayany *et al.* 2001	Israel		(-60%)[1)]	
Law and Wu 2003	Canada		no change	
Martens *et al.* 2007b	Netherlands	little change		
O'Malley *et al.* 2006	USA			no change

1) no proper statistical analysis given

5.6.3 Impact on drug expenditure

Across UK studies, seven studies showed that fundholders spent less on drugs, compared to non-fundholding practices (Table 5-16). The magnitude of reduction was slightly greater in drug expenditure than utilisation, about 3~13%, indicating that fundholders prescribed less expensive medications rather than issuing less prescriptions. The utilisation of generics was increased by 5~21% in five out of six studies, which was linked to a significant decline in prices in one study which was rated as high quality (Table 5-16).

By and large, savings were largest in the first year of being a fundholder in all waves, reducing over time (Harris and Scrivener, 1996; Whynes *et al.*, 1997). Dispensing fundholders were more likely to be affected than those that were non-dispensing (Bradlow and Coulter, 1993).

One Swiss university plan was successful in controlling expenditure growth by introducing a gatekeeper and a global budget on a capitation basis (Etter and Perneger, 1998). Drug expenditure was decreased by more than 40%, compared to those of a comparison plan with a FFS payment system. A Chinese payment experiment presented a similar result. Fourteen hospitals in Hainan where 'a prepayment scheme' was introduced, a sort of a monthly global budget, appeared to reduce expenditure on costly drugs by about 46%, compared to hospitals still operating on a fee-for-service basis (Yip and Eggleston, 2004).

Despite such encouraging results from included studies, a few methodological points are worth mentioning here. Positive results might be confounded by selection bias. For example, UK fundholding GPs, in particular those in the first wave, already showed better prescribing practices before becoming fundholders. Hence, prescribing behaviour of fundholders may be an inherent characteristic, not a policy achievement. Selection could occur in patients as well as providers. In Switzerland, heavy consumers tended to move away from a restricted plan into a more generous one when a capitation based budget scheme was implemented. Overall, studies were rated as poor quality.

Dissimilar to cases thus far, a global budget scheme in Sweden may not have brought about the intended changes either in drug utilisation or prices (Granlund *et al.*, 2006).

The authors suggested that there might be no room for further savings on drugs because the new budget scheme introduced in the region where had been affected by several cost containment strategies. In Taiwan, drug expenditure increased significantly rather than decreased after the implementation of a global budget scheme in hospitals (Lee *et al.*, 2006). Taiwanese authors drew the conclusion that savings were not seen because incentives were not directly aimed at prescribers in their drug budget scheme. In Canada, incentivised pharmacists could not change prescribers to a lower-priced therapy (Law and Yu, 2003).

An Israeli itemised budget constraint programme slowed the growth of drug costs by 60% over three years, compared with expenditure in the district as a whole (Elhayany *et al.*, 2001). However, such savings were offset by administrative expenses. Saving effects weakened and expenditure in ex-fundholding practices returned to the original levels with the discontinuation of the intervention.

5.6.4 Impact on other service use

The effect of budgetary regulation on referral rates to higher levels of care or more expensive services substituted for medications was not investigated in the included studies. On this issue, a previous review including less-well controlled studies, suggested that fundholding may not be associated with the increase of referral rates (Gosden and Torgerson, 1997), which is supported by a large scale quasi-experimental study exploring the effect of fundholding after the abolition (Dusheiko *et al.*, 2006). However, the association of pharmaceutical use and other service use resulted from incentives on professionals is unclear in these studies.

5.6.5 Summary: Evidence about incentives

The present review shows that budgetary constraints could be an effective strategy in containing spending for drugs when direct and constant incentives were given to prescribers. According to British studies exploring individual general practice budgets, prescribers may accomplish modest savings by prescribing less-costly medications, for example generics, rather than reducing the absolute prescribing volume. However, readers should bear in mind that these findings were from studies rated as moderate to low quality. Although this review included more studies from varied settings than the

previous Cochrane review (Sturm *et al.*, 2007), there were few differences in conclusions concerning the policy impact and little improvement in the quality of evidence available.

5.7 Distribution of samples

Three studies explored the association between free drug samples and prescribing practices in the US (Annex 15). One study used an ITS analysis; two employed CBA designs. All studies used a claims database maintained by a national or organisational body and tackled short-term effects over less than 3 years. Studies were rated as moderate to low quality.

Evidence from the retrieved studies showed that free drug samples might not be sufficient to modify physicians' prescribing behaviour. Doctors did not show a significant increase in prescribing generics, even after receiving free generic samples over a three-year period (O'Malley *et al.*, 2006; Scott *et al.*, 2007). Likewise, restrictions on access to free drugs stocked at physicians' offices did not achieve meaningful changes in the utilisation of non-formulary drugs (Mukamal *et al.*, 2002).

5.8 Mandatory generic substitution

One study rated as moderate quality examined the impact of mandatory generic substitution in Sweden, under which pharmacists were to dispense the cheapest substitutable products on the benefit list (Annex 15). Andersson *et al.* (2007) examined the policy impact on drug expenditure over more than two years, using a segmented regression analysis of nation-wide data. The study showed a sharp decrease in both public and private expenses on pharmaceuticals, which lasted two years after the implementation. There is no further information as to whether the policy influenced utilisation, prices or other service use.

5.9 Repeat prescribing

One study, rated as moderate to low quality, explored the impact of British repeat prescribing using an RCT study design for a year (Bond *et al.*, 2000) (Annex 15). It shows that pharmacists maintaining repeat prescribing brought out some

improvements in the quality of medication care by detecting adverse medication problems without increasing relevant medical services such as GP visits and hospitalisations. However, effects in drug volume and expenses seem negligible.

5.10 Separation of prescribing and dispensing drugs

One study, rated as moderate to high quality, tackled the impact of the separation policy in Taiwan, using a CBA design (Chou *et al.*, 2003) (Annex 15). The authors compared two regions that adopted the separation policy in 1997 with another two regions where there had been no changes.

This study showed that the Taiwanese separation policy might lower drug utilisation and expenditure only in clinics without pharmacists on-site. Patients attending such clinics were about 3 times more likely to have no prescriptions in the post-separation period, compared to patients in the control settings. Overall drug spending was reduced by 12% in clinics with no pharmacist over the study period. However, such changes were not found when all study clinics were included in the analysis. The authors suggested that physicians still prescribed and dispensed drugs on their premises by hiring pharmacists rather than modifying their prescribing behaviour, indicating no real separation in such premises.

5.11 Discussion

From the search of two major electronic databases and references from included studies, 117 studies were identified, which explored the impact of pharmaceutical regulations influencing providers. Half of the reviewed studies investigated educational interventions aimed at prescribing practices, followed by studies examining reimbursement policies and incentives for providers. Only a few studies addressed other measures such as distribution of free drug samples, mandatory generic substitution, repeat prescribing and the separation policy.

Overall, this review found the following from included studies:

- Studies exploring the impact of educational interventions were generally rated as moderate quality; those exploring the impact of reimbursement restrictions were of mixed quality but showed little variation in the findings according to

quality; those exploring the impact of incentives were of moderate to low quality. Thus, caution should be made when interpreting the findings of this review.

- Providing prescribing information achieved a limited success in correcting prescribing behaviour. Nevertheless, the improving patterns were likely to be associated with the intended outcomes (decrease or increase) in the utilisation of targeted drugs and lowering drug expenditure. The magnitude of reduction in drug expenditure was generally modest, between 10~20% and diminished over time.
- Educational interventions could lower drug expenditure when they focused on cost-effective information. In addition, if the information was either well-focused on problematic medications with good scientific grounds, on improper behaviour with individual-specific data, or supported by professionals, involved more multi-directional participants, disseminated repeatedly, and/or through multiple devices, it could also improve drug utilisation profiles.
- Educational approaches are unlikely to influence other resource use, overall health, or patient satisfaction.
- Greater and relatively invariable savings were seen in reimbursement policies among the included interventions. There were considerable reductions in restricted drug use with a slightly smaller increase in preferred drug use, resulting in marginal drops in overall utilisation. The effects of increasing use of less costly alternatives were likely linked to reducing drug expenditure. Among reimbursement policies, the withdrawal of inappropriate drugs from the benefit lists was less likely to change drug utilisation and expenditure than others.
- Few studies tackled changes in private expenditure after introducing reimbursement policies; there is limited evidence showing that step-therapies or limited uses could lower out-of-pocket payment.
- Some evidence indicates that reimbursement policies could increase other service use within a short term.
- Budgetary policies might lower drug expenditure only when they provided direct and constant financial benefits for prescribers.
- UK fundholding might have lowered drug expenditure by around 5~15% by increasing less-costly alternative prescriptions, not by decreasing the absolute prescribing volume. The greatest changes were achieved in the first year of involvement and weakened over time. However, it seems doubtful whether these were true savings or exaggerated by selection bias, because there were apparently different characteristics between fundholders and non-fundholders and little

change in price variables reflecting the effects of using less costly alternatives.

- There are few studies exploring other types of intervention. Unlike pre-existing beliefs, evidence from the included studies showed that doctors did not seem to be affected by free drug samples, these studies were rated as poor quality; mandatory generic substitution could lower both public and private expenditure; pharmacist-maintaining repeat prescribing brought little change in overall utilisation; the separation policy might lower drug utilisation and expenditure only in a strictly separated condition between prescribers and dispensers in Asian surroundings.

A shared aspect of policy interventions on providers is that savings were generated from the increasing use of less costly alternatives and decreasing a handful of expensive products, rather than a decline in overall utilisation. Impact from educational programmes and incentive schemes were smaller, compared to those from reimbursement policies in drug costs. From the doctors' viewpoint, it may be the same with educational interventions, in fact, competing with industry sources of information. In real terms, one of the most important informants is the drug company. In the US, it was estimated that drug companies spent $7.3 billion on detailing activity and provided $15.9 billion worth of drug free samples to physicians in 2004 (Schweitzer, 2007b). Continuing medical education programmes have been supported by drug companies to a considerable extent (Angell, 2005). Thus, Witt *et al.* (2004; p253) argued, "the method of academic detailing could easily be dismissed if it was not for the fact that the medical industry spends vast amounts on marketing efforts that include detailing".

Although the administrative interventions showed worthwhile decreases in drug costs in comparison with other voluntary-based measures, the query about actual savings is debatable. Administrative restrictions could raise more concerns about secondary consequences, being mostly compulsory measures with little consideration for patient-specific clinical characteristics. If they foster using other healthcare resources, the net saving would be much less.

A factor causing confusion in the calculation of savings in educational programmes may be administrative expenses. For instance, this review found that educational efforts might be positively associated with modifying prescribing behaviour toward evidence-based practices. Such changes, as hoped, brought a positive economic effect. However,

can savings really be calculated without considering programme expenses? Even if individual contacts or computerised technologies achieve greater changes in prescribing practices, it would not make economic sense in cases where spending exceeds saving – so called "policy cost-effectiveness" (Mason *et al.*, 2001). However, evidence of net benefit is almost lacking in this review. In the included studies, only two studies addressed this subject and failed to show the positive net effects after taking off the administrative costs except one sub-case.

In addition, little attention was given to questions like whether pharmaceutical regulations affect patients' costs and if so, how much those are and whether or not such measures influence equity among social groups. Linked to these issues, the Swedish mandatory generic substitution policy and two step-therapy studies showed a decline in expenses to both insurer and patient. It is worthy of note, given that other policies appeared to accrue extra expenses to patients.

In South Korea, a variety of efforts influencing providers are currently made including positive lists, prescribing budgets, computerised DUR systems and generic prescribing (Chapter 2). They seem to encompass every possible option that this review found across countries. This review yields little information directly relevant to Korean pharmaceutical policy, but demonstrated that many known and unknown factors are able to affect policy outcomes. Moreover, the questions about the association between the policy interventions and health remain unanswered. Therefore, the vital factor in policy-making efforts is to evaluate outcomes and consequences through robustly designed experimental or quasi-experimental analyses of empirical data from the Korean population.

Bearing in mind the limited generalisability of the findings, the following information should be considered in Korean pharmaceutical policy-making:

Although prescribing feedback has been implemented for nearly a decade in Korea, it is thought that few actual alterations have been achieved in prescribing practices (Chapter 2). The impact of this policy has been inadequately evaluated. Hence, it may be difficult to discover the true causes for its ineffectiveness despite that Korean prescribing feedback has regularly delivered individualised data to prescribers. Given the findings from this review, one of the important reasons may be that standardised,

centralised information has not been supported by prescribers, who may have a number of clinical reasons to prefer individual patient databases. This review shows that it seems worthwhile in future focusing primarily on problematic prescribers with clear clinical reasons rather than giving feedback to every prescriber.

The current review also shows that inappropriate coverage decisions may yield unwanted policy consequences. At present, Korean authorities work on a new positive list grounded in cost-effectiveness (Chapter 2). Simultaneously, concerns are growing over the quality of pharmacoeconomic evaluation studies available in Korea. Choi (2008) asserted several challenges concerning economic evaluation in her recent article. First, studies are conducted on integrating local cost data and foreign clinical data, owing to the lack of randomised clinical studies in the Korean context. Second, funding and experts are scarce for the validation of such mixed research. Third, drug companies often resist disclosing the raw data of their economic studies, which is vital for validation. In this respect, it should be borne in mind that poor economic studies may result in undermining the value of economic evaluation and increasing overall costs to the healthcare system if expensive but marginally effective drugs are not ruled out.

Finally, it was observed that various measures explored in the reviewed studies contained costs by encouraging utilisation of generics. However, this was not always the case. For instance, the Spanish series of papers demonstrated that an increase in generic prescribing could not affect drug costs as shown in Table 5-7 (Sicras-Mainar and Pelaez-de-Lono, 2005; Sicras-Mainar *et al.*, 2007; Sicras-Mainar *et al.*, 2004). Presumably, this was due to the low baseline use of generics in Spain (European Generic Medicines Association, 2004), subsequently, in the study nursing homes (about 8%). In such surroundings, generic utilisation might hardly affect overall drug expenditure, even though generic use increased by 50%. Thus, for better policy outputs relating to generic policies, it seems essential to discover the situation of the Korean generic market before taking a step forward.

Among evaluated interventions, budgetary interventions seem promising as policy options encouraging generic use. However, a careful interpretation should be made because current evidence is derived from studies rated as moderate to low quality and mostly from the UK, with a substantially different healthcare system from Korea. There

may be huge administrative challenges in Korea where most providers operate on a private basis in contrast with the UK NHS. Alternatively, measures limiting the less cost-effective drugs, including prior-authorisations or step-therapies, may be recommendable if common sense is exercised about 'less cost-effective drugs' in society like 'antibiotics for the common cold' (Chapter 2). If it merely selects some drugs because they are expensive, it may raise policy resistance and social inequity.

5.12 Summary

This review found that existing evidence about the impact of pharmaceutical policies influencing healthcare providers is concentrated on three types of intervention: educational approaches; reimbursement restrictions; and incentives. Although the included studies used rigorous study designs, they were of very mixed quality. Greater caution should be made with the studies exploring incentives that showed poor quality in general. Little attention has been paid to other policies such as free drug samples, generic prescribing/ substitution, alternative prescribers or the separation policy. Evidence from studies suggests that voluntary-based interventions including educational and budgetary measures are associated with limited and short-term success in lowering drug expenditure. Policies restricting drug reimbursement may be linked to greater impact in lowering drug expenditure. In most cases, impact on drug utilisation was selective. Although few studies tested the policy impact on the use of other resources, overall health and private expenses, there are some concerns that inappropriate reimbursement decisions may lead to an increased use of other resources, possibly linked to deteriorating health. Korea has a relatively short history in implementing pharmaceutical policies that influence healthcare providers. It should not be overlooked that there are clear limitations to generalising foreign experience to the Korean context. Further discussion about methodological aspects of the reviewed studies and implications for the current research are continued in Chapter 7.

CHAPTER 6: THE EFFECTS OF PHARMACEUTICAL REGULATIONS INFLUENCING INDUSTRY

6.1 Introduction

The objective of this chapter is to present findings from the systematic review concerning pharmaceutical policies regulating industry. In brief, studies for this review were identified from two major databases, MEDLINE and EMBASE, and included if the article (1) explored the effects of pharmaceutical regulations aimed at influencing industry; (2) examined the effects of such interventions on at least one of the relevant outcomes depicted in Chapter 3; (3) analysed primary or secondary data; and (4) performed this with one of three most robust designs, RCT, ITS, or CBA. Details of methods were presented comprehensively in Chapter 3.

6.2 Overview of included studies

In the search for pharmaceutical policies regulating industry (Annex 4), 265 studies were identified (Figure 6-1). Thirty were retained after the initial screening of titles and abstracts. And of them, 19 studies finally met the inclusion criteria (Table 6-1). The majority of these studies are devoted to evaluating pricing controls: reference-pricing programmes (n=13), other price controls (n=3). Single studies explored the effects of a formal quest for cost-effectiveness information on reimbursement decisions, patent expiry and profit control. Reasons for exclusion are reported in Figure 6-1 and Annex 6.

6.3 Policies regulating industry

For several decades, governments have been controlling pharmaceutical prices to regulate industry (Jacobzone, 2000; Mrazek and Mossialos, 2004). They commonly set, cut, or agree prices for drugs. For example, in the studies reviewed, an American Medicaid agency set an upper limit of reimbursement for prescribed drugs, which is one of the principles of pricing mechanisms in Korea.

Figure 6-1: Flow diagram of studies (industry)

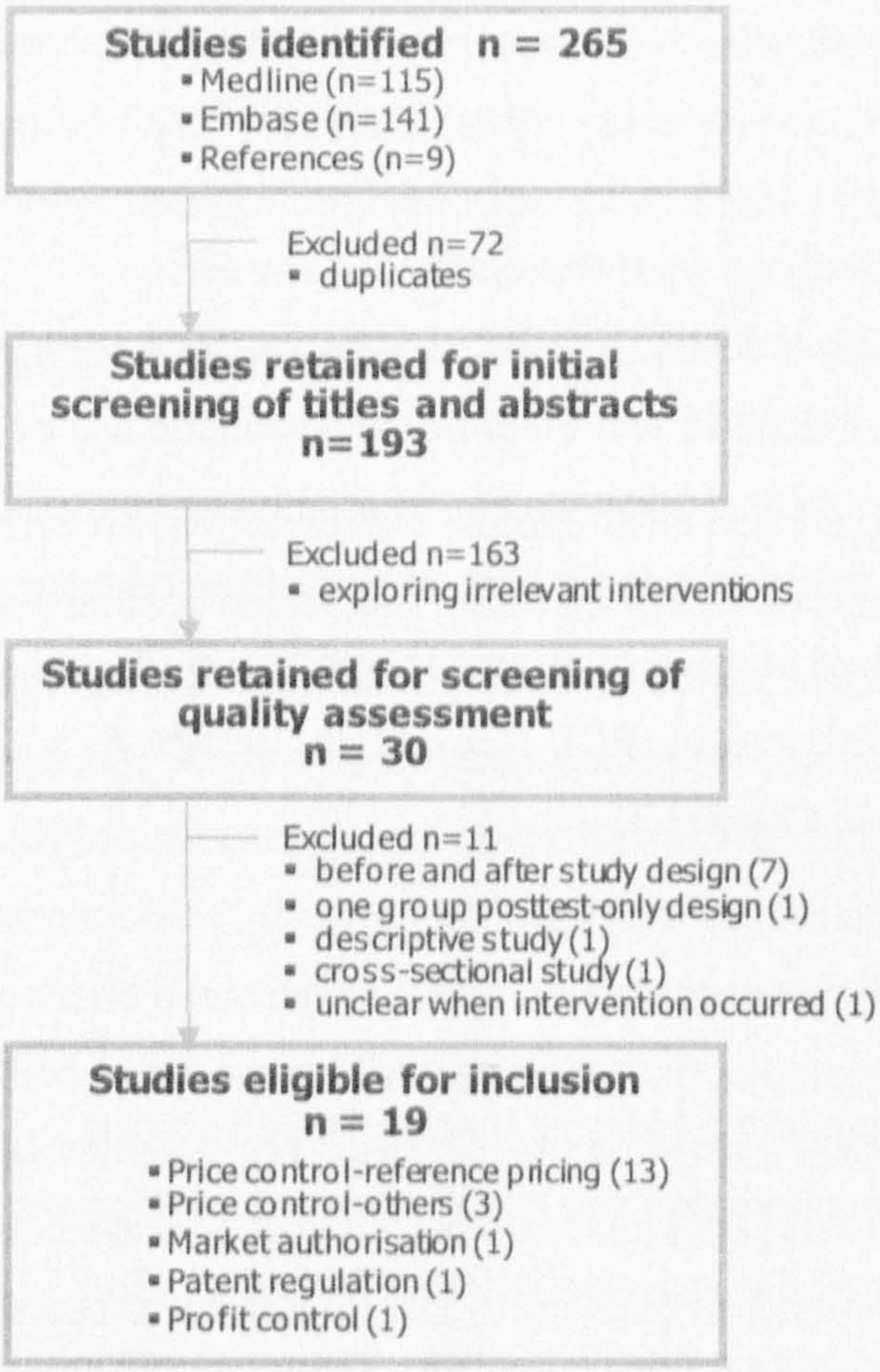


Table 6-1: Studies included

Intervention		Studies
Reference pricing	13	Andersson *et al.* 2006, Bergman and Rudholm 2003, Grootendorst and Stewart 2006, Grootendorst *et al.* 2001, Grootendorst *et al.* 2005, Hazlet and Blough 2002, Mabasa and Ma 2006, Marshall *et al.* 2002, Pavenik 2002, Puig-Junoy 2007, Schneeweiss *et al.* 2002b, Schneeweiss *et al.* 2002c, Schneeweiss *et al.* 2003
Other price control	3	Almarsdottir *et al.* 2000, Lee *et al.* 2006, Sawyer 1983
Formal quest of cost-effectiveness information	1	Lundkvist *et al.* 2006
Patent regulation	1	Boersma *et al.* 2005
Profit control	1	Borrell 1999

Since Germany, introduced a reference-pricing system in 1989, which indirectly controlling prices for drugs, it has been expanded to a number of countries. In reference-pricing systems, a reimbursement price is set for drugs and patients have to pay for the difference between the cost of the product prescribed and the reference price. Three of the most influential policy factors that determine the impact size are: how to group pharmaceuticals; how to compute reference prices; and whether or not to include patented drugs (Lopez-Casasnovas and Puig-Junoy, 2000). This review identified studies evaluating the impact of reference-pricing programmes implemented in Germany, Sweden, Spain and some Canadian provinces. Early German and Canadian, and Spanish systems classified drugs by chemically active ingredients and the Canadian and German systems classified further by therapeutic classes. The German reference-pricing programme broadened the drug groups to therapeutic effects. The reference price may be the lowest daily cost (Canada), the average price of drugs in a category (Germany), the average price of the three lowest price drugs in a category (Spain), or the lowest priced drug plus a certain amount of mark up (10% in Sweden). New and innovative drugs are excluded by reference-pricing programmes in these countries.

A small number of countries regulate industry through controlling the profits of drug producers. In the British Pharmaceutical Price Regulation Scheme (PPRS), companies are allowed freedom of pricing for their products and voluntarily negotiate target profits from sales of drugs to the NHS with the authority. In 2005, the target profits were 21% on a Return on Capital basis and 6% on a Return on Sales basis (Department of Health, 2006b). According to the target, manufacturers earning excessive profits may be required to reduce prices of drugs provided to the NHS.

Licensing or reimbursement decisions are long-lasting ways of regulating industry alongside price control. Licensing is a drug approval procedure, processed in most countries with the criteria of safety and clinical efficacy. No studies exploring this policy were identified. In recent years, governments have increasingly required cost-effective evidence in reimbursement decisions, through which the government wishes to curb expensive but marginally innovative new drugs. The global patent system was enforced in 1986 to encourage R&D investment by awarding temporary monopoly power on successful innovation for new drugs. Basic characteristics of included studies and outcomes from the review are discussed by intervention in the following sections.

6.4 Reference-pricing schemes

6.4.1 Characteristics of included studies

Basic characteristics of included studies are presented in Annex 16. The majority explored the impact of reference-pricing introduced in 1990s in Canada. Most Canadian studies were rated as moderate to high quality and involved elderly beneficiaries on a PharmaCare plan in British Columbia as an intervention population, while Mabasa and Ma (2006) analysed the effects of a similar pricing regulation of PPIs on members of an employer-sponsored drug plan in Ontario. The remaining four studies were from other nations, such as Germany, Sweden and Spain, and were rated as moderate to low quality.

All but two studies employed ITS designs. Most of these used monthly data, whilst two utilised quarterly data (Bergman and Rudholm, 2003; Pavenik, 2002) and one utilised quarterly (before) – monthly (after) data (Andersson *et al.*, 2006). One study used a CBA design (Mabasa and Ma, 2006). Schneeweiss and colleagues explored secondary outcomes of the policy using a CBA design alongside ITS analyses for the primary outcomes (Schneeweiss *et al.*, 2003; Schneeweiss *et al.*, 2002c).

Eleven studies used aggregated claims data held by national or provincial-level authorities; two non-Canadian studies employed market sales data constructed by IMS Health. Two studies explored the impact of longer than 5 year-term policies. Others followed up the policy effects at short- or intermediate-term.

6.4.2 Impact on drug utilisation

Evidence from retrieved studies demonstrates that reference-pricing programmes may be effective in reducing the volume of non-reference drugs and increasing the volume of reference drugs. As a result, modest or little impact in overall use has been shown (Table 6-2).

Reference-pricing schemes could carry less-desirable substitution effects. Grootendorst *et al.* (2005) reported that they observed an increased use of costly opiates after applying reference-pricing to NSAIDs, however, their aggregate data could not provide

further evidence whether oplates were being prescribed as a substitute for restricted NSAIDs, or prescribed due to treatment failure on the part of the lower cost NSAIDs. In this respect, two studies exploring the histamine-2-receptor antagonists (H_2RIs) the reference-pricing, showed that prior-authorisation of PPIs, introduced simultaneously, might be helpful to curb potential increases in other substitutable noncost-effective medications (PPIs in this case) (Hazlet and Blough, 2002; Marshall *et al.*, 2002).

Table 6-2: Impact of reference-pricing schemes on drug utilisation

Study	Setting	Study drugs[1)]		Drug utilisation[2)] Overall	Therapeutic class	Restricted drugs	Reference drugs	Related drugs
Andersson *et al.* 2006	Sweden	Overall		no change	no change ~lower			
Pavenik 2002	Germany	*oral antidiabetics*		no change[3)]		lower	no change	
		antiulcerants		no change[4)]		lower	higher	
Puig-Junoy 2007	Spain	statins			no change ~lower			
Grootendorst and Stewart 2006	Canada	ACEIs, CCBs			no change			
Grootendorst *et al.* 2001	Canada	nitrates, CCBs			no change	(-12~-68%)	(+86~+124%)	
Grootendorst *et al.* 2005	Canada	NSAIDs	same active ingredient		no change			no change ~ lower
			therapeutic class		no change			no change ~ higher
Hazlet and Blough 2002	Canada	H_2RAs (PPIs)			no change			no change[5)]
Mabasa and Ma 2006	Canada	PPIs			(-20%)			
Marshall *et al.* 2002	Canada	H_2RAs (PPIs)		(+12%)[6)]	(+14%)	(-51%)	(+316%)	no change[5)]
Schneeweiss *et al.* 2002b	Canada	ACEIs		no change[7)]	lower	lower	higher	
Schneeweiss *et al.* 2003	Canada	dihydropyridine CCBs		no change[7)]	lower	lower	higher	

1) ACEIs; angiotensin converting enzyme inhibitors, CCBs; calcium channel blockers, H_2RAs; histamine-2-receptor antagonists, NSAIDs;nonsteroidal anti-inflammatory agents, PPIs;proton-pump inhibitors
2) *In cases no proper statistical evidence given but more than 10% differences reported, the results are in perantheses.*
3) all oral antidiabetics
4) all antiulcerants
5) special authority for PPIs implemented concurrently
6) all gastrointestinal (GI) drugs; an increase of the use of cisapride was leading to an increase of all other GI preparations use
7) all antihypertensives

6.4.3 Impact on drug expenditure and prices

As shown in Table 6-3, encouraging the utilisation of less costly drugs through reference-pricing was linked to a considerable decline in payers' spending on drug

classes of 11% to 50% in Canada. Greater effects were seen in the scheme with therapeutic class clustering rather than chemical identical grouping. The magnitude of effect has decreased over time (Grootendorst and Stewart, 2006; Schneeweiss *et al.*, 2003). A far smaller impact has been observed in studies rated as poorer quality, undertaken in other settings such as Spain and Sweden.

Table 6-3: Impact of reference-pricing schemes on drug expenditure and price

Study	Setting	Clustering		Drug expenditure		Price[1)]
		same active ingredient	therapeutic class	Payer[1)]	Out-of-pocket[1)]	
Andersson *et al.* 2006	Sweden	Y		no change		lower
Bergman and Rudholm 2003	Sweden	Y				no change ~ lower (-16~-21%)
Pavenik 2002	Germany	Y (1989)	Y (1991)			no change ~ lower
Pulg-Junoy 2007	Spain	Y		lower (-2.2%)		lower
Grootendorst *et al.* 2005	Canada	Y		lower (-11%)	higher	no change ~ higher
			Y	lower (-44%)	higher	no change ~ lower
Grootendorst and Stewart 2006	Canada		Y	no change ~ lower		no change
Grootendorst *et al.* 2001	Canada		Y	lower (-22 ~ -50%)	(+390%)	(-11~ -39%)
Mabasa and Ma 2006	Canada		Y	(-26%)		(no change)
Marshall *et al.* 2002	Canada		Y	(-45%)	(+16%)	(-52%)
Schneeweiss *et al.* 2002b	Canada		Y	(-19%)		
Schneeweiss *et al.* 2003	Canada		Y	(-12%)		

1) In cases no proper statistical evidence given but more than 10% differences reported, the results are in perantheses.

In contrast to policy expectation, reference-pricing may result in a minimal price reduction (Table 6-3). Included studies came from Canada indicated that reductions in payers' expenditure might be achieved substantially by raising patients' out-of-pocket payment. Grootendorst and colleagues estimated that elderly patients' out-of-pocket payments represented about 8~20% of insurers' savings in their studies (Grootendorst *et al.*, 2001; Grootendorst *et al.*, 2005). As a result, people of low income status may

be more likely to give up their medication (Schneeweiss *et al.*, 2003).

Pavenik (2002) suggested that brand prices might be lowered further where a larger generic market had been established, as in Germany and Sweden (Bergman and Rudholm, 2003). A Spanish study, rated as moderate quality, however, demonstrated that prices tended to converge at a reference price; there was an immediate price reduction in products above the reference line, but little impact in those initially below the level (Puig-Junoy, 2007). The author argued that the drug price might be dropped not by price competition, but by regulatory decisions, i.e. "the method of calculation of the reference price" in the heavily regulated Spanish market.

6.4.4 Impact on other service use and clinical variables

Four Canadian studies investigated whether restricting the use of costly drugs carried any change in other medical services utilisation or clinical variables (Table 6-4). None found any meaningful changes in relevant variables within a 12-month study period.

Table 6-4: Impact of reference-pricing schemes on other clinical variables

Study	Population	Study drugs[1)]	Variables	Effects	Follow-up[2)]
Hazlet and Blough 2002	Elderly	H_2RAs (PPIs)	Office visits	lower	S
			ER visits	no change	
			hospitalisations	no change	
			length of stay	no change	
Schneeweiss *et al.* 2002b	Elderly	ACEIs	drug discontinuation	no change	S
Schneeweiss *et al.* 2002c	Elderly	ACEIs	physician visits	no change	S
			emergency hospitalisations	no change	
			nonemergency hospitatisations	no change	
			long-term care admissions	lower	
			mortality	no change	
Schneeweiss *et al.* 2003	Elderly	dihydropyridine CCBs	physician visits	no change	S
			emergency hospitalisations	no change	
			nonemergency hospitatisations	no change	
			other services expenditure	no change	

1) ACEIs; angiotensin converting enzyme inhibitors, CCBs; calcium channel blockers, H_2RAs; histamine-2-receptor antagonists, PPIs;proton-pump inhibitors
2) S equal or less than 12 months

6.4.5 Summary: Evidence for reference-pricing schemes

Based on Canadian studies, rated as higher quality in general, this study found that reference-pricing schemes could reduce pharmaceutical spending with few changes in overall utilisation, suggesting less deterioration in patient accessibility. Savings may be achieved through partially increasing the use of less costly medication, namely reference drugs, and, in parallel, increasing patient expenses. Hence, it seemed to discriminate against patients who faced unavoidable extra out-of-pocket expenses in some quarters. Greater effects were observed in reference-pricing schemes that grouped drugs by therapeutic class compared to by the same active ingredient. There is some evidence for lowering prices in pharmaceutical products above the reference price in the market. However, empirical data suggests that the opposite trend could be possible if the price was below the reference line. Few studies reported unwanted consequences, but the impact of reference-pricing on overall heath and other healthcare resources seem still warranted, given that most evidence came from one Canadian province and none were truly dedicated to addressing consequences in health.

6.5 Other price controls

Three retrieved studies were dedicated to investigating regulations relating to other price controls in three different settings (Annex 17). All employed an ITS design to investigate the association between the new policy and drug costs using government-level claims data over a relatively long period, 2~7 years.

Evidence from included studies suggests that price controls may hardly affect drug spending (Table 6-5). Although one Taiwanese study rated low quality suggested a minimal decline after some of the national pricing scheme changes, the other two studies rated as higher quality did not support the changes.

An early US study examining the impact of the Maryland Maximum Allowable Cost (MAC) limit on multisource drugs showed a temporal decrease in total drug expenditure after the change. However, the authors concluded that it might be due to fewer beneficiaries wanting to get drugs in a newly introduced copayment schedule rather than the new pricing policy (Sawyer, 1983).

Table 6-5: Impact of various price controls on drug expenditure

Study	Setting		Drug expenditure (Payer)
Almarsdottir *et al.* 2000	Iceland	deregulation of OTC price set	no change
Lee *et al.* 2006	Taiwan	1st ~ 3rd mechanisms[1)]	no change
		4th ~ 6th mechanisms[2)]	lower
Sawyer 1983	USA	total expenditure	lower
		costs/patient	no change

1) International and inter-brands price comparison, market price survay
2) market survey, generic grouping, flat payment rates

6.6 Formal request for economic evidence

One study addressed the association between the formal requirements for cost-effectiveness information in reimbursement decisions and time lags before authorisation using an ITS design with yearly data from regulatory authorities, but the quality of the study was poor (see Annex 18 for the basic characteristics).

Lundkvist and colleagues (2006) investigated 242 new chemical entities (NCEs) approved in Finland and Sweden from 1995 to 2003 and found that the new procedure tended to prolong the time until final decision only in the first year of implementation. Additionally, NCE drugs launched by the bigger manufacturers or with a bigger volume of sales appeared to go more quickly through the authorisation procedure. The authors concluded that a crucial determinant of time taken in the new authorisation procedure might be linked to the capacity for obtaining requested information.

6.7 Patent regulation

In the Netherlands, Boersma *et al.* (2005) investigated the trends in the use of generics after patent expiry for enalapril, fluoxetine and ranitidine and the price changes of these medications over 6 years using a time-series analysis of the InterAction Database which holds prescription records covering approximately 300,000 Dutch patients (Annex 18). Evidence from the study rated as moderate quality showed that drug costs per DDD dropped markedly by about 50~70% after patent expiry, mainly due to the increasing use of generic alternatives.

6.8 Profit control

One included study explored the rate-of-return (ROR) regulation in the UK PPRS using an ITS design with an annual price index between 1980 and 1994, which was rated as being of moderate to low quality (Borrell, 1999) (Annex 18).

Evidence from the study suggests that changes in the ROR cap have had little impact on drug price indices; a 1% change in the ROR cap has generated only a 0.15% change in the aggregate price index overall. Despite the small impact, the author suggested, "the UK regulation of the price of medicines has encouraged innovative UK-based pharmaceutical firms to diversify into competitive pharmaceutical market" (p301).

6.9 Discussion

After searching two major electronic databases and relevant references, 19 studies examining the effects of pharmaceutical policies influencing industry were identified. About three-quarters of the retrieved studies explored the effects of price controls on drug utilisation and expenditure. Few studies addressed the impact of profit control, market and patent regulations and those studies that did were rated as poor quality. Approximately half of the studies came from North America, thanks to Canadian exploration of reference-pricing; the other half came from Western Europe, with just one study from elsewhere. This study drew conclusions about the impact of reference-pricing primarily based on the Canadian studies, since these were largest in number and rated as higher quality.

Overall, this review found the following from included studies:

- Reference-pricing schemes may achieve savings partly by increasing the use of less costly medication, and, in parallel, increasing patient expenses. There are certainly greater effects when clustering drugs by therapeutic class in comparison with active ingredient. Evidence supporting the impact of reference-pricing schemes on price decreases is currently weak.
- Few studies report unwanted consequences, though evidence about policy consequences still seems to be lacking.
- While price control is routinely used, it has rarely been evaluated. From three

included studies, little positive evidence was found that direct pricing measures were associated with altering the trend of increasing drug expenses.

- Few rigorous evaluations were found which investigated other regulations such as patents, market authorisation, or profit control. Thus, few or no inferential conclusions can be made through this review.

Although this study conducted a comprehensive search without limiting interventions, studies exploring interventions other than price controls were rarely identified. Hence, figures in this study look very similar to the previous Cochrane review addressing pricing policies (Aaserud *et al.*, 2006a). This study included a small number of extra studies that are either awaiting review by the Cochrane authors or were derived from electronic searches in relation to price controls.

The previous reviewers argued that policy details could yield considerably different outcomes in reference-pricing schemes (Danzon and Ketcham, 2003; Lopez-Casasnovas and Puig-Junoy, 2000). This review highlighted the association between policy differences and impact in Table 6-3 (see Annex 16 for more details). There were certainly greater effects in clustering drugs by therapeutic class in comparison with the same active ingredient. The relationship between the other two policy variables and impact was inconclusive, because there were insufficient included studies to compare with one another. Four non-Canadian studies did not provide comparable information about effect size. No studies were identified from countries such as Australia, the Netherlands or New Zealand, where on-patent drugs are included in groupings. In addition, it was impossible to test previous reviewers' arguments that the new regulation might lead to a cutback in R&D activity by the industry in this review, since there were no relevant outcomes measured in the included studies.

Out-of-pocket payments increased by a large amount after reference-pricing, reflecting that patients (or prescribers) consumed costly drugs above the reference line by paying extra out-of-pocket. No further information was available about what makes them endure extra costs.

Although price control has been implemented in various countries for several decades, rigorous evaluation seems to be lacking. Existing evidence suggests there is little effect in drug costs with a single-faceted price control approach. This may be partly because

the price factor affects little the recent pharmaceutical expenditure growth. Nefarma data indicates that price factors contributed little (about -1~1%) to the growth of total expenditure (about 4~12%) in several major European countries (Mossialos *et al.*, 2004). Overall, the findings of this review support the Guillen and Cabiedes (2003; p12) remarks; "price-control policies do not guarantee expenditure control when they are not accompanied by control of quantity".

Price control has been one of the most central and longest lasting pharmaceutical polices in South Korea (Chapter 2). According to the recent government document, the fraction of price factor accounted for -0.67% out of 13.7% total drug expenditure growth in 2003/4 in Korea, which is similar to the European figure from Nefarma above (Ministry of Health & Welfare, 2006c). This implies that price control may also be less effective in the Korean situation.

The Korean government tried but failed to introduce a reference-pricing system in 2002. The causes of failure were universal policy resistance and an initial grouping that was too broad to make clinical sense (Lee and Lee, 2007). Owing to the constantly rising trend of drug costs, a reference-pricing system has recently been re-highlighted in the hope of influencing all relevant stakeholders. The most recent report suggested refinement to the new reference-pricing system; by 1) introducing in a stepwise manner; 2) grouping drugs by chemical active ingredient; and 3) setting the weighted average prices of drugs in a category as the reference price (Lee and Lee, 2007). They also recommended a gentle transformation for lowering the reference line and amending grouping to therapeutic classes. Their initial suggestions, however, do not sound very promising in terms of economics. As the Korean authors mentioned in their context, Norway abolished its reference-pricing system due to cost-ineffective outcomes when considering administrative expenses (Haga and Sverre, 2002). This review clearly demonstrated that reference-pricing systems clustered by the same active ingredient have shown a minimal impact on drug costs, even though they set the reference price at much tighter levels than 'a weighted average price' that the Korean authors suggested. In this regard, it is worrisome that a reference-pricing system may merely increase private expenses and, consequently, augment social inequity.

6.10 Summary

Despite frequent exploitation, robust assessment of policies regulating the drug industry are rarely performed and little is known about the policy impact. Most evidence found in this review related to a reference-pricing scheme in one Canadian province. This review found that reference-pricing reduced drug costs with little change in overall utilisation. Therapeutic class clustering may achieve greater savings than that of the same chemical ingredient. Included studies showed that the reference-pricing might result in little change in clinical variables or other service use, but at the expense of a high increase of private costs. Limited evidence from included studies suggests little success in other price control programmes. Given the negligible share of the price factor in the recent drug expenditure growth, the effects of price control are expected to be small in South Korea. Further discussion of the methodological aspects of reviewed studies and implications for the present research are continued in Chapter 7.

CHAPTER 7: LESSONS FROM INTERNATIONAL EXPERIENCE: METHODOLOGICAL ISSUES AND KEY FINDINGS FROM SYSTEMATIC REVIEWS OF THE LITERATURE

7.1 Introduction

Chapter 3 through 6 systematically appraised published research to explore what is known about the effects of various pharmaceutical regulations on expenditure and utilisation of drugs and other health services. In total, 176 studies were reviewed and evaluated critically. This chapter discusses methodological aspects of the included studies and highlights the findings from the systematic reviews. At the end, implications for the empirical research are discussed.

7.2 Methodological issues

7.2.1 Overall study design

Sixty-seven studies used CBA designs; 71 employed ITS designs; and 41 used RCT designs. Details for study designs used in each intervention are displayed in Figure 7-1 overall and in Table 7-1 by intervention. Some variation in quality rating was seen by study design. CBA studies were rated of moderate quality; RCT studies were rated of moderate to high quality; but ITS studies were rated of mixed quality.

Slightly more than a third of ITS studies were equipped with a control series, and most of these came from the North American context. It seems natural that researchers in Canada and the US are more likely to find a proper comparator than those elsewhere. In the North America, since regulations are likely to be implemented at state- or private health plan-level, each state (or plan) may act as a good comparator for another. Given the difficulty of randomisation in social sciences (Chapter 2), an unexpectedly large portion of studies, more than 20%, employed RCT designs. The majority of RCT studies investigated educational measures. It may be because studies addressing educational measures involve a relatively small population, making it more feasible to randomise participants, whether in the intervention or control.

Figure 7-1: Study design in the included studies

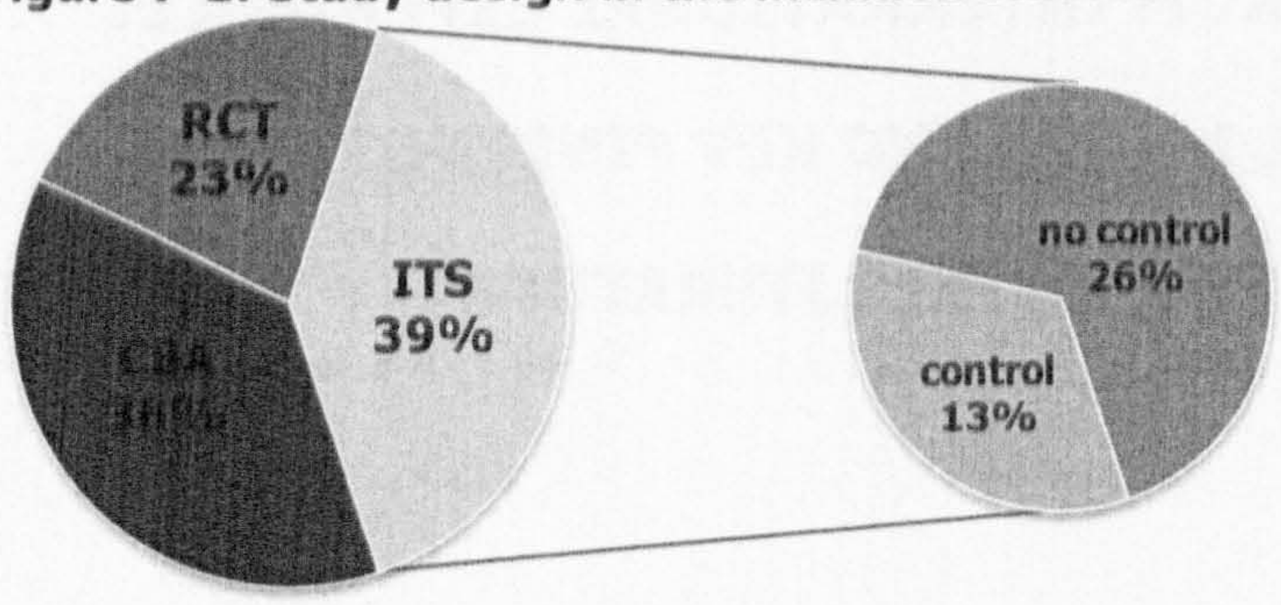


Table 7-1: Study design by type and intervention

	RCT	CBA	ITS		Total
			control	*no control*	
number of studies	41	67	24	47	179[1)]
by intervention	41	67	24	53	185[2)]
patients					***46***
cost-sharing	2	8	4	16	30
tiered formulary		7	2		9
prescription caps			3	2	5
educational approach	1				1
OTC switch				1	1
providers					***119***
educational approaches	36	21	3	3	63
reimbursement restrictions	1	11	6	15	33
incentives		14	2	1	17
distribution of samples		2	1		3
mandatory generic substitution				1	1
repeat prescribing	1				1
SPD[3)]		1			1
industry					***20***[1)]
reference pricing		3	3	8	14[1)]
price control (others)				3	3
profit control				1	1
market authorisation				1	1
patent regulation				1	1

1) Schneeweiss *et al.* 2003 is included two times in CBA and ITS (no control) respectively and O'Malley *et al.* 2006 is included three times in CBA.

2) Four studies are included two times (Almarsdottir *et al.* 2000, Andersson *et al.* 2006, Gurwitz *et al.* 1995, Starmans *et al.* 1994) and two studies three times (O'Malley *et al.* 2006, Lee *et a*l. 2006)

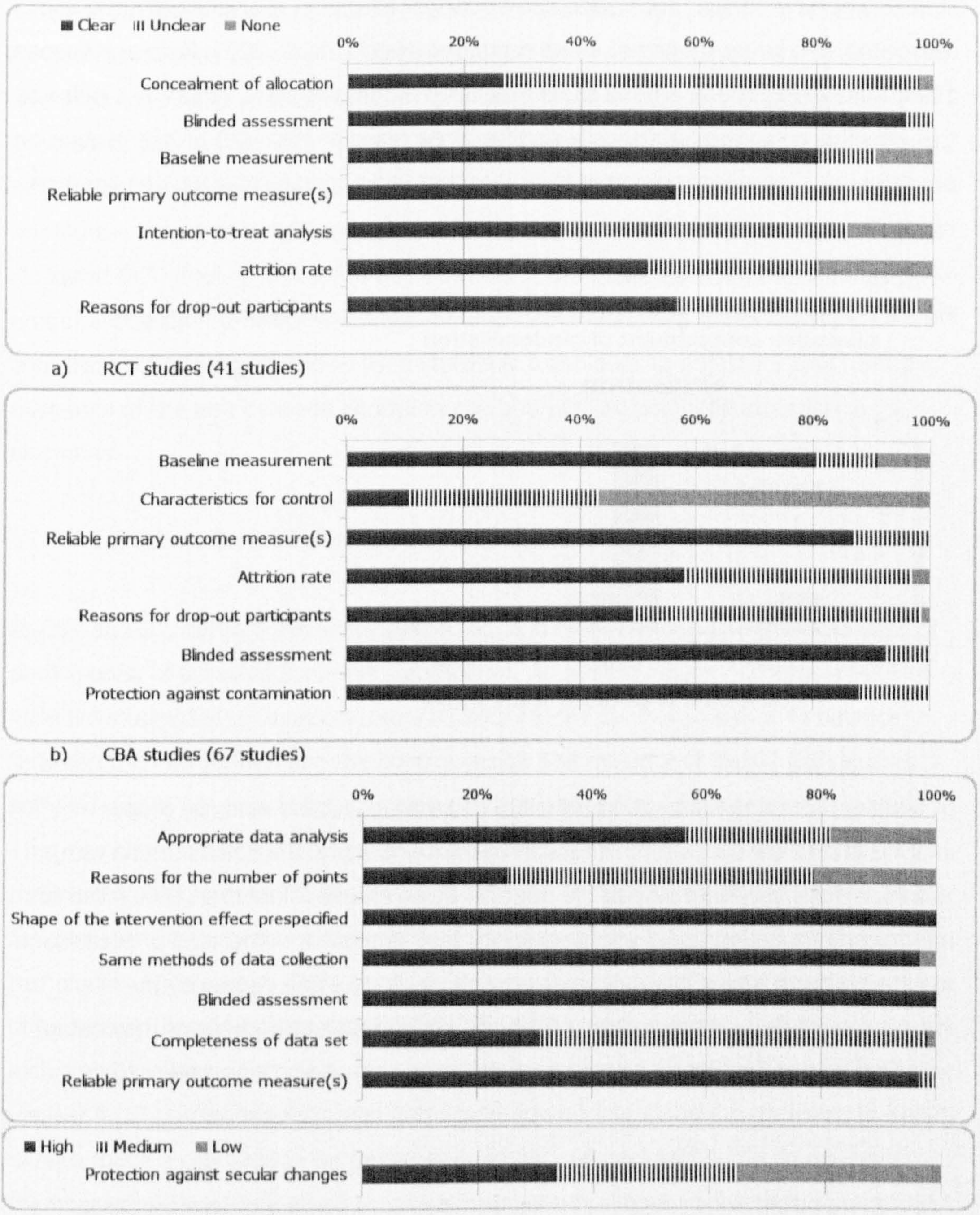
3) separation of prescribing and dispensing of drugs

7.2.2 Sources of bias

7.2.2.1 Randomised controlled trials

As shown in Figure 7-2, a crucial element to securing the internal validity in an RCT design is undoubtedly randomisation.

Figure 7-2: Outcomes in quality assessment



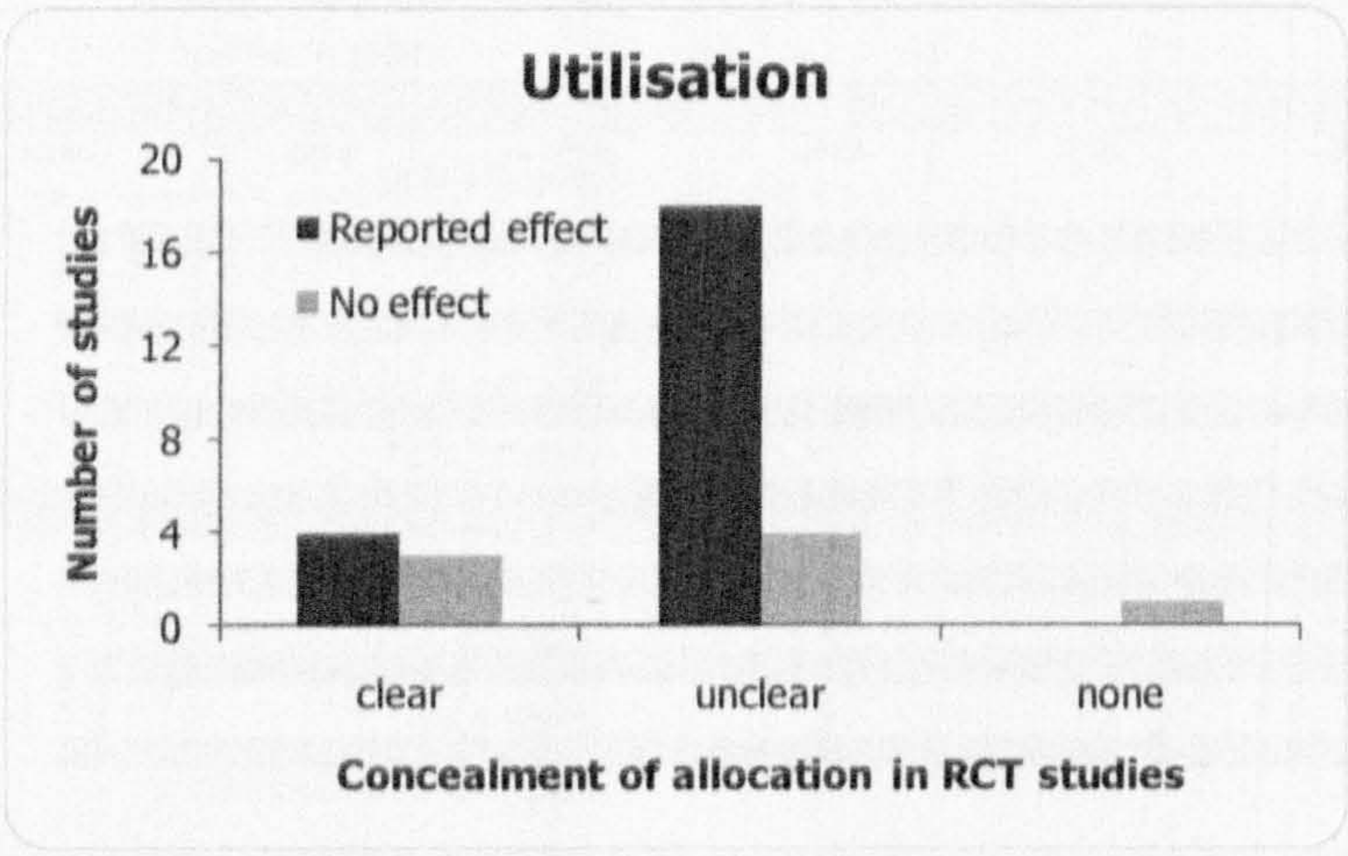
a) RCT studies (41 studies)

b) CBA studies (67 studies)

c) ITS studies (71 studies)

More than 70% of included studies failed to provide an appropriate statement concerning allocation concealment. There are a number of meta-epidemiological studies that have shown that inadequate or unclear allocation concealment are associated with larger treatment effect estimates (Hewitt *et al.*, 2005; Kunz and Oxman, 1998; Kunz *et al.*, 2007). Among studies included in these reviews, Figure 7-3 indicates that effective outcomes (statistically significant decrease or increase) of intervention on drug use were more likely reported in studies that failed to assure adequate allocation concealment compared to those using adequate methods.

Figure 7-3: Reported effectiveness of RCT studies in proper versus improper allocation concealment of randomisation



In addition, sound randomisation is maintained throughout the study by proper analysis and follow-up (e.g., an intention-to-treat analysis and a small attrition rate). However, many reviewed studies did not fulfil these criteria. More than 50% failed to offer clear information about an intention-to-treat analysis or withdrawal of participants. Along with these issues, the outcomes may be biased to some degree by the Hawthorne effect – participants might change their behaviour because of they being watched by investigators, not because of the given educational information (Gale, 2004).

Another important issue raised in randomised studies is clustering. In most cases, the unit of randomisation was groups of people rather than individuals. This might be due to the nature of the interventions, which were designed to improve doctors' prescribing behaviour (Divine *et al.*, 1992). Hence, the unit of randomisation was often the doctor or the practice, and thus the intervention was applied to groups of patients, a cluster rather than an individual.

Cluster allocation is a useful tool for researchers to avoid potential contamination between participants and to convey the intervention efficiently. However, cluster randomisation sees a recurrence of practical problems such as lack of clarity of informed consent for cluster members and invalidation of standard statistical procedures (Donner and Klar, 2004). Actual policy impact at a clustered level can be augmented by analysing at individual level using standard statistical procedures. Among the included 41 RCT studies, all but six used cluster randomisation. Among 35 clustered-RCT studies, 16 carried out analyses at the clustered level, the same as the unit of allocation – of which 4 studies showed further statistical considerations concerning clustering; 9 studies used statistical techniques to adjust for bias from the mismatch of the unit between allocation and analysis; 10 paid little attention to clustering.

7.2.2.2 Controlled before and after studies

In CBA studies, authors frequently neglected to present the baseline characteristics of participants, or provided irrelevant information. As seen in Figure 7-2, almost 90% of included studies failed to report characteristics for the control group, or to balance between the intervention and the control group. The majority of the 67 CBA studies suffered due to baseline imbalance between the intervention and the control groups. This may be a common challenge in policy evaluation. Studies exploring the UK fundholding programme provide a typical example of this (Ess *et al.*, 2003). To adjust for discrepancies between groups, included studies often employed various statistical techniques. Difference-In-Difference (DID) analysis was a popular way of adjusting for differences in baseline characteristics (n=37). Adjustment was also performed by including baseline performance as a covariate in regression (n=13). However, it was unclear in 17 studies whether they performed appropriate statistical analyses; five studies made a comparison between pre and post numbers within the group, rather than between groups; six studies simply investigated post-mean differences with little consideration for baseline differences. No statistics were found in the other six studies.

7.2.2.3 Interrupted time-series studies

In included studies, internal validity in ITS studies was determined primarily by two

factors: the quality of the data sources they could access and how well they controlled for underlying trends. Both seem closely linked. For proper control of background trends, it is necessary to use sufficient data points. In an ITS design, vital factors including data points, study length, or measurement units were subject to data sources available at the time of the study. As Figure 7-2 shows, a rationale for the number of data points was rarely given in reviewed studies. Where information was supplied, it was due to data availability and external changes in policy surroundings, such as the abolition of study policy or the introduction of other relevant policies. None of which were under the control of the investigators. Large variations in the quality ratings of ITS studies shown in the current reviews may ascribe to these external limitations. In this review, only a third of ITS studies were considered to have enough data points to control for secular changes – more than 50 before and after (ARIMA models) or more than 12 before and after covering 4 seasons (segmented regression models) (Figure 7-2).

Nearly 80 per cent of studies used monthly data and 3 used weekly data. But, nine studies used quarterly data and three studies used annual data. Two studies used a different method of data collection before and after the intervention. Starmans *et al.* (1994) used biannual data for the first five years but annual data for the last 4 years due to the limit of available data. They performed a weighted least squares technique to correct the disparity of data but the reliability of such correction seems questionable. Andersson *et al.* (2006) employed quarterly data before and monthly data after the intervention without providing further information.

Faced with such limitations, constructing controlled time-series is another way to increase reliability. In a study investigating a Canadian reference-price scheme, Grootendorst and Stewart (2006) demonstrated that before and after time-series design could overestimate policy effects by about double, compared to the case with a comparable control state. Although controlled time-series is definitely helpful to enhance scientific rigour in policy studies, it may not be always feasible. Policies are frequently implemented at the same time nationwide, which makes it difficult to find a comparable population which is not influenced by the policy change. That must be one of the most important reasons that two thirds of included studies have no controls.

Schneeweiss *et al.* (2002a) suggested the importance of a transition period just after

the policy introduction to avoid overestimation of the policy impact due to temporary 'shorter prescription duration' after medication changes. Also, unusual responses by stakeholders, such as stockpiling, could produce spurious results shortly before or after policy changes (Ray, 1997). Among the included studies, only 14 ITS studies incorporated a transition period of around a few months. Although this review lessened bias from transition time by including studies with more than a 6 month follow-up, cautious interpretations are still recommended for studies with a short follow-up period.

For sound research, another important issue is to employ appropriate statistical methods. Table 7-2 illustrates statistical techniques employed in the ITS studies and appropriateness of analysis based on quality assessment. Two thirds of included studies carried out segmented regression analysis, of which 26 studies adjusted for autocorrelation by applying estimated generalised least squares (EGLS) assuming first-order autocorrelation among error terms (Ostrom, 1990). Seven studies justified ordinary least-squares (OLS) estimates by checking the absence of autocorrelation through formal statistical tests such as the Durbin-Watson d-statistic (DW) (Durbin and Watson, 1950, 1951; Savin and White, 1977). One study partially applied EGLS estimation in the presence of autocorrelation. Fifteen studies applied OLS with little information concerning their strategy for controlling for correlated error terms. Seventeen studies employed an autoregressive integrated moving average (ARIMA) approach. It was unclear in five studies what statistical analyses were undertaken.

Table 7-2: Statistical techniques and appropriateness of analysis

Statistic techniques	Number of studies	Assessment of quality				
		clear	unclear	*reasons of unclear*	none	*reasons of none*
ARIMA[1)]	17	14			3	<20 data points in pre-intervention period
Segmented regression						
EGLS[2)]	26	20			6	<12 months before and after intervention
OLS[3)]	22	5	11	little information about correcting correlation	4	<12 months before and after intervention
			2	annual data		
EGLS+OLS	1	1				
Unclear	5		5	lack of information		
Total	*71*	*40*	*18*		*13*	

1) autoregressive intergrated moving average
2) estimated generalised least-squares
3) ordinary least-squares

Thirteen studies performed either ARIMA technique with less than 20 pre data points, (Cochrane Effective Practice and Organisation of Care Review Group, 2002), or segmented regression with less than a 12-month period before and after the intervention (Wagner *et al.*, 2002), raising concerns about potentially inadequate control over pre-existing trends. Eleven studies failed to provide proper information about how they dealt with the autocorrelation in OLS estimates or gave spurious DW values. The association between the approach to the analysis and research outcomes was inconclusive due to the lack of homogeneity.

7.2.2.4 Inter-design issues

Soumerai *et al.* (1989) demonstrated striking contrast in conclusions between well-designed and inadequately controlled studies; less adequate designs were much more likely to produce significant outcomes. In this review, any potential differences among research designs might be overwhelmed by the heterogeneity of included studies such as setting, policy details or length of study. Among the retrieved studies, one interesting result was exhibited by Schneeweiss *et al.* (2004) who examined reimbursement policy. They found different outcomes from their RCT study and observational study; the former returned a non-significant decrease in drug expenses for study drugs, whilst the latter showed a significant fall in the same outcome.

7.2.3 Other threats to validity

7.2.3.1 Setting

Strikingly, a large number of included studies were conducted in North America as seen in Table 7-3. Among 176 studies, nearly 56 per cent came from North America and about a third came from Western Europe. Only one out of ten studies came from elsewhere.

Table 7-3: Number of studies by setting

	Western Europe	North America	Others	Total
number of studies	61	98	17	176[1)]
by intervention	64	101	19	184[2)]
patients				***46***
cost-sharing	10	16	4	30
tiered formulary		9		9
prescription caps	1	4		5
educational approach	1			1
OTC switch		1		1
providers				***119***
educational approaches	29	25	9	63
reimbursement restrictions	1	31	1	33
incentives	12	2	3	17
distribution of samples		3		3
mandatory generic substitution	1			1
repeat prescribing	1			1
SPD[8)]			1	1
industry				***19***
reference pricing	4	9		13
price control (others)	1	1	1	3
profit control	1			1
market authorisation	1			1
patent regulation	1			1

1) acutal number of studies without any duplication

2) number of included studies by intervention but Schneeweiss *et al.* 2003 is included once: Four studies are included two times (Almarsdottir *et al.* 2000, Andersson *et al.* 2006, Gurwitz *et al.* 1995, Starmans *et al.* 1994) and two studies three times (O'Malley *et al.* 2006, Lee *et al.* 2006).

7.2.3.2 Follow-up period

Table 7-4 displays the period studies have followed policy outcomes after the implementation. Approximately 54% of studies investigated the policy impact in a single year after the intervention. Almost all studies (97%) addressed less than 5 years. The ITS studies were more likely to address a longer time period, whereas evidence

from North America was more concerned with short-term effects. Overall, there is a notable lack of evidence of long-term policy effects. Follow-up periods are also presented in Annex 19 by intervention.

Table 7-4: Follow-up length by study design

Study design	Follow-up period			Total
	≤ 12 months	> 12 months & ≤ 60 months	> 60 months	
Total (%[1)])	99 (54)	79 (43)	7 (4)	185[2)]
RCT	33	8		41
CBA	39	28		67
ITS (control)	14	10		24
ITS (no control)	13	33	7	53

1) *rounded*
2) number of included studies by intervention; Schneeweiss *et al.* 2002 is included twice

7.2.3.3 Outcome variables

Table 7-5 displays the outcome variables examined in the reviewed studies (see Annex 20 for details). It shows that a fairly small number of studies were dedicated to exploring the indirect consequences of regulations such as the impact on other service use or on health. Most studies paid a great deal of attention to expenditure from the payers' perspective and neglected changes in private expenses.

Table 7-5: Outcome variables appeared in the included studies

Outcome variables	No. of studies	
	(n=184[1)])	%
Utilisation	*137*	74
Expenditure	*89*	48
Out-of-pocket	*17*	9
Other services use	*28*	15
Heath outcomes	*7*	4

1) number of included studies by intervention but Schneeweiss *et al.* 2003 is included once

Few studies explored direct variables relating to health outcomes due to the lack of patient-level data. In this regard, some authors measured changes in other service use and interpreted the outcomes as a reflection of clinical health. Are these proxies properly representative? Office visits could be increased when patients change medication, regardless of their health conditions, because doctors usually want to

monitor them more closely just after altering a course of therapy (Schneeweiss *et al.*, 2002a). Moreover, these were mostly short-term studies. The health of many patients might deteriorate after discontinuation or change of medication, but not to the extent that they visit an emergency room or are hospitalised. Also, the prevalence of disease could affect such utilisation. The effects of change in the use of medication for rare diseases would not be easily detected by proxies.

Similar limitations were also found in studies measuring health outcomes. Five studies assessed blood pressure and arguments over the use of surrogate end-points also apply here (Freemantle *et al.*, 2004).

7.2.3.4 Data sources

As seen in Table 7-6, the majority of studies used administrative claims data hence the usual limitations from using such datasets apply here (Fairman and Motheral, 2000; Ray, 1997). Ecological issues appeared most frequently across reviewed studies. Conducting research with aggregated data definitely has many advantages, but it makes it hard to determine whether the effects are translated accurately at an individual level. In real terms, the impact of every single policy on each patient might differ due to their socio-economic positions or health condition, missing important messages from individual patients and possibly misguiding policy-makers in the wrong direction.

Table 7-6: Data sources by study design

Data Source	RCT	CBA	ITS (control)	ITS (no control)	Total (n=185[1])(%)
national- or state-level aggregated claims data	14	32	14	41	101 (54)
health plan aggregated claims data	6	24	6	4	40 (22)
institutional pharmacy data	10	5	1	1	17 (9)
commercial data	2	3	3	4	12 (7)
academic pharmacy data	3	1		1	5 (3)
individual pharmacy data	5	1			6 (3)
others	1	1		2	4 (2)

1) number of included studies by intervention but Schneeweiss *et al.* 2003 is included twice

Regarding data sources, probably the most challenging aspect in assessing quality was that there was a clear limitation to confirming the reliability of datasets employed in each study. Authors rarely discussed the reliability of the databases they used. This issue seems more serious in data managed by private health plans, because much less information is known about such datasets. More effort needs to be made in reporting and discussing the quality of data used in these study designs.

7.2.3.5 Funding sources

There have been some concerns that a source of funding may be associated with study outcomes in drug trials (Jefferson *et al.*, 2009; Jorgensen *et al.*, 2008; Lexchin *et al.*, 2003). Despite that this review found little evidence of the relationship between funding and results, it was impossible to remove all doubts. Primary authors occasionally interpreted similar outcomes differently in context. For instance, an industry-funded study found the increase in physicians' visits during the first 6-months after introducing formulary and drew the following conclusion:

The observed range of increases in hospital and physician visits is evidence for the possible existence of an unintended consequence of PDL implementation by state Medicaid programs. (Murawski and Abdelgawad, 2005, pSP35)

In contrast, a remark from a publicly-funded study concerning the upsurge in office visits in the three months after reference-pricing was as follows:

The insurance coverage restriction for PPIs .... led to substantial utilization changes and savings without negatively affecting major clinical outcomes. (Schneeweiss et al., 2006; p386)

Any meaningful divergence could be masked by the heterogeneity of studies. Additionally, influences from a source of funding appear more complex in health service research. Unlike drug trials, it may not be appropriate to group sources of funding only into public and commercial bodies. Public funders include not only purely research-oriented public bodies, but also government bodies that play a central role as payers in the market. Given the reality, it seems difficult to ensure that governments are necessarily neutral in the case of 'public' money for research activity. Likewise, 'private' money from commercial health plans may be used differently from that in the drug industry.

7.3 Key findings from the systematic reviews

The reviewed studies were of mixed quality and showed clear weaknesses in design despite being more robust study design to start. Studies concerning cost-sharing/ reimbursement restrictions were in particular of mixed quality; those concerning educational interventions/ tiered formularies/ reference-pricing schemes were generally rated as moderate quality; those addressing incentives were rated as moderate to low quality. Therefore, the findings should be considered based on this quality constraint. The following conclusions are drawn about the impact of pharmaceutical regulations.

- **First,** existing robust evidence is concentrated in a few policies and settings. Studies examining cost-sharing, educational approaches, North American reimbursement policies, English individual general practice budgets and Canadian reference-pricing appeared frequently. The effects of many other policy measures remain largely untouched in the included studies. Thus, empirical evidence is still needed for relevant interventions in this arena.

Cost-sharing or educational measures were evaluated in varied settings. Cost-sharing schemes have a long history – more than half a century – and thus more chance of being evaluated. A study exploring educational approaches is relatively easily constructed. It can also be conducted with a small number of participants. Random allocation is more likely and effects are often realised within a short period. Additionally, clinical researchers may be more familiar with this kind of project, as it can be constructed to look very similar to a clinical trial.

Reimbursement policies are popular in various health plans in North America and highly evaluated within the US and Canadian contexts. Also, the researchers exploring reimbursement policies in these surroundings seem to have strong advantages in building research projects in a rigorous manner, because various private health plans and state-level drug benefit programmes have been used as good comparators for each other. Equally importantly, there is a greater opportunity of funding by various payers who wish to confirm or simulate any effects generated by their policies. Similar arguments are true in the Canadian reference-pricing scheme.

Other pharmaceutical policies have been inadequately evaluated. For example,

conventional price control programmes seem to be poorly studied even though they have as long a history than cost-sharing and wider exploitation. Overall, not only price controls, but most regulations primarily targeted at industry activity generally appear to be less well studied. Many factors may cause this. It may be harder to access industrial data owing to business privacy issues. It could also be tougher to build a rigorous quantitative study. Hence, issues concerning the pharmaceutical industry have often been explored in qualitative ways (e.g.Braithwaite, 1984c), which is out of the scope of this review.

- **Second,** outcome variables in the studies concentrate on benefits, but few studies measured undesirable consequences. Hence, although this review found little explicit evidence on the association between restricted regulations and health or other resource use in the short-term period, conclusions are debatable. The long-term outcomes concerning these issues are unknown. Moreover, some restrictions were certainly tied to curbing patient access to essential drugs for chronic conditions, which might be associated with compromising health, or increasing other subsidised, sometimes more expensive resources, over longer periods. Furthermore, small but evident adverse trends were seen in vulnerable populations and these occasionally reached a statistically significant level during the authors' study period.

- **Third,** savings were more evident in policies that directly limited patient demand or prescriber practices, such as cost-sharing, prescription capping, tiered formularies, reimbursement policies and reference-pricing schemes. Only a modest decrease was seen in voluntary-based measures such as educational approaches or budgetary constraints. However, questions remain regarding whether or not administrative regulations still make economic sense from a societal perspective after considering a budget shift to private individuals and its consequences; and if educational programmes are still cost-effective after including administrative expenses.

Although policy effects varied considerably in size across studies, there were some apparent differences in the mechanisms of savings across policy interventions. Saving was primarily driven by a decrease of absolute volume in regulations limiting patient demand, such as flat rate cost-sharing and prescription capping. They hardly improve patients' purchasing behaviour toward cost-effective alternatives. A price drop in reference-pricing and other price control measures may not be as great as anticipated;

there is only limited evidence of price decreases for the former.

In contrast, volume decrease is seen less often in measures designed to encourage appropriate prescribing and purchasing. In differential cost-sharing structures, such as tiered formularies or reference-pricing programmes, or tools orienting prescribing behaviour such as educational measures or reimbursement policies, saving was achieved by the increasing use of less costly drugs combined with the decrease of expensive drugs. As a result, although few changes were seen in overall volume, sizable saving for payers was observed in drug costs.

Any form of cost-sharing regulations, including tiered formularies and reference-pricing, may partly achieve cost containment by shifting the budget to private individuals. In this regard, lower income groups seem to be particularly vulnerable because the financial burden of out-of-pocket expenditure tends to fall more heavily on these groups. Generally, better-off consumers seem to be inflexible to price increase in medication. Decreases were often observed in disadvantaged groups who lowered their consumption of essential as well as optional drugs. Thus, any policies possibly increasing out-of-pocket expenditure are carefully tracked to explore if they reduce social equity for saving costs.

- **Fourth,** fostering generics use has been shown to yield positive economic returns in a variety of interventions. In consequences, pharmaceutical policies encouraging the use of cost-effective drugs, for instance, generics or first-line therapies are increasingly highlighted.

The review showed that pricing policies might hardly have any influence on the rising trend of drug costs, given the predominant causes of the trend – volume growth. On the other hand, policies restricting patient demand might have adverse effects on overall health. In this regard, generics have been of increasing value in pharmaceutical policies.

Strategies aimed at increasing generics were found in various policies, including educational approaches, reimbursement policies, tiered formularies and reference-pricing programmes based upon policy details, and generic substitution or prescribing. In budgetary policies, British studies examining fundholding programmes suggested

that fundholders saved money by increasing generic use with little change in absolute drug volume.

In this regard, it is anticipated that policies directly encourage generics use, for instance, mandatory generic prescribing, which would result in greater financial savings, but those policies appear less frequently (National Economic Research Associates, 1998; Vogler *et al.*, 2008). One of the key reasons is probably prescribers' lack of acceptance of those interventions (Banahan and Kolassa, 1997; Brust *et al.*, 1990; Tilyard *et al.*, 1990). Budgetary and educational strategies are perhaps regulations imposing least limitations on the authority of prescribers. Others may be moderate because generic drugs are just one of the options in measures such as reimbursement policies and doctors still take main responsibility of the choice of pharmaceuticals. But generic substitution or prescribing may impose heavy restraints on prescribers because the selection of final products is in the control of dispensers or consumers.

Doubts about the quality of generic products can be another reason. Even though a globally accepted standard has been developed, for example a 'bio-equivalence test', some studies argue that this may not be sufficient to prove that the clinical effectiveness of generics is equal to their original counterparts (Borgheini, 2003; Meredith, 2003). Interchangeable clinical efficacy is undoubtedly a vital condition in generic policies, or generic use may result in increasing the use of other resources and/or deteriorating health.

Along with proven clinical efficacy, two factors seem to be required to achieve savings in drug costs by generic substitution. First, the generic market should be large enough, or an increase in the generic share would generate little change in overall costs as shown in Spanish studies (Sicras-Mainar and Pelaez-de-Lono, 2005; Sicras-Mainar *et al.*, 2007; Sicras-Mainar *et al.*, 2004). Second, generic products should be priced at a significantly lower level (Kanavos, 2007; Lee *et al.*, 2008), otherwise, policies encouraging use of generics may not necessarily lead to the reduction of drug costs.

- **Lastly,** despite rigorous efforts made so far to evaluate the impact of pharmaceutical policies across certain countries, several limitations may affect both their internal validity (e.g. data availability, inappropriate study procedure, statistical

problems, etc.) and their external validity (heterogeneity in interventions or in settings).

The range of changes varies considerably across studies even within a single, homogeneous measure, indicating that there must be interactions among a number of potential endogenous and exogenous factors. The typical examples for the former may be methodological devices such as comparators, measurement units, study drugs, length of study period or study populations. Those for the latter may include intervention details, or a structure of health systems that were built on the political, societal and economic milieu in each study setting.

Although included studies may provide some direction for policy-makers interested in adopting foreign regulations in their pharmaceutical segments, it should not be assumed that policy performance can be predicted precisely based on this information. In future research, an analysis standard (e.g. measurement units, etc.) needs to be set for reliable cumulative outcomes by reducing heterogeneity in methodology.

Table 7-7 summarises the included studies by the observed impact of the intervention for each outcome variable assessed.

Table 7-7: Observed effects of interventions on outcome variables

Intervention (n=number of studies)	**Effects**				
	public expenditure	*private expenditure*	*utilisation*	*price*	*other resource utilisation*
policies influencing patients					
Cost-sharing (n=30)	decrease	possibly increase	decrease		possibly increase in the vulnerable population
Tiered formularies (n=9)	decrease	increase	selective		little change
Prescription caps (n=5)	decrease	possibly increase	decrease		increase in the vulnerable population
Educational (n=1)	possibly decrease		selective		
Over-the-counter switch (n=1)			selective		
policies influencing providers					
Educational approaches (n=63)	limited decrease		selective		little change
Reimbursement restrictions (n=33)	decrease except delisting	decrease in step-therapies or limited uses	selective		mixed
Incentives (n=17)	limited decrease		possibly increase of generic utilisation	little change	
Distribution of samples (n=3)			little change		
Mandatory generic substitution (n=1)	decrease	decrease			
Repeat prescribing (n=1)					little change
Separation policy (n=1)	little change overall but decrease in clinics without pharmacist on-site		little change overall but decrease in clinics without pharmacist on-site		
policies regulating industry					
Reference-pricing schemes (n=13)	decrease	increase	selective	possibly decrease	little change
Price controls (n=3)	little change				
Formal request for economic evidence in market authorisation (n=1)	prolong the time until final decision in the first year of the implementation				
Patent regulation (n=1)				decrease after patent expiry	
Profit control (n=1)				little change	

7.4 Study limitations

There are several limitations to this study:

First, this review sets a strict limit on study designs, which is both a weakness and a strength of this work. Including the three most robust study designs lessened the potential heterogeneity between well- and poorly-designed studies and improved the reliability of review outcomes. Among the identified studies, 20% in the patient category, 36% in the provider category and 33% in the industry category were excluded due to poor study designs. Whilst study design was used as an exclusion criteria, and limited to more robust designs, there was still great variability in the quality ratings. On the other hand, it might exclude many potentially worthwhile pieces of research. For example, studies exploring the impact of educational regulations influencing patients or direct-to-consumer advertising might be conducted qualitatively. More importantly, excluding studies with weaker designs may neglect studies from other developing or middle-income countries that could be useful information for Korea.

Second, as with any literature review, this study may be limited by inherent publication biases to publish only statistically significant results and by a language barrier although there was no restriction made on language in the search criteria.

Third, two electronic resources may not be enough to explore such a variety of policies even though the loss of potential studies was reduced by hand-searching relevant references.

Fourth, the quality of the study was assessed principally based upon the original authors' description. It was challenging to confirm the quality of pharmaceutical claims used in the reviewed studies, particularly those held by private health plans, which might primarily affect the validity of reviewed studies using ITS designs.

Fifth, per cent changes presented in this review may not be comparable across included studies. Each study employed various measurement units, for example, days per prescription versus the number of defined drug doses per patient. Cautious interpretation is thought essential and numbers presented should be considered only as a reference.

Finally, at the time of planning, it was intended that a meta-analysis would be undertaken but this proved impossible given the heterogeneity in each study from the policy intervention and the method of presenting results, to the study population. Thus, many of the conclusions of this review were necessarily qualitative. It was particularly difficult to draw general conclusions with educational interventions since they were too varied and the authors' information was often too simple. Varying characteristics and behaviours of outreach visitors might have affected physician behaviour, making comparisons more challenging. Equally importantly, it was unlikely to be practicable that the complexity of the prescribing environment and any changes in the market, such as strong promotion of related drugs, was taken into account when interventions were compared.

7.5 Lessons for this study

This review has illustrated some implications for the external validity of existing evidence in pharmaceutical policy studies. Existing rigorous evidence is limited to a handful of settings. Most settings had relatively high economic status, a well-established welfare network, and a profitable, competitive drug industry. There is practically no evidence from countries comparable with South Korea.

Other populations with different social conditions may exhibit different behavioural responses to pharmaceutical policies. For example, people are more likely to be affected by cost-sharing in studies from settings showing weakness in social welfare (including Nepal, Taiwan and the US). Moreover, policies may be devised with different interests and motivations across national settings. Decisions are often affected by political, social and economic internal and external conditions that vary across settings. According to the profitability of the drug industry, there may be divergences in the decisions of individual governments as to how to balance healthcare and industrial goals. For instance, governments with profitable companies, such as the US, tend to allow more freedom to the industry in terms of drug pricing, especially for originators. Because of these underlying differences, even a single policy, for example, the reference-pricing scheme, could be surprisingly diverse in details by country, which may produce dissimilar policy effects. Thus, Klein (1997; p1268) remarked "no two laboratories are the same" in policy studies.

In line with this argument, variations appeared consistently and were considerable in terms of policy outcomes and authors' arguments across studies, even within these limited settings. Hence, the results from one setting are not easily generalised to another in policy studies.

In this regard, careful assessment should be made of any prospects for success in pharmaceutical regulations when they are applied to other settings apart from the original. Given the low transferability of policy outcomes and the lack of available evidence, there is a pressing need for studies to probe pharmaceutical policy outcomes under the inherent surroundings and their interactions in Korea. Nevertheless, to date the study of pharmaceutical policy has been given little attention in South Korea. Therefore, in the following part, this thesis will explore Korean drug policies with empirical data to study how similar policy issues are exhibited and dealt with in a Korean context.

Firstly, the impact of two pharmaceutical regulations will be examined quantitatively. Of the three most robust study designs, ITS is the most appropriate approach because there is no comparable population free from policy change in Korea. Secondly, Korean policy-makers will be interviewed to address further policy issues.

Additionally, there are several lessons for improving the quality of quantitative investigations. First, the use of less well-controlled time-series analysis may lead to spurious outcomes, often overestimated. To cope with this potential problem and to verify policy effects, it is advisable to crosscheck time-series data by different analytical techniques. Second, outcome variables for drug utilisation tend to be particularly sensitive to measurement units (e.g. dose/capita, prescriptions/capita, days/prescription, etc.). Real changes can be misinterpreted in examining changes with aggregated volume if the researcher fails to account for population changes. Also, measuring the policy impact with prescription numbers can overlook changes in prescription sizes, resulting in incorrect conclusions. Thus, the trend of population changes should be taken into account. Alongside this, measurement units reflecting utilisation changes more accurately are advised (e.g. defined dose). Third, policy impact on expenditure should be considered from a societal perspective.

PART 3 EMPIRICAL RESEARCH:

LOCAL REALITY

CHAPTER 8: DESIGN OF POLICY EVALUATION: INTERRUPTED TIME SERIES ANALYSES

8.1 Introduction

So far, discussion has been around theoretical backgrounds and international evidence concerning the performance of pharmaceutical regulations. The third part of the thesis moves debate into the local context. The goals are to explore the impact of pharmaceutical policies in South Korea. Empirical investigation in the thesis is approached both quantitatively and qualitatively.

The quantitative studies investigate the effects of two recent Korean pharmaceutical policies. The impact of these policies is examined using an interrupted time series (ITS) design. The qualitative study tackles the contextual elements surrounding decision making and implementation of policy.

Chapter 8 provides insight into a methodological framework for the ITS analysis, which begins with exploring the general background of design and analysis, then outlines the data sources used in statistical analysis. It ends by demonstrating the specification of ITS models for the data employed in the current project.

8.2 Interrupted time series experimental design

A time series is a sequence of observations made on a single variable at successive time intervals. Interrupted time series refers to a particular form of time series which is *interrupted* by a manipulated intervention such as a policy (Wagner *et al.*, 2002). It can be charted as:

$$\ldots\ \ldots\ O_{I-5}\ O_{I-4}\ O_{I-3}\ O_{I-2}\ O_{I-1}\ X\ O_{I+1}\ O_{I+2}\ O_{I+3}\ O_{I+4}\ O_{I+5}\ \ldots\ \ldots$$

where, $O_{I\pm p}$ denotes an observation at time p after (+) or before (-) the intervention and X denotes an intervention introduced at time I. As seen in the above sequence, the intervention breaks the time series into two segments, a pre-intervention and a post-intervention period. An ITS analysis aims to explore whether or not the time series has

changed after the intervention. Effects are commonly investigated in terms of *level* and *slope* changes. Changes in level indicate that the intervention may be associated with an immediate impact at the point of inception, while changes in slope suggest that the intervention may affect the rate of increase or decrease in the trend of the series (Wagner *et al.*, 2002). Effects can also be characterised in other ways, such as the permanence – continuous or discontinuous, or the shape – immediate or delayed (Shadish *et al.*, 2002c).

In pharmaceutical policy studies, ITS is frequently employed – as demonstrated in the systematic reviews presented in Chapter 4 through 6. Trends of drug utilisation or spending can be constructed into time series which provide ideal models for observing whether policy changes cause visible and measurable changes in existing trends (Shadish *et al.*, 2002c). Particularly, as already discussed in Chapter 2, the time series design is a favourable option when randomisation is infeasible as a policy has already been introduced, since it is still effective under such condition in reducing many internal threats to validity (Shadish *et al.*, 2002c). Therefore, as mentioned in Chapter 7, time series design may be the most rigorous option available for this project because the policies of interest were introduced at the same time nationwide, so that randomisation is impossible.

With the lack of randomisation to control confounding factors, the validity and feasibility of ITS is primarily determined by the quality of the data source and the number of available data points. As discussed in Chapter 7, the scope of investigation using an ITS design is clearly limited by the data available at the time it is carried out. Available data is often inflexible in terms of outcome variables collected, region, interval available for analysis and/or the length of the data points because in many cases it is established not for research purposes but for other administrative aims.

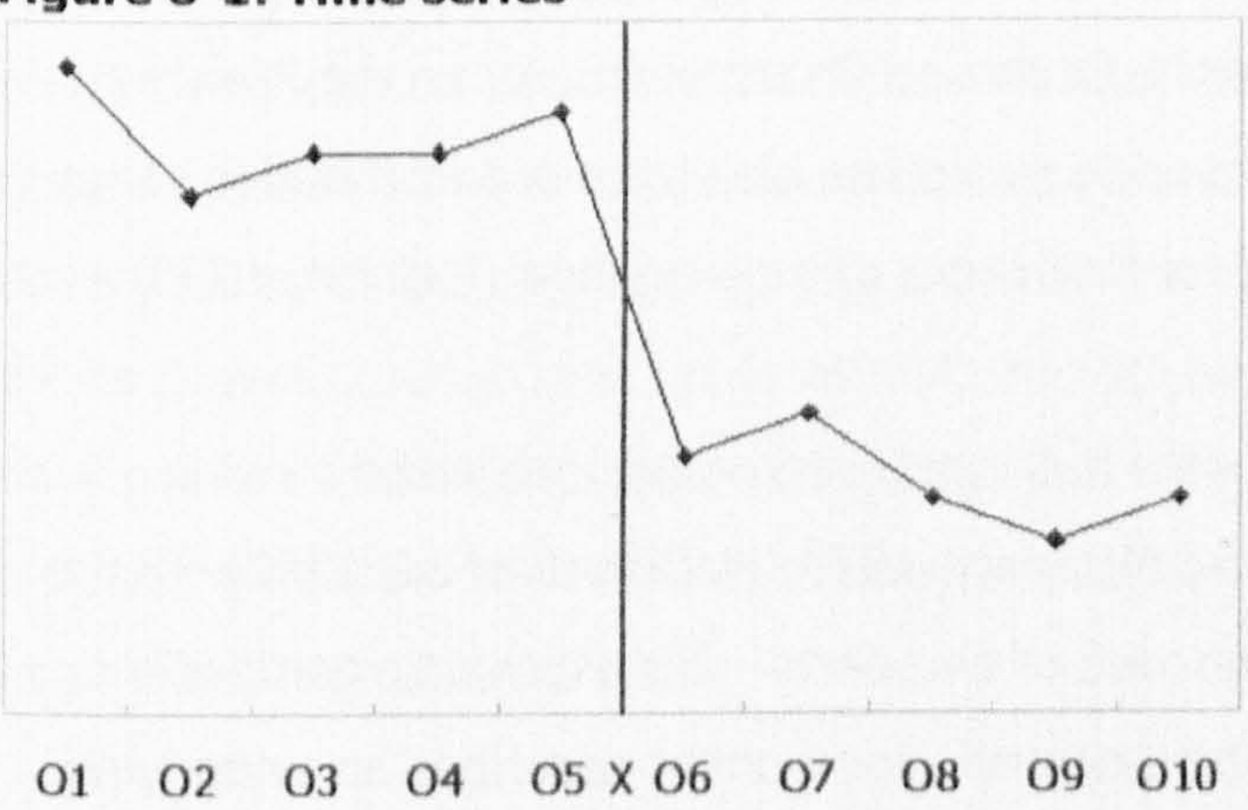
A short time series may fail to rule out problematic confounders such as selection or maturation. It may be hard to determine how many data points are sufficient, but textbooks suggest a rule of thumb of 50 observations or more (Box and Jenkins, 1976; Cook and Campbell, 1979a; McCleary *et al.*, 1980b). According to the most widely referenced example, more than 100 data points are recommended to give an accurate estimation of autocorrelation among error terms and to facilitate correct model identification (Shadish *et al.*, 2002c). However, it is difficult to generalise the exact

number of data points required for any ITS analysis and it may depend on specific details within the individual studies; for example, the number of data points required may depend on the statistical methods used. The Cochrane EPOC group suggests that ARIMA techniques require at least 20 observations in the pre-intervention period (Cochrane Effective Practice and Organisation of Care Review Group, 2002), while Wagner *et al.* (2002) suggest that a segmented time series regression analysis requires 12 monthly data points before and after the intervention.

8.3 Outline of time series analysis

In a time series design, changes can be detected by a visual inspection of the series after plotting the dependent outcome variable against time (Figure 8-1).

Figure 8-1: Time series



However, a visual inspection cannot remove changes caused by chance or other concurrent confounding factors such as seasonal fluctuation. In order to control for such factors, several statistical techniques have been developed for policy evaluation (McCain and McCleary, 1979; Ostrom, 1990; Wagner *et al.*, 2002).

One approach gaining popularity in health services research is a segmented regression analysis, which fits a least squares regression line to each segment of the outcome variable against time, and assumes a linear relationship between time and the outcome within each segment (Wagner *et al.*, 2002). A segmented regression model provides several advantages. It requires a relatively short time series. Wagner *et al.* (2002) suggest 12 monthly data points before and after the intervention. It allows clear and easy interpretation of the outputs from hypothesis tests based on ordinary least

squares (OLS) or estimated generalised least squares (EGLS) estimations.

There are some concerns about the appropriateness of least squares methods for analysing time series data. While one of the main assumptions of the OLS regression is that error terms are independent (Gill, 2000), it has been recognised that error terms from time-dependent data are often correlated because each observational value in a chronologic time sequence variable is likely to be correlated to the next (Ostrom, 1990). Correlation of error terms leads to the underestimation of standard errors, which means that the *t*-ratio is inflated producing an artificially low *p* value and therefore increasing the chance of rejecting the null hypothesis (McCain and McCleary, 1979). Hence, when using segmented regression it is important that the presence of autocorrelation is explained and corrected if possible. To detect autocorrelation, there are several diagnostic statistics, such as Durbin-Watson *d* statistic (DW) (Hamilton, 2006). When the presence of autocorrelation through diagnostic tests becomes apparent, EGLS estimations (such as the Cochrane-Orcutt estimator or the Prais-Winsten estimator) have been employed to overcome bias from autocorrelation. They correct standard errors in the model for first-order autocorrelation (Ostrom, 1990).

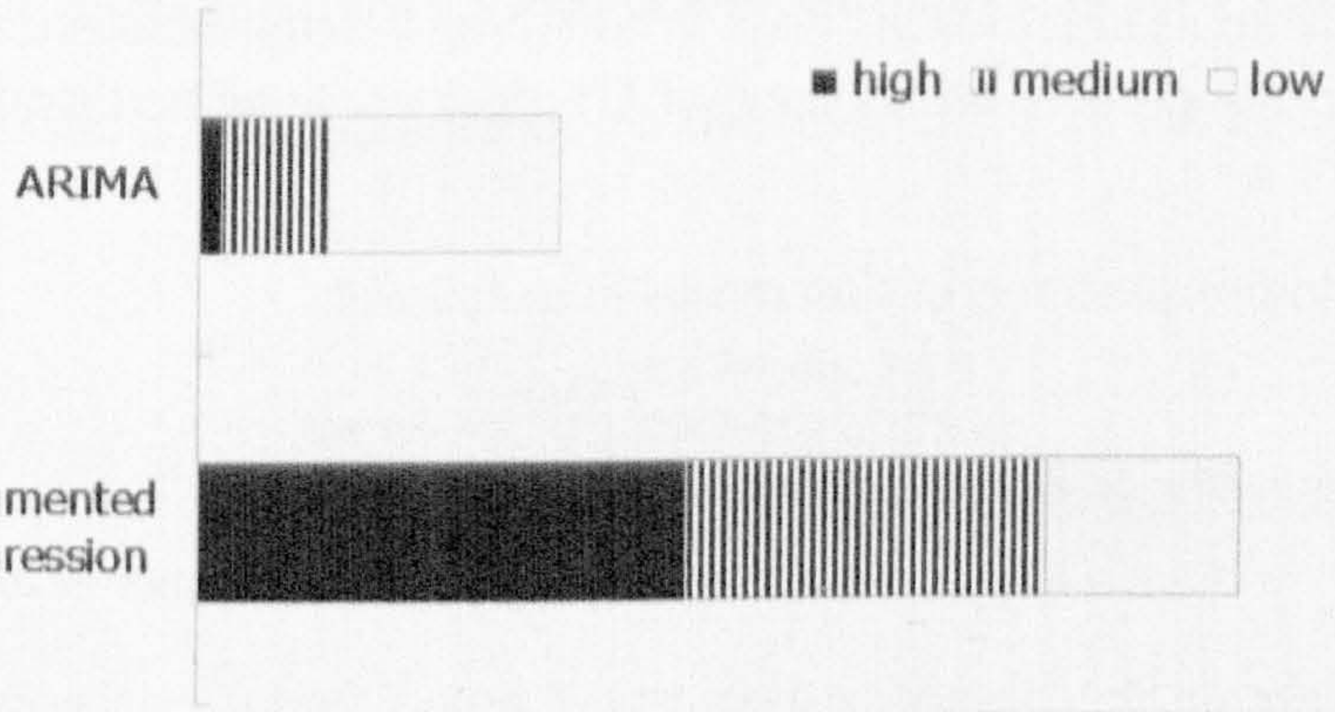
Another approach for analysing ITS data is the autoregressive integrated moving average (ARIMA) process (McCain and McCleary, 1979; McDowall *et al.*, 1980). In the ARIMA strategy, a time series is comprised of two parts – the stochastic component and the deterministic component. The stochastic component describes an underlying process of unobserved errors, often called a noise component of the model. The deterministic component describes the systematic behaviour of the time series (McCain and McCleary, 1979). ARIMA modelling is an iterative process of identifying the most appropriate model for each time series and then testing this model (McCleary *et al.*, 1980c).

There are some concerns about the use of ARIMA methods. While ARIMA modelling may be an appropriate method, it may not permit easy interpretation (McCleary *et al.*, 1980b). Moreover, if the modelling procedure is too sophisticated, there may be room for error according to the performer's ability. Velicer and Harrop (1983) demonstrated that highly trained experts were able to identify appropriate ARIMA models in only 28% of study time series. Even automated methods may not guarantee precise model identification (Stadnytska *et al.*, 2008).

Furthermore, relatively long observations are required in the ARIMA approach for an appropriate model because models are built empirically from the data itself (McCleary *et al.*, 1980b). The Cochrane EPOC group suggests that ARIMA techniques require at least 20 observations in the pre-intervention period (Cochrane Effective Practice and Organisation of Care Review Group, 2002). Without doubt, the more data points the better for the identification of accurate models for statistical analysis. One study found that model accuracy was 16% higher in cases with 100 observations compared to other cases with 40 observations (Velicer and Harrop, 1983).

In policy studies, researchers are usually limited by the data available at the time of undertaking the analysis, which includes the length of the data points, interval available for analysis, and outcome variables collected. Policies are often implemented immediately and consecutively, and eliminated unexpectedly, which is out of the researchers' control. Hence, time series with sufficient data points may not always be possible and this may create more problems for ARIMA analysis as it requires longer observations for building appropriate models. The reviewed ITS studies in Part 2 of this thesis showed that studies using ARIMA analysis were more likely to give insufficient data points compared to those using segmented regression (Figure 8-2). Furthermore, a poorly conducted ARIMA analysis may be more misleading than a well performed segmented regression analysis.

Figure 8-2: The appropriateness of data points in the reviewed ITS studies



model	ARIMA	Segmented regression
high	≥ 50 data points before and after	≥ 12 data points before and after including 4 seasons
medium	20 ≤ data points < 50 before and after	4 ≤ data points < 12 before and after including 4 seasons
low	not meet the above criteria	

In summary, both approaches seem to have different strengths and weaknesses. McCleary *et al.* (1980b; p20) suggested the following guideline in the choice of analysing tools:

> When relatively long time series are available, an empirical ARIMA approach will ordinarily give the best results. But when relatively long series are not available, regression approaches informed by prior research and/or theory will give the best results.

The time series under study in the present project comprise 66 monthly data points with a relatively short follow-up period, 18 months for the first but only 11 months for the second intervention. In this respect, a combination of approaches may generate the best results, which is also in line with lessons learnt from the existing literature (Chapter 7). To maximise benefits and minimise difficulties from each approach, the current study employs a segmented regression as its primary analysis, and when appropriate, models are crosschecked using an ARIMA method. The practical issues and concepts of the two approaches are presented in the following sections.

8.3.1 Segmented regression analysis

A segmented regression analysis is a method for statistical modelling time series data in which more than two "segments" are shaped by "a change point" (Wagner *et al.*, 2002). A change point dividing time series data into two compartments is an identifiable exogenous event such as a pharmaceutical policy. Two parameters are examined as mentioned in the general background of ITS designs: level and slope.

The simplest segmented interrupted regression model is as follows:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention + \beta_3 \times time\ after\ intervention_t + \varepsilon_t \quad \text{(Eq. 1)}$$

(Wagner *et al.*, 2002)

where,

- Y_t ; a dependent outcome variable of interest at time t
- $time_t$; a continuous variable indicating time in basic time intervals (week, month or year) at time t from the start of the observation period
- **intervention** ; an indicator for a particular time point occurring before (intervention=0) or during and after (intervention=1) the intervention

- **time after Intervention$_t$** ; a continuous variable counting the number of time intervals after the intervention at a particular time point, coded 0 before the intervention and 1 at the time of introduction, 2 at the second time point after the intervention and so forth
- β_0 ; a baseline level of the outcome at time zero
- β_1 ; a baseline trend of the outcome before the intervention
- β_2 ; a level change of the outcome immediately after the intervention from the end of the preceding segment
- β_3 ; a change in the trend of the outcome after the intervention, compared with the baseline trend before the intervention
- ε_t ; an error term at time t, representing the random variability not explained by the model

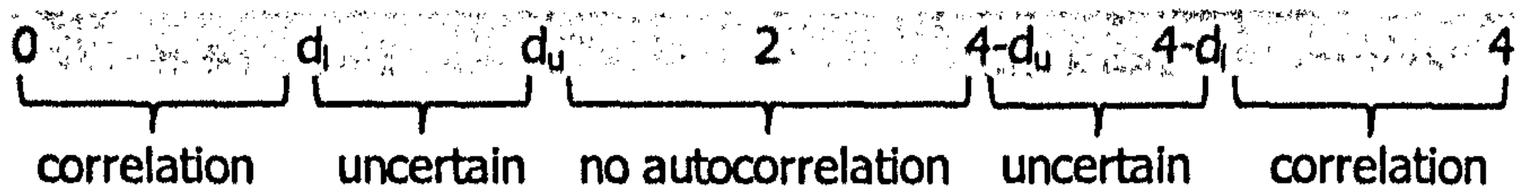
Statistical outputs from a segmented regression analysis are easily understandable. From the above model, β_2 is a coefficient for the level change, representing an abrupt intervention effect; β_3 is that for the change in trend after the intervention, representing a gradual change in the value of the outcome during the segment. The sum of β_1 and β_3 represents the post-intervention slope.

As stated above, autocorrelation poses bias for the use of simple OLS. To test for its presence in a specified model, the present analysis used the DW statistic. The DW statistic tests whether or not the residuals from a linear regression or multiple regression are independent and is designed to detect errors that follow a first-order autoregressive process. It tests the null hypothesis H_0 that the errors are uncorrelated against the alternative hypothesis H_1 that the errors are correlated with the next. The test statistic is computed based on the residuals from the least squares estimates as follows

$$d_w = \frac{\sum_{t=2}^{T}(e_t - e_{t-1})^2}{\sum_{t=1}^{T} e_t^2}.$$ (Verbeek, 2008; p110)

where $e_t = Y_t - \hat{Y}_t$ and Y_t and $\hat{Y}_t$ are, respectively, the observed and predicted values of the outcome variable for individual time t, which is the ratio of the sum of squared differences in successive residuals to the residual sum of squares (Gujarati, 2003). The critical value is around two, when there is no serial autocorrelation (Savin and White, 1977).

Figure 8-3: Five regions for values of Durbin-Watson *d*



In the presence of a positive autocorrelation the value of the test statistic tends to be small, while in the presence of a negative autocorrelation it will be large (Durbin and Watson, 1951). The critical values for the test statistic are dependent on both the number of data points and the number of independent variables contained in the model from which the residuals are derived (Savin and White, 1977). To arrive at the decision on the presence of autocorrelation, the significance level of d – the upper (d_u) and lower (d_l) limits – were established as shown in Figure 8-3. If DW values fall between d_u and $4-d_u$, the OLS estimates can be accepted without fear of a loss of efficiency or bias in the estimated variances. If DW values fall between d_l and $4-d_l$ and outside of the range of d_u and $4-d_u$, it is inconclusive and careful consideration should be made regarding the OLS estimates (Ostrom, 1990). The acceptable values of DW d will be presented for each specified model in each section.

8.3.2 Autoregressive integrated moving average process

ARIMA modelling is an iterative process involving identification, estimation, and diagnosis (McCain and McCleary, 1979). Annex 22 demonstrates the overall process with an example. The procedure begins with the development of a noise model to account for the underlying stochastic component: trend or drift, seasonality, and autocorrelation in the variable under study by examining the correlogram such as the autocorrelation function (ACF) and partial autocorrelation function (PACF) plots. Once a tentative noise model is identified, the parameters (Box 8-1) of the model are estimated and diagnosed as to whether all parameters are within each of the criteria and the residuals are not different from white noise. If any of these basic criteria is not satisfied, the model appears to be unacceptable and the procedure should be repeated.

Box 8-1: Definition of ARIMA parameters

An ARIMA model has three structural parameters, p, d and q, and they are presented as ARIMA (p,d,q) in documents. The lower-case p specifies the number of autoregressive terms, d specifies the number of times a series must be differenced, and q specifies the number of moving average terms. If time-series exhibit systematic periodic shifts as a pattern of behaviour repeats itself, it is desirable to incorporate a seasonal structure into the regular ARIMA (p,d,q) model in order to adjust for seasonality. The seasonal model is ARIMA $(p,d,q)(P,D,Q)_S$ where p, d, and q are the regular structural parameters, P,D,Q, and S the seasonal structural parameters. The upper-case P, D, and Q denote seasonal autoregressive terms, seasonal differenced, and seasonal moving average terms respectively. The S denotes the length of the period, for instance, which equals 4 for quarterly data, 12 for monthly data and so on. (McCain and McCleary, 1979)

After an appropriate noise model is specified, the intervention model is added to test the effect of the interventions. The impact assessment model may be written as follows:

$$Y_t = N_t + f(I_t) \qquad \text{(McCleary } \textit{et al.}\text{, 1980a)(Eq. 2)}$$

where,

- $\mathbf{Y_t}$; a dependent outcome variable of interest at time t
- $\mathbf{N_t}$; a noise component at time t
- $\mathbf{f(I_t)}$; an intervention component

There are generally three patterns of intervention models (McDowall *et al.*, 1980):

1) abrupt and permanent; $Y_t = \omega f(I_t) + N_t$ (Eq. 3)

2) abrupt and temporary; $Y_t = \delta Y_{t-1} + \omega f(I_t) + N_t$ (Eq. 4)

3) gradual and permanent; $Y_t = \delta Y_{t-1} + \omega f(I_t) + N_t$ (Eq. 5)

where,

- $\mathbf{Y_{t-1}}$; a dependent outcome variable of interest at time t-1
- ω ; a parameter interpreted as the magnitude of changes at the moment of intervention
- δ ; a parameter, determining how gradually the series changed

The adequacy of the intervention model is also tested by residuals analysis. Despite white noise residuals in the tentative noise model, the full impact assessment model is not acceptable if residuals are different from white noise. The model-building procedure is repeated until a parsimonious and statistically acceptable impact assessment model is generated (McCain and McCleary, 1979).

8.4 Data

Aggregated monthly claims data for drug consumption were provided by the Health Insurance Review & Assessment Service (HIRA) for the period January 2003 through June 2008. Data included claims that provided services between January 2003 and June 2008, and were submitted to the HIRA until September 2008. For the present study, a dataset was reconstructed on the basis of the date of service because the claims dataset has been principally constituted on the date of claim. Data provided for this study covers drug expenses, the unique number of patients dispensed and total number of units dispensed. Drug expenses are defined as net drug ingredient costs plus dispensing fees and include payments from public funds and legal patients' copayments. Medications dispensed in episodes covered by auto insurance, veterans' insurance and workers' compensation insurance are excluded from these statistics. For a better understanding of data sources, the procedure for making pharmaceutical claims is detailed in the following section.

8.4.1 Pharmaceutical claims database

Since 1995 in South Korea, National Health Insurance (NHI) covers about 98 per cent of the population (NHIC and HIRA, 2007). The remaining population, probably the most poor in the country, are covered by the national Medical Aid Plan (MAP) (Korean Statistical Information Services, 2006). The National Health Insurance Corporation (NHIC) is an organisation responsible for administration of the NHI and the MAP in terms of eligibility, billing and management of health insurance funds. Retail pharmacists and dispensing doctors (only in limited, pre-designated arrangements by law since 2000) are reimbursed directly by the NHIC, based on the prescription obtained from the patient after going through evaluation by the HIRA (Figure 8-4).

The HIRA administers a computerised database, which takes prescription information regularly reported by both the prescriber and the dispenser within the scope of the NHI and the MAP. The database covers information on beneficiaries, prescribers, dispensers, fees and dispensing (prescribing) of drugs, payment and reimbursement decisions. Refund of claims is the responsibility of the NHIC as mentioned. Before refunding, the HIRA determines whether claims are reimbursed, partly reimbursed or declined.

Figure 8-4: Claims flow diagram

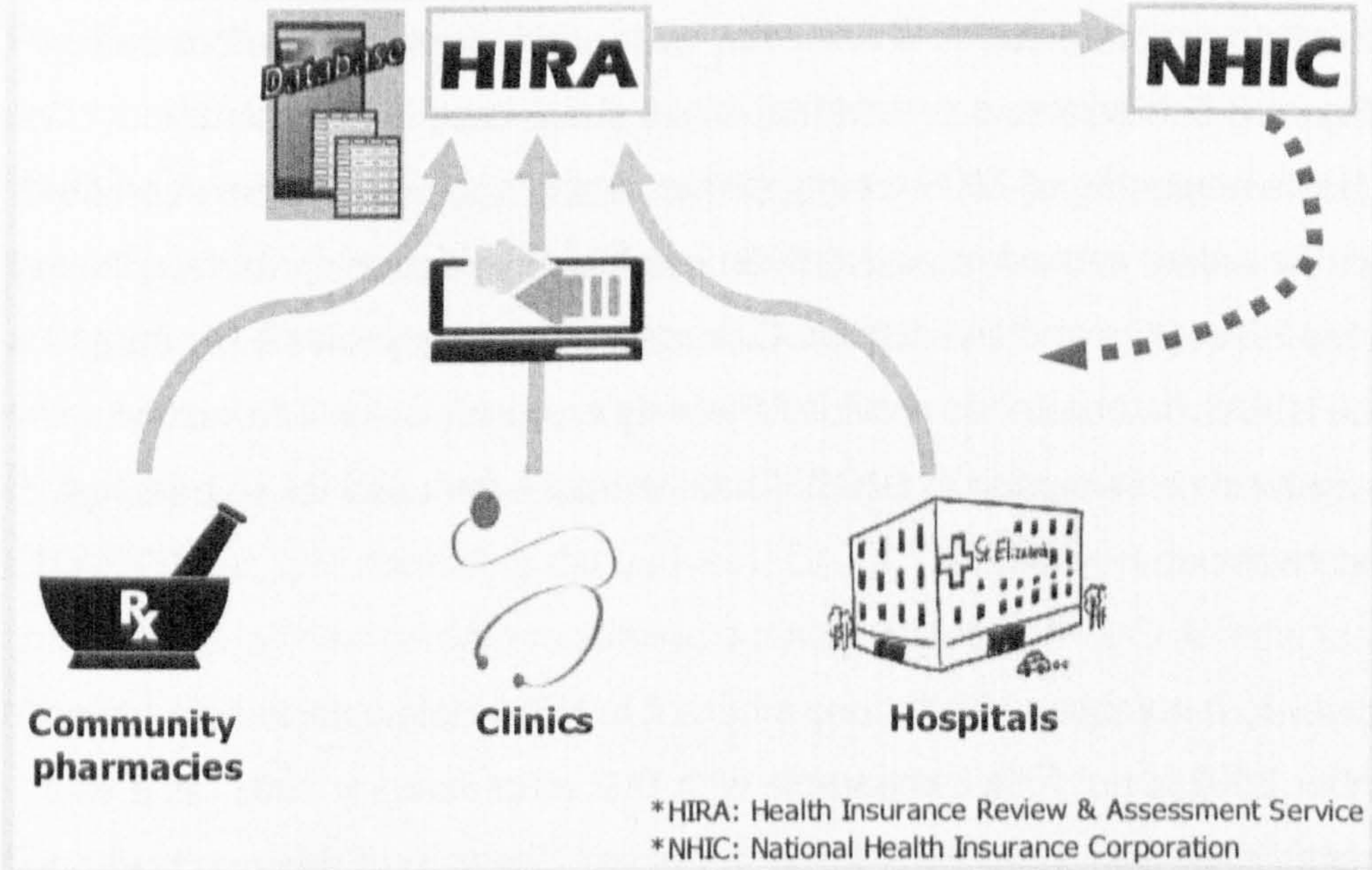
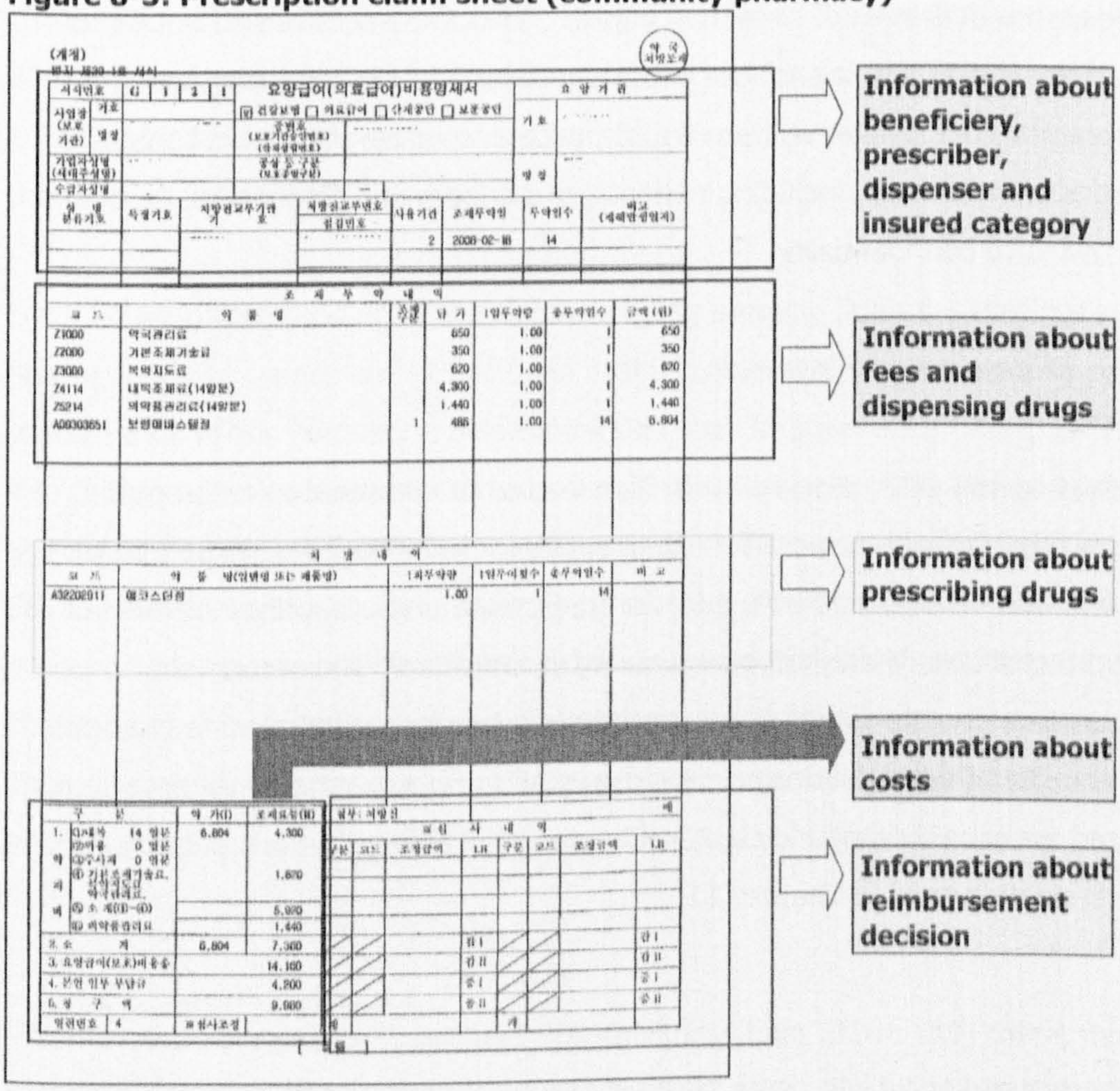


Figure 8-5: Prescription claim sheet (community pharmacy)



To make the decision, the HIRA assesses all medical and pharmacy claims to see that they meet the national guidelines in terms of both quality and quantity. Every provider should hand in all prescription claims online or by post and be assessed before being reimbursed. Figure 8-5 illustrates a prescription claim sheet used in community pharmacies. At the beginning of 2005, nearly 90 per cent of major providers submitted claims through the online networking system, an established electronic interface linking databases to the HIRA (Kim and Lee, 2006). Currently, the prescription claims data recorded in the HIRA's database has provided the only comprehensive information about pharmaceutical consumption in South Korea, so has been used for a variety of scientific research.

There are, however, a number of limitations inherent in HIRA claims data. First, data before December 2002 is not fully comparable with that after January 2003, as it was defined differently and maintained by a different system. Because of this practical difficulty, data before December 2002 was not used for the present project. Second, it does not cover the utilisation of over-the-counter (OTC) drugs, consumed outside of the scope of the NHI. Third, it has little precise information about the diagnosis for which a given prescription was written. Fourth, access to information about the characteristics of individuals, including patients, prescribers and dispensers, is prohibited owing to confidentiality.

8.4.2 Time series of interest

In this study, two sets of time series were constructed to investigate Korean policy interventions. The first set includes four time series for individual drug expenditure, individual utilisation or aggregated population prescribed and unit prices in terms of overall pharmaceuticals, which will be examined in Chapter 9. The second set comprises time series established in two therapeutic subclasses to examine the policy impact on the use of essential drugs and generics. For these purposes, six time series will be tested for each therapeutic class in Chapter 10. The implications of both analyses will be discussed in Chapter 11.

8.4.2.1 Choice of therapeutic subclasses

For the second set of time series, two therapeutic classes (antihypertensives and antihyperlipidemics) were chosen. Antihypertensives were defined as medications in WHO Anatomic Therapeutic Chemical (ATC) group C02 (antihypertensives), C03 (diuretics), C07 (beta-blocking agents), C08 (calcium channel blockers), C09 (agents acting on the Renin-Angiotensin system). Antihyperlipidemics were defined as medications in WHO ATC group C10AA (HMG CoA reductase inhibitors), C10AB (Fibrates), C10AC (Bile and sequestrants), C10AD (Nicotinic acid and derivatives), C10AX (Other lipid modifying derivatives), C10BA (HMG CoA reductase inhibitors in combination with other lipid modifying agents), C10BX (HMG CoA reductase inhibitors, other combinations).

Classification of each chemical ingredient sold in the Korean market was made according to the taxonomy provided by the HIRA in 2007, which linked most chemical substances to the WHO classification (Health Insurance Review & Assessment Service, 2007f). Korean national classification was also used for the unclassified products[13]. A list of insured products was obtained from the Maximum Allowable Cost list released by the HIRA in July 2008[14].

For a better understanding of the Korean coding system, Table 8-1 displays an example product and the names and codes used in the Korean market. Norvasc,® a product produced by Pfizer, containing amlodipine besylate 5mg per each tablet, is categorised into C08 (calcium channel blockers) in the WHO ATC system, 219 (other cardiovascular agents) in the Korean system and was granted the Insurance Code A03102361 or E01890381 during the study period. There may be several insurance codes for one product in Korea because the authority grants a new code to the same product if any change occurs in its legal market authorisation certificate for documentation reasons. Thus, the present study considered all insurance codes for each product to include all products during the study period.

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[13] Korean National Code 210 (consisted of 9 sub-codes from 211 to 219) covers most kinds of cardiovascular drugs including blood pressure lowering agents and blood lipid lowering agents.

[14] available at http://www.hira.or.kr/common/dummy.jsp?pgmid=HIRAF010104000000

Table 8-1: Example codes and names for a pharmaceutical product

International Nonproprietary Name	WHO ATC Classification	Korean National Code	Korean Insurance Code	Brand Name (Unit)	Manufacturer
amlodipine besylate	C08CA01	219	A03102361	Norvasc (5mg Tab.)	Pfizer Korea
			E01890381	Norvasc (5mg Tab.)	Pfizer Korea

In total, 464 lipid-lowering agents and 1,997 blood pressures lowering agents were identified, of which 351 and 1409 products were claimed at least once during the study period from January 2003 to June 2008 (see Table 8-2).

8.4.2.2 Classification of brand-named and generic drugs

This study defined generic drugs using the European Parliament regulation, which characterises generic medicines as follows:

> "Generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bio-equivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. (*Directive 2001/83/EC Article 10, paragraph 2, point (b)*)

A brand-named drug in this study was used as a synonym for an original drug, and was defined as a drug having been held or holding a patent for new chemical entities unless it was marketed before 1987, when patent regulation had not yet been introduced in South Korea. For products approved before 1987, a product was regarded as a brand-named drug if it was marketed for the first time among the same chemical substances internationally. A drug that was granted a patent on the manufacturing process, but not on the active ingredient was considered a generic drug. Similarly, a drug with a different salt from the original drug (a type of me-too drug), for example, amlodipine camsylate (e.g. Amodipine®) or amlodipine maleate (e.g. Anidipine®), was regarded as a generic drug of amlodipine besylate (Norvasc®). Two products would be

considered brand-named drugs if both contain the same active ingredient, but this active material was distributed by a different innovative delivery system from the other. An example of this would be a tablet or a capsule versus a delayed release tablet or a patch; however, there were no such cases in identified products. Generic drugs refer to all drugs except brand-named drugs defined above.

Pharmaceuticals were divided into brand-named and generic drugs by the two step procedure in order to mirror the real world more accurately. At the first step, products were principally grouped according to the following four sources of information about individual product's origin:

- the Korean bio-equivalent reference drug list;
- original drug information from database held by one university affiliated hospital in Korea;
- patent information from Orange book (US FDA, http://www.fda.gov/cder/ob/), or European Public Assessment Report (EMEA, http://www.emea.europa.eu/htms/human/epar/a.htm);
- information about licensing agreements between local producers and international manufacturers from several medical newspapers

The Korean bio-equivalent reference drug list has been established for the Bio-equivalence Validation Programme (BVP) and regularly updated by the HIRA since 2000. The BVP was introduced in 2000, to verify the quality of generic products. In this process, generic producers are obliged to prove that their product has a bio-equivalence profile equal to their reference drugs in the list. Reference agents are selected when they meet three conditions; 1) original drugs; 2) products holding the first market approval among products with the same ingredient; and 3) products the most popular in the market (*KFDA Official Instruction 2007-23, provision 3-2*). Reference products on the list may not always be original drugs, if they were selected because of the second and third conditions.

Owing to such limitation, other sources of patent information were sought. A database held by the pharmacy department in one respected teaching hospital was employed to supplement the first sources. The database has been established on the basis of information provided by marketing staff from each drug company. However, it does

not cover some of the products never prescribed in this particular hospital. Consequently, the Orange book published by US FDA and the European Public Assessment Report published by European Medicines Agency (EMEA) were also considered alongside the other information. In addition, several medical newspapers were scanned for information on licensing agreements between local producers and international originators, because, until recently, it was usual for an international originator to launch products via a local producer, sometimes more than one at a time, with different market names. If information from the stated procedure was insufficient, then each manufacturer or marketer was contacted for more accurate information for grouping.

At step two, the final list was confirmed by two registered pharmacists currently working in a teaching hospital and a community pharmacy in Korea.

Finally, 284 brand-named drugs and 1,125 generic drugs were identified among 1,409 drugs for lowering blood pressure. As for lipid lowering drugs, 60 brand-named drugs and 291 generic drugs were isolated (Table 8-2). Annex 21 presents an example of the classification for amlodipine derivatives.

Table 8-2: Number of brand-named and generic drugs identified by ATC code

ATC code		Brand drugs	Generic drugs	ATC code		Brand drugs	Generic drugs
antihypertensives				***antihyperlipidemics***			
C02	antihypertensives	29	69	C10AA	HMG CoA reductase inhibitors	33	237
C03	diuretics	29	73	C10AB	Fibrates	10	39
C07	beta-blocking agents	42	335	C10AC	Bile acid sequestrants	1	2
C08	calcium channel blockers	70	320	C10AD	Nicotinic acid and derivatives	9	4
C09	agents acting on the Renin-Angiotensin system	114	327	C10AX	Other lipid modifying derivatives	2	9
	unclassified		1	C10BA	HMG CoA reductase inhibitors in combination with other lipid modifying agents	2	
				C10BX	HMG CoA reductase inhibitors, other combinations	3	
	subtotal	284	1125		subtotal	60	291
Total			***1409***	***Total***			***351***

8.4.3 Definition of outcome variables

Outcome variables explored in this thesis include drug expenditure, utilisation, and unit

prices:

- **Drug expenditure** is operationally defined as the average monthly costs per patient, which includes both payers' expenditure and patients' legal copayments. From the empirical data under study, it was observed that total costs appeared to be high in winter, while costs per patient tended to be high in summer. It may be a result of an increase in patients with slight illnesses, such as the common cold, in spring and winter. Presumably, patients were prescribed less expensive, symptom-relief preparations, which could affect total expenditure in such periods. The present study employed a measure of per capita expenditure rather than total costs in expenditure to control such variations. In parallel, analysing the net expenditure including payers' and patients' expenses avoids bias from the budget shift which is likely to occur in policies limiting patient demand, such as cost-sharing (Chapter 7).
- **Drug utilisation** is operationally defined in two ways: aggregated number of individuals dispensed and units per patient. Although the 'units per patient' is a measure commonly used when investigating the utilisation of pharmaceuticals in empirical research, the true effects could be masked in a case where both the number of patients and the total drug consumption are reduced (or raised) by a similar magnitude as seen in Table 8-3. Opposite responses (decrease versus increase) in total units or the number of patients dispensed generate the same answer in units per patient. It may be particularly confusing if the researcher attempts to test the impact of cost-sharing given the way it functions, which is to decrease patient demand for drugs through suppressing patient visits or adherence to prescription filling (Chapter 4). Hence, both measures will be used in conjunction to investigate individual use as well as drug accessibility in this study.

Table 8-3: Relationship between participation and units per patient

	time point A	time point B	time point C
number of units dispensed	100	120	50
number of patients dispensed	100	120	50
units per patient	**1**	**1**	**1**

- The **unit price** of pharmaceuticals is operationally defined as the costs per unit.

The definitions and calculations for each of the dependent variables are outlined below:

- ***Total costs reimbursed for pharmaceuticals*** is defined as the sum of payers' and patients' costs on drugs dispensed on a monthly basis, including fees.
- ***The number of patients dispensed*** is counted as each unique patient having one or more claims during the study period on a monthly basis.
- ***Total number of units dispensed*** is defined as the sum of (units × frequency × days dispensed) for each pharmaceutical during the study period on a monthly basis. A unique unit for each pharmaceutical product is designated in the pharmaceutical reimbursement list and generally defined depending on the formulation of the product, for example, 1 tablet, 1 capsule, 1 pack, 1ml, 1 ampule, 1g, and so forth.
- ***Costs per patient*** are defined as the total costs reimbursed for pharmaceuticals divided by the number of patients dispensed in the corresponding month.
- ***Units per patient*** are defined as the total number of units dispensed divided by the number of patients dispensed in the corresponding month.
- ***Costs per unit*** are defined as the total costs reimbursed for pharmaceuticals divided by the total number of units dispensed in the corresponding month.

8.5 Modelling framework

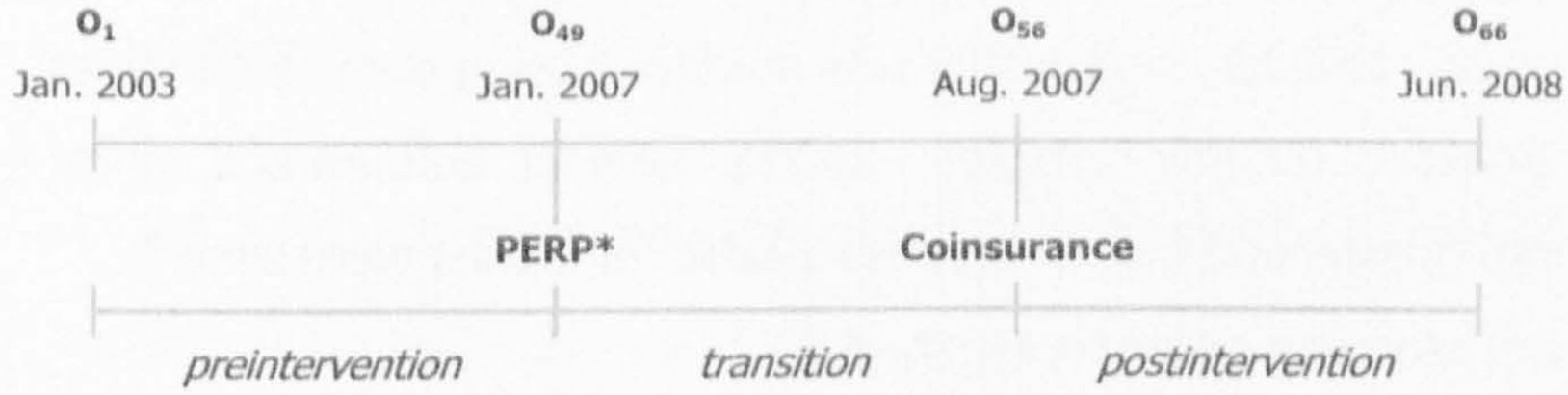
Two pharmaceutical policies were evaluated in this thesis: the Pharmaceutical Expenditure Rationalisation Plan (PERP) and the extension of coinsurance. Each policy was described in detail in Chapter 2.

8.5.1 Segmented regression model

8.5.1.1 Basic segmented regression model

A basic segmented regression model included independent variables to test the size and statistical significance of time series changes in level and slope after policy interventions. The data were segregated into three discrete periods for analysis: from January 2003 to December 2006 – a pre-intervention period; from January 2007 to July 2007 – the period after PERP enforcement began, a transition period; from August 2007 to June 2008 – the period after coinsurance extension implemented, a post-intervention period as diagrammed in Figure 8-6.

Figure 8-6: Introducing date of policies of interest in data period



* PERP refers to the Pharmaceutical Expenditure Rationalisation Plan

Thus, the following segmented regression model was established:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \varepsilon_t \quad \text{(Eq. 6)}$$

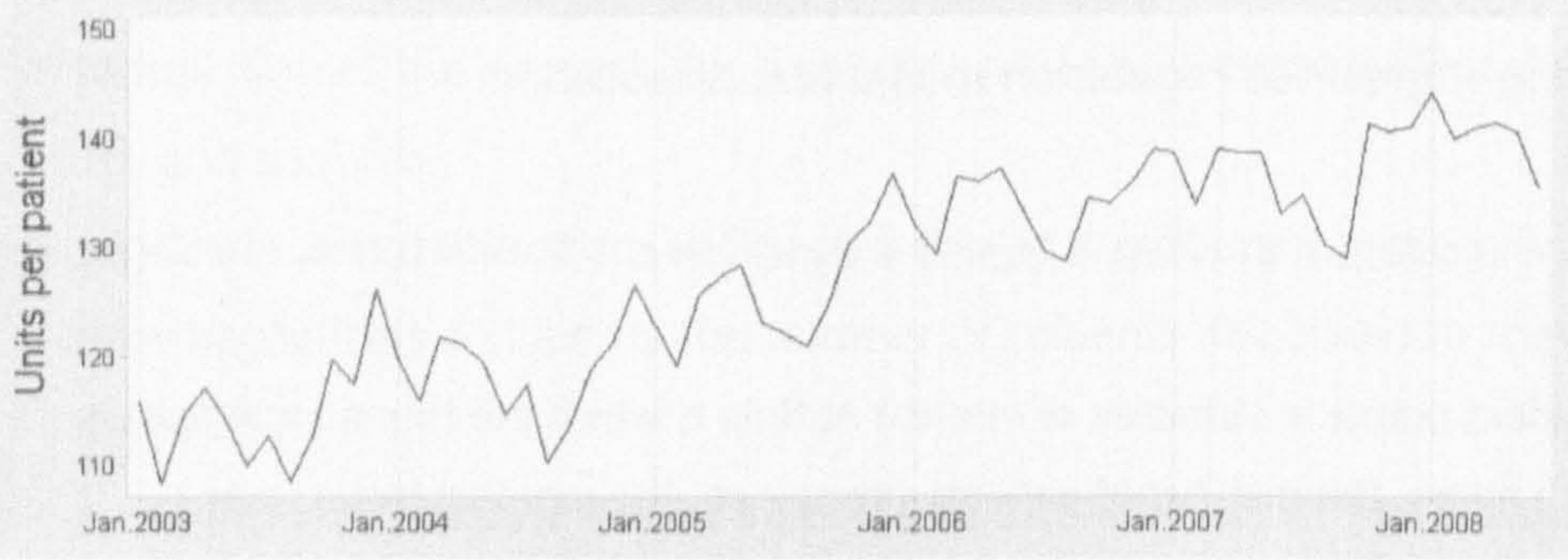
where,

- $\mathbf{Y_t}$; dependent outcome variables of interest at time t, which are the monthly mean costs per patient, the number of patients prescribed, the monthly mean units prescribed per patient and the monthly mean costs per unit
- $\mathbf{time_t}$; a numerical month variable beginning in January 2003 (month=1) and extending to June 2008 (month=66)
- **Perp** ; a dummy variable for the PERP (the first policy change of interest) coded 0 before January 2007 and 1 from January 2007
- $\mathbf{Perp_t}$; a continuous variable representing time after the PERP and coded 0 before January 2007 and 1 to 18 from January 2007 to June 2008
- **Co** ; a dummy variable for the coinsurance (the second policy change of interest) coded 0 before August 2007 and 1 from August 2007
- $\mathbf{Co_t}$; a continuous variable representing time after the coinsurance and coded 0 before August 2007 and 1 to 11 from August 2007 to June 2008
- $\boldsymbol{\beta_0}$; baseline level of the outcome at time zero
- $\boldsymbol{\beta_1}$; baseline trend of the outcome before the interventions
- $\boldsymbol{\beta_2}$; a level change of the outcome immediately after the implementation of PERP
- $\boldsymbol{\beta_3}$; a change in the trend of the outcome after the PERP, compared with the baseline trend
- $\boldsymbol{\beta_4}$; a level change of the outcome immediately after the expansion of coinsurance
- $\boldsymbol{\beta_5}$; a change in the trend of the outcome after the coinsurance, compared with the trend after the PERP
- $\boldsymbol{\varepsilon_t}$; error term at time t

8.5.1.2 Seasonally adjusted segmented regression model

Accompanying the policy variables, seasonality was modelled using dummy variables where appropriate. Seasonal dummy variables – spring, summer, autumn and winter – were incorporated into the general model because sizable variations were seen in prescription data by season (for instance, Figure 8-7).

Figure 8-7: Units per patient (January 2003 ~ June 2008)



Seasonality is a usual feature in monthly prescription data. Less patients may see their doctors during certain times of the year (for example, summer) and more during others (for instance, winter). South Korea has four clear seasons. March to May as classed as spring, June to August as summer, September to November as autumn and December to February as winter. Such seasonality needs to be controlled for in any ITS analysis because it usually becomes an important source of variability. Moreover, the data employed contains different seasonal profiles, for example more winter and spring months in the post-intervention period which could potentially confound any apparent intervention effect.

Figure 8-7 displays a time series for units per patient between January 2003 and June 2008. Monthly measures were plotted by period to inspect the distributions visually. It shows a clear peak in winter months. Seasonal dummy variables were used to control seasonal fluctuations. After stepwise elimination of non-significant terms, only one variable representing summer was included in the final model. This was also the case for other outcome variables showing apparent seasonality. Finally the following model was specified for those time series:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \beta_6 \times S + \varepsilon_t \quad \text{(Eq. 7)}$$

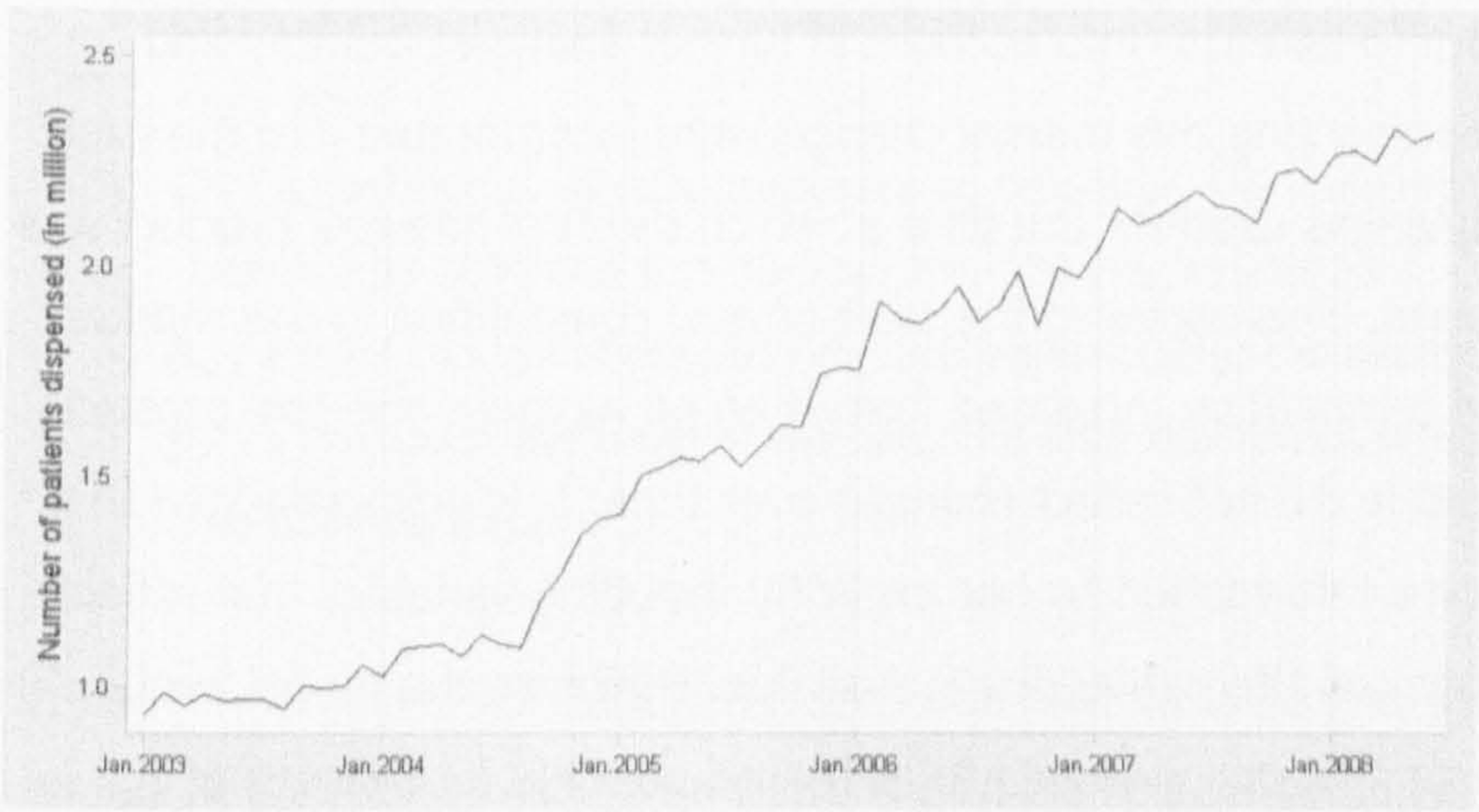
where,

- β_6 ; coefficient for a summer variable
- **S** ; a dummy variable for summer months coded 1 for June, July and August and 0 for others

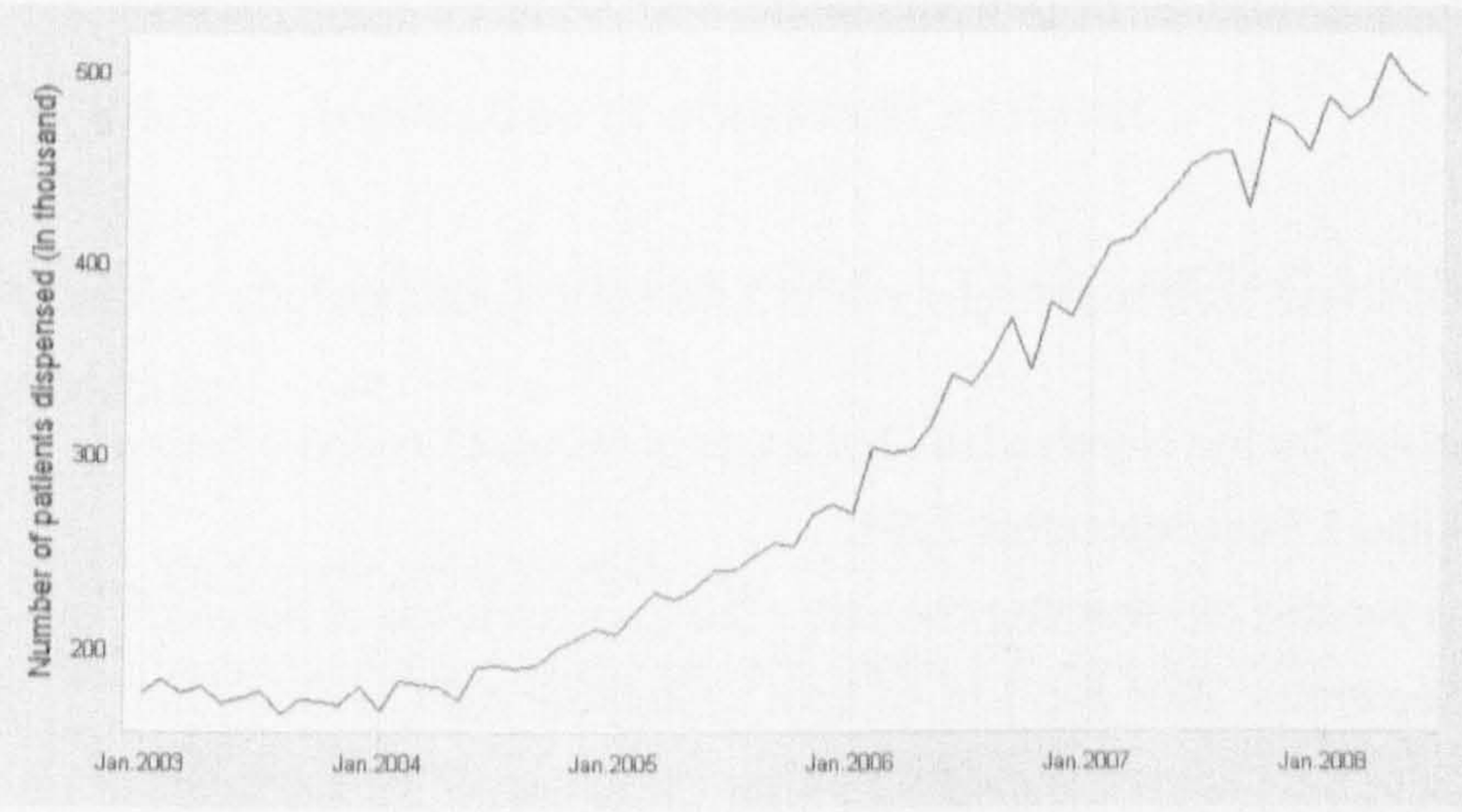
8.5.1.3 Segmented regression model by therapeutic subclass

On first inspection, the time series from the two therapeutic subclasses produced quite different trend lines with little seasonal variation observed. Substantial increases were detected in mid 2004 for the time series for the number of patients dispensed (Figure 8-8).

Figure 8-8: Number of patients dispensed



a) Number of patients dispensed ***generic*** antihypertensives



b) Number of patients dispensed ***brand-named*** antihyperlipidemics

In the Korean market, there were big changes with study drugs in 2004. With antihypertensives, the first 'me-too' drug of Norvasc® was launched in September 2004.

A 'me-too' drug denotes a product containing a slightly modified active ingredient, but generating the same clinical effect as the original product. Norvasc® is a Pfizer's brand name for amlodipine besylate, which is a long-acting calcium channel blocker (CCB) and one of world's blockbusters in 2000s (Pfizer Inc., 2006). It had been at the top of the Korean prescription drug market over all products until 2005 (Korea Health Industry Development Institute, 2007).

Since 2004, many 'me-too' products had sharply encroached upon the market share of Norvasc®. The market share of a front-running product among the me-too drugs of Norvasc® was placed 8th in 2005 and rose to 4th place with a 30% increase in 2006 amongst all prescription market products (HIRA document cited by DailyPharm, 2009). Because the magnitude of change caused by me-too drugs was considerable in the market, it was necessary to take this into account in further analysis. Dummy and continuous variables representing this market change were incorporated into the basic model. A dummy variable was used for the time at which the first 'me-too' product was introduced into the market. This captured the start of new competition in this market. Although the degree of competition increased from then on as more 'me-too' products were available, the variable did not reflect changes over time. It is acknowledged that the analysis has lost some information by not explicitly including variables that reflect the change of the number of alternative drugs available. However, the model kept independent variables for non-policy events to as few as possible for reasons of parsimony. The following model (named the *antihypertensives segmented regression model*) was specified for 'the number of patients dispensed' series in antihypertensives:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \beta_6 \times Nv + \beta_7 \times Nv_t + \varepsilon_t \qquad \text{(Eq. 8)}$$

where,

- **Nv** : a dummy variable for the launch of me-too drugs of Norvasc® coded 0 before September 2004 and 1 from September 2004
- **Nv_t** : a continuous variable representing time after the launch me-too of Norvasc® and coded 0 before September 2004 and 1 to 46 from September 2004 to June 2008
- **β_6** : a level change of the outcome immediately after the launch of me-too drugs of Norvasc®
- **β_7** : a change in the trend of the outcome after the launch of me-too drugs of Norvasc®, compared with the baseline trend

In the antihyperlipidemics market, Crestor® (rosuvastatin branded by AstraZeneca) was launched in July 2004 into the Korean market (DailyPharm, 2004a). The market share of Crestor® jumped from 76th to 20th place with a 135% increase among all prescription market products between 2005 and 2006 (HIRA document cited by DailyPharm, 2009). To control such a substantial change in the analysis, dummy and continuous variables representing the launch of Crestor® were incorporated into the basic model similarly to the case with antihypertensives. The final model (named the *antihyperlipidemics segmented regression model*) was specified for 'the number of patients dispensed' series in antihyperlipidemics:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \beta_6 \times Cr + \beta_7 \times Cr_t + \varepsilon_t \qquad \text{(Eq. 9)}$$

where,

- **Cr** ; a dummy variable for the launch of Crestor® coded 0 before July 2004 and 1 from July 2004
- **Cr_t** ; a continuous variable representing time after the launch of Crestor® and coded 0 before July 2004 and 1 to 48 from July 2004 to June 2008
- **β_6** ; a level change of the outcome immediately after the launch of Crestor®
- **β_7** ; a change in the trend of the outcome after the launch of Crestor®, compared with the baseline trend

The empirical regression model for each outcome variable was specified through the procedure described so far. Details for the model specification will be presented together with individual analysis in the following chapters.

8.5.2 Application of statistical analyses

Identified segmented regression models were examined statistically in the following procedure:

1. OLS estimation performed;
2. autocorrelation was explored using the DW statistic;
3. if the data were found to be autocorrelated, segmented regression analysis was repeated by EGLS estimation using the Prais-Winsten estimator;
4. the sensitivity of segmented regression analysis was crosschecked using an ARIMA process whose model specification procedure is addressed in the following section.

8.5.3 ARIMA model specification

In the present studies, ARIMA models were constructed for a sensitivity analysis to crosscheck results. The following conceptual intervention components were established as Equation 10.

$$f(I_t) = \omega_1 Perp + \omega_2 Co \qquad \text{(Eq. 10)}$$

where,

- **$f(I_t)$;** an intervention component
- **Perp ;** *1) for the abrupt, permanent and the gradual, permanent change*: a dummy variable for the PERP (the first policy change of interest) coded 0 before January 2007 and 1 from January 2007, *2) for the abrupt, temporal change*: a pulse variable coded 0 before January 2007, 1 for January 2007 and 0 again for the rest period
- **Co ;** *1) for the abrupt, permanent and the gradual, permanent change*: a dummy variable for the coinsurance (the second policy change of interest) coded 0 before August 2007 and 1 from August 2007, *2) for the abrupt, temporal change*: a pulse variable coded 0 before August 2007, 1 for August 2007 and 0 again for the rest period
- **ωs ;** coefficients for the magnitude of changes

To incorporate the intervention components into the specified noise models, it was necessary to choose an intervention transfer function (Equation 3 through 5 In 8.3.2). The Intervention models were built firstly according to the analysis results from the regression models, because they were considered a reasonable *a priori* notion as to the nature of the policy impact. However, the identification was not limited to the regression results, but broadened if necessary by exploring the graphical appearance of actual data and forecasting numbers from the tentative noise model.

The adequacy of the final models was tested statistically by the Box-Ljung Q test of residuals (McCain and McCleary, 1979). The model-building procedure was done repeatedly until a parsimonious and statistically acceptable impact assessment model was generated. Box 8-2 outlines the series of steps employed in the study. Annex 22 addresses these in greater detail with the example analysis of the 'costs per patient' time series.

Box 8-2: Steps for ARIMA modelling

1. Visual examination of the time plot of the data series of interest
2. Examination of correlogram to identify a 'noise' model
3. Estimation of parameters and check with the basic criteria
4. Examine residuals from the obtained model and assess adequacy
5. Fit the intervention component to the identified 'noise' model
6. Diagnosis for the residuals of the full impact assessment model

(McCain and McCleary, 1979)

8.6 Summary

This chapter described a methodological tool for the empirical quantitative studies conducted in the thesis. Quantitative studies in this thesis employed a segmented ITS analysis to investigate the impact of the Korean pharmaceutical policy interventions, which was crosschecked where requested by the ARIMA approach. National insurance claims data were provided by the HIRA, a Korean medical services audit body. Specific segmented regression models were identified for each time series of interest, taking seasonal variations and market dynamics into account. Finally, three adjusted models were specified alongside a basic segmented regression model, which were seasonally adjusted segmented regression models, and antihypertensives and antihyperlipidemics segmented regression models. In parallel, this chapter briefly outlined the specification of ARIMA models. More detailed, specific methods, descriptive summaries and results are presented in Chapter 9 and 10.

CHAPTER 9: ASSESSING THE EFFECTS OF LOCAL PHARMACEUTICAL POLICIES ON THE PHARMACEUTICAL MARKET

9.1 Introduction

The objective of this chapter is to present results from the first empirical study. The impact of two recent pharmaceutical policies upon overall pharmaceutical expenditure, utilisation and prices are explored. The two policy interventions are the Pharmaceutical Expenditure Rationalisation Plan (PERP) and the extension of coinsurance for outpatients' prescription drugs that has been implemented in South Korea. Neither policy has been evaluated since implementation.

9.2 Policy changes

9.2.1 Pharmaceutical Expenditure Rationalisation Plan

The PERP was implemented on 29 December 2006, about 8 months after it was suggested in May 2006. The PERP is a comprehensive package of pharmaceutical regulations and consists of four sub-domains, which are *price control, volume control, quality control* and *the restructure of the pharmaceutical market* (see Chapter 2 for policy details). Many of the measures in the PERP are little more than existing regulations which previously were scattered here and there. However, some of them, such as a positive list or a price-volume agreement, were measures dismantling the traditional regulation structure. The present study aims to explore the impact of the new reimbursement pricing and listing system.

In brief, the PERP employed price-volume agreements for the pricing of all patent drugs based on the evidence of cost-effectiveness. One year after the first decision, the volume of each product consumed in the healthcare sector is assessed based on data from pharmaceutical claims. Off-patent drugs are reduced in price by 20% when the first generic counterpart is submitted for the listing. This was applied to all existing off-patent drugs when the new system was implemented, reflected in the Maximum

Allowable Costs (MAC) edition of January 2007. The pricing system for generics maintained the same rules as before. Prices for generics are set at a 20~30% reduced price to their brand-named counterparts. In actuality, the new system cuts the price of the off-patent original drugs by 20% making the price of generic products equal to 64% of the price of the original counterpart in the previous system.

The reimbursement listing system replaced a negative list with a positive one. However, few changes have been observed in the total number of pharmaceuticals in the list, as discussed in Chapter 2. Hence, the present study found few real changes brought about by the new listing system.

9.2.2 Coinsurance

From 2001 to 2007, patients paid a fixed copayment of 1,500KRW (£0.75) per prescription, unless the total drugs cost per single prescription (including a dispensing fee) exceeded 10,000 KRW (£5) (see Chapter 2 for more details). In August 2007, a fixed copayment for patients aged between 6 and 64 was replaced by the 30% coinsurance scheme. In other words, non-elderly patients have to pay 30% of total drug costs per prescription even though the total amount of expenses is under the previous 'upper limit'. Because of the new cost-sharing schedule, the actual increase in the out-of-pocket rate was about 50% from 20% to 30% in prescriptions previously under the fixed-copayment scheme. The elderly population continue to pay a fixed copayment same as before. A slightly lower cost-sharing rate began to apply to children under six, which since August 2007 has been 70% of the adults charge.

9.3 Objectives of study

The aim of the PERP was to contain pharmaceutical expenditure primarily by achieving cost-effective purchasing (Ministry of Health & Welfare, 2006c). In PERP, price cutting of off-patent pharmaceuticals was followed by curtailing prices of corresponding generic products, consequently lowering the average price of overall medications in the market. Decreasing the average price of medications was expected to lower expenditure on pharmaceuticals.

The copayment change aimed to contain pharmaceutical costs by increasing price

sensitivity in patients, targeting those with temporary symptoms such as the common cold (Ministry of Health & Welfare, 2007a). Increasing out-of-pocket expenditure might discourage patients from seeking drugs in unnecessary cases, thus decreasing pharmaceutical consumption. Decreasing volume might subsequently lead to containing pharmaceutical expenditure.

The effects of the two policy interventions on pharmaceutical expenditure and utilisation are still unknown. Therefore, this study seeks to examine whether the policies achieved the intended policy objectives.

9.4 Methods

9.4.1 Study design and data source

The design of the study is an observational, retrospective, interrupted time series analysis of 66 monthly observations from January 2003 to June 2008. Aggregated monthly data concerning drug consumption and expenditure were provided by the Health Insurance Review & Assessment Service (HIRA) (see Chapter 8 for details).

9.4.2 Outcome measures

The primary outcome variable was drug expenditure per capita to test if two study interventions achieved their ends, I.e. 'cost containment'. Variables reflecting drug utilisation and unit drug price were investigated as secondary outcomes to explore if they did lower costs how they did so. Drug utilisation was defined in two ways: *'units per patient'* and *'total number of patients dispensed'*. Unit drug price was defined as *'costs per unit'*. Details of definitions and calculations are presented in Chapter 8.

9.4.3 Statistical Analysis

9.4.3.1 Primary analysis

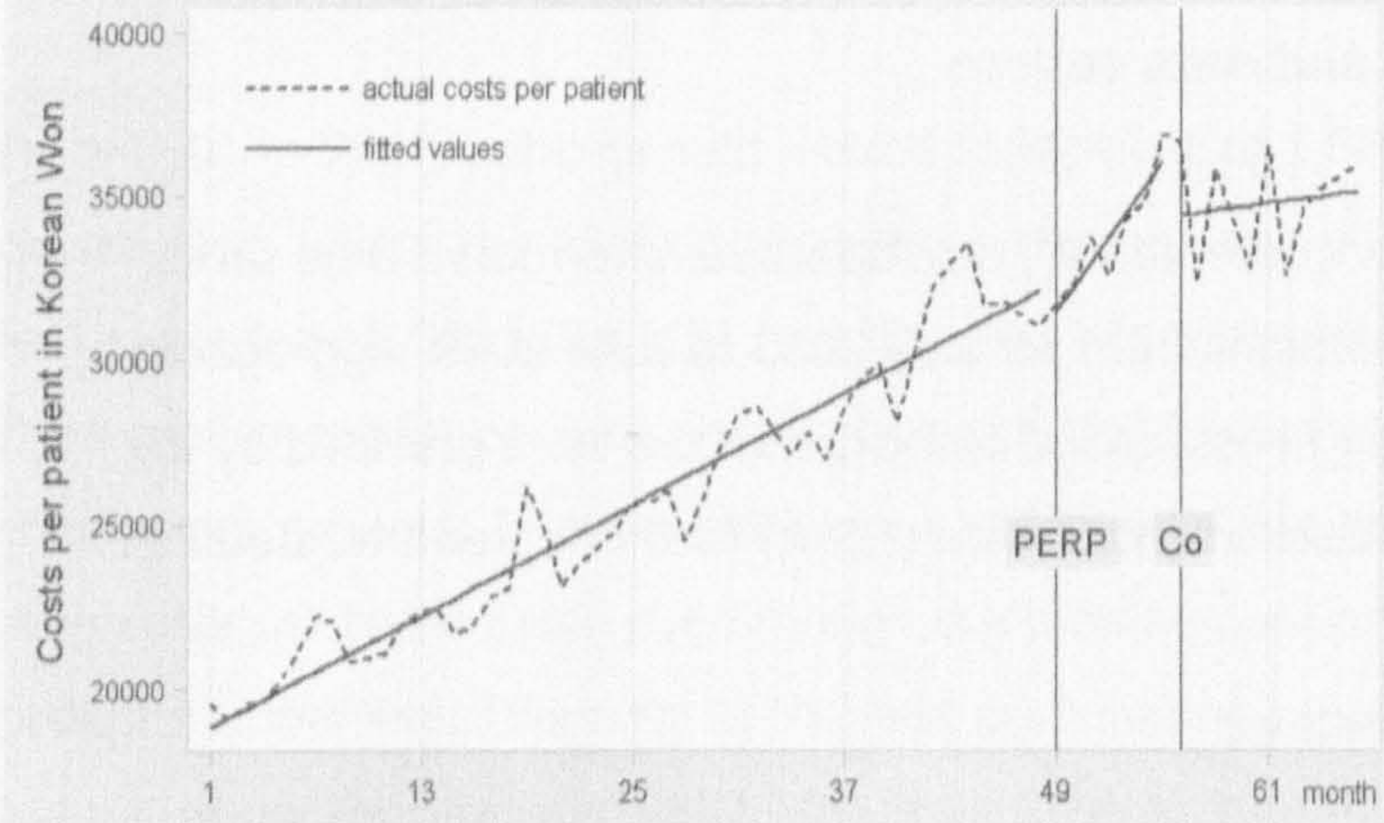
To measure the size and statistical significance of time series changes associated with the implementation of these interventions, segmented regression models were primarily used (Chapter 8). Time series for each dependent variable was established

and visually examined for any extreme variations potentially confounding policy outcomes. Considerable seasonal fluctuations were noted in all outcome variables. Hence, both general and seasonal models were applied to all outcome variables to determine the best framework. Details of definitions and coding were explained in Chapter 8 (see 8.5 for modelling framework). As a reminder, the basic segmented regression model (Equation 6) and seasonally adjusted segmented regression model (Equation 7) were as follows:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \varepsilon_t \quad \text{(Eq. 6)}$$

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \beta_6 \times S + \varepsilon_t \quad \text{(Eq. 7)}$$

Figure 9-1: Drug costs per patient from January 2003 through June 2008



A visual investigation of the fitted data against the actual value suggested that the seasonally adjusted segmented regression model was superior for all time series concerned. For example, monthly average drug costs per patient were plotted in Figure 9-1. It displays the time series of actual costs per patient for pharmaceuticals by month (dashed line) along with the corresponding fitted values (solid line) from OLS estimation by applying the basic model. From the analysis, a sharp increase in trend was suggested after the PERP ($p=0.033$). However, it seems erroneous given seasonal fluctuations – drug expenditure repeatedly increased during the first half of every year and tended to fall during the second half (Figure 9-1). In the years before the introduction of PERP, a rising trend in the first half was offset by a decreasing trend in the second half. Contrary, there was only the first half of the year after the PERP, in the segment before the implementation of the second intervention, denying the offset by a decline in the second half. In this sense, an increasing trend measured by a simple

segmented regression model can hardly be ascribed solely to the PERP implementation. To control for such seasonality, a seasonally adjusted segmented regression model was applied and this suggests non statistically significant changes in the trend after the first policy change.

The Durbin-Watson *d* statistic (DW) was used as a test for serial correlation of error terms. Table 9-1 displays critical values for two tentative models at the significance level of 5%. If DW values clearly indicated the presence of autocorrelation after applying ordinary least squares (OLS), the models for such variables were corrected for first-degree autocorrelated errors using the Prais-Winsten estimator.

Table 9-1: Durbin-Watson critical values for the regression models

	d_l	d_u	2	$4-d_u$	$4-d_l$
decision	uncertain	no autocorrelation		uncertain	
critical value					
general model	1.438	1.767		2.233	2.562
seasonal model	1.404	1.805		2.195	2.596

(Source: Savin and White, 1977)

A *p*-value of less than or equal to 0.05 was considered statistically significant. To explore the goodness of fit of the segmented regression models, the proportion of variability in the data set that was accounted for in the model was also calculated (adjusted R^2). The segmented regression was carried out using STATA version 10.0 (StataCorp LP, 2007).

9.4.3.2 Sensitivity analysis

For crosschecking the significant results from segmented regression models, autoregressive integrated moving average (ARIMA) models were constructed and analysed. Using an iterative process as described in Annex 22 until changes in the orders of the autoregressive, integrated, and moving average processes resulted in no further improvement in fit and the autocorrelation of errors was not statistically significant. Finally, the ARIMA$(0,1,1)(0,1,0)_{12}$ model was specified from the pre-intervention data for the noise compartment in all relevant variables. Using the tentative noise model, projections for the post-intervention period were formed to provide estimates in the absence of interventions. After the visual examination of actual and fitted data, it was found that there was little reason to assume gradual,

permanent or abrupt, temporal intervention effects. Thus, the simplest intervention model (abrupt, permanent) was added to represent the effect of the interventions. The Box-Ljung Q statistic was used for residual analysis to gauge serial autocorrelation of error terms. The ARIMA process and statistical analysis was carried out using R version 2.11.0 (The R foundation for statistical computing, 2010). The best-fit models were compared with closely competing models to determine the impact of alternative models on the intervention effect, and the estimates of intervention effect were robust. Although the coefficients varied somewhat, its direction and significance remained robust across closely competing models.

9.5 Results

9.5.1 Overall trends

Figure 9-2 and Table 9-2 demonstrate overall trends in aggregated drug costs, the volume and the population who were dispensed drugs at least once during the study period. During a 5-year period, total costs almost doubled from 465 billion KRW in 2003 to 913 billion KRW in the first half of 2008. The annual growth rate of expenditure was highest, nearly 20%, in 2005 and has shown a downturn since then.

Volume rose by 42% and the number of patients dispensed increased by 16% in the corresponding period. Both also showed the highest growth in 2005, about 12% and 5% respectively. The pattern of the trend was similar in these two variables. Considerable fluctuations were discerned by month with a peak during the spring (April and May) and winter seasons (November and December); the lowest was in summer (June, July and August) and February.

Figure 9-2: Total costs for pharmaceuticals, total number of patients dispensed and total number of units dispensed from January 2003 to June 2008

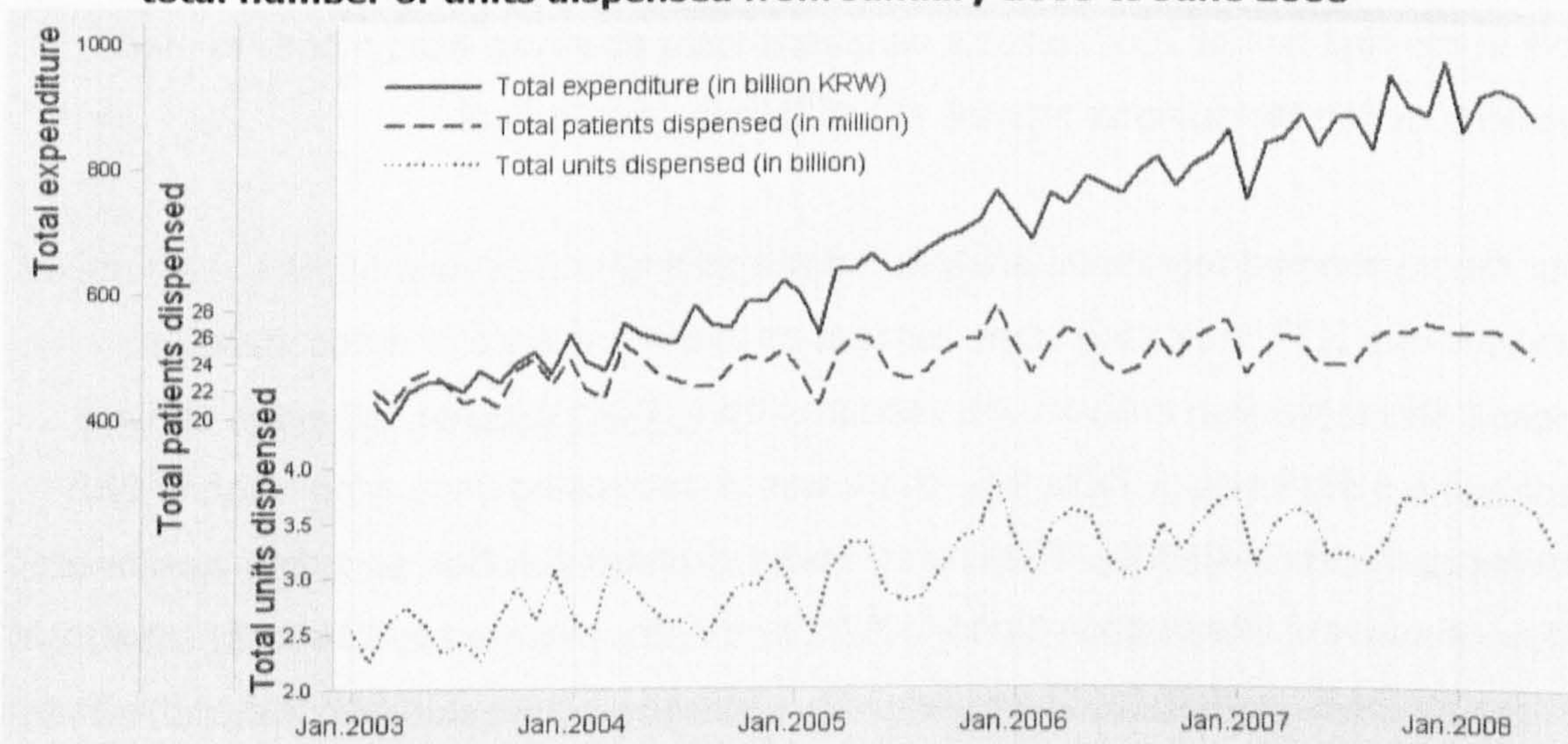


Table 9-2: Descriptive summary of overall changes in expenditure, number of patients and utilisation on pharmaceuticals during the study period

	Total costs for pharmaceuticals (in billion KRW[1])		Total patients dispensed (in million)		Total units dispensed (in billion)	
Year	Mean (95% CI[2])	Annual changes (%)	Mean (95% CI)	Annual changes (%)	Mean (95% CI)	Annual changes (%)
2003	465.15 (443.98, 486.32)	-	22.45 (21.72, 23.18)	-	2.58 (2.44, 2.73)	-
2004	548.43 (524.88, 571.99)	17.9	23.39 (22.61, 24.17)	4.17	2.77 (2.64, 2.91)	7.42
2005	655.97 (622.58, 689.36)	19.61	24.46 (23.33, 25.58)	4.57	3.10 (2.88, 3.31)	11.65
2006	769.11 (745.76, 792.45)	17.25	24.91 (24.20, 25.63)	1.86	3.34 (3.20, 3.48)	7.83
2007	862.82 (834.81, 890.84)	12.18	25.40 (24.63, 26.17)	1.94	3.47 (3.32, 3.63)	3.99
2008[3]	913.10 (880.57, 945.63)	5.83	26.06 (25.41, 26.71)	2.61	3.66 (3.52, 3.81)	5.48

1) KRW refers to Korean won.
2) CI refers to confidence interval.
3) From January to June

9.5.2 Impact on drug expenditure

Monthly 'costs per patient' had increased from 20,713 KRW in 2003 to 34,006 KRW in 2007 with an average annual growth rate of 13%. It was observed that the annual growth rate continued to rise until 2005, then fell from 15% in 2005, 10% in 2007 to 3% in the first half of 2008. Sizable variations were observed from month to month, peaking during the summer months and bottoming out in April.

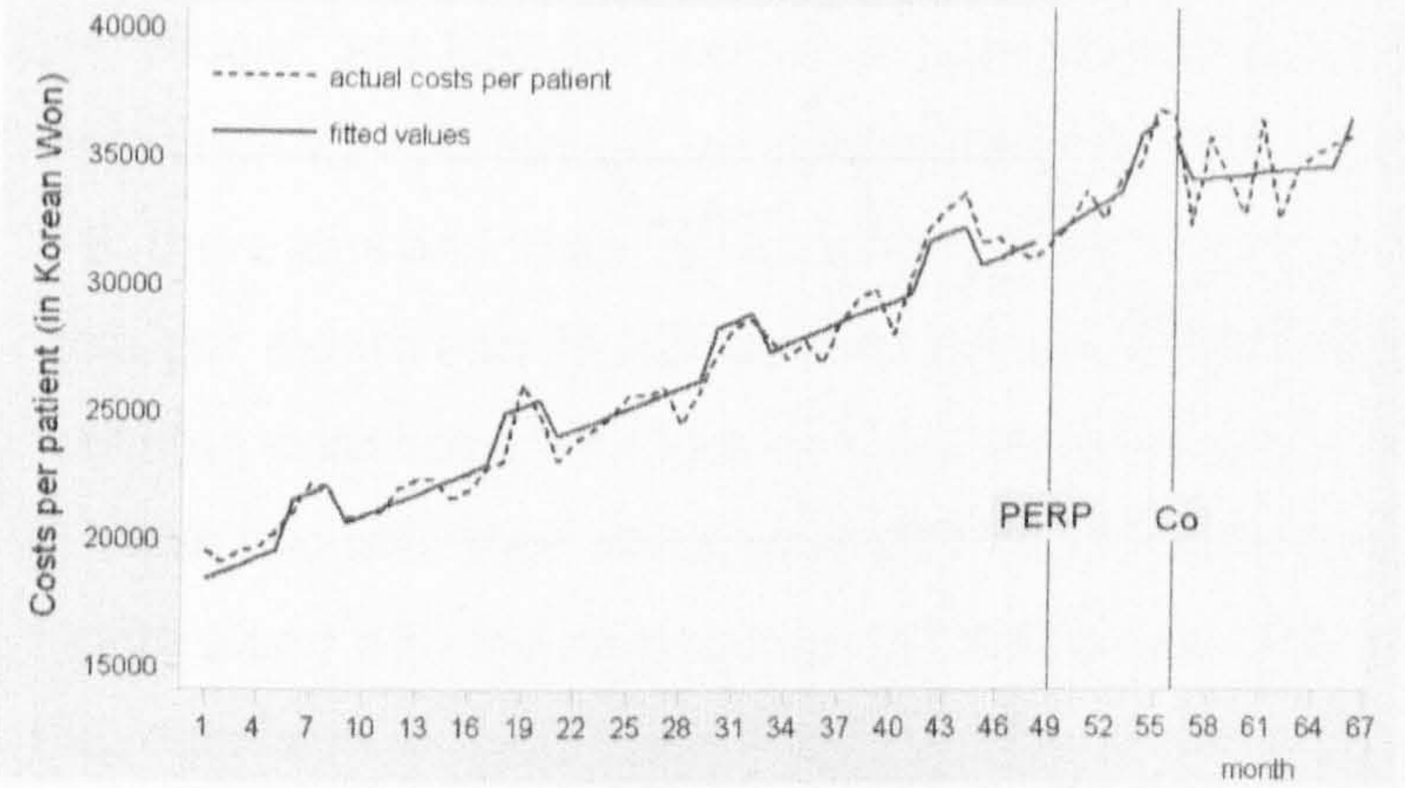
For the segmented regression analysis, after applying OLS estimation, the value of DW statistic was 2.37, indicating some concern as to the presence of autocorrelation. Hence, the regression analysis was repeated using Prais-Winsten estimator, and outputs are displayed in Table 9-3. There was an increasing underlying trend of 281 KRW per month ($p<0.001$). The upward trend of pharmaceutical spending was lowered after the second intervention by 368 KRW per month, which was statistically significant at the 5% level ($p=0.030$). There was little evidence of change in trend after the first policy and in levels after both interventions. Figure 9-3 presents the time series of actual 'costs per patient' on pharmaceuticals by month along with the corresponding fitted values from estimated generalised least squares (EGLS) estimation.

Table 9-3: Regression coefficients for costs per patient

(unit; Korean won)	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value	DW *d*-statistic
Intercept β_0	18155.82	17717.14	18594.49	82.82	<0.001	1.93
Baseline trend β_1	280.89	265.77	296.00	37.18	<0.001	
Level change after PERP β_2	-181.16	-1590.33	1228.00	-0.26	0.798	
Trend change after PERP β_3	167.30	-137.42	472.03	1.1	0.276	
Level change after coinsurance β_4	-650.58	-2142.84	841.68	-0.87	0.387	
Trend change after coinsurance β_5	-367.88	-699.56	-36.19	-2.22	0.030	
Summer β_6	1745.52	1276.82	2214.22	7.45	<0.001	

* Estimated generalised least squares estimation

Figure 9-3: Observed and estimated costs per patient before and after interventions



9.5.3 Impact on unit prices

The average 'costs per unit' had increased over time with the annual growth rate of 8% until 2007. Cumulatively it rose by 38% from 181 KRW in 2003 to 249 KRW in the first half of 2008. The annual growth rate was highest in 2004 at about 10% and no less than 7% until 2007. By contrast, the upward trend appeared to cease during the first half of 2008, when it was 0.13%.

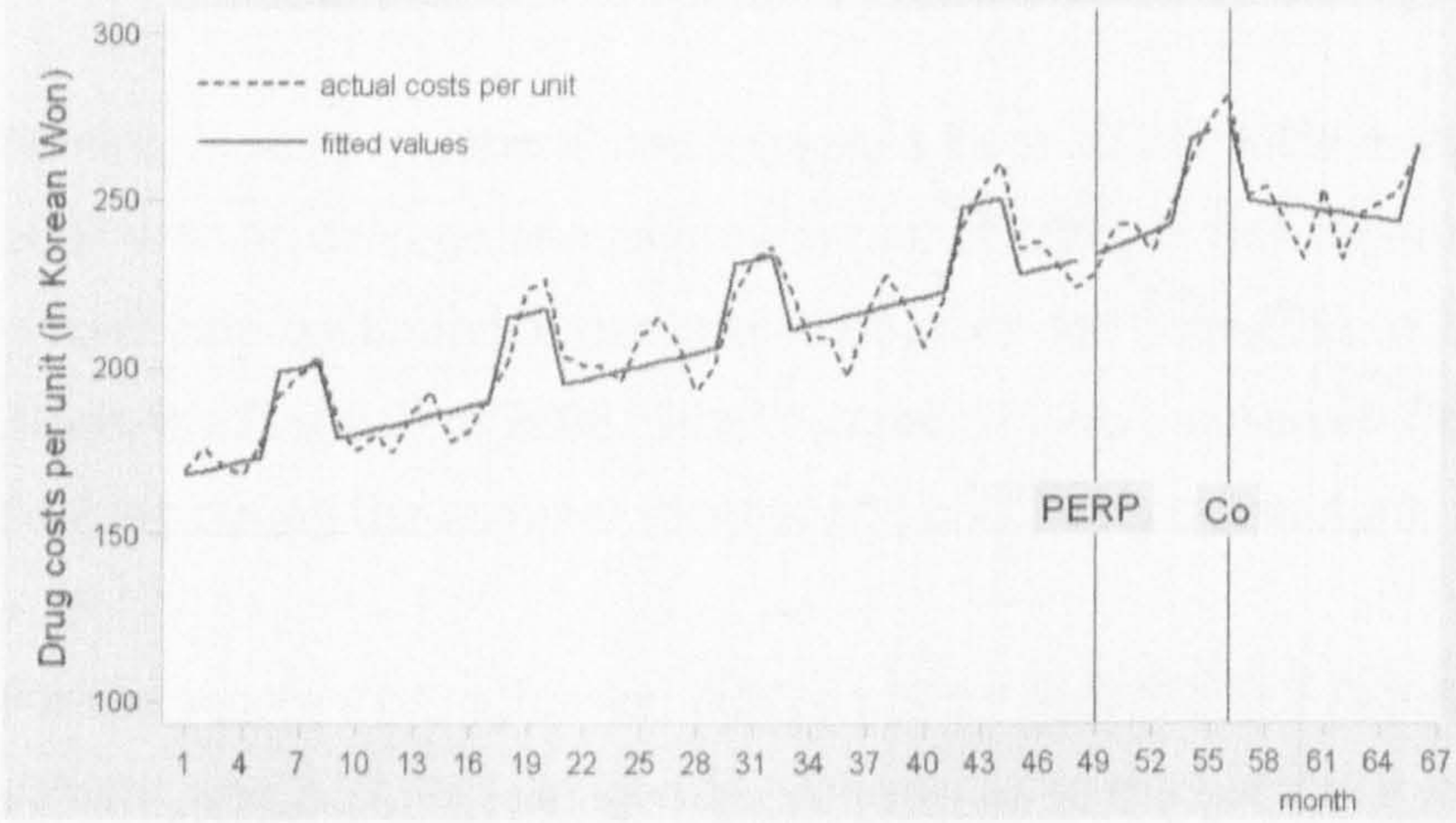
Table 9-4 displays the results from the segmented regression analysis for the 'costs per unit'. The value of DW statistic was 1.79 giving little reason for concern about autocorrelation. There was an increasing underlying trend of 1.36 KRW per month ($p<0.001$) in the pre-intervention period. Overall, the results demonstrate no statistically significant changes either in levels or in slopes after the policy introductions. There was some weak evidence to suggest a downturn in the slope after the restructuring of cost-sharing schedule ($p=0.085$) (Figure 9-4).

Table 9-4: Regression coefficients for costs per unit

(unit; Korean won)	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value	DW *d*-statistic
Intercept β_0	166.4405	161.8334	171.0475	72.29	<0.001	1.79
Baseline trend β_1	1.3571	1.1979	1.5164	17.05	<0.001	
Level change after PERP β_2	-0.1129	-14.1029	13.8770	-0.02	0.987	
Trend change after PERP β_3	0.8236	-2.1808	3.8281	0.55	0.585	
Level change after coinsurance β_4	4.0350	-10.6147	18.6847	0.55	0.584	
Trend change after coinsurance β_5	-2.9230	-6.2590	0.4130	-1.75	0.085	
Summer β_6	23.8978	19.3253	28.4703	10.46	<0.001	

* Ordinary least squares estimation

Figure 9-4: Observed and estimated costs per unit before and after interventions



Because the PERP had not clear effect on the model it is possible that the coinsurance assessment may be misspecified. To explore this issue further, the analysis was repeated without the PERP terms in the regression analysis (Table 9-5). The results from this analysis suggest a statistically significant decrease in the month to month cost per unit after the introduction of coinsurance (p=0.004).

Table 9-5: Regression coefficients for costs per unit without the PERP term

(unit; Korean won)	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value	DW *d*-statistic
Intercept β_0	165.6436	161.3939	169.8933	77.94	0.000	1.77
Baseline trend β_1	1.3969	1.2682	1.5257	21.7	0.000	
Level change after coinsurance β_4	8.2326	-2.3655	18.8307	1.55	0.126	
Trend change after coinsurance β_5	-2.1391	-3.5886	-0.6897	-2.95	0.004	
Summer β_6	24.2404	19.8787	28.6020	11.11	0.000	

* Ordinary least squares estimation

9.5.4 Impact on drug utilisation

Monthly 'units per patient' increased from 115 units in 2003 to 141 units in the first half of 2008 with the average annual growth rate of 5%. The cumulative growth rate was 22% in the corresponding period. Considerable variations were observed from month to month, with a peak during December and April and bottoming out in August and September. The number of patients dispensed had grown annually by 4~5% until 2005, but the growth rate stayed at below of 2% since then. It rose by 2.6% in the first half of 2008.

The DW values of the two outcome variables after OLS estimation were 1.56 for 'units per patient' and 1.92 for 'number of patients dispensed', respectively. Hence, EGLS estimation was performed for the former to correct autocorrelation. As shown in Table 9-6, there was an increasing underlying trend in both dependent variables, about 0.54 units per month and 78,207 patients per month respectively ($p<0.001$ for both). There was little evidence of changes in either levels or slopes after both policy interventions in these two utilisation variables. Figure 9-5 exhibits time series of both variables by month along with the corresponding fitted values. The removal of the PERP terms in the regression analysis made marginal differences to the results for the level change immediately after the introduction of coinsurance in 'units per patient', but this result was not statistically significant ($p=0.077$) (Table 9-7).

Table 9-6: Regression coefficients for utilisation variables

	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value	DW *d*-statistic
Units per patient						
Intercept β_0	111.5273	109.5237	113.5331	90.59	<0.001	1.94
Baseline trend β_1	0.5414	0.4756	0.6142	12.68	<0.001	
Level change after PERP β_2	-1.1239	-7.6123	4.5627	-0.34	0.737	
Trend change after PERP β_3	-0.0458	-1.2858	1.3289	-0.06	0.949	
Level change after coinsurance β_4	-4.0883	-10.6374	2.1118	-1.19	0.237	
Trend change after coinsurance β_5	0.1491	-1.3622	1.5410	0.18	0.857	
Summer β_6	-5.5226	-7.9420	-3.9627	-5.22	<0.001	
Number of patients dispensed						
Intercept β_0	22300000	21700000	23000000	68.92	<0.001	1.92
Baseline trend β_1	78207	55792	100623	6.98	<0.001	
Level change after PERP β_2	-825037	-2794337	1144263	-0.84	0.405	
Trend change after PERP β_3	-11625	-434546	411296	-0.06	0.956	
Level change after coinsurance β_4	471425	-1590746	2533596	0.46	0.649	
Trend change after coinsurance β_5	-46034	-515629	423560	-0.2	0.845	
Summer β_6	-1799130	-2442784	-1155476	-5.59	<0.001	

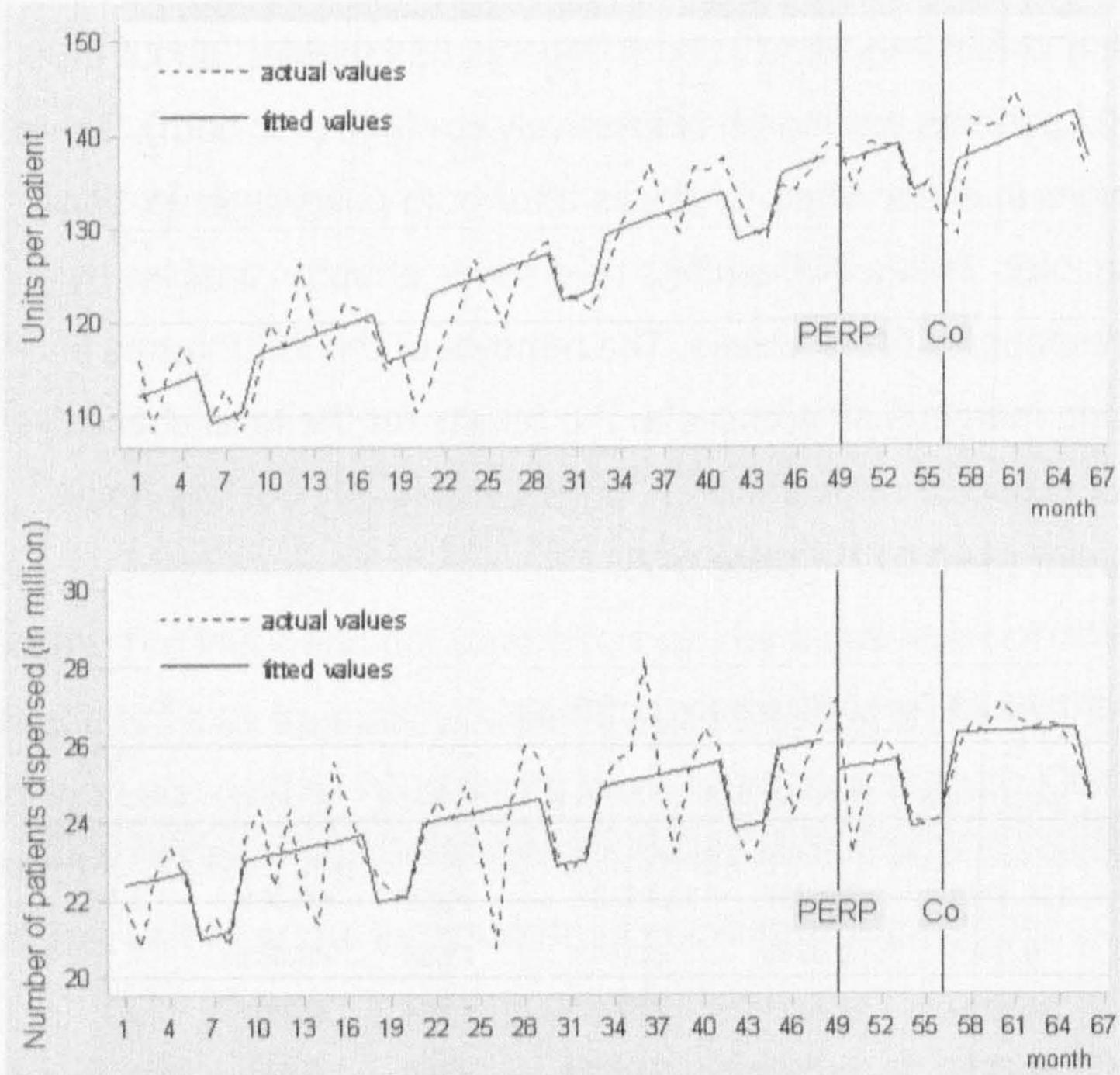
* Estimated generalised least squares estimation for 'units per patient'; Ordinary least squares estimation for the 'number of patients dispensed'

Table 9-7: Regression coefficients for units per patient without the PERP term

	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value	DW *d*-statistic
Intercept β_0	111.8139	109.5139	114.1138	97.210	0.000	1.94
Baseline trend β_1	0.5249	0.4550	0.5948	15.010	0.000	
Level change after coinsurance β_4	-4.8141	-10.1657	0.5375	-1.8	0.077	
Trend change after coinsurance β_5	0.1066	-0.6298	0.8430	0.29	0.773	
Summer β_6	-5.5073	-7.5568	-3.4579	-5.370	0.000	

* Estimated generalised least squares estimation

Figure 9-5: Observed and estimated units per patient (above) **and number of patients dispensed** (below) **before and after interventions**



9.5.5 Sensitivity analysis

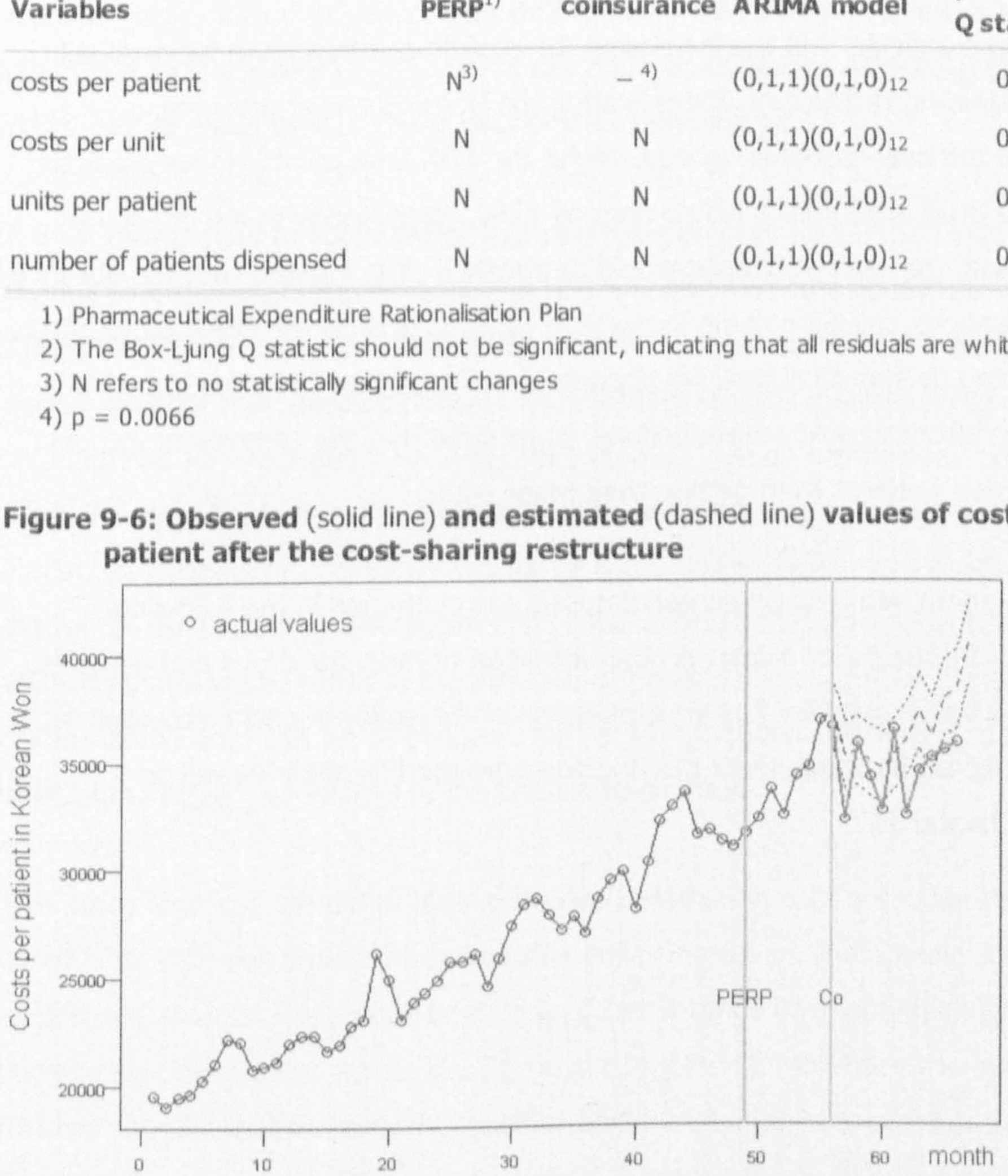
Results from the ARIMA models are shown in Table 9-8, highlighting a significant decrease in individual drug costs only after the copayment increase. Figure 9-6 shows that the forecasted series (black dashed) with 95% confidence intervals and the actual series (gray solid) after the new cost-sharing period. It is seen that there is an apparent difference between the two during the second intervention period.

Table 9-8: Summary of ARIMA analysis of the significance of the policy effects

Variables	PERP[1)]	coinsurance	ARIMA model	p value for Q statistic[2)]
costs per patient	N[3)]	– [4)]	$(0,1,1)(0,1,0)_{12}$	0.3136
costs per unit	N	N	$(0,1,1)(0,1,0)_{12}$	0.6283
units per patient	N	N	$(0,1,1)(0,1,0)_{12}$	0.7603
number of patients dispensed	N	N	$(0,1,1)(0,1,0)_{12}$	0.6850

1) Pharmaceutical Expenditure Rationalisation Plan
2) The Box-Ljung Q statistic should not be significant, indicating that all residuals are white noise.
3) N refers to no statistically significant changes
4) p = 0.0066

Figure 9-6: Observed (solid line) **and estimated** (dashed line) **values of costs per patient after the cost-sharing restructure**



9.6 Summary of findings

The time series of interest included 66 time points (January 2003 to June 2008) for expenditure, unit prices and utilisation of pharmaceuticals. The policy changes came at the 49th (PERP) and 56th (coinsurance) time point. Each policy aimed to achieve cost-effective purchasing and reduce unnecessary drug utilisation respectively, striving to lower drug expenditure. Thus, the present study examined whether the new policies achieved the intended effects in drug costs, prices or utilisation of pharmaceuticals, employing ITS design.

The ITS analyses indicate that the increasing trend of drug expenditure fell gradually after the cost-sharing restructure. Extrapolating the trend to a year after the introduction of the new cost-sharing scheme (at the 67th time point), it was predicted that per capita drug expenditure would drop by 12%, compared with the previous system. However, the level of savings would be nearly nil if compared with the absence of both interventions, implying some increase in drug costs after the PERP, although it was not detected by statistical test. No discernable effects were observed in overall drug utilisation after the policy introductions, suggesting that the copayment increase might not prevent patients from getting their medication.

Closer investigations with disaggregated datasets are continued in the following chapter to explore the policy impact on the utilisation of essential drugs and generics, which provides opportunity for further exploration of the policy impact discovered in the present chapter. Implications of the findings from the ITS analyses will be discussed in Chapter 11.

CHAPTER 10: ASSESSING THE EFFECTS OF LOCAL PHARMACEUTICAL POLICIES ON ESSENTIAL DRUGS UTILISATION AND THE KOREAN GENERICS MARKET

10.1 Introduction

The objective of the present chapter is to present results from the second empirical study. The first empirical analyses found little impact in most of the outcome variables after the policy introductions, except that the new cost-sharing structure might lower pharmaceutical expenditure. However, there are many issues remaining to be addressed to make sure of the impact of the study policies.

It was unclear how the copayment increase lowered pharmaceutical costs without any change to the overall drug utilisation in South Korea. With the copayment increase, there are three possible scenarios underlying patient behaviour. First, a rise in out-of-pocket expense may prevent patients from visiting medical institutions to obtain prescriptions for medication. Second, patients may give up having their prescriptions filled. Third, patients may ask their doctors to prescribe other medical services or, fourth, to recommend a cheaper version of the drugs to avoid extra charges. Of these, the fourth assumption could reduce drug costs with little change in overall drug utilisation, and would result in the increase of generic use as well as the decline in brand-named drug use. In this regard, further investigation was essential for a better understanding of the findings in the preceding chapter.

This study explored the policy impact on two therapeutic subclasses for chronic conditions. It seems important to examine policy impact on therapeutic subclasses in at least three aspects. First, experience from other settings invariably highlights a considerable divergence across drug groups (Chapter 4). Moreover, the systematic reviews suggest that the consequences of demand-side policies often occur by limiting essential drug utilisation (Chapter 4). Hence, it seems crucial to investigate the policy impact on patient access to essential medication. Second, Korean patients may respond differently from those in more affluent countries. Korean patients pay greater out-of-pocket expenses in relative terms and those with chronic conditions pay even more (Chapter 2). Thus, the concern is that Korean patients may show a greater

decrease in their use of essential medication even with a small increase in copayment. Third, the subset of data, usually less heterogeneous, would provide more opportunity to understand the results of the preceding time series analyses. In this study, the two groups of medication were divided further into generic and brand-named drugs, increasing the possibility of explaining a marginal decline in the price variable by testing if the copayment increase encourages use of generics.

10.2 Access to essential medications

Reducing less-essential drug consumption is the primary goal of policy programmes limiting patient drug utilisation, such as copayments for prescription drugs (Chapter 1). Empirical evidence, however, shows that demand-side policies may unexpectedly affect the utilisation of essential drugs as well as discretionary drugs in conditions such as an excessive increase in copayments. They may also potentially reduce social equity by having a disproportionate effect on disadvantaged groups, for instance the elderly who are highly vulnerable to financial constraints are more likely to need medication for chronic illnesses (Chapter 4). Restricting essential drugs can have an adverse influence on overall social health by allowing the development of more serious conditions. In addition, concerns arise that it may result in an increase in the net cost of illness prevalent in society from an economic standpoint.

This study focused on antihypertensives and antihyperlipidemics as it has been well established by several long-term studies that blood pressure and blood lipid disorders are clearly related to subsequent cardiovascular morbidity and mortality (Anderson *et al.*, 1987; Franco *et al.*, 2005; Kannel, 1996; McCarron *et al.*, 2000; Shaper *et al.*, 1985; Stamler *et al.*, 1993; Verschuren *et al.*, 1995). Thus, early detection and control of hypertension and dyslipidemia can improve health status and increase longevity by reducing the risk of cardiovascular diseases (Ingelsson *et al.*, 2008; National Cholesterol Education Program Expert Panel on Detection, 2002). Drug therapy plays an important role in controlling these risks and has been developed relatively well (Chobanian *et al.*, 2003; Cooper *et al.*, 2008; National Cholesterol Education Program Expert Panel on Detection, 2002; Nestel *et al.*, 2008). In this regard, policy interventions placing obstacles to the utilisation of these drugs may do more harm than good for overall health.

There were two additional reasons for limiting to two therapeutic classes. Firstly, medications for hypertension are currently placed in first position in terms of value, which was about 9% of the Korean prescription market in 2005 (Ministry of Health & Welfare, 2006c). Those for lipid disorder occupied the first position in terms of growth rate of value, which was over 380% between 2001 and 2005 (Ministry of Health & Welfare, 2006c). Secondly, it was necessary to narrow the range of study pharmaceuticals to gain insight into the dynamics of the generic market. It is extremely difficult to categorise all products into brand-named and generic drugs because as yet there is no national indicator classifying brand-named and generic medications in Korea.

10.3 Generics utilisation

For economic reasons, generic drugs nowadays get more attention in the pharmaceutical arena. They are regarded as a promising option to expensive brand-named drugs since pharmaceutical costs have continued to rise in some decades (Chapter 4 through 6). Correspondingly, policies encouraging the use of generic medicines have increasingly been highlighted across countries (General Accounting Office, 1991; King and Kanavos, 2002; Mrazek and Frank, 2004; Simoens and De Coster, 2006; Vogler *et al.*, 2008).

A generic drug is identical or bio-equivalent to an original drug, which is produced and distributed after the expiry of the originator's exclusive right. As generic producers do not incur the R&D costs, generic products are typically sold at lower prices than their brand-named counterparts. As a result, the generics share in value is generally lower than the generics share in volume (European Generic medicines Association, 2007). For this reason, it has been suggested that money be saved by substituting generics for brand-named drugs (Fischer and Avorn, 2003, 2004b; Karim *et al.*, 1996; Simoens and De Coster, 2006).

In South Korea, generic drugs had first been considered for industrial rather than budgetary reasons. Recently, a sharp rise in drug expenditure pressed Korean policy-makers to pay more attention to policies fostering the use of generics (Chapter 2). On this issue, recent evidence from Taiwan suggests that greater use of generics may not necessarily be associated with reducing drug costs if the price of generics is not significantly low (Lee *et al.*, 2008). Not surprisingly, the savings can be greater in

countries which show the market share of generics to be higher in volume and lower in value (Mrazek and Mossialos, 2000; Simoens and De Coster, 2006).

Thus, there is urgent need to determine the size of the Korean generic market before developing generic policies any further. At the moment, however, adequate information about the generic market is lacking. One previous local study reported that there was little difference in the market share of generics in volume (42.8%) from that in value (39%) in South Korea (Huh *et al.*, 2006). The authorities estimated about 40% of value ascribed to generics in the Korean market between 2004 and 2006, but they did not provide information on volume (HIRA internal report cited by You, 2007). None of them dealt comprehensively with the Korean generic market. They used an unclear definition of generics as well as analysing only a very short period of data – only one or two months per year.

10.4 Objectives of study

This study firstly seeks to examine whether the two interventions prevent patients from accessing their essential medication. Secondly, it aims to investigate the impact of the policy interventions on generic use in the study medication, with the intention of tackling not only the relationship between the study interventions and the use of less costly drugs, but also to promote a better understanding of the Korean pharmaceutical market.

10.5 Methods

10.5.1 Study design and data source

The design of the study is an observational, retrospective, interrupted time series analysis of 66 monthly observations from January 2003 to June 2008. Aggregated monthly data concerning drug consumption of two therapeutic classes were provided by the Health Insurance Review & Assessment Service (HIRA). For reconstructing the subsets of data, the list of the Korean Insurance Code for each product under therapeutic subclasses and generic and brand categorisation were provided by the researcher. (Chapter 8 depicted general aspects of the data, reasons of choice of two subclasses and the process of classification of generics.)

10.5.2 Outcome measures

After classifying brand-named and generic drugs, three sets of data were finally established in each therapeutic class: overall, generic and brand-named drugs. To examine the impact of two policy interventions on individual drug use and patient accessibility, two outcome variables were employed: *units per patient;* and *number of patients dispensed.* Therefore, six time series were finally constructed for each therapeutic class. Details of definitions and calculations for outcome variables are illustrated in Chapter 8.

10.5.3 Statistical Analysis

10.5.3.1 Primary analysis

To measure the size and statistical significance of time series changes associated with the implementation of study interventions, segmented regression models were used (Chapter 8). Time series for each dependent variable was established and examined visually for any extreme variations potentially confounding policy outcomes. As little seasonal variation was observed, the simple segmented regression model (Equation 6) was applied to 'units per patient' time series. The antihypertensive or antihyperlipidemics segmented regression model (Equation 8 or 9) taking market changes into account was applied to the time series of 'number of patients dispensed' in two therapeutic subclasses. Details of the specification of models, definitions and coding were explained in Chapter 8 (see 8.5 for modelling framework). As a reminder, models were:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \varepsilon_t \quad \text{(Eq. 6)}$$

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \beta_6 \times Nv + \beta_7 \times Nv_t + \varepsilon_t \quad \text{(Eq. 8)}$$

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times Perp + \beta_3 \times Perp_t + \beta_4 \times Co + \beta_5 \times Co_t + \beta_6 \times Cr + \beta_7 \times Cr_t + \varepsilon_t \quad \text{(Eq. 9)}$$

The Durbin-Watson *d* statistic (DW) was used as a test for serial correlation of the error terms. Table 10-1 displays critical values for these models at the 5% significance level. If DW values clearly indicate the presence of autocorrelation after applying ordinary least squares (OLS), the models for such variables were corrected for first-

degree autocorrelated errors using the Prais-Winsten estimator.

Table 10-1: Durbin-Watson critical values for the regression models

	d_l	d_u	2	$4-d_u$	$4-d_l$
decision	uncertain	no autocorrelation		uncertain	
critical value					
general model	1.438	1.767		2.233	2.562
therapeutic subclass model	1.37	1.843		2.157	2.63

(Source: Savin and White, 1977)

A *p*-value of less than or equal to 0.05 was considered statistically significant. To explore the goodness of fit of the segmented regression models, the proportion of variability in the data set that was accounted for in the model was also calculated (adjusted R^2). The statistical analysis was carried out using STATA version 10 (StataCorp LP, 2007).

10.5.3.2 Sensitivity analysis

For crosschecking the hypothesis test of the segmented regression models, autoregressive integrated moving average (ARIMA) models were constructed and analysed. After iterative processes (see Annex 22 for the example procedure), a tentative model for each data structure was specified from the pre-intervention data for the noise compartment in all relevant variables. Using the tentative noise model, projections for the post-intervention period were formed to provide estimates in the absence of interventions. After the visual examination of actual and fitted values, there was little reason to assume gradual, permanent or abrupt, temporal intervention effects. Thus, the simplest intervention model (abrupt, permanent) was added to represent the effect of the interventions. The Box-Ljung Q statistic was used for residual analysis to gauge serial autocorrelation of error terms. The ARIMA process and statistical analysis were carried out using R version 2.11.0 (The R foundation for statistical computing, 2010). The best-fit models were compared with closely competing models to determine the impact of alternative models on the intervention effect, and the estimates of the intervention effect were robust. Although the coefficients varied somewhat, the direction and significance remained robust across closely competing models.

10.6 Results

10.6.1 Overall trends

Table 10-2 presents overall changes in expenditure, number of patients dispensed and utilisation of antihypertensives and antihyperlipidemics during the study period, which are displayed in Figure 10-1 and 10-2.

Drug costs doubled from 62 to 120 billion KRW in blood pressure lowering drugs. Those in lipid lowering drugs were even greater, four times higher from 10 to 40 billion KRW. Spending on antihyperlipidemics increased two times faster than that of antihypertensives during the corresponding years – 31% and 14% respectively. Annual growth rate has declined in antihypertensives, while it remained greater than 30% in antihyperlipidemics until 2007.

Table 10-2: Overall changes in expenditure, number of patients and utilisation of two study therapeutic subclasses during the study period

	Total costs over pharmaceuticals (in billion KRW[1])				Number of patients dispensed (in million)			Number of units dispensed (in million)		
Year	Mean (95% CI[2])			Annual changes (%)	Mean (95% CI)		Annual changes (%)	Mean (95% CI)		Annual changes (%)
Antihypertensives										
2003	62.0	(58.9	65.0)	-	3.05	(2.95 3.14)	-	154 (148	160)	-
2004	75.4	(72.6	78.2)	21.61	3.52	(3.42 3.62)	15.49	179 (174	185)	16.23
2005	88.6	(85.3	92.0)	17.51	4.09	(3.97 4.20)	16.11	205 (198	212)	14.53
2006	102.0	(99.4	104.0)	15.12	4.61	(4.53 4.68)	12.81	231 (226	236)	12.68
2007	113.0	(110.0	117.0)	10.78	4.99	(4.90 5.09)	8.36	250 (243	257)	8.23
2008[3]	120.0	(116.0	124.0)	6.19	5.24	(5.13 5.34)	4.86	263 (255	272)	5.20
Antihyperlipidemics										
2003	10.4	(9.74	11.1)	-	0.343	(0.326 0.360)	-	12.9 (12.2	13.6)	-
2004	14.0	(13.1	14.9)	34.62	0.432	(0.412 0.453)	25.98	16.3 (15.5	17.2)	26.36
2005	19.5	(18.2	20.8)	39.29	0.566	(0.537 0.594)	30.88	21.4 (20.2	22.7)	31.29
2006	27.2	(25.6	28.8)	39.49	0.740	(0.707 0.773)	30.80	28.6 (27.1	30.2)	33.64
2007	35.7	(34.0	37.4)	31.25	0.922	(0.891 0.953)	24.64	36.9 (35.2	38.6)	29.02
2008[3]	40.1	(38.5	41.7)	12.32	1.008	(0.974 1.041)	9.27	41.6 (40.0	43.2)	12.74

1) KRW refers to Korean won (2000 KRW=£1 in June 2008).
2) CI refers to confidence interval.
3) From January to June

Figure 10-1: Overall trends in antihypertensives

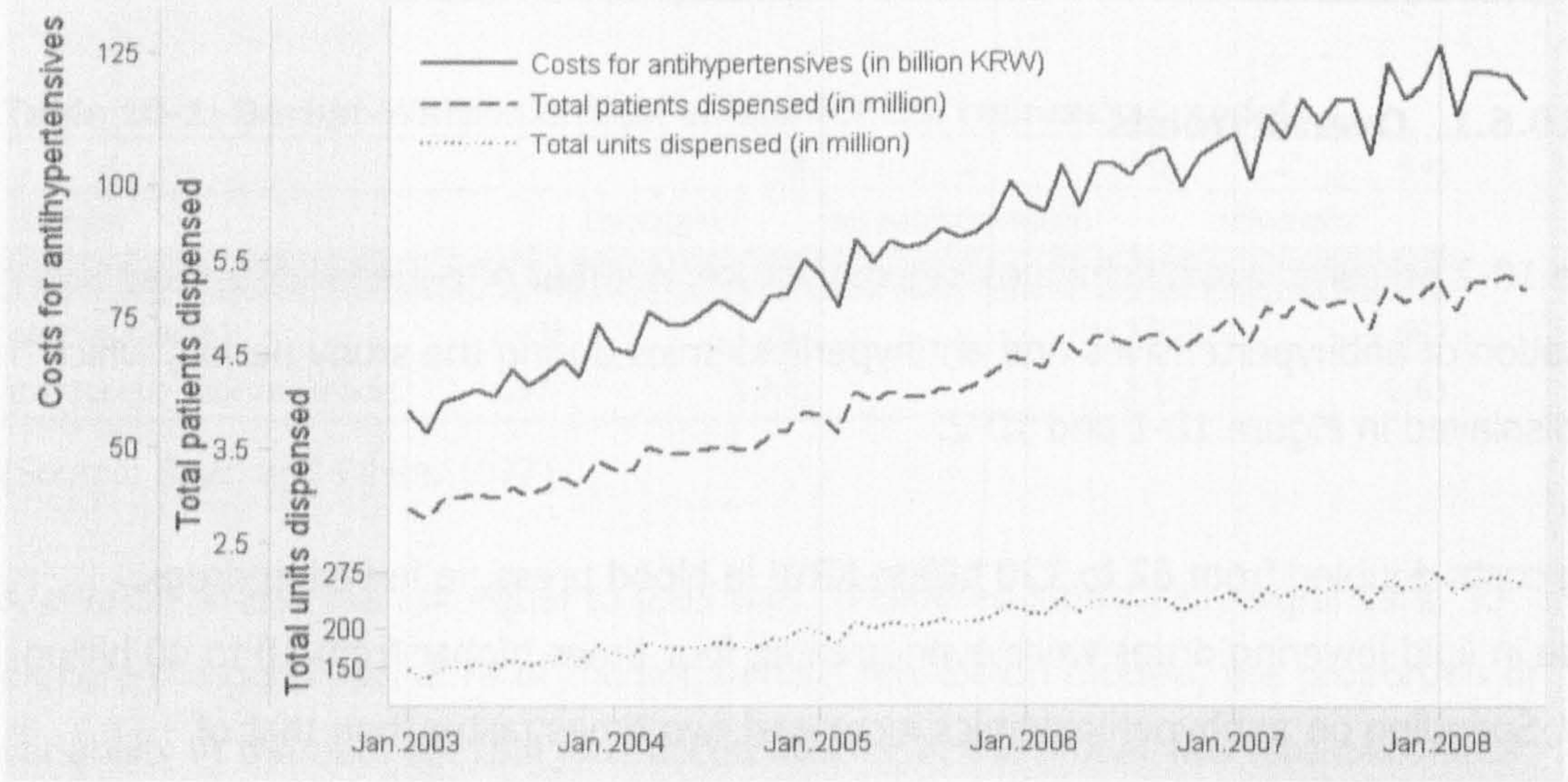
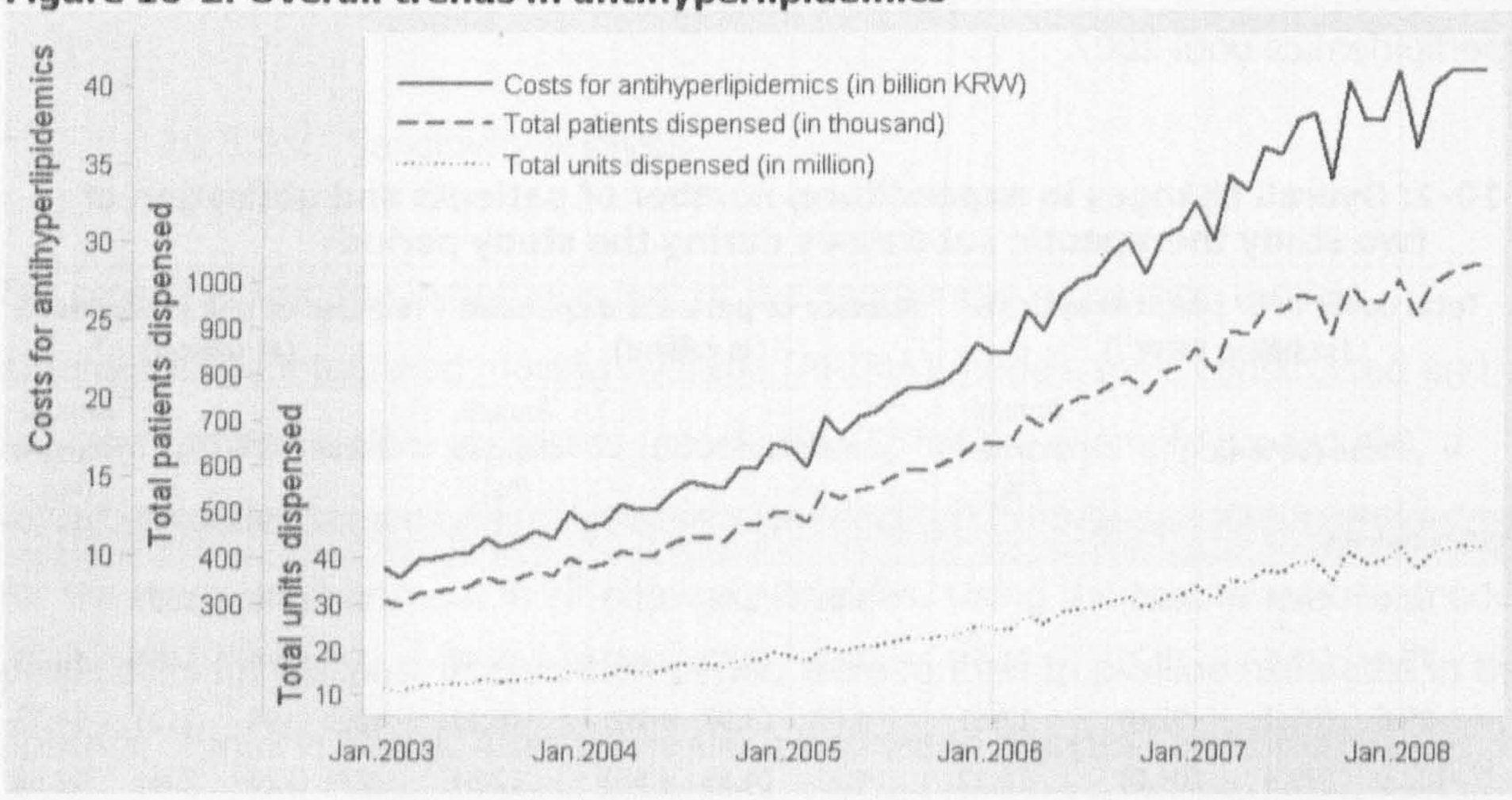


Figure 10-2: Overall trends in antihyperlipidemics



The number of patients dispensed antihypertensives on a monthly basis had increased over time until 2006 with an average annual growth rate of 13%. Cumulatively, it rose by 72% from about 3 million in 2003 to 5.2 million in the first half of 2008. The figure for patients dispensed antihyperlipidemics had increased to an annual growth rate of 28% between 2003 and 2007. Cumulatively, it tripled from about 0.34 to 1 million during the study period. Very similar rising trends were observed in volume changes. Dispensed drug units had increased by 71% in antihypertensives and 222% in antihyperlipidemics during this period, the annual growth rate being 11 and 27%, respectively.

10.6.2 Market share of generics

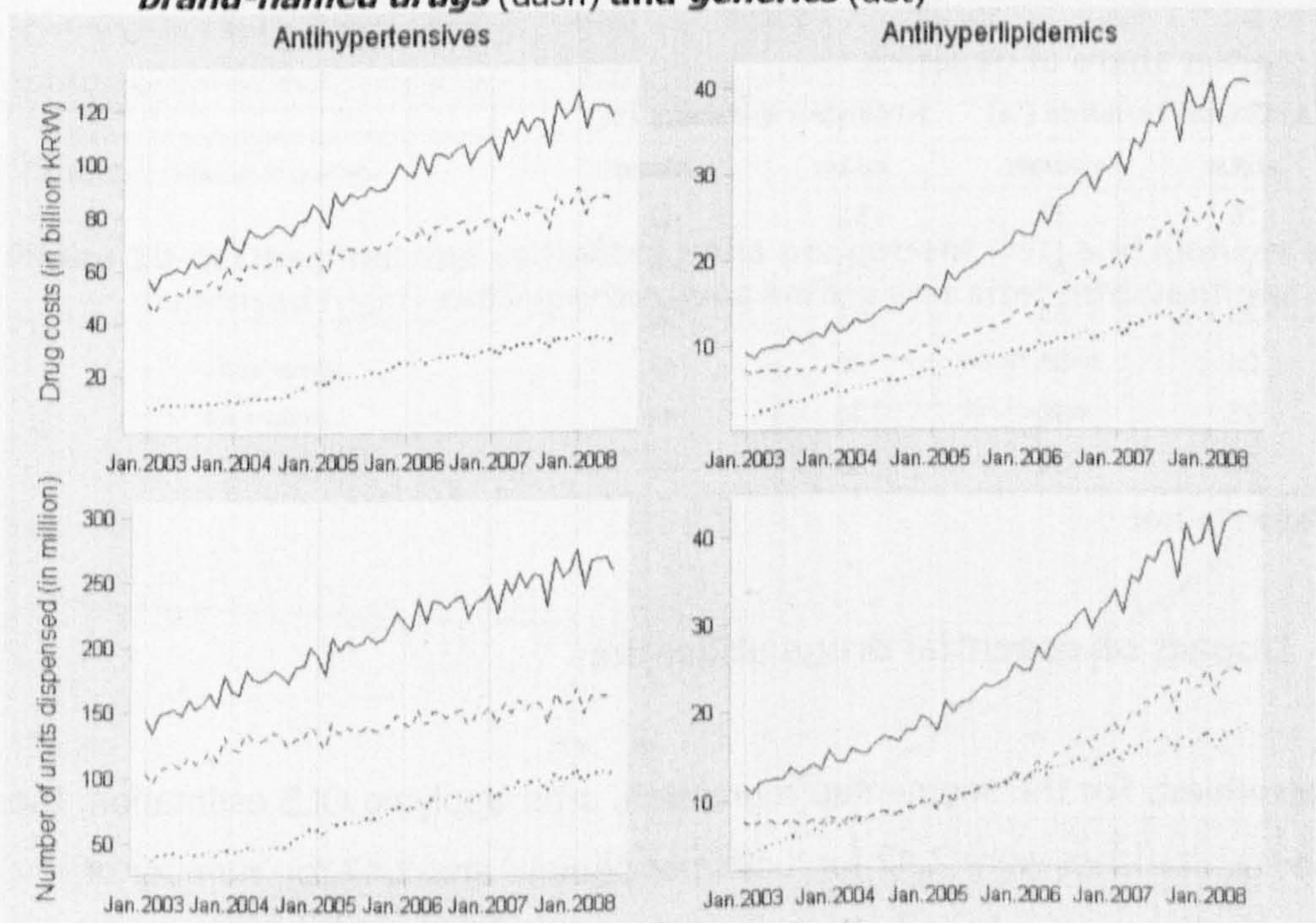
Table 10-3 and Figure 10-3 display overall changes in expenditure and utilisation of the two therapeutic subclasses under study by brand-named and generic drugs during the study period.

Table 10-3: Overall changes in expenditure and utilisation of two study therapeutic classes by brand-named and generic groups during the study period

	Antihypertensives				Antihyperlipidemics			
	costs (in billion KRW)		*units (in million)*		*costs (in billion KRW)*		*units (in million)*	
Year	brand drugs	generics	brand drugs	generics	brand drugs	generics	brand drugs	generics
2003	52.30	9.64	112.0	41.9	7.14	3.26	7.4	5.5
2004	62.20	13.20	130.0	49.4	8.34	5.62	8.3	8.1
2005	67.90	20.70	137.0	67.8	11.50	8.04	10.7	10.7
2006	75.10	26.90	147.0	83.7	16.60	10.60	15.1	13.5
2007	81.30	31.80	154.0	95.9	22.70	12.90	20.9	16.1
2008[1)]	86.00	33.80	160.0	103.0	26.20	13.80	24.1	17.5
Annual growth rate (%)								
2003	-	-	-	-	-	-	-	-
2004	19	37	16	18	17	72	11	47
2005	9	57	5	37	38	43	29	33
2006	11	30	7	23	44	32	41	26
2007	8	18	5	15	37	22	38	19
2008[1)]	6	6	4	7	15	7	15	9

1) From January to June

Figure 10-3: Number of units dispensed in two study drug classes by *overall* (solid), *brand-named drugs* (dash) and *generics* (dot)



The generic use of antihypertensives rose greatly in 2005 by 37% compared to the preceding year, and then declined to 7% in the first half of 2008. The utilisation of brand-named drugs has changed much less over time and the growth rate has been between 4 and 7% since 2005.

Generic use of antihyperlipidemics rose by 47% in 2004, declining sharply to 9% in the first half of 2008, while that of brand-named drugs remained high between 30 and 40% from 2005 to 2007. Brand-named drug utilisation declined to 15% in the first half of 2008. The growth rate of spending on generics was greater than the utilisation growths in both study medications in each year except 2008, as shown in Table 10-3.

Table 10-4 describes the changes in market share of generics in two study medications. In the antihypertensives market, the volume share of generics rose from 27 to 39% during the study period. In the antihyperlipidemics market, the differences between brand-named drugs and generics were narrowing until 2005 (half and half) and then returned to exactly the same level as in 2003 – 42% generics and 58% brand-named drugs in the first half of 2008. In terms of value, expenditure on generics in antihypertensives continues to increase from 16 to 28%, while antihyperlipidemics increased until the middle of the study period and then fell to a similar level as in 2003, which was similar to the volume changes.

Table 10-4: Market share of generics

	Antihypertensives (%)		Antihyperlipidemics (%)	
Year	*value*	*volume*	*value*	*volume*
2003	16	27	31	42
2004	17	27	40	49
2005	23	33	41	50
2006	26	36	39	47
2007	28	38	36	44
2008[1)]	28	39	35	42

1) From January to June

10.6.3 Impact on essential drugs utilisation

Antihypertensives: For the segmented regression, after applying OLS estimation, the values of the DW statistics were 2.42 for 'units per patient' and 2.47 for 'number of patients dispensed' respectively, indicating some concern about the presence of

autocorrelation. Hence, the regression analyses were repeated using the Prais-Winsten estimator, results from these models are displayed in Table 10-5.

Monthly utilisation has changed little over time, maintained at around 50 units for an individual patient during the study period. This was in accord with the findings from the segmented regression analysis, indicating little change in the baseline trend of individual utilisation after the policy interventions (Table 10-5).

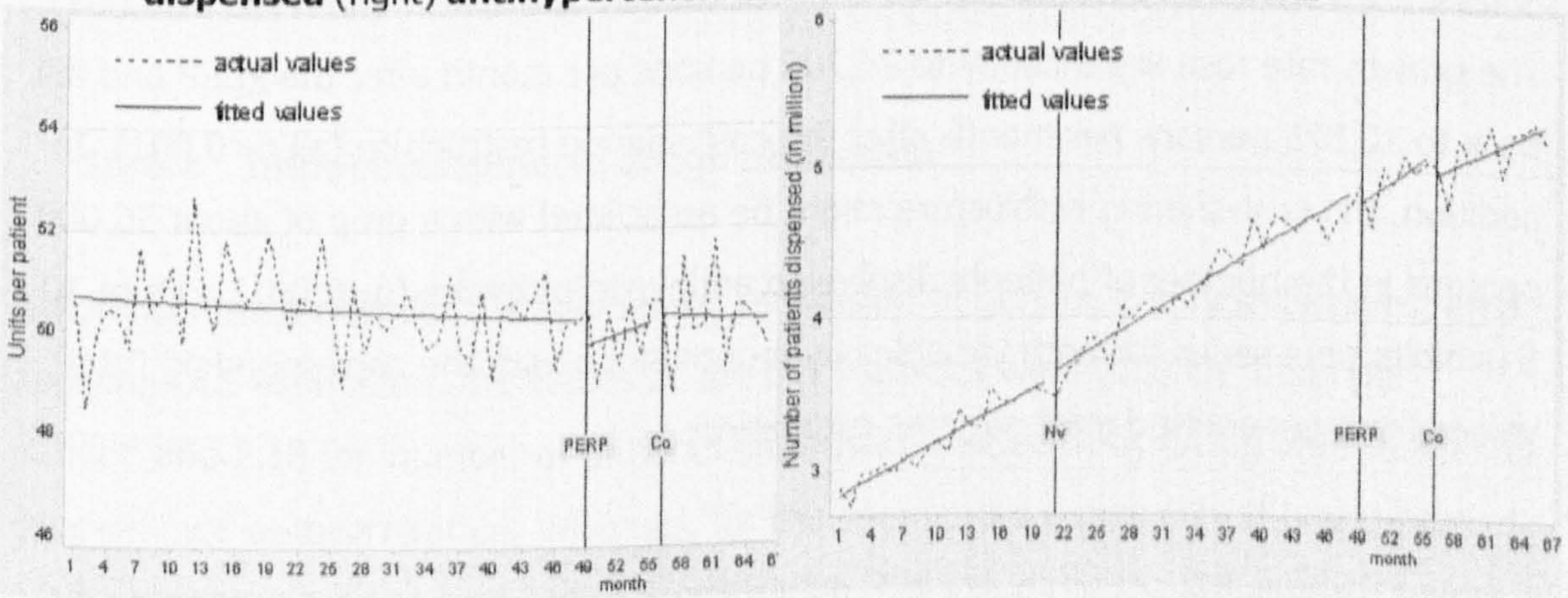
Table 10-5: Regression coefficients for overall Antihypertensives

	Coefficient[1)]	95% Confidence Interval		*t*-statistic	*P*-value	DW *d*-statistic
Units per patient						
Intercept β_0	50.6998	50.3138	51.0857	262.78	<0.001	2.01
Baseline trend β_1	-0.0100	-0.0238	0.0037	-1.46	0.149	
Level change after PERP β_2	-0.5900	-1.8286	0.6485	-0.95	0.344	
Trend change after PERP β_3	0.0877	-0.1764	0.3518	0.66	0.509	
Level change after coinsurance β_4	0.1366	-1.1873	1.4606	0.21	0.837	
Trend change after coinsurance β_5	-0.0883	-0.3775	0.2010	-0.61	0.544	
Number of patients dispensed						
Intercept β_0	2797167	2715560	2878775	68.61	<0.001	1.94
Baseline trend β_1	38529	31697	45362	11.29	<0.001	
Level change after PERP β_2	-108603	-278732	61527	-1.28	0.206	
Trend change after PERP β_3	7000	-28099	42098	0.40	0.691	
Level change after coinsurance β_4	-149442	-325073	26189	-1.70	0.094	
Trend change after coinsurance β_5	-17379	-55600	20843	-0.91	0.367	
Level change after Norvasc[2)] 'me-too' drugs	43740	-58867	146348	0.85	0.397	
Trend change after Norvasc[2)] 'me-too' drugs	5719	-2170	13608	1.45	0.152	

1) Estimated generalised least squares estimation

2) Norvasc; amlodipine besylate

Figure 10-4: Observed and estimated units per patient (left) **and number of patients dispensed** (right) **antihypertensives before and after interventions**



The number of patients who were dispensed antihypertensives had been steadily increasing over time ($p<0.001$), but was hardly affected by policy interventions or market surroundings. A temporary drop was seen after the copayment increase, but this was not statistically significant ($p=0.094$). Figure 10-4 exhibits time series for both variables by month along with the corresponding fitted values from generalised least squares estimation.

Antihyperlipidemics: For the segmented regression, after applying OLS estimation, the values of the DW statistics were 2.33 for 'units per patient' and 2.74 for 'number of patients dispensed' respectively, indicating some concern about the presence of autocorrelation. Hence, the regression analyses were repeated using the Prais-Winsten estimator, results from these models are displayed in Table 10-6.

Monthly 'units per patient' were slowly rising at baseline, differing from antihypertensives (see Table10-6; $\beta_1=0.03$, $p<0.001$). The trend has increased considerably since 2006. The growth rate of monthly units per patient rose about 2% in 2006 compared to a year before and has remained higher than 3% after 2007. The statistical analysis indicated that the trend of 'units per patient' increased about six times from 0.03 to 0.18 by 0.15 (Table 10-6), showing a sizable upsurge in the time series line after the first intervention (Figure 10-5). This, however, was not statistically significant ($p=0.110$) and few changes were seen either in trends or in levels after the policy interventions.

The number of patients who were dispensed antihyperlipidemics steadily increased by 7,220 persons per month before the launch of Crestor® (rosuvastatin) and was almost doubled to 13,700 persons per month after the launch of the new statin (all $p<0.001$). The growth rate rose significantly to 24,705 persons per month after the PERP and fell back to 10,573 persons per month after the cost-sharing restructure (all $p<0.001$). In addition, the cost-sharing restructure might be associated with a drop of about 56,000 persons in the number of patients dispensed antihyperlipidemics ($p<0.001$). Figure 10-5 exhibits time series for both variables by month along with the corresponding fitted values from generalised least squares estimation.

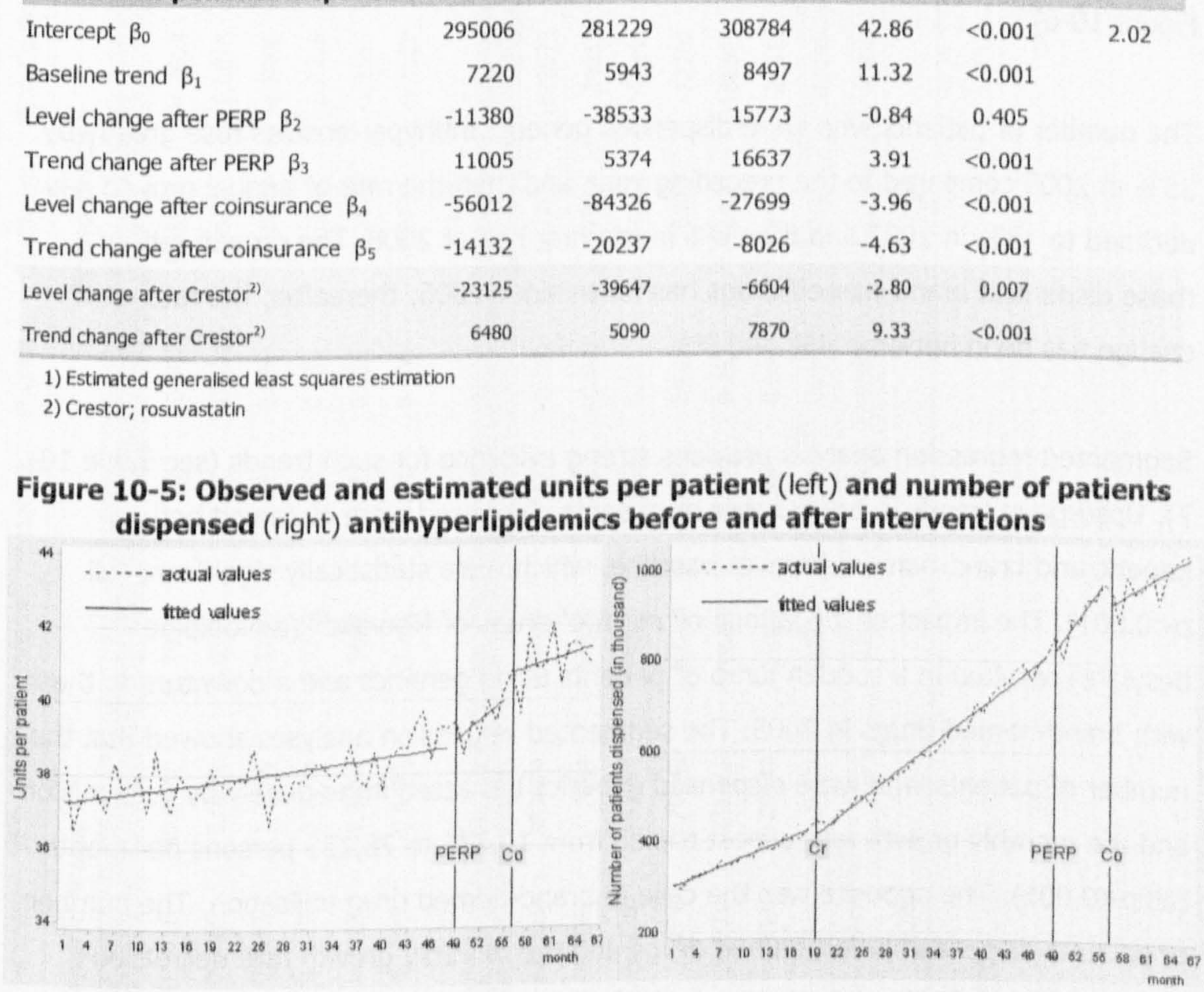
Table 10-6: Regression coefficients for overall Antihyperlipidemics

	Coefficient[1)]	95% Confidence Interval		*t*-statistic	*P*-value	DW *d*-statistic
Units per patient						
Intercept β_0	37.2463	36.9733	37.5193	272.91	<0.001	1.94
Baseline trend β_1	0.0302	0.0205	0.0399	6.22	<0.001	
Level change after PERP β_2	0.0345	-0.8386	0.9076	0.08	0.937	
Trend change after PERP β_3	0.1511	-0.0350	0.3372	1.62	0.110	
Level change after coinsurance β_4	0.6788	-0.2536	1.6111	1.46	0.151	
Trend change after coinsurance β_5	-0.1146	-0.3187	0.0895	-1.12	0.266	
Number of patients dispensed						
Intercept β_0	295006	281229	308784	42.86	<0.001	2.02
Baseline trend β_1	7220	5943	8497	11.32	<0.001	
Level change after PERP β_2	-11380	-38533	15773	-0.84	0.405	
Trend change after PERP β_3	11005	5374	16637	3.91	<0.001	
Level change after coinsurance β_4	-56012	-84326	-27699	-3.96	<0.001	
Trend change after coinsurance β_5	-14132	-20237	-8026	-4.63	<0.001	
Level change after Crestor[2)]	-23125	-39647	-6604	-2.80	0.007	
Trend change after Crestor[2)]	6480	5090	7870	9.33	<0.001	

1) Estimated generalised least squares estimation

2) Crestor; rosuvastatin

Figure 10-5: Observed and estimated units per patient (left) **and number of patients dispensed** (right) **antihyperlipidemics before and after interventions**



10.6.4 Impact on generic drugs utilisation

Antihypertensives: For the segmented regression of generic antihypertensives, after applying OLS estimation, the values of the DW statistics were 2.20 for 'units per patient' and 2.18 for 'number of patients dispensed', respectively, giving little reason for concern over autocorrelation. Whereas, for the segmented regression of brand-named antihypertensives, after applying OLS estimation, the values of the DW statistics were 2.33 for 'units per patient' and 2.61 for 'number of patients dispensed' respectively,

indicating some concern about the presence of autocorrelation. Hence, the segmented regression analyses for brand-named antihyperlipidemics were repeated using the Prais-Winsten estimator. Statistical results are displayed in Table 10-7.

Monthly 'units per patient' were slowly rising in both generic and brand-named drugs during the study period, while the growth rates were negligible. Statistical analysis showed that there was little evidence of change in either levels or slopes ascribed to the policy interventions in the pattern of individual utilisation (see Table 10-7 and Figure 10-6).

The number of patients who were dispensed generic antihypertensives rose greatly by 35% in 2005 compared to the preceding year, and then the rate of annual growth has declined to 13% in 2007 and then 6% in the first half of 2008. The growth rate of those dispensed brand-named drugs has fallen since 2005; thereafter, the rate of change has been between 4% and 8%.

Segmented regression analysis provides strong evidence for such trends (see Table 10-7). Upsurge in trends in the number of patients dispensed were observed both in generic and brand-named drugs at baseline, which were statistically significant (all $p<0.001$). The impact of the launch of 'me-too' drugs of Norvasc® (amlodipine besylate) resulted in a sudden jump of patients using generics and a downturn in those with brand-named drugs in 2005. The segmented regression analyses showed that the number of patients who were dispensed generics increased immediately by 0.15 million and the monthly growth rate almost tripled from 10,776 to 28,133 persons per month (all $p<0.001$). The opposite was the case in brand-named drug utilisation. The number of patients dispensed brand-named drugs and the monthly growth rate decreased sharply (all $p<0.001$), while the amount of change was mild in comparison with those seen in generic drugs. The policy interventions did not alter existing patterns for generic, or brand-named antihypertensives (Table 10-7 and Figure 10-6). There was a considerable drop in the level after the new cost-sharing scheme in brand-named antihypertensives, however this was not statistically significant at the conventional 5% level ($p=0.064$).

Table 10-7: Regression coefficients for generic and brand-named antihypertensives

	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value
	Generic drugs [1]					***Brand drugs*** [2]				
Units per patient										
Intercept β_0	41.3716	40.9447	41.7984	193.88	<0.001	54.8154	54.3614	55.2694	241.52	<0.001
Baseline trend β_1	0.0380	0.0228	0.0531	5.01	<0.001	0.0151	-0.0010	0.0313	1.88	0.066
Level change after PERP β_2	0.0125	-1.2854	1.3104	0.02	0.985	-1.0767	-2.5206	0.3672	-1.49	0.141
Trend change after PERP β_3	0.1037	-0.1718	0.3792	0.75	0.454	0.0347	-0.2729	0.3423	0.23	0.822
Level change after coinsurance β_4	0.1418	-1.2256	1.5092	0.21	0.836	0.1578	-1.3815	1.6972	0.21	0.838
Trend change after coinsurance β_5	-0.1290	-0.4371	0.1791	-0.84	0.406	-0.0727	-0.4107	0.2654	-0.43	0.669
DW *d*-statistic	2.20					1.98				
Number of patients dispensed										
Intercept β_0	928705	883874	973537	41.47	<0.001	1867767	1823572	1911963	84.6	<0.001
Baseline trend β_1	10776	7034	14519	5.76	<0.001	27919	24218	31619	15.1	<0.001
Level change after PERP β_2	-44720	-133685	44245	-1.01	0.318	-53042	-145841	39757	-1.14	0.257
Trend change after PERP β_3	-2164	-20542	16214	-0.24	0.815	6944	-12202	26090	0.73	0.471
Level change after coinsurance β_4	-51001	-141662	39660	-1.13	0.265	-90506	-186561	5549	-1.89	0.064
Trend change after coinsurance β_5	-9111	-29540	11317	-0.89	0.376	-6533	-27312	14247	-0.63	0.532
Level change after Norvasc[3] 'me-too' drugs	154569	98585	210554	5.53	<0.001	-114903	-170464	-59343	-4.14	<0.001
Trend change after Norvasc[3] 'me-too' drugs	17357	12986	21728	7.95	<0.001	-11777	-16041	-7513	-5.53	<0.001
DW *d*-statistic	2.18					1.99				

1) Ordinary least squares estimation

2) Estimated generalised least squares estimation

3) Norvasc; amlodipine besylate

Table 10-8: Regression coefficients for generic and brand-named antihyperlipidemics

	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value	Coefficient	95% Confidence Interval		*t*-statistic	*P*-value
	Generic drugs [1]					***Brand drugs*** [2]				
Units per patient										
Intercept β_0	33.3521	33.1038	33.6005	268.64	<0.001	40.9866	40.7230	41.2502	311	<0.001
Baseline trend β_1	0.0053	-0.0035	0.0142	1.21	0.232	0.0925	0.0832	0.1019	19.73	<0.001
Level change after PERP β_2	-0.3047	-1.1005	0.4910	-0.77	0.447	-0.6831	-1.5344	0.1682	-1.61	0.114
Trend change after PERP β_3	0.0770	-0.0926	0.2467	0.91	0.368	0.1613	-0.0203	0.3430	1.78	0.081
Level change after coinsurance β_4	0.2624	-0.5878	1.1126	0.62	0.539	0.7984	-0.1134	1.7101	1.75	0.085
Trend change after coinsurance β_5	-0.0843	-0.2702	0.1016	-0.91	0.368	-0.1009	-0.2993	0.0976	-1.02	0.313
DW *d*-statistic	1.94					2.03				
Number of patients dispensed										
Intercept β_0	118485	109917	127054	27.68	<0.001	177317	164350	190283	27.37	<0.001
Baseline trend β_1	6819	6025	7613	17.19	<0.001	306	-892	1504	0.51	0.611
Level change after PERP β_2	-15114	-31807	1579	-1.81	0.075	6886	-17298	31069	0.57	0.571
Trend change after PERP β_3	4079	618	7539	2.36	0.022	6202	1188	11216	2.48	0.016
Level change after coinsurance β_4	-37810	-55127	-20493	-4.37	<0.001	-13212	-37982	11558	-1.07	0.290
Trend change after coinsurance β_5	-5119	-8894	-1343	-2.71	0.009	-8626	-14208	-3045	-3.09	0.003
Level change after Crestor[3]	-6589	-16876	3699	-1.28	0.205	-15006	-30492	479	-1.94	0.057
Trend change after Crestor[3]	22.30	-844.86	889.46	0.05	0.959	6517	5196	7837	9.88	<0.001
DW *d*-statistic	1.82					2.01				

1) Estimated generalised least squares estimation

2) Estimated generalised least squares estimation for 'units per patient'; Ordinary least squares estimation for the 'number of patients dispensed'

3) Crestor; rosuvastatin

Figure 10-6: Observed and estimated units per patient (above) **and number of patients dispensed** (below) **generic and brand-named antihypertensives before and after interventions**

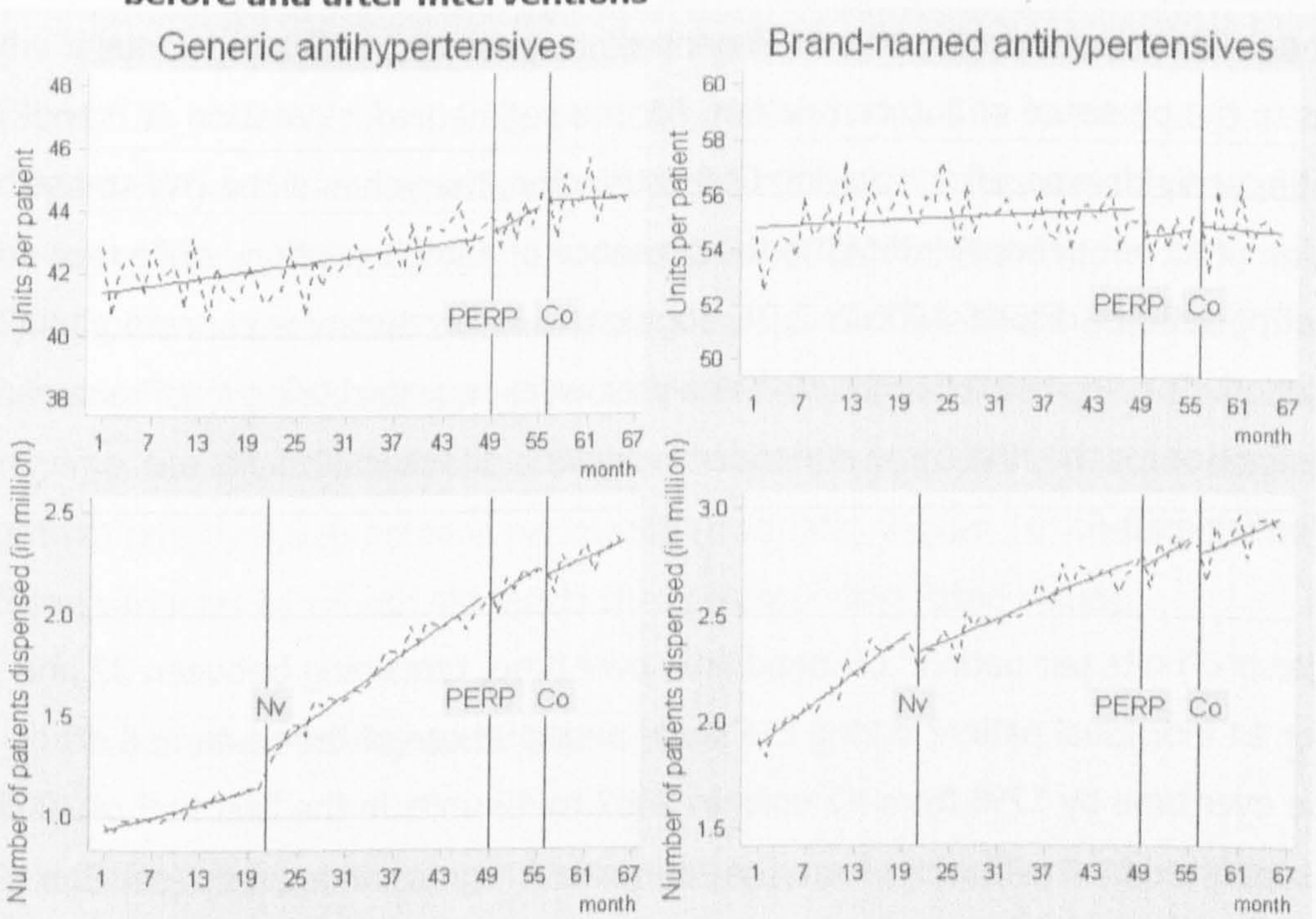
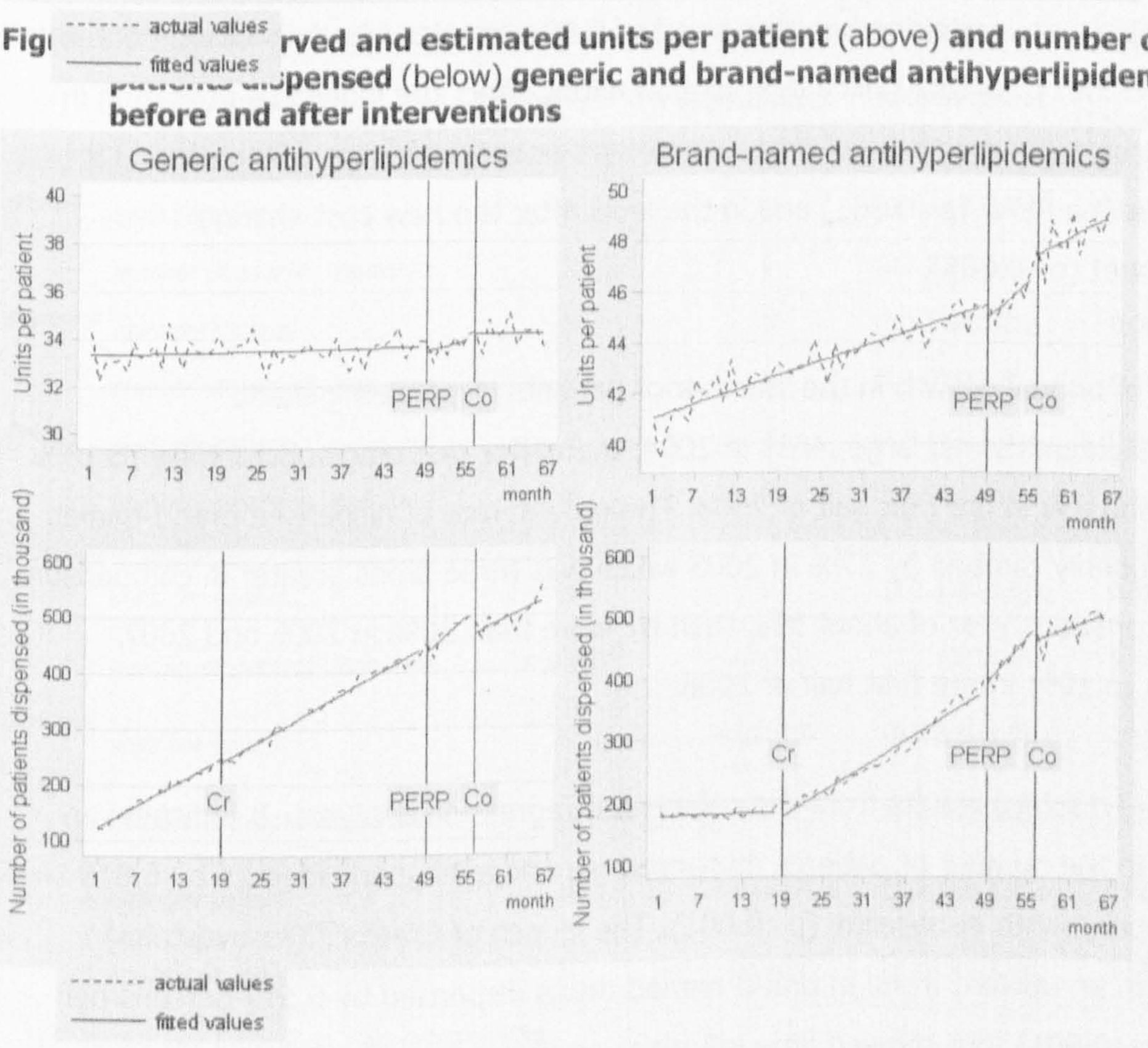


Figure 10-7: Observed and estimated units per patient (above) **and number of patients dispensed** (below) **generic and brand-named antihyperlipidemics before and after interventions**



Antihyperlipidemics: For the segmented regression of generic antihyperlipidemics, after applying OLS estimation, the values of the DW statistics were 2.33 for 'units per patient' and 2.25 for 'number of patients dispensed', respectively, indicating some concern as to the presence of autocorrelation. For the segmented regression of brand-named antihyperlipidemics, after applying OLS estimation, the value of the DW statistic was 2.50 for 'units per patient', indicating the presence of autocorrelation, while that for 'number of patients dispensed' was 2.01, suggesting little reason for concern about autocorrelation. The segmented regression analyses were repeated using the Prais-Winsten estimator for the first three dependent variables. Statistical results are displayed in Table 10-8.

Monthly generic 'units per patient' changed little over time, remaining between 32 and 34 units for an individual patient during the study period; those of brand-named drugs slowly rose over time by 17% from 42 units in 2003 to 49 units in the first half of 2008. This was supported by the findings from the segmented regression analysis (see Table 10-8 and Figure 10-7), indicating no statistically significant changes in generics ($p=0.232$) but an increasing baseline trend of 0.09 units per month in brand-named drugs ($p<0.001$). Neither policy intervention might affect the individual utilisation in generic drugs. In brand-named drugs, there was a weak evidence of increase in the slope after the PERP ($p=0.081$) and in the level after the new cost-sharing arrangement ($p=0.085$).

The rate of annual growth in the 'number of patients dispensed' generic antihyperlipidemics was large, 46% in 2004, thereafter declining substantially to 18% in 2007 and 8% in the first half of 2008. The growth rate of dispensed brand-named drugs suddenly climbed by 27% in 2005 which was three times greater in comparison with the previous year of about 8%; then by more than 30% in 2006 and 2007, dropping to 10% in the first half of 2008.

Table 10-8 displays results from the segmented regression analyses. It indicates an upsurge in the number of patients dispensed generic antihyperlipidemics by 6,819 persons per month at baseline ($p<0.001$). The launch of Crestor® (rosuvastatin) resulted in an upward trend in brand-named drugs dispensed by 6,517 persons per month ($p<0.001$), but showed little influence on dispensing of generic antihyperlipidemics.

Segmented regression analyses suggested that the PERP might raise the growth rate of the number of patients dispensed in both generic and brand-named antihyperlipidemics (β_3=4,079, p=0.022; β_3=6,202, p=0.016, respectively). The 'number of patients dispensed' generic antihyperlipidemics indicated that the cost-sharing reschedule might be related to an abrupt drop in the level (about 38,000 persons, p<0.001) as well as a 5,119 persons per month decline in the slope (p=0.009). Those dispensed brand-named antihyperlipidemics might not be affected immediately by the new cost-sharing scheme, but the influence could be greater over time, showing a larger drop in the growth rate by 8,626 persons per month (p=0.003). Figure 10-7 exhibits time series of these variables by month alongside the corresponding fitted values.

10.6.5 Sensitivity analysis

Results from the application of the ARIMA models are reported in Table 10-9.

Table 10-9: Summary of ARIMA analysis of the significance of the policy effects

Variables		PERP[1),3)]	coinsurance[3)]	ARIMA model	p value for Q statistic[2)]
antihypertensives					
overall	units per patient	N	N	$(0,1,1)(0,1,0)_{12}$	0.0702
	number of patients dispensed	N	N	$(0,1,1)(0,1,0)_{12}$	0.1908
generics	units per patient	N	N	$(0,1,1)(0,1,0)_{12}$	0.0632
	number of patients dispensed	N	N	$(1,1,0)(0,1,0)_{12}$	0.6188
brand	units per patient	N	N	$(1,1,1)(0,1,0)_{12}$	0.4418
	number of patients dispensed	N	N	$(1,1,0)(0,1,0)_{12}$	0.1186
antihyperlipidemics					
overall	units per patient	N	N	$(1,1,1)(0,1,0)_{12}$	0.3568
	number of patients dispensed	+ (0.033)	− (0.002)	$(1,1,1)(0,1,0)_{12}$	0.2558
generics	units per patient	N	+ (0.023)	$(0,0,0)(0,1,0)_{12}$	0.9288
	number of patients dispensed	N	− (0.018)	$(0,1,1)(0,1,0)_{12}$	0.1718
brand	units per patient	N	+ (0.057)	$(1,1,1)(0,1,0)_{12}$	0.6044
	number of patients dispensed	N	− (0.020)	$(1,1,1)(0,1,0)_{12}$	0.2845

1) Pharmaceutical Expenditure Rationalisation Plan
2) The Box-Ljung Q statistic should not be significant, indicating that all residuals are white noise.
3) P values are in parantheses; N refers to no statistically significant changes.

Figure 10-8: Actual and estimated values of outcome variables after the policy interventions

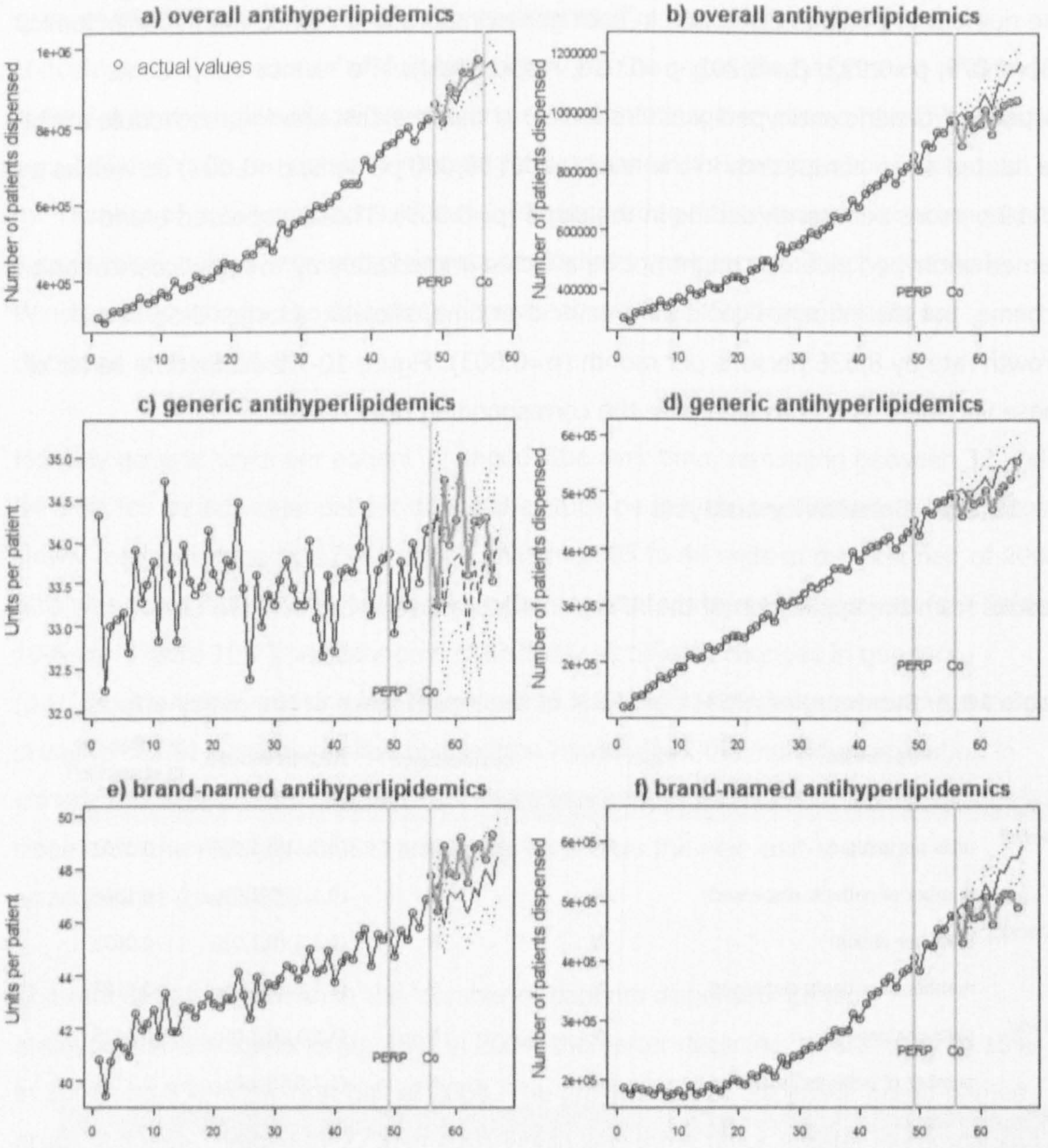


Figure 10-8 shows the outcome variables along with the forecasted series with 95% confidence intervals. Circles with a solid line represent the observed outcome during a given time period. In the post-intervention period, circles with grey lines represent the observed outcomes and black solid lines represent the expected association had the policy change not occurred. Dashed lines represent 95% confidence intervals of the forecasted series.

ARIMA models suggested little impact on antihypertensives and a significant growth in

the 'number of patients dispensed' overall antihyperlipidemics after the PERP (Figure 10-8a). Consistent results were also seen in the 'number of patients dispensed' overall, generic and brand-named antihyperlipidemics, which might decline after the new cost-sharing programme (Figure 10-8b, d, and f respectively). The increasing pattern of the individual utilisation of brand-named antihyperlipidemics after the cost-sharing restructure was identified through the ARIMA process (Figure 10-8e).

Some divergences were observed in results relating to the 'number of patients dispensed' generic or brand-named antihyperlipidemics after the PERP, and generic 'units per patient' after the new cost-sharing structure. The increased trends in the former two variables after the PERP were not demonstrated by the ARIMA models. Although ARIMA analysis suggests some increase in generic 'units per patient' after the new cost-sharing, it may be difficult to be conclusive with a short-term analysis given a large fluctuation by month (see Figure 10-8c).

10.7 Summary of findings

The time series of interest included 66 time points between January 2003 and June 2008 in the use of two medications for chronic conditions – antihypertensives and antihyperlipidemics. The policy changes came at the 49th (the PERP) and 56th (coinsurance) time point. Each policy aimed to produce cost-effective purchasing and reduce unnecessary drug utilisation respectively, without compromising patient accessibility to essential drugs. The present study examined whether: firstly, the new policies restrict patients from obtaining their essential medications; secondly, whether they encourage patients to consume less costly drugs.

The ITS analyses suggest that the policy interventions exercised different effects in the two essential drug groups. They seemed rarely to affect patient accessibility to antihypertensives, but exhibited apparent changes in access to antihyperlipidemics. The statistical investigation showed that the PERP might encourage patients to get antihyperlipidemics. The number of patients who were dispensed lipid-lowering drugs rose about 7% during the 7-month period (between the 49th and 55th time point), compared to the absence of the PERP. The trend was reversed after the copayment increase. Extrapolating the statistical results to a year after the introduction of the copayment increase (at the 67th time point), it was predicted that patients filling their

prescriptions would decline by approximately 18%, compared to before the new cost-sharing scheme.

The intervention influenced patient access to generic and brand-named antihyperlipidemics in a different fashion. Patients dispensed generics were likely affected immediately, while those dispensed brand-named drugs were influenced gradually. The magnitude of influence was greater in brand-named lipid-lowering drugs during a given time period, which would result in a greater reduction in brand-named drugs use in a one-year period. A year after the new cost-sharing schedule (at the 67th time point), a 14% drop in the number of patients prescribed generic antihyperlipidemics was expected, compared to the absence of the policy, including an 8% drop in the first month of implementation. In the corresponding period, a 19% decline was anticipated in those prescribed brand-named antihyperlipidemics compared to the absence of the policy. Implications from the findings from the ITS analyses will be discussed in the following chapter.

CHAPTER 11: LESSONS FROM PHARMACEUTICAL POLICY EVALUATION IN SOUTH KOREA

11.1 Introduction

Chapter 8 through 10 investigated the impact of two Korean pharmaceutical policies. The present chapter discusses the limitations of the analysis presented in Chapter 8 to Chapter 10. The discussion then moves on to focus on the implications of the findings from the analysis in terms of the policy impact and consequences. The chapter concludes with a discussion of the implications for the Korean generic market and future areas of research.

11.2 Study limitations

11.2.1 Issues with avallable data

Insurance claims data taken by the Health Insurance Review & Assessment Service (HIRA), the national medical services audit body, are the most credible and comprehensive data currently in South Korea. They are mostly collected through a computerised network between the HIRA and healthcare institutions. The lag between time that services are provided and claimed is no longer than 2 months according to the internal information from the HIRA. Because the data was extracted with a time gap of 3 months, the amount of claims potentially omitted were expected to be low.

As the two pharmaceutical policies tested in this study were introduced recently, data were only available for a short post-intervention period. With prescription profiles spanning 18 months from the first policy change (Pharmaceutical Expenditure Rationalisation Plan, PERP) and 11 months from the second policy change (coinsurance), it was impossible to determine the long-term impact of the policies.

Furthermore, because of the short follow up period there were few post-intervention data points and this reduces the statistical power of the tests of change in level and trend. One example of this could be for the cost per unit, despite being able to observe a considerable change in the trend in the cost per unit after coinsurance the

segmented regression results gave a large standard error and the results failed to reach statistical significance at the 5% level (see Figure 9-4).

Owing to the short follow-up, the models employed in this study assumed an immediate impact of the policies. However, in the real world, it may be natural to suppose that there would be a time lag between the introduction of the policies and the impact of these policies. It would have been desirable, if there were sufficient data points for this, to include a time lag in the analysis to allow assessment for a delay in the impact of these policies.

The interventions were implemented consecutively over a short period hence the data were not sufficient to distinguish the impact of one policy from another. To disentangle the effects of the PERP and coinsurance, it would require development of outcome variables which would respond to the PERP but not to the coinsurance or vice versa. One example of this would be the real market prices for pharmaceutical products rather than the cost per unit. Another example in relation to the positive list would be to explore if there is any causal relationship between the change in the number of products in the benefit list over time and the change in pharmaceutical expenditure or utilisation.

11.2.2 Issues with interrupted time series analyses

This study used two statistical approaches to overcome the limitations of the short post-intervention data period and to improve the reliability of the statistical results. The relatively short post-intervention period has consequences for the model specification process, especially in the ARIMA approach. Even the best-fitting models provided only limited improvement in fit or residual analyses over competing models. Taking this limitation into account, the analyses presented in the previous chapters used the ARIMA technique only as a secondary analysis tool, which supported the results from the segmented regression.

With the segmented regression, an 11-month post-intervention period would not be expected to create such serious problems as for the ARIMA models. Within the segmented regression, the presence of autocorrelation was carefully tested and corrected. However, in the two situations where the PERP was clearly not having an

effect on the model, there was some concern that the equation modelling the effect of coinsurance could be misspecified. If the model was misspecified, then the standard error of the coinsurance variables may be affected, leading to an incorrect test of its significance. When the models were repeated without the PERP terms one of the models suggested a statistically significant change; however, the results were inconclusive as the ARIMA analysis did not support this result. In all but five of the regression models the adjusted R^2 values were greater than 0.9; In the remaining five cases the adjusted R^2 values were not less than 0.6, thus indicating that all segmented regression models fitted well the observed data.

11.2.3 Issues with outcome variables

This study used the aggregate number of dispensed units for each active ingredient, which might differ in dosages. This variable was used as a proxy for quantity, as it allowed me neither to calculate the quantity of the active ingredient, or the number of defined daily doses (DDD), nor to calculate meaningful average prices. However, units used in this study were a more accurate proxy in comparison with the aggregated number of prescriptions, units have been frequently employed as a proxy measure in policy evaluation research (Kanavos *et al.*, 2004). The limitation of the aggregated number of prescriptions is that the policy impact could be misinterpreted if prescribers increase prescription sizes to reduce prescription numbers and vice versa (Holloway *et al.*, 2001; Starmans *et al.*, 1994). The 'units' employed in this study are clearly defined by law and generally equal to a usual one dose, which are able to reflect utilisation alteration regardless of size or volume changes.

In relation to brand/generic classification, it was possible that drugs were misclassified as brand-named or generic drugs due to the absence of official indicator for the classification in South Korea. However, the guideline used in this study was carefully developed by employing multi-faceted information available in the market, which is much more accurate than those used in existing Korean studies. For example, Huh *et al.* (2006) and Yoon (2008) considered that the most expensive drug among pharmaceuticals containing the same ingredient was defined as an original drug. However, one recent study found that 31 products among 181 selected brand-named subjects were priced lower than their generic alternatives in 2005 (You, 2007). Lim (2002) and You (2007) defined a first marketed product as an original drug in the

Korean market. Their method seems to need further consideration of which is an original version across countries, not only in the Korean market, because most new entities now tend to be developed by transnational companies. Cho *et al.* (2001) defined products on the Korean bio-equivalent reference drugs list[15] as an original drug. However, reference agents on the list could not always be regarded as a brand-named drug, as already discussed in the Methods section (Chapter 8). Shin and Choi (2008) utilised the same definition as that of Cho *et al.* (2001), but they supplemented the shortcomings in the list by employing the price guide and direct contact with the manufacturers if necessary, which is most similar to the current study.

11.2.4 Issues with the generalisation of the findings

Lastly, the findings from this study may be generalised to a limited extent. First, it must be cautioned in extrapolating the results beyond the study timeframe, which is approximately one year following the copayment increase. Reported decreases must be interpreted with care. It is not known whether those models with significant linear slopes after the policy change represented new equilibriums or would continue in the predicted direction. Analyses based on longer-term data would need to be undertaken to answer this question. Second, as these analyses used aggregated claims data, it cannot be assumed that the findings are evenly shown across individuals. Third, caution should be exercised in generalising the findings from two chronic medications to other therapeutic classes. Patients may exhibit different behavioural responses to a copayment increase when they use medications in other therapeutic classes, particularly drugs for temporary symptomatic illnesses or drugs for acute, possibly fatal illnesses. Each of the different therapeutic classes may have been sold in considerably different market conditions, which may influence the use of drugs substantially.

11.3 Implications for policy impact

Theoretically, it has been thought that a rise in out-of-pocket payments could lower drug costs by discouraging demand for medication (Chapter 1). This hypothesis was

[15] The Bio-equivalence Validation Programme (BVP) was introduced to verify the quality of generic products focusing on bio-equivalence in 2000. In this process, local manufacturers should prove that their product is equal to bio-equivalence profile of a product with the same ingredient on the bio-equivalent reference drugs list.

supported by international evidence available from the systematic review (Chapter 4). A body of evidence suggests that the fall in pharmaceutical expenditure generally remains within a limited range and is often smaller than the decline in volume after an increase in copayment (Chapter 4). Interestingly, the ITS analysis found the opposite to be the case. The analyses of Korean claims data indicated that the copayment increase might lower drug costs without any visible change in drug utilisation. This can be explained if the copayment increase encouraged the use of less costly drugs in the Korean prescription market, as opposed to international lessons which suggested few substitution effects toward cost-effective medications by the cost-sharing strategy (Chapter 7).

Subsequent investigation, however, suggested that the apparent fall in costs might be associated with a decline in utilisation of costly therapies, such as antihyperlipidemics, rather than a rise in utilisation of less costly alternatives. Empirical investigation of the two therapeutic classes demonstrated that the impact of the new cost-sharing programme might vary across therapeutic classes. For example, the policy might not affect patient access to antihypertensives, but possibly to have prevented access to antihyperlipidemics. Although a greater decrease was seen in patients with brand-named antihyperlipidemics, there was little evidence to suggest that the new cost-sharing schedule led patients to shift from brand-named drugs toward generics.

It was unexpected that there was no immediate change in the drug price variable after the PERP, given that the new price cut lowered drug prices for out-of-patent drugs and their generic versions by 20% immediately after the introduction. There could be two explanations for this. First, the new scheme might apply to too small a number of products to generate detectable impact on the market. However, this seems a little unrealistic as the new scheme included almost every product on the market except a few products still within their patent in the Korean market.

A second explanation is the new price cut scheme might increase the availability of expensive drugs. That is to say, it might encourage prescribers or patients to consume more costly products that were previously restricted mainly because of their prohibitive prices. As a result, rising expenditure on relatively expensive drugs offset the savings generated by cutting prices, which was highlighted in the subsequent investigation. The reduced prices after the PERP might allow patients greater access to

antihyperlipidemics, which are relatively expensive in the Korean market.

This finding is in accordance with existing evidence showing the trend of drug utilisation in the recent decade in Korea. After the separation policy, Korean doctors became more likely to prescribe original drugs, which has created expenditure inflation to a substantial degree (Chapter 2). Summary statistics of the current claims data also suggest that pharmaceutical expenditure has expanded faster than growth in utilisation over the five year period of the study. According to the recent government paper, the growth rate of drug costs was 13.7 per cent between 2003 and 2004 and factors contributing to the growth included a rise in volume (76 %) and the introduction of new, more expensive drugs (24% and 10% respectively). Pharmaceutical prices and savings by use of less expensive alternatives showed a slight decrease and contributed adversely to the growth by about 5 per cent during that time (Ministry of Health & Welfare, 2006c).

Thus, findings from the present study concerning the rising baseline trend of 'costs per unit' may be reflected by the increasing trend towards new, more expensive drugs rather than a real increase in market prices. The impact of price cuts may be masked by the trend in consumption and even facilitate it by lowering drug prices.

11.4 Implications for policy consequences

The finding that the new cost-sharing schedule may be associated with an unintended decrease in the use of antihyperlipidemics was unexpected, because the copayment increase was limited to cases in which total expenditure per single prescription was less than 10,000 KRW (about £5). It was anticipated that the new cost-sharing structure was less likely to influence the use of medication for chronic conditions. From the prescription claims data used in this study, the average cost per patient per month was 20,000 ~ 23,000 KRW (£10 ~ 11.5) for antihypertensives and 30,000 ~ 40,000 KRW (£15 ~ 20) for antihyperlipidemics, suggesting that patients taking antihypertensives or antihyperlipidemics were unlikely to be influenced by the new policy change. One explanation for the decrease may be that consumers perhaps misunderstood the new policy as a simple increase in copayment, discouraging them from filling their prescriptions after the policy introduction. Alternatively, the concurrent increase in the medical services fee may have discouraged patients from visiting their doctors.

Then, why were patients more likely to reduce their use of lipid-lowering drugs? The first possible explanation is that the high price of antihyperlipidemics discouraged drug consumption. Antihyperlipidemics are generally a costly medicine; average expenditure per patient was about 30% higher in 2003 compared with antihypertensives and the difference had become even greater – nearly twice as high in 2008 in the Korean insurance market.

Additionally, it may be due to the different clinical characteristics of the two chronic conditions. In practice, patients have a better understanding of the pathology of high blood pressure and can recognise the benefits of medication more directly. Symptoms are easily recognised and patients are usually trained to check their blood pressure at home. On the other hand, the pathology of dyslipidemia is complex and symptoms are generally less easily recognised. Serious conditions such as cardiovascular diseases or stroke are usually established over a longer time period. Hence, patients are more likely to think that antihypertensives are more crucial medications, compared to antihyperlipidemics. A body of evidence indicates that the demand for medication could be more flexible when patients perceive them to be less essential (Chapter 4).

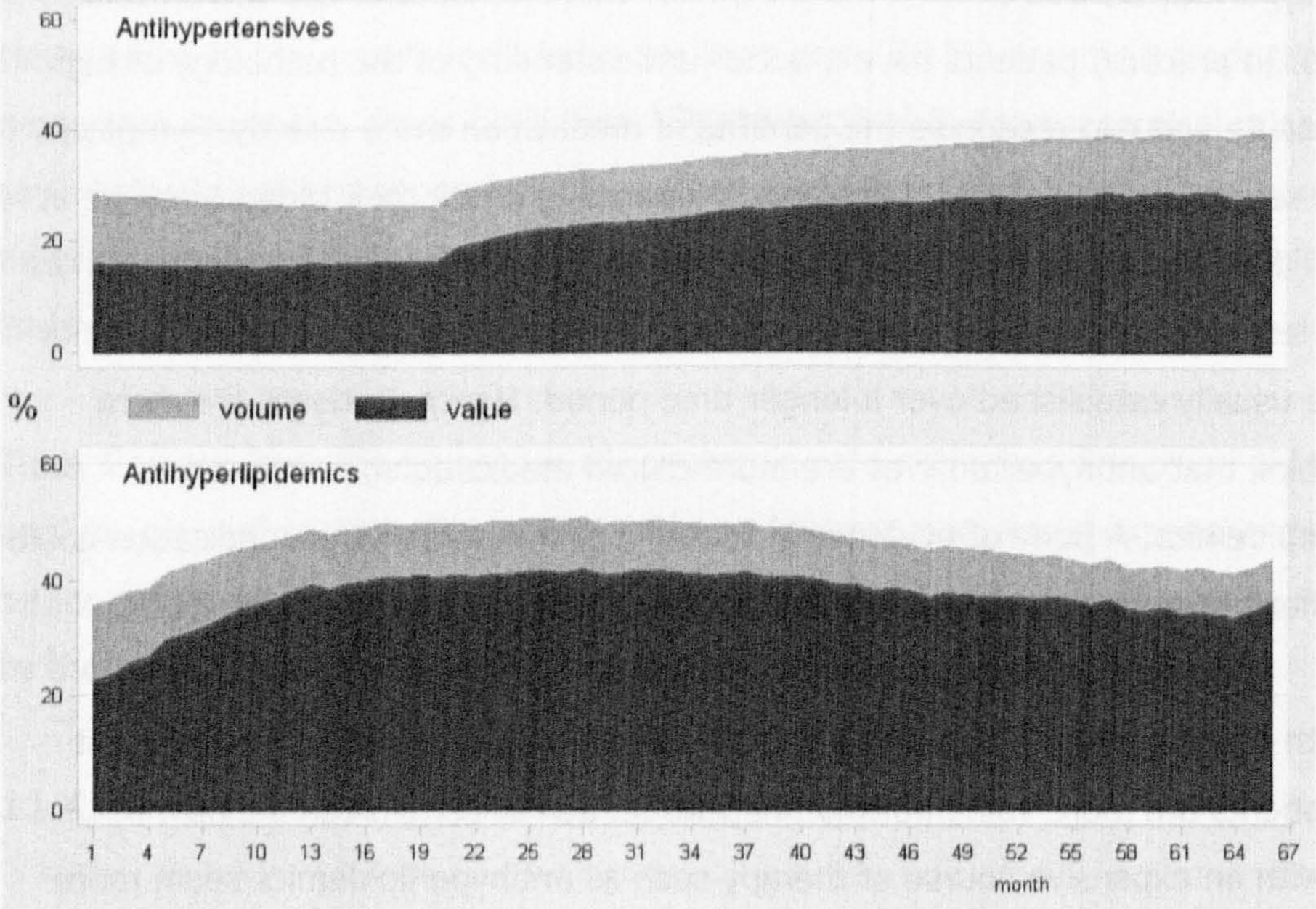
In line with this, two features found in the current analysis may reflect the fact that Korean patients are more vulnerable to financial burden in certain conditions. First, patients with an expensive course of therapy such as antihyperlipidemics seem more sensitive to the interventions, increasing drug consumption after the price cut, and reducing it after the subsequent copayment increase. Second, small but immediate effects in those taking generic antihyperlipidemics similarly suggest the potential loss of equity by denying patients access to essential medications to a larger extent in the low-income group, who may have been more likely to use generics (Federman *et al.*, 2006).

11.5 Implications for the Korean generic market

Alongside the policy evaluation, this analysis also found a few notable traits of the Korean generic market, worthy of discussion here. First, the market share of generics of the two study medications had maintained between 30 and 50 per cent over the study period. This seems a considerably high figure, given that there have been few

intensive generic policies in South Korea (Chapter 2). Spending on generics increased rapidly between 2003 and 2005 in antihypertensives and before 2004 in antihyperlipidemics, as seen in Figure 11-1. The trend was often governed by products newly launched after patent-expiry of several best selling drugs, for example, Zocor® (an original brand of simvastatin) in the antihyperlipidemics market, and some 'me-too' drugs in the antihypertensives market, rather than policy regulations.

Figure 11-1: Generic market shares in antihypertensives (above) **and antihyperlipidemics** (below) **in South Korea from 2003 to 2008**

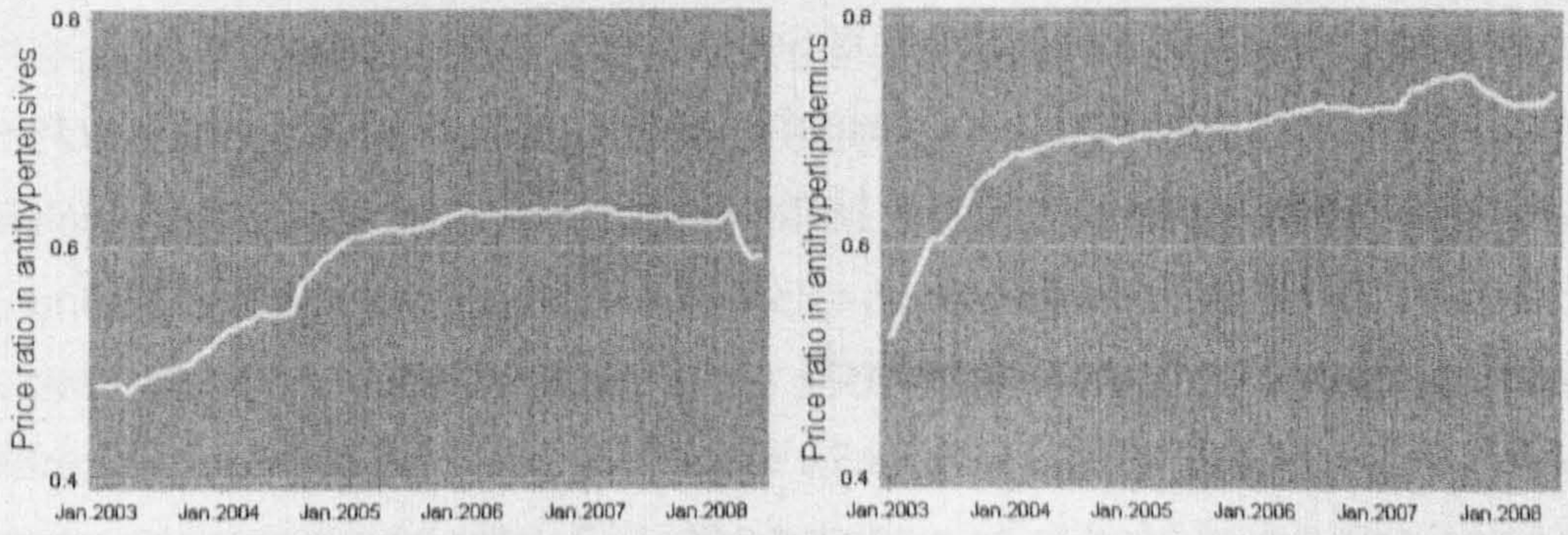


Second, the present study indicates that the gap between the value and volume of generic share in the two chronic medication markets has been constant at around 10 per cent in Korea. Previous studies suggested a smaller difference of less than 5 per cent. There have been two studies exploring the changes in total pharmaceuticals grouped into brand-named and generic drugs in Korea. One used the same claims data as the current study but over a different period (2002-2005) and included all claimed pharmaceuticals. It reported annual data of the market share of generics, which was 40~43% in volume and 35~39% in value (Huh *et al.*, 2006). The other study also performed a comprehensive analysis of pharmaceutical claims, but in a single month in 2007, and it demonstrated that generics occupied 44% in volume and 41% in value in the Korean market (Yoon, 2008). It may be hard to make a head-to-head comparison between these two studies and the current because both studies used a different

classification tool from that used here. Moreover, they included all pharmaceuticals and the current study included only two chronic therapeutic classes. Despite such differences, the volume estimates only differ slightly. The current study suggests that the value of generics of antihypertensives took about a 10% smaller segment compared with all generics in the previous studies, indicating that the antihypertensives market is probably more competitive than others (e.g. antihyperlipidemics). This is understandable as the antihypertensives market has a longer history, various sub-therapeutic classes and greater generic availability; and hence, there may be more choice of drugs.

Three further studies have explored the determinants of the market share of generics (Lim, 2002; Shin and Choi, 2008) or the first approval drugs (You, 2007). These are hard to compare with the current study because they used a different dataset, small numbers of selected panel data. Variations in the generics share were very broad, from 20 to 75% in volume and 40 to 75% in value by item.

Figure 11-2: Price ratio of generics against brand-named drugs in South Korea



* Price ratio = Costs per unit of generics/Costs per unit of brand-named drugs

Figure 11-2 demonstrates the price ratio of generics against brand-named drugs[16] between 2003 and the first half of 2008. It clearly shows that the generic price had increased considerably. However, such a marked increase is unlikely to have occurred in countries like South Korea, which has implemented price control over several decades (Chapter 2). According to the recent government paper, the market price has been negatively associated with drug expenditure (Ministry of Health & Welfare, 2006c). In line with this, two previous studies stated that such an increasing trend may be

[16] Price ratio of generics against brand-named drugs = Costs per unit of generics/Costs per unit of brand-named drugs

associated with the increasing use of expensive generics rather than an augmentation of market prices (Lee, 2006; You, 2007). Thus, the price ratio here may indicate an increase in the use of new, more expensive generics, rather than a real price increase in the marketplace.

The figures overall imply that generic prices may be as expensive as those for brand-named drugs in some therapeutic classes in the Korean market. Therefore, under current market conditions, it is questionable whether the growth of generic volume in the Korean market leads efficiently to a fall in drug expenditure. It becomes much clearer when making comparisons with figures from other settings where generic policies are thought promising. According to two recent reports from Europe, countries such as Denmark, Germany, the Netherlands, UK and Sweden, with relatively small expenditure on pharmaceuticals, have 2~3 times larger volume share in comparison with value in the generic market (European Generic medicines Association, 2007; Simoens and De Coster, 2006). Sweden, in particular, has a similar sized generic market to Korea in terms of volume at about 44%, but much less in value, around 14% in 2004. In Sweden, the share of drug expenditure of total health costs was 12.5% in the same year, which is about a half of that of South Korea. In this respect, it is important to address not only how to increase the volume of generics but also how to decrease the price of expensive generics in Korea.

11.6 Implications for future research

Clearly, this research would need to be extended with 1~2 years longer observations in order to clarify the policy impact. Two medications for chronic illnesses seem insufficient to explore the market dynamics. Hence, wider analyses involving various therapeutic classes would be informative. Exploring changes in symptom-relief remedies would be particularly interesting. It would also be interesting to investigate the impact and consequences of policies on overall health status, other aspects of health service utilisation and private expenses beyond the National Health Insurance scope. This is essential in relation to the copayment programme, because international and local evidence indicates that limiting patient demand may result in reducing social equity and deteriorating social health in some conditions (Chapter 4 and 10). Specific issues requiring further study include: the underlying causes of the reduction in antihyperlipidemics use; the causes of differential effects by drug class; the effects of

the decline in antihyperlipidemics use on long-term health outcomes; and the factors encouraging the use of expensive generics in the Korean market.

11.7 Summary

Empirical analyses of prescription claims data showed that the two policy interventions may be associated with a decrease in drug expenditure, but only to a marginal degree. They seem to contain costs not by the intended mechanisms (i.e. lowering prices or encouraging cost-effective consumption), but by reducing patients access to expensive medications regardless of clinical necessity. Thus, concerns were raised about potential impacts of overall health under such circumstances, for example, chronic illnesses in the lack of understanding by patients or in higher costs for a course of therapy. Additionally, some features, such as a sizable response in the antihyperlipidemics market or an immediate response in generic use to policy change, suggest potential loss of equity by denying patients access to costly essential medication for financial reasons.

The present investigation indicates that the gap between value and volume shares in the case of two large markets for medication for chronic conditions has been maintained steadily at around 10% in Korea, which is far smaller than that in some countries enjoying large savings by policies encouraging generics use. There has been a clear and considerable increase in the price of generics against brand-named drugs, translated into two possibilities: a faster increase in generic prices or a higher market share of expensive generics. In such market conditions, it is possible that generic policies would be less effective in containing costs.

CHAPTER 12: EVIDENCE-BASED PHARMACEUTICAL POLICY-MAKING IN THE KOREAN CONTEXT: A QUALITATIVE STUDY

12.1 Introduction

The purpose of this chapter is to present a qualitative investigation into the difficulties of evidence-based pharmaceutical policy-making in the Korean context from the policy-maker's perspective. In the current qualitative study, the policy-maker was defined broadly, including not only personnel who actually make decisions about policy, but also people who influence policy decisions in the Korean policy-making process.

A substantial literature indicates that the cost crisis in pharmaceuticals has been caused primarily by increased consumption (Mossialos *et al.*, 2004; Strunk and Ginsburg, 2004). Linked to this, systematic reviews illustrate that the pharmaceutical policy agenda has expanded from controlling patients using copayment schemes or restricting drug suppliers through price control, to limiting doctors' prescribing practices (Chapter 4 through 6).

A matter of prime interest in regulating prescribing practices is currently to encourage the use of lower cost alternatives without compromising quality of care (Chapter 5). In addition, as it becomes aware of access to medications possibly being reduced by flat-rate cost-sharing programmes, interests are increasing about developing various tools that are able to encourage less pricy alternatives such as generics instead of reducing utilisation (Chapter 4 to 6). It has been suggested that price control might be powerless when confronted with entrepreneur activity in the industry, for instance marketing for newer, more expensive medications (Healy, 2006; Jacobzone, 2000; Lovell, 2006). So, more efforts have been made to reduce prices by promoting competition in the market. Examples may include reference-pricing schemes (Chapter 6).

During the 2000s, faced with rising drug expenditure, the Korean government has tried to contain costs by the simultaneous introduction of several policy interventions (Chapter2). It is, however, unknown whether effective policies have been implemented to tackle the main cause of expenditure inflation in Korea. For instance, evidence from

claims data invariably suggests that first it is necessary to change doctors' prescribing behaviour. Nevertheless, the Korean government, as seen in Chapter 2, has focused more on measures influencing patient demand or reimbursement prices, rather than on those affecting prescribing behaviour overall.

Obviously, interventions controlling patient demand and prices have achieved only a marginal impact in containing costs in Korea (Chapter 9). It may be too early to draw any conclusions from the programmes currently under examination. However, given the global evidence from the systematic reviews of one-off effects in controlling patient demand and direct pricing, it seems unlikely that much greater impact would be realised afterwards. Moreover, some unwanted consequences were seen after the recent policy changes, such as a considerable restriction in the use of essential drugs, and a decline in the use of generics as well as brand-named drugs (Chapter 10).

In recent years, a variety of attempts to influence prescribing behaviour has increasingly taken place. However, many of them remain in the early stages of development (Chapter 2). Even within a single plan, for example, the Pharmaceutical Expenditure Rationalisation Plan (PERP), measures influencing prescribing practices are less likely to take effect than others, such as pricing (Chapter 9). This raises some questions. What are the factors that can cause a conflict between evidence and policy decisions in South Korea? To what extent does the evidence have an effect on the policy-makers? What other factors, if any, influence policy-making, and to what extent? While needs exist, few studies have addressed these subjects scientifically so far.

Results from the systematic reviews illustrated that a few strategies might be effective for containing pharmaceutical expenditure in other settings. However, it is unclear whether such strategies would be effective as well as feasible in Korea. Thus, there is a pragmatic need to identify the barriers, feasibility and implications of some promising policies from other settings in the local context to achieve further improvement in the pharmaceutical arena.

12.2 Research questions

This study was designed to address the following question from policy-makers' perspective:

What makes it difficult to formulate evidence-based policy-making in South Korea?

Within this question, the intention was to:

- investigate participants' views on current policies and evidence available to policy-makers;
- explore the factors that influence policy decisions;
- explore participants' opinions of the potential policies available to policy-makers.

12.3 Methods

12.3.1 Study design

For the study, semi-structured interviews were carried out with key influential personnel in Korean pharmaceutical policy-making. Semi-structured in-depth interviews are performed "on the basis of a loose structure consisting of open-ended questions" (Britten, 2006; p13). Whilst the topic area to be explored is determined at the outset and some questions can be pre-determined, qualitative semi-structured interviews also allow for some questions or topics to be developed within the interviews, allowing the respondents to raise issues important to them and that were not considered in advance by the researcher. In this sense, they differ from structured interviews which "involve tight control over the format of the questions and answers" (Denscombe, 2007a; p175). Fundamentally, this study was not designed to develop theoretical concepts relating to the topic area. Rather, it aimed to probe pragmatic issues among experts, making semi-structured interviews the best choice for the study.

12.3.2 Participants

Potential participants were selected from among the appropriate members of the key groups associated with pharmaceutical policy-making in Korea, with the intention of identifying those who are the most relevant to the research aims. Purposive sampling was employed – such non-probability sampling is often used in a small sized, exploratory qualitative studies (Denscombe, 2007c). In purposive sampling, the interviewees are strategically sampled because they are "information-rich cases"

(Patton, 1990a).

To find key names efficiently, a snowballing technique was used (Patton, 1990a). Experts involved in the pharmaceutical policy-making process comprise of a group of people, who are often difficult to contact directly. Hence, personal connections are valued in this field and snowballing is thought an effective way to increase the likelihood of obtaining interviews (Marshall and Rossman, 2006). These 'information-rich' key people were identified by asking a number of different informants to recommend colleagues for the study. A few key names were mentioned repeatedly, and they were considered as valuable potential interviewees and approached to take part. To ensure maximum variation and diversity across relevant organisations in the sample (Patton, 1990a), types of potential participant were loosely categorised by the organisations to which they currently belonged. At the same time, their previous career was also considered in the categorisation.

Potential participants were chosen based on appropriateness, relevant experiences, and, of course, their willingness to engage in discussion. The selection criteria included:

- experience of the pharmaceutical policy-making process;
- current or recent involvement in the pharmaceutical policy-making process in South Korea either as a policy-maker or as an advisory committee member;
- experience of academic research into Korean pharmaceutical policies;
- willingness to discuss personal views;
- interests in pharmaceutical policies.

A total of 49 potential participants were identified through the process, of which 16 were approached. Nine individuals finally participated in the research, but among them, one failed to be followed up after the questionnaire (see the following section for details in the procedure of data collection). Recruitment was ended as it appeared that saturation had been reached in terms of the views expressed, with similar opinions and concepts repeatedly recurring in study topics (Guest *et al.*, 2006).

12.3.3 Data collection

Data was collected between July and September 2009 through a semi-structured, self-administered questionnaire and an in-depth telephone interview. A small pilot of the questionnaire and interview process was undertaken with selected, interested interviewees known to the researcher, who fulfilled the inclusion criteria and had expressed a willingness to act as subjects.

Participants were approached with a request for an interview. An initial letter of approach was emailed to the selected individuals, summarising the proposed research and inviting participation. This approach was made via a member of the network of contacts, or interviewees. Individuals were followed up by telephone or email to confirm receipt of the initial invitation, and to ask whether they would consider participating. Following agreement to participate, a covering letter was sent by post with: 1) the information sheet detailing the content of the research; 2) two copies of the consent form; 3) the topic guide for participants (Annex 23); and 4) a semi-structured questionnaire (Annex 24). Individuals were followed up to confirm receipt of these documents. After the return of the signed consent form and completed questionnaire, a telephone interview was carried out.

A semi-structured, preliminary questionnaire was developed and sent to participants to complete in advance of the interview. This served two purposes. First, it was expected that a preliminary questionnaire would be useful in reducing the time spent on interviewing, and soothing the participants' anxieties relating to the time commitment related to the study participation. Second, it was expected that preliminary questionnaires would be useful triggers for discussion during the interviews (Adamson *et al.*, 2004). They would ensure the interviews were highly focused, making it possible for the researcher to interview participants within limited time (Patton, 1990b).

The interview guide and questionnaire consisted of four domains: individual characteristics; opinions about existing evidence and evidence-based policy-making; pragmatic experience in policy-making; and recommendations for future policy. All respondents were asked identical questions in the same sequence, but interviews evolved further, concentrating more on key responses from the questionnaires.

Additionally, as the study recruited participants using a purposive sampling method, it allowed for allocation of extra questions relating to each participant's expert field, if deemed necessary for the study (Denscombe, 2007c).

Each interviewee was interviewed once. Each interview took place over the telephone lasting 40 to 60 minutes on a one-to-one basis. All interviews were conducted by the same researcher. The discussion was audio-recorded for transcription. Interviews were subsequently transcribed verbatim. There was no further follow up of participants for collecting primary data, but where necessary, further contact by telephone or email was made on a case-by-case basis to verify vague dialogue or to identify further participants. A log of all contacts was kept, for audit purposes.

12.3.4 Ethics

Consent was freely given, and was not coercive for any reason. Participants were informed they could discontinue the interview whenever they wanted to. The consent form was sent to participants with the following documents and a semi-structured questionnaire to ensure participants were fully informed of their role within the research.

- **Participant Information Sheet** detailing the process of the interview;
- **Topic Guide** highlighting the areas for discussion.

Interviewees, for their records, retained one copy of the consent form and signed and returned a second copy to the researcher for filing as part of the audit trail. The researcher's contact details were available throughout the research, to allow participants the opportunity to discuss any issues arising. The researcher was available to answer any further questions they might have, both prior to consent and once permission had been obtained for the interview to take place. Consent was an ongoing process (Lawton, 2001), and was verbally re-obtained and recorded during the interview, thus appearing in the transcripts.

Interviews were transcribed anonymously and the interviewees' identities were protected by the allocation of a respondent code. Their names were not reported at

any stage and organisations were described only in the broadest terms in order to protect individual's identity while maintaining the context of information in the research. Additionally, participants had opportunities to see transcripts and excerpts destined to be used in the final report. Any information they gave during the interview was not reported if they expressed any unwillingness to disclose. Personal details had been securely retained for contact purposes only and all information collected about participants during the course of the research was kept strictly confidential. The only people who had access to their identities were the named researchers who ensured that steps were taken to maintain security and confidentiality. Tapes and paper copies of the transcripts were stored in a locked filing cabinet in the investigator's office, to be destroyed when no longer required. Access to data stored on computers was password restricted to the researchers. Data will be stored until the project is completed in its entirety and securely archived until disposal.

Prior to being undertaken, the research was reviewed and obtained approval from The Department of Health Sciences Research Governance Committee, The University of York.

12.3.5 Data Analysis; framework approach

The data was analysed employing a framework approach, developed by the National Centre for Social Research as a tool for policy and evaluation analysis (National Centre for Social Research, 2010). A framework is an analysing tool to find answers to qualitative questions deductively, involving a series of well-organised steps and increasingly used in qualitative research (Pope *et al.*, 2000; Ritchie and Spencer, 1994). The framework technique, which is relatively formulaic, allows for examination of the analysis to take place, indicating high transparency of the procedure (Ritchie and Spencer, 1994). Moreover, for the same reason, the framework approach allows rapid, targeted progress in qualitative analysis, which reduces the burden of time-consuming and labour intensive tasks for analysers.

Data analysis was done through an iterative process including familiarisation, identifying a thematic framework, indexing, charting, mapping, and interpretation (Ritchie and Spencer, 1994). After completing each interview, tape-recorded data was

transcribed by the researcher. Transcription from voice to hard-copies took a considerable time, involving listening to tapes and reading transcripts several times. While undertaking this, the researcher had time to become familiar with the raw data. Additional reading of transcripts was also carried out to list key ideas and to find recurrent themes. At this stage, the data were bracketed according to the emerging concepts and subjects. Alongside this, brief notes on each concept and subject were tagged.

The data was examined several times until meaningful clusters of text were identified. Each identified cluster (theme) was given a unique code. A qualitative data analysis software, ATLAS.ti version 5 (GmbH Berlin) was used for coding. When all the data had been coded thoroughly, key characteristics of the coded data were considered and pulled together. For assuring a picture of the data as a whole, an Excel spreadsheet was built for each theme, which displayed quotes or expressions, summarised the vital idea of theme, and contained further details of sub-themes.

Following initial coding, the data were then examined for potential patterns or underlying relationships between themes and sub-themes, in order to develop higher order constructs. Where necessary, the transcripts were revisited and themes compared and contrasted in order to search for common structure, inter-connections and implications. The process was repeated several times. Finally, three higher order themes emerged, which were evidence, challenges and prospects. Each main theme was comprised of 2 or 5 sub-themes (see Figure 12-1). *A priori* themes were combined, restructured or displaced by new ones emerging from the data.

For reporting, the original language was translated into English by an independent translator. There is little evidence that translation would alter the qualitative analysis, though some concerns may still arise as to whether translation is accurate and portrays the subtle meanings of the original language (Marshall and Rossman, 2006). To reduce such concerns and to gain a better understanding of delicate nuances, a separate translator, who is a Korean and has a near-native command of English, was engaged. Quotations in the original language are presented in Annex 25 in parallel with the English version.

12.4 Results

12.4.1 Characteristics of participants

For this study, eight interviews were undertaken with key persons involved in drug policy-making and evaluation in South Korea. The questionnaire was completed by nine participants, but one participant (p022) did not agree to be interviewed without giving a reason. These answers were included only in the questionnaire analysis. Their characteristics are illustrated in Table 12-1.

Table 12-1: Basic characteristics of participants

Participant	Working for	Length	Background
p006	government body	10<	Pharmacy
p014	advisory research body	5~10	Pharmacy, Health Sciences
p017	advisory research body	10<	Pharmacy, Health Sciences
p019	advisory research body, academia	10<	Pharmacy, Health Sciences
p022	government body	<5	Nursing
p028	government body	10<	Pharmacy
p030	government body	10<	Pharmacy
p047	advisory research body, academia	5~10	Pharmacy, Health Sciences
p048	government body, academia	5~10	Pharmacy, Health Sciences

Participant numbers (e.g. p006) are arbitrary, and were simply allocated in the order in which names were initially identified during the snowballing process. In table 12-1, 'Working for' indicates organisations in which participants have been engaged so far, 'Length' denotes time period that participants have been engaged on relevant tasks and 'Background' reflects their academic discipline. Half of the participants have worked for government bodies at national level and have experienced policy planning and implementation. The rest have worked in an advisory role in either advisory research bodies or academia. All but one participant had a pharmacy background and among them, five participants had received further training in Health Sciences. Participants in government bodies tended to take responsibility closely related to current major pharmaceutical policies and were regarded as appropriate key policy-makers. Those in advisory organisations had published related subjects across a range

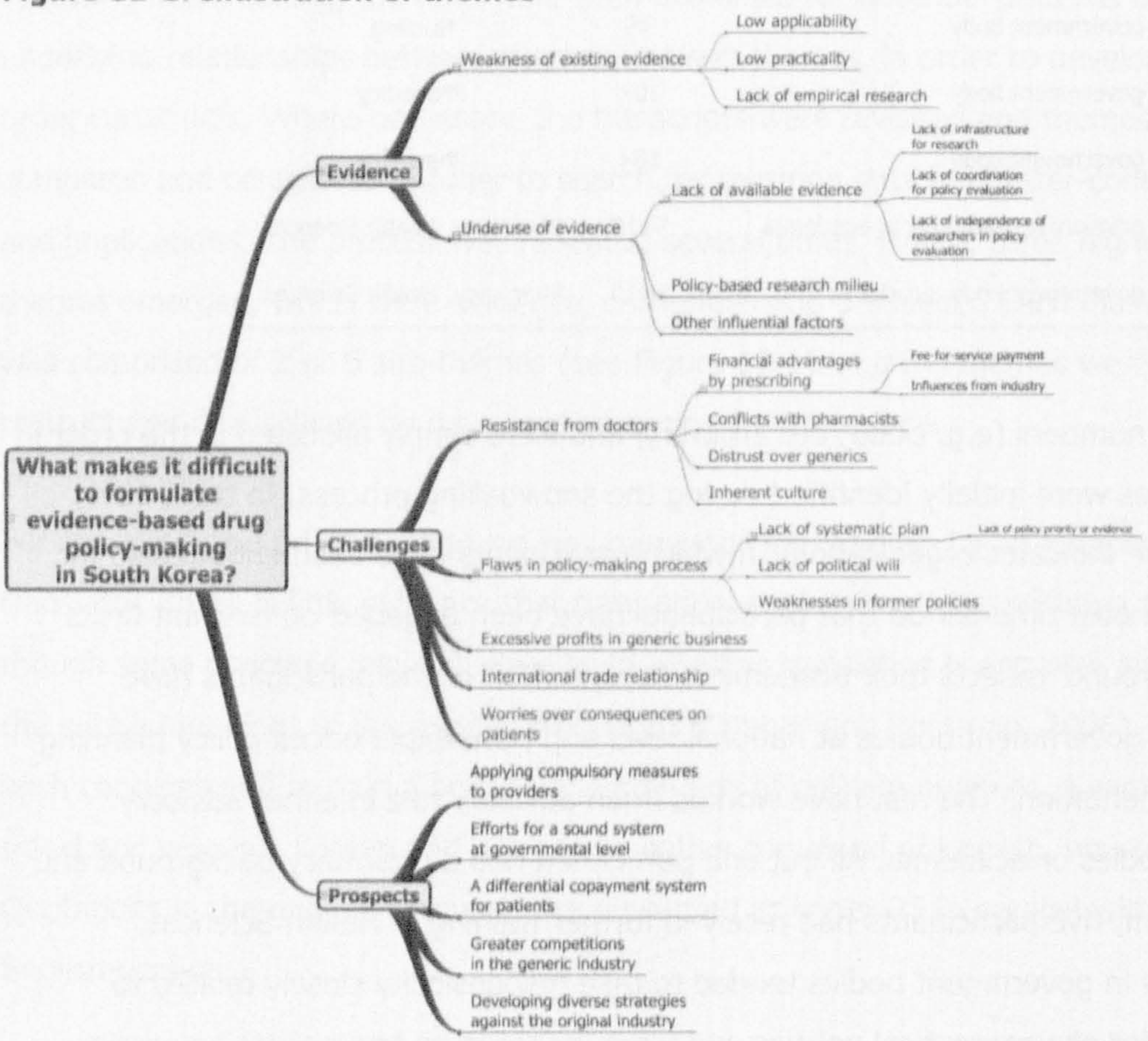
of media including government-funded research documents, newspapers and academic journals and, hence, were regarded as influential personnel affecting Korean pharmaceutical policy-makers. Thus, all participants could be considered appropriate key persons in the Korean pharmaceutical arena.

12.4.2 Emerging themes

Themes emerging from interviews were categorised into three core subjects as follows:

- ***Evidence*** showed the weaknesses of existing evidence and policy cycles undermining scientific evidence in the Korean pharmaceutical arena.
- ***Challenges*** identified practical difficulties that Korean policy-makers have often faced in drug policy-making.
- ***Prospects*** brought together suggestions for future drug policy and an effective policy-making process.

Figure 12-1: Illustration of themes

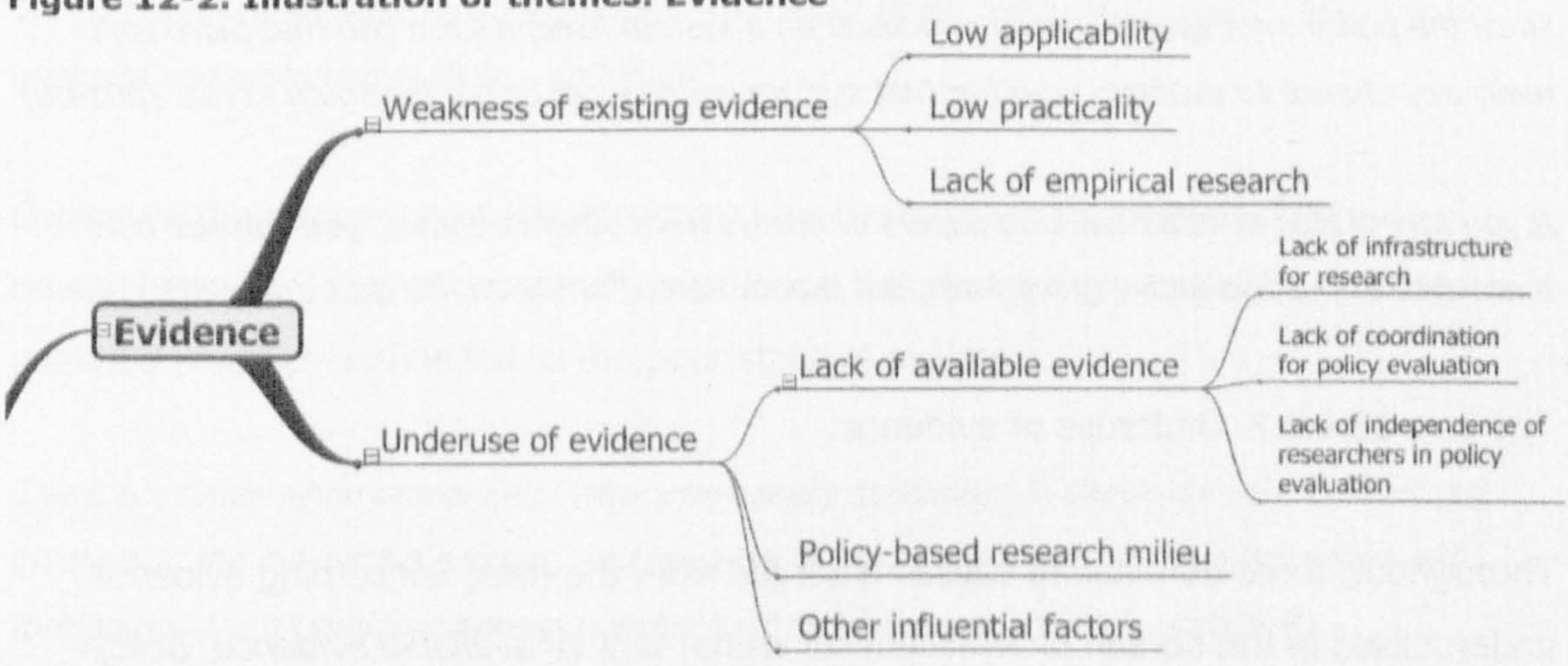


Within core themes, a number of sub-themes were identified as shown in Figure 12-1. Due to the extent of this illustration, a closer depiction of each theme is presented in the corresponding section (see Figure 12-2, 12-3 and 12-5). Each theme is dealt with in the following sections in turn. In terms of the quotations, the references at the end of each indicate the participant reference number, followed by the paragraph numbers where the quotation occurs in the transcript. The paragraph numbers were generated by a qualitative data analysis software, ATLAS.ti version 5 (GmbH Berlin), which was used as a data management tool. For example, the first quotation in the next section is referred to as (p030:8), which indicates that it was said by participant 030, and that the comment occurs on the eighth paragraph of the transcript.

12.4.3 Evidence for pharmaceutical policy-making

Discussions regarding the first theme, '**evidence**', showed the weaknesses of existing evidence and uncovered the fact that scientific evidence has been underutilised in Korean drug policy-making. Subsequently, dialogues tackled several sub-themes concerning the cause of the underuse of evidence, including the scarcity of available evidence due to the lack of infrastructure, coordination and independency, policy-based research milieu and the presence of other influential factors (Figure 12-2).

Figure 12-2: Illustration of themes: Evidence



12.4.3.1 Weaknesses of existing evidence

The weaknesses of current evidence suggested by respondents can be grouped into three categories. First, evidence from abroad seems less useful owing to difficulties

adapting it to the local context. The perception was that there were many factors making every policy intervention produce different outcomes depending upon details or social environments.

...even if the evidence were objective, it's hard to apply it simply because of the difference between Korean system and other countries' systems (p030:8)

Second, evidence produced in Korea is also considered impractical, since most studies conclude with general remarks and, as a result, fail to present any practical suggestions. This was particularly stressed by participants engaged in the planning or implementing of policies, who might welcome a practical prescription.

If you look at the outcomes of most evidence produced in Korea, they usually tend to cover just the general aspects of it and leave out all the details. (p006:6)

Third, it is rare to conduct empirical follow-up after introducing a foreign policy, or to investigate the policy impact in the local context from various angles. So far, policy has most likely been studied focusing on 'the system itself', rather than on its lessons for Korea. Closely linked to this was the sub-theme, 'policy-based research milieu', which was discussed further in the following section.

Since the policy monograph is mostly focused on a system itself, it's too bad that there isn't really any chance to evaluate whether that system would work or not for South Korea. (p014:8)

If you take a look at other working papers or essays from other countries, you can see how there are various evaluative procedures, we [South Korea] rarely do like that. (p048:6)

12.4.3.2 Underuse of evidence

Throughout, three dominating causes emerged from the data, concerning evidence underutilised in the Korean pharmaceutical arena: *lack of available evidence, policy-based research milieu* and *presence of other influential factors*.

Lack of available evidence: The difficult situation initially met by participants in the policy process was the scarcity of relevant evidence.

It's also not being used because, so far, there basically hasn't been enough evidence available on other previous policy-making processes for us to learn from and use as an example whenever we have to make certain future decisions... (p047:4)

The opinions from interviews made it clear that the principal factor placing a hurdle in the way of evidence-based policy-making is the lack of available evidence. The underlying causes of the shortage, participants identified, were threefold: *lack of infrastructure for research; lack of independence of researchers; and lack of coordination* in policy evaluation.

Most participants felt that the dearth of basic infrastructure might cause available evidence to be limited or less valuable. In detail, their statements were omni-directional, including the lack of fundamental relevant research, such as *"epidemiology relating to chemical substances or epidemiologic researches [on local population] (p030:10)", "head-to-head data on drugs (p030:10)", "evidence on how to allocate the budget [to discuss a prescribing budget] (p019:24)", "costs data in relation to an economic evaluation (p019:8)", and "[for prior authorisation] [a standard of judgment] on whether this person really needs this or not (p028:60)"*; the lack of workforce - qualified researchers and training programmes; the lack of experience in the establishment and evaluation of policy and the translation evidence into policy.

We just don't really have much experience with all of these policy evaluations... like how to evaluate and systematise them... (p006:40)

Central to the discussion of infrastructure was the demand for properly trained researchers. Participants repeatedly mentioned this during interview. The shortage of qualified researchers has led to the poor state of evidence.

There are times when researchers who aren't really specialists in the social science field get involved in the evaluating process, and because of this, they simply make comparison with foreign policies or evaluate Korean policies tend to be too generalised... (p019:8)

Participants working as planners or implementers asserted that they often felt that it was necessary to guide public funded-researchers with intensive discussions, since the quality of most researchers might not be sufficient otherwise.

Most researchers don't necessarily understand very well about the policy direction. So, whenever we ask them to write out policy reports to researchers, we normally request them to focus and verify the topics we mostly discuss and write about. (p028:14)

Less-qualified researchers were thought to rely on guidance from the authorities. To some degree, even the ability of eligible researchers suffered from a lack of independence in policy evaluation. Firstly, it seems to be unavoidably restricted because of the shortage of resources like time, background references, colleagues for inter-disciplinary research, or fundamental data that are essential to aid the diversity of research. Participants such as a researchers or advisors regretted the shortage within the researcher pool that often prevented them from undertaking in-depth analysis of practice.

I'd like to do more about the evidence you mentioned before, such as evidence on a certain policy evaluation or a system evaluation that we could use in the future. But it's not easy for us to pursue in-depth research because policies continue to change, and also there aren't enough networks for us to reach out to those who might be able to help. (p014:8)

Secondly, respondents argued that currently researchers in Korea are inevitably governed by sources of funding or data. Under these circumstances, the quality of studies tend to be of lower standard, respondents arguing that funders (mostly administrative government bodies) were likely to require descriptive or general outcomes advocating their own arguments, rather than those from a robust scientific analysis.

Either the government or other organisations in South Korea that would recruit researchers for policy research prefer more descriptive methods than in-depth analytic ones, they just want things to be explained descriptively and in certain ways they want them to be explained. (p048:6)

In order to improve the quality of evidence, participants felt that it would be essential to construct a systematic research framework with long-term planning. One participant in particular spent considerable time describing the definition of coordination in policy evaluation. She elucidated it in three ways: to plan a policy from simulation to evaluation prior to introduction; to set out priority among policies and research to avoid wasteful duplication of effort in close collaboration among relevant government bodies;

and to construct datasets systematically. She argued that the lack of research coordination could cause inferior research outcomes compared with inputs in this field. Her concepts reappeared in other participants' interviews albeit in a slightly patchy and different manner. Related comments from other participants are *"needs a live, close network among research institutions (p030:10)"*, *"hasn't been enough evidence available ... to make certain future decisions (p047:4)"*, *"the short-term and fragmented policy evaluation (p014:4)"* and *"doing another before evaluating a policy introduced ahead (p048:4)"*. The following statement from one participant illustrates, how it has been difficult to consider for evaluation at the policy planning stage in practice.

The evaluation for that would be the successor's responsibilities ... (p028:22) It normally takes about three to five years to figure out if policies are really working or not, but policy-makers usually end up being replaced after that amount of time. (p028:24)

Policy-based research milieu: Besides the three direct causes addressed earlier, it was claimed that the deficit of evidence had been exacerbated by the weakness of the Korean policy cycle. In South Korea, the policy-based research milieu has been constructed on three characteristics of the policy-making process: the limited time available to make decisions; the lack of accountability for bad decision-making; and the lack of transparency in the process of decision-making.

There are often sudden requests for policy reform, then, [policy-makers] have to come up with the request and carry it out in a very limited amount of time. (p006:4)

There are a number of those [government bodies] who are mainly focused on their group-interest, well, especially with drug pricing policies (p048:46)

Evidence does not just appear when needed although, as one participant appropriately commented, it is required in a timely manner to influence policy-making.

So when it comes to policy-making process, we end up using research materials or data that are either already done by someone else, or already on the market. I just don't think we really have any choice but to rely on experts' opinions. (p006:4)

It is important to conduct research consistently and to build routine information systems to improve knowledge, regardless of exogenous environments such as political

imperatives. Participants testified that such sound research environments have hardly been put in place in current policy-making conditions. In this decade, as several participants mentioned, the government has been under pressure from the cost crisis, which required policy-makers to take action in some form. In such conditions, several policies have actually been introduced without careful consideration for the local situation.

since we are usually pressured for time, we try to introduce all these American and European policies, just add to, even if they are not necessarily the best ones for our country (p030:58)

They basically already liked what they saw in that short period of time, so they don't really seem to care too much about fully comprehending foreign policies or the systems that they're interested in as long as they like [the foreign systems]. (p014:4)

Additionally, evidence could be used selectively, and sometimes misused, according to its intended purpose – such as supporting or justifying policies already introduced.

there were many cases where those evaluations have been made public mainly focused on the 'good aspects' of them. (p014:4)

Participants occasionally expressed disappointment about current conditions, arguing that they were discouraging and made for poor performance in research activity.

All these factors are related, and result in hindering the in-depth, diverse evaluation of policies and impeding research capacity. Within this vicious cycle, policy-makers are often faced with poor evidence at the time of use, which hamper 'evidence-based' policy-making.

Presence of other influential factors: In order to explore how scientific evidence is regarded in policy-making, participants were asked to rank factors influencing policy decisions. Additional in-depth discussions over the factors influencing policy-making provided a clearer idea about aspects other than evidence. Certainly, various factors might be ahead of scientific evidence in consideration of policy. Some of the participants felt there was little point in ranking factors, especially those placed in the lower positions such as fifth or below, since they thought the power of influential factors altered according to the steps in the process. For example:

At first, opinion leaders and other people, such as a group of consumers, would announce something like 'these are the problems in a policy, and it should be reformed.' However, when it comes to the process of carrying out the policy, cases from other countries or pre-existing evaluations are taken into consideration. In the next step, other example cases and evidence grounds may play an important role, and then, the pharmaceutical industry or some interest groups would play a part in deciding how strongly they enact... (p047:6)

Depending on the organisations and tasks in which each participant had been engaged, considerable differences were observed. Different opinions also emerged as a result of the participant's interpretation of the query. For instance, some participants replied from a personal viewpoint, others made more generalised comments. Some responded with answers they felt would be welcomed, others tried to show the reality of their workplace.

Table 12-2: Factors influencing policy decisions

	1st	2nd	3rd	4th
p006	Consequences on pharmaceutical industry	Interest groups	Scientific evidence	Opinion leaders' perspective
p014	Opinion leaders' perspective	Overseas experience	Political context	Scientific evidence
p017	Interest groups	Consequences on pharmaceutical industry	Political context	Consequences in other resources use
p019	Political context	Interest groups	Opinion leaders' perspective	Consequences on pharmaceutical industry
p022	Consequences on pharmaceutical industry	Conventional precedents	Opinion leaders' perspective	Scientific evidence
p028	Political context	Conventional precedents	Overseas experience	Impacts on expenditure
p030	Conventional precedents	Overseas experience	Political context	Consumers' groups
p047	Conventional precedents	Political context	Scientific evidence	Overseas experience
p048	Political context	Overseas experience	Impacts on expenditure	Impacts on patients

Table 12-2 shows the factors that each participant rated from one to four. Political consideration appeared most frequently and had the highest ranking, followed by

overseas experience, conventional precedents, and considerations for the pharmaceutical industry and opinion leaders' perspectives, in that order.

Participants felt that political imperatives were be the most powerful factor. They recognised that policy is inevitably formulated in the context of political agenda not only in healthcare, but also in all other areas. Overseas experience is often used as a 'backup' for interventions introduced according to political imperatives.

The conventional precedents largely included four different situations: 1) *preceding cases* for micro-level decisions, such as whether or not a drug was included in the insurance benefit list; 2) *previous policies* providing justification for new policies; 3) *former experience* in policy implementation such as the example of the reference-pricing scheme, the failure of which discouraged policy-makers to re-attempt introduction of this policy despite a growing opinion in favour of the scheme; 4) *existing policies* with which the new policy must interplay.

Another major factor was 'consequences in the pharmaceutical industry'. Participants expressed the view that the Korean government tended to price generic drugs generously, expecting a profitable industry return through innovation.

Our country has, in some ways, intended to maintain the domestic industry by setting generous prices for generics (p017:64)

Consequences in the pharmaceutical industry were given more weight in policy decisions. The opinions relating to the pharmaceutical industry were strongly linked with the challenges caused by the generic industry, which is addressed under the next theme.

Participants also rated opinion leaders' perspectives in relatively highly. They suggested that this factor played a leading role in several big changes to date, including the separation policy and the formal economic evaluation.

Interestingly, fewer participants thought that influences from interest groups, such as doctors or manufacturers, could be stronger than scientific evidence, which seems contrary to the fact that most participants kept mentioning difficulties resulting to

policy resistance from such groups. The following remarks may show the reasons for such differences.

Since the influence of a pharmaceutical company is not explicit in outside... (p047:6)

I didn't really have to face it directly. However, if I had been involved in either the NHIC or in the HIRA, then I would've understood the importance of it. (p014:12)

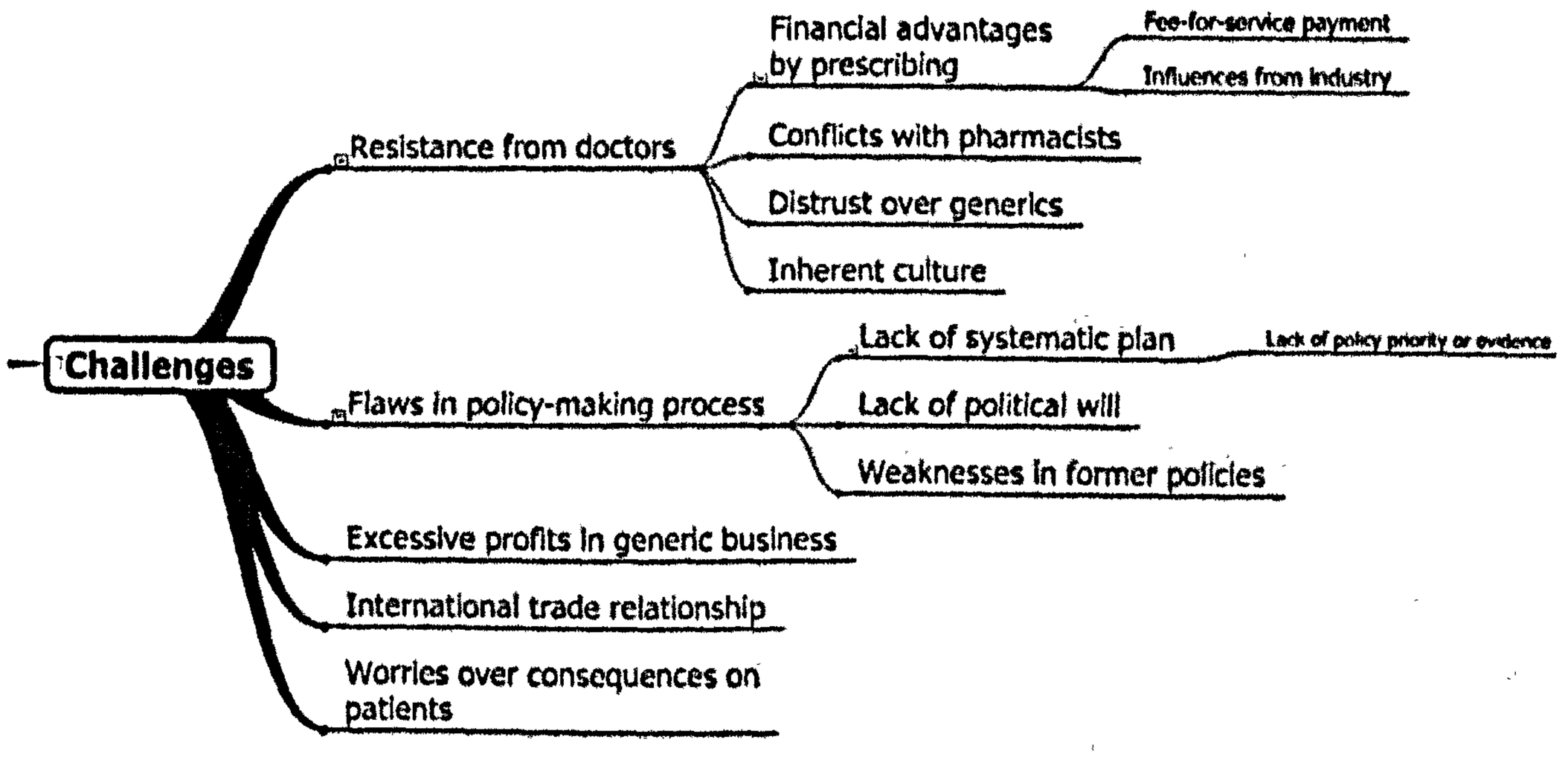
It's like saying this is one of my top priorities. But if I had to rate this objectively, then it would be much more influenced by interest groups. (p028:18)

A clear implication from discussions is that there is a variety of factors potentially influencing policy decisions, often stronger than reliable evidence. It means that other factors can override good evidence, presumably more frequently than one would imagine.

12.4.4 Contemporary challenges in pharmaceutical policy-making

The second major theme dealt with **'challenges'** that participants have faced within the process of policy-making in the Korean context.

Figure 12-3: Illustration of themes: Challenges



Five factors were stressed repeatedly by participants: policy resistance from doctors; inherent flaws in policy-making process; excessive profits in generic business;

International trade relationship; and worries about increasing inequity (Figure 12-3). Issues relating to doctors appeared most frequently. Participants identified underlying causes of doctors' perceptions against drug policies, citing four sub-themes: financial advantages by prescribing; professional conflicts with pharmacists; distrust over generics; and the inherent culture commonly observed in auto-regulated professionals.

12.4.4.1 Doctors' resistance

All participants spoke of physicians' antagonism in a variety of subjects. They acknowledged that medical professionals' opinions strongly affect the Korean drug policy process, not only planning or introduction, but also success or failure. Some participants felt that a policy, regardless of its scientific grounds, would rarely achieve the policy objectives if doctors disliked and undermined it.

I think gaining the acceptance of doctors is crucial when it comes to carrying out a policy, (p017:20)

The main issue is not about the efficiency of medical services in a healthcare system, but about getting the approval of doctors'. (p006:24)

Four causes for doctors' resistance were specified in participants' arguments. First, doctors find it hard to agree with the necessity of pharmaceutical policies to contain costs because they currently receive financial advantages by prescribing more drugs. On the issue of financial benefits, two factors were thought important – a current payment system and an under-the-table deal between doctors and manufacturers. Participants pointed out that policies aiming to reduce pharmaceutical expenditure could cause a decline in doctors' income under the current fee-for-service payment system. In this situation, many medical professionals find no motivation to behave in accord with cost-containment policies. Of equal importance may be the source of economic interest resulting from lobbying by drug companies.

The biggest problem is that doctors prescribe certain drugs because they have an economic interest in doing so. (p048:52)

I don't think doctors who had previously been getting illegitimate financial benefits by giving out new drugs or keeping changing prescriptions would change to generic prescriptions

suddenly because of a policy. (p014:36)

Second, they do not want to weaken their power over pharmaceuticals against pharmacists. Conflicts between doctors and pharmacists have been another obstacle in pharmaceutical policy-making since the Separation of Prescribing and Dispensing of drugs (SPD). Domination of pharmaceuticals may include several issues, though most participants focused on the fact that such power is likely associated with financial advantages, such as bribes or improper material support from the industry. In other words, the individual with the power of product choice is directly linked to the one receives the benefits provided by the industry. This is actually the same argument as the preceding issue. In this respect, participants considered that pharmacists also might behave similarly to doctors if they took a dominant position of power in the pharmaceutical market. This is the primary reason that participants responded negatively to generic prescribing. They argued that it would fuel an extreme dispute in society without creating any real benefits.

Since there's already too much conflict between doctors and pharmacists, I think it's best to stay neutral rather than firing them by favouring one side over another. (p047:14)

The third cause was doctors' deep-seated distrust of the quality of generics, which drives them to undermine any strategy fostering generic utilisation. Participants felt this has become an important barrier which must be eliminated very soon if generic policies are to be introduced.

I don't think people in our country, especially the service providers, still believe that the quality of generics is just good as other brand-named drugs. I think this is what is holding us back from enforcing all these useful policies that are out there. (p047:16)

In response to the doctors' doubts over the quality of generics, participants suggested slightly different causes. More participants ascribed them partly to the forged bio-equivalence test episode which happened in 2006 and partly to insufficient follow-up measures of Korea Food & Drug Administration (KFDA) after marketing. In some of the participants' responses, it was basically doctors' misunderstanding of the bio-equivalence test or their far-fetched and ill-founded arguments.

Doctors don't really believe in bio-equivalence test itself. But the thing is, you can't say that all bio-equivalence tests are completely absurd, and the scientific facts they've learned in medical school are absolutely right. (p014:36)

Fourth, doctors are likely to adopt an unfriendly attitude because of an intrinsic view that prescribing activity is an exclusive right and that new measures undertaken by the government threaten these rights. Hence, some participants felt that it might be hard to amend prescribing practices with a couple of momentary interventions because their prescribing behaviour had usually been established over a long period since their years at medical school.

12.4.4.2 Flaws in policy-making process

Another key challenge identified during discussion, was that there were some inherent flaws in existing policies and the policy-making process, possibly preventing policy programmes from being successful. In this regard, three sub-themes were established; *lack of a systematic plan*, *lack of political will* and *lack of appropriate measures to foster the utilisation of less costly drug variations*.

Respondents gave a variety of anecdotal episodes that indicated the absence of an overall strategy could lead to drug policies being less successful. Episodes included, for example, the cacophony between schooling contents and policy programmes, the failure in the introduction of a reference-pricing programme, the delayed progress of the positive list system, the dissonance among policy programmes, and the loopholes in some established programmes.

Doubts concerning the value of a prescribing budget were closely linked to this issue. In theory, participants felt that prescribing budgets might be a useful alternative to the current payment system. However, in further discussion, they were unanimous in pointing out that it might not be currently feasible because there have been few considerations concerning appropriate budget allocation both at research- and administrative-level.

I'm not sure if we are going to be able to carry this [prescribing budget] out in a short period of time. We don't really have any ideas or previous research on how to allocate the budget... I just

don't think we're ready yet. (p017:42)

Participants often concluded that the absence of systematic planning of policies resulted from the dearth of available evidence. Another example frequently cited was that there has been little guidance backed by robust evidence in pricing agreements. As a result of this, discussion between the authority and manufacturers tends to be in difficulty by being either operated under monopsony power or governed by the influence of the industry.

I've heard that there have been some cases where certain negotiations were made under such monopsony. (p006:20)

It's no surprise that pharmaceutical companies dominating that type of information draw people into their circles with their logic and reason. (p006:26)

The lack of political will seems to make the situation worse. Many participants vented disappointment when they spoke out on this issue. According to their observations, a weakened political will generated the following consequences in practice:

First, it often distorts the original proposal of policies even after implementation. For instance, according to one participant closely involved in the positive pharmaceuticals list, the master plan and affiliated economic evaluation was weakened over time by downsizing products on the must-do list as political will was discoloured by a variety of interests. Second, it prohibits programmes from being applied in practice as according to original intentions. Third, it avoids establishing policies with which powerful stakeholders such as doctors are in disagreement. The second and third aspects are well described in the following statement.

So basically, there is already a structure for this, but just not in a more concrete way. Also, they can't really do anything when it comes to the cultural aspect of medical professionals, which I think is the most vital part. (p014:39)

Participants argued that pricing-centred policies had become one of the greatest weaknesses in the current system. They recognised that the current rising trend in drug expenditure had been mainly driven by an upsurge in drug utilisation (see Annex 26h). In addition, participants felt that a product shift towards more costly drugs might

be as important a factor as volume in rising pharmaceutical costs. They suggested that the trend could be curbed not by pricing policies, but by policies encouraging the utilisation of less-costly drugs such as generics.

The problem with South Korea's current policies is that they're price-centred, controlled ones, so they keep on lowering the price anyway. But there's a limit to that. We need policies that can encourage us to use drugs, or ingredients that are not as expensive. (p006:22)

12.4.4.3 Excess profits in generic business

Thirdly, participants suggested that generic prices have remained at a premium in Korea with the purpose of fostering innovation; however, the surplus might not be put into R&D activity, but would allow manufacturers to lobby professionals to prescribe their products. Currently, a generic product can be listed on the reimbursement list only if it provides a 20~30% price cut over its brand counterpart. Under the current pricing structure, they argued, it would be more attractive for manufacturers to spend money on lobbying prescribers to augment their profits than to invest in the research and development of new drugs.

since generics are relatively at a premium price, the manufacturers continue to be in generic business for profit rather than to invest that money towards researching and developing new drugs, it's natural from the manufacturers' perspective. (p017:64)

I don't think the drug itself is very pricy. However, one of our country's biggest problems is that we tend to use drugs that are relatively high in price. This is because expensive drugs have more surpluses, which can cause illegal financial rebates in the end. (p019:24)

On the whole, these factors may not be separated, but are closely linked. Generous generic prices may produce surplus, allowing lobbying activity for prescribing excessive brand generics and/or for generous pricing. As a result, generic producers can maintain the growth of expensive generics markets and/or the pricing system allowing premium prices for generics, which produce further profits for lobbying activity.

12.4.4.4 International trade relationship

The fourth issue was related to the original industry. Participants invariably expressed

concern about the lethargic situation in South Korea. This seems to be caused by the fact that the original industry is mostly comprised of transnational corporations (TNCs). Almost every powerful 'big pharma' has its headquarters in the US or Europe where Korea has its top trade partners. The situation was broader in perspective and included other businesses, such as the automobile industry, not just healthcare.

In line with this, one participant emphasised a concern about accessibility to essential medications, giving anecdotal examples of unethical business by original producers having refused to offer their products for some years.

South Korea still doesn't have much control when it comes to certain leading products, and there's a chance that international companies might even refuse to offer their products to us. (p019:36)

Another participant testified that this situation has also prohibited the Korean government from introducing policies encouraging the use of generics because some policies can be appealed against as protective policies. For this reason, he supported a reference-pricing scheme, arguing that it might be less likely to be regarded as discrimination against TNCs because their products could be fully reimbursed by reducing prices below the reference price.

Since America has plural insurers, they tend to implement generic policies easily with thinking in the way that someone else will eventually use the brand name anyway. However, [we have a single central insurer so] if we use generic policies, then it would end up being misunderstood as protective trade policies. (p028:40)

12.4.4.5 Worries over consequences on patients

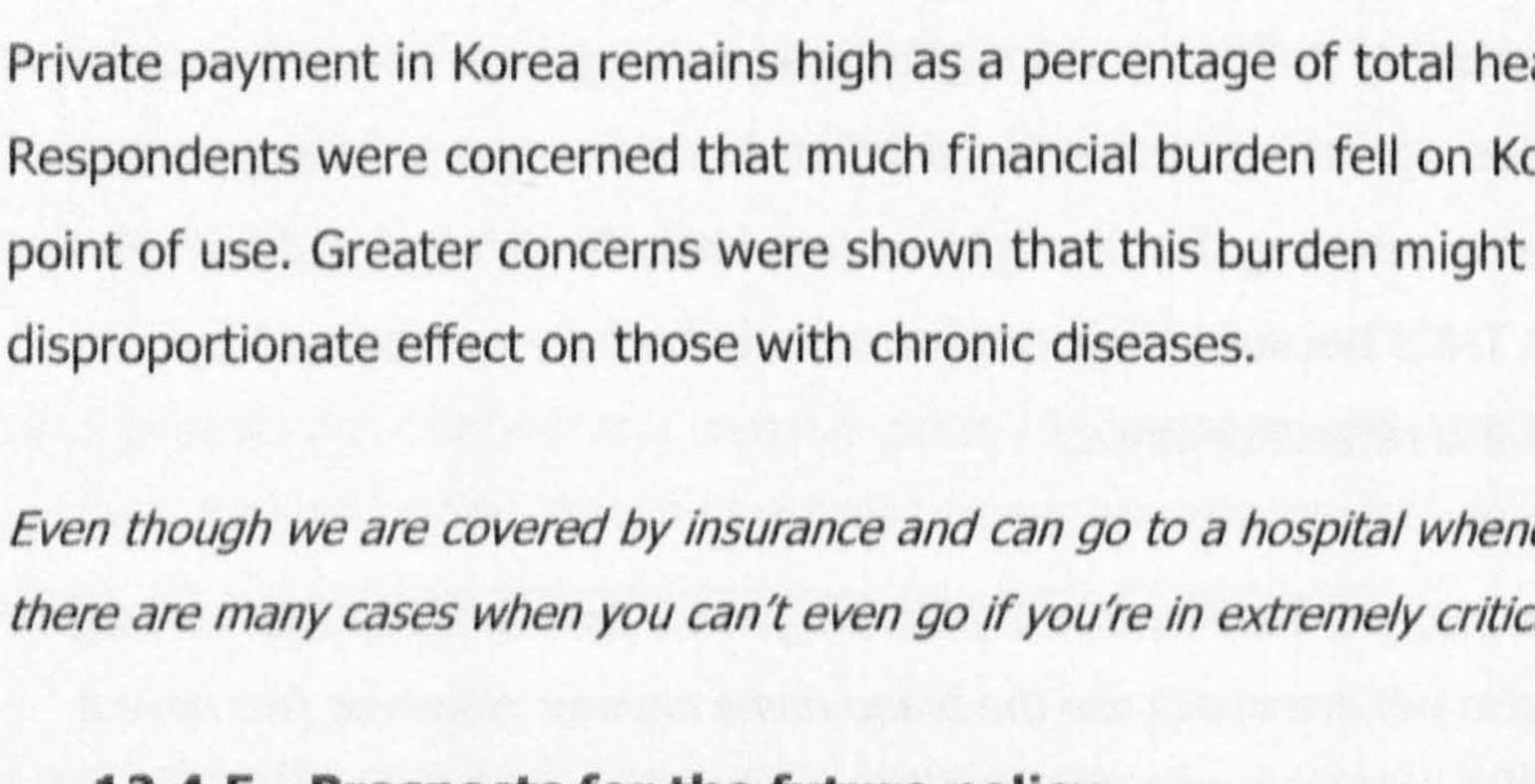
Lastly, it appeared that participants paid considerable attention to the potential consequences of policies on equity such as reducing accessibility to medication. The following remark reflects the basic thought of participants.

I think it should be the final factor that we carry out this or that which doesn't harm in consumers. (p030:16)

Participants who currently or previously were engaged with government bodies voiced

explicit opinions over this issue during interviews. Other participants expressed this in implicitly, either in the questionnaire or in interviews. Figure 12-4 indicates that participants regard equality in medication use as more important than cost control.

Figure 12-4: Should-be-tackled issues in the future policies



Private payment in Korea remains high as a percentage of total health expenditure. Respondents were concerned that much financial burden fell on Korean patients at the point of use. Greater concerns were shown that this burden might have a disproportionate effect on those with chronic diseases.

Even though we are covered by insurance and can go to a hospital whenever we have to, still there are many cases when you can't even go if you're in extremely critical condition. (p048:42)

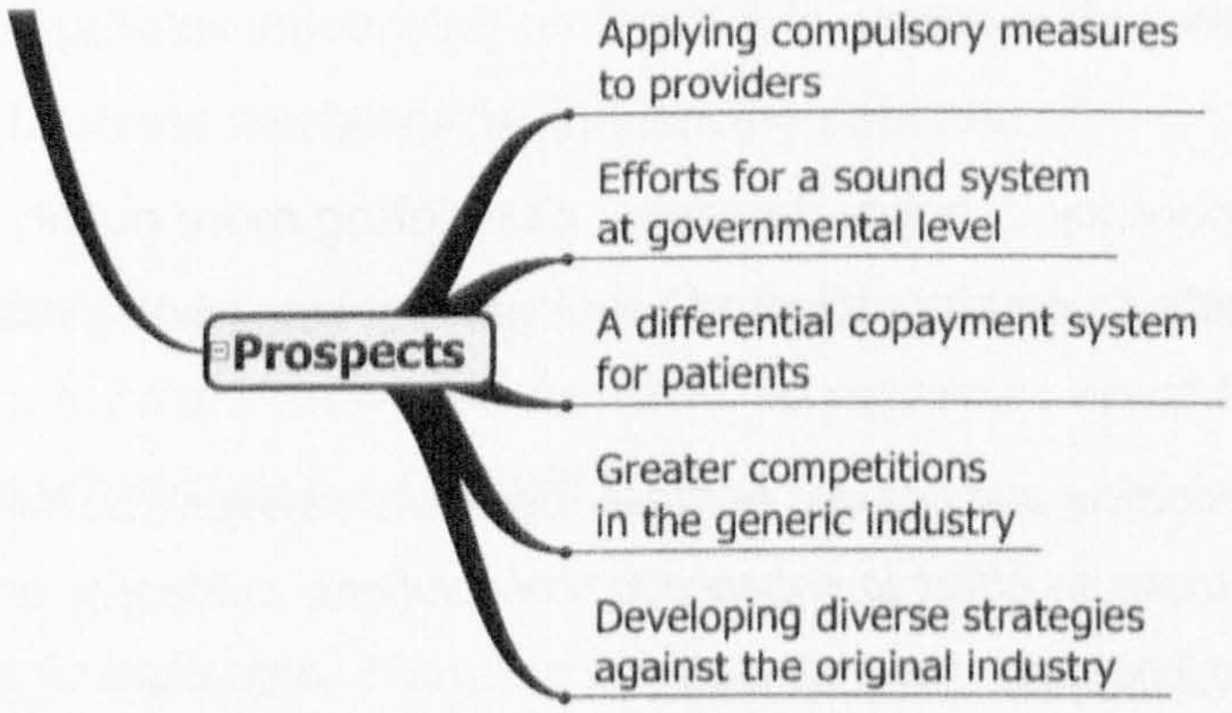
12.4.5 Prospects for the future policy

The last theme brought together ideas about the '**prospects**' of pharmaceutical policy-making in South Korea from the participant's perspective. Running parallel to the subject of challenges were the prospects for future policy. Participants' perceptions for future policy were primarily formed based on their opinions of the drawbacks in this area. Hence, participants frequently referred to challenges and prospects together.

They suggested distinctive approaches to each of the five stakeholders in the pharmaceutical arena. These included: applying more compulsory measures to providers; efforts for a sound system at government level; a differential copayment system for patients; bringing greater competition to the generic industry; and

developing diverse strategies against the original industry (Figure 12-5).

Figure 12-5: Illustration of themes: Prospects



Overall, participants felt that multiple approaches were needed. They often stressed that no individual measure would be sufficient and were keen to suggest a range of methods that would influence stakeholders in different ways. The important point that they invariably made during interviews, was a balance between influences and interests, with the prime purpose of improving people's welfare.

Whether you're a doctor or a pharmacist or a consumer, I just hope they all can at least try to understand each other instead of focusing on either their own personal benefit, or their group... (p030:57)

I think it's important for people to be open-minded and try to find what's best for our nation people. (p019:40)

Providers. Participants proposed to introduce compulsory measures applicable to healthcare providers from two main angles. First, mandatory standards could foster less-costly alternatives, as well as reducing professionals' power in product choice. Examples of mandatory standards included letting patients play a more active role in choosing, and setting a clear, pre-determined standard, such as mandatory substitution with the lowest priced product at the dispensing stage. Second, they insisted on imposing strict punitive measures not only to the industry, but also to providers, in order to curb improper relationships between them. Otherwise, they thought, it might be hard to achieve proposed policy impact, whatever they were.

Authorities. Participants felt that government bodies ought to make a greater effort

in constructing a robust system across the whole of the pharmaceutical arena. The discussions dealt with a variety of topics that should be top priority for the Korean pharmaceutical system, such as the value of evidence, trust, transparency, public funding and consideration for the vulnerable.

Among them, ideas over transparency in policy decisions, channelling more public funding into evaluation and welfare security attracted more general remarks as follows:

though this may sound a very theoretical and like one of those "Confucius sayings..".....the government should continuously make an effort to enhance logical solutions, rationality, or clarity when carrying out policies. (p006:32)

More practical dialogue concerned evidence and trust. Central to the discussion of evidence was the role of the government in establishing a system that may take comprehensive responsibility for synthesis and dissemination of policy evidence. They expected that the system could facilitate the whole process of policy-making from planning to evaluation.

I think it's important for the government to focus not only on the quantity aspect of establishing, evaluating, and promoting the policy evidence, but also on processing it in a more systematic way. (p047:4)

Among others concerns in the issue of trust, participants stressed the urgent need to convince society of the quality of generic products. They invariably argued that many generic policies could not be promoted with full confidence until a good process of quality control is accomplished. They suggested that KFDA should strengthen the standard of manufacturing practice and introduce a follow-up monitoring system. With this as a basis, KFDA must show greater confidence in the quality of generics to acquire social support.

Patients. A dual approach was suggested for controlling patient demand. On one hand, efforts should be made to enlighten patients on the issue of finite resources in healthcare. On the other, a differential copayment system was proposed, which required higher copayment for the use of symptom-relief drugs. This was linked to the concerns about social inequity, which were universal among participants. Some participants, in this respect, felt that a reference-pricing programme might help to

increase patients' price sensitivity without restricting their access to medication.

Not surprisingly, participants who were sceptical about regulating professionals – they viewed policies influencing professionals unworkable in the short term – were more likely to stress measures for influencing patients.

Technically, the most important thing to do is to place both doctors and pharmacists under control, but that's easier said than done. So consumers would be the ones who would be directly affected by it.... (p030:35)

Generic industry. Many participants strongly adhered to a direct price control, showing a deep concern about corrupt transactions in the market as follows:

I can't really think of a good way to ensure this price competition unless we get rid of all the illegal trading we discussed so far. (p048:58)

A few practical suggestions, such as a significant initial price cut and elimination of unqualified products from the market, were made to encourage greater price competition. Participants agreed that this competition included all products, regardless of originality, if patents had expired.

After patents expire, I think the price competition should be more in force. I also think -- consumers pay much more than a marginal cost on the products not resulted from the R&D just in order that such extra expenses can help maintain a certain industry--is really unnecessary. (p047:22)

Original industry. Participants generally felt there was a great necessity to develop diverse strategies in order to manage trans-national originators, but with little idea of how to go about this. Some ideas appeared to control the original industry, for example, imposing limitations on data exclusive rights, or introducing a performance-based risk-sharing scheme recently introduced in some nations such as Australia. However, in general, they failed to make pragmatic suggestions.

12.5 Discussion

In order to implement an effective strategy, it is essential to probe nation-specific factors influencing policy and policy-making, as policy outcomes can vary according to "the interactions" among those factors (Guillen and Cabiedes, 2003). This was echoed in the systematic reviews, which showed that each policy intervention was introduced with a quite different figure and produced diverse results across settings. In South Korea, despite substantially different environments in the pharmaceutical arena, there is little information on how factors interplay with the drug policies or how policy-makers determine and evaluate them. In this study, participants discussed how and why policy research has remained a neglected field in Korea, identifying three main themes: evidence; challenges; and prospects.

12.5.1 Issues over evidence

Participants have recognised the increasing need for good quality evidence in policy decision making. Whilst this need was identified, Korean policy-makers often seemed faced with limitations to the research evidence they could use in practice. Quality of available evidence is generally acknowledged as being poor and single-faceted.

One notable aspect observed during discussions was that participants tended to speak less positively about policies in which they were more closely involved. Presumably, because they, 'insiders', had greater opportunity to know about the facts and the 'negative' aspects of the case, they were more critical. 'Outsiders' may have fewer chances to do this. This may be fostered by two situations. First, the government is more likely to release favourable evidence. Second, there is scant research that deals with the negative aspects of policy that generally needs a further step analysis. This is understandable when considering the quantitative analyses in the preceding chapters. The unexpected consequences of polices – for instance, limiting patient access to essential drugs – has not been recognised in the first general analysis (Chapter 9 and 10).

Given this limitation, although participants generally expressed positive views regarding the selected policies (see Annex 26f), these might not reflect the reality of those policies. But it might be shaped by the limited available evidence, suggesting a

considerable bias in the current perceived policy impact. In line with this, the evidence they quoted frequently overlapped, implying that the source of information may not be sufficiently diverse. Whilst discussing selected policies, participants seldom cited references using a scientifically advanced analysis, but mostly gave simple aggregated numbers or anecdotal episodes. They occasionally supplied groundless or intuitional comments.

Discussions were frequently theoretical when evidence was lacking. In general, opinions on recent policy, for example the PERP, were more likely to reflect participants' expectations, rather than the real impact of the intervention. Irrespective of the programme, comments about consequences mostly concerned the shortcomings of the policy programmes themselves. Few participants spoke about the side effects of the policies on other pragmatic variables (for example, utilisation or costs in relevant healthcare services, or drug accessibility).

Faced with the limitations of available evidence, some suboptimal sources of information, such as a policy monograph mainly detailing a foreign system, remain the important tools for supporting policy decisions. Careful consideration seems to be crucial with this type of information in order to learn from "reflecting on information", not from "exotic information" (Klein, 1997; Rose, 2005). Linked to this, Wilson *et al.* (2007) argued that evidence should be considered from a broader perspective than "hard facts and figures", including judgment, opinion and belief, research, data generation, and analysis.

Throughout the interviews, it was apparent that evidence had not played a central role in drug policy-making in South Korea. Political and industrial perspectives often ruled the policy cycle. An interesting facet of this subject was that fewer participants ranked interest groups before scientific evidence. However, this does not seem to represent reality, but rather what they felt should be done or what they would try to do from a personal perspective. It became clear during interviews that participants, in fact, frequently reiterated the influence of interest groups in the drug policy process.

Strong unscientific influences may, in part, be fostered by the fact that available evidence was not sufficient to form a store of knowledge for future programme developments, more effective intervention implementations, and enlightened policy-

making. Therefore, the need to produce evidence is an ongoing issue, and is expected to continue, if the evidence gap is to be filled.

12.5.2 Challenges and prospects

Table 12-3 presents core prospects suggested by participants along with key challenges they recognised. In general, policy-makers did not just take account of costs, although overall they were in agreement that economic forces often precipitated policy changes.

Table 12-3: Challenges and prospects emerged during interviews

Challenges	Prospects
Resistance from doctors	Controlling the dominant power
	Increasing a consumers' role
	Legal discipline on illegal profits
Flaws in the process	Systematic planning
	Building proper infrastructures
Overplus in generic business	Promoting competition
International trade relationship	Making a policy strategy diverse
Potential decline of patients' welfare	A differential copayment system
	Increasing public awareness on the issue of a finite resource

It would appear that participants had experienced some of the greatest difficulties with powerful professionals, whose resistance to policy implementation might not be a situation unique to Korea. It was certain that the threat of physicians undermining an unpopular programme and choosing not to practice under certain conditions was one of the great barriers in most healthcare systems (Ameringer, 2002; Harrison and Wistow, 1993; Salter, 2004a). Also, underlying factors specified as the sources of resistance seem to overlap with findings in other settings (Brust *et al.*, 1990; Sekimoto *et al.*, 2006).

Interestingly, participants often perceived certain factors to be much stronger in Korea, including illegitimate profits, conflicts among professionals, and distrust of generics. It is unclear the extent to which such perceptions are supported by robust evidence in this study, as the discussion was mainly on an intuitive basis and little research is available that provides background information on this. Despite such limitations, it may not necessarily be groundless. The point is that such difficulties seem a vital underlying

cause why many potential policies have gone no further than the pilot stage, a typical example of which was generic prescribing. Arguments by sceptics on generic prescribing were exactly in line with the challenges stated so far, and very practical, while those from supporters were more likely to be theoretical (see Annex 26g). It is thought that opinions from sceptics may be closer reality. The reality is that the programme was severely opposed by doctors as soon as it was put into place in 2007, although only as a pilot attempt within a single hospital (DailyPharm, 2007a). The majority of doctors expressed strong concern about the safety and effectiveness of generic medicines and the role of the pharmacists who would take responsibility for product selection under the new programme (DailyPharm, 2007b, 2007c).

Suggestions from participants on how to hold back the resistance from powerful professionals can be separated into two types: limiting professional autonomy; and legal discipline. In addition, the need for a new paradigm in medical education was called for, although that voice was relatively weak.

Notably, considerations about efforts to find a point of agreement between the authorities and the professionals were surprisingly faint. Participants entered into little argument concerning the issue that reliable evidence would generate good persuasive power (Cookson, 2005). For instance, most arguments over the perception of the safety and effectiveness of generic medicines were not expanded beyond the bio-equivalence test. Many participants showed feelings of helplessness towards the misconception of the bio-equivalence test among doctors, but they rarely sought other ways of verifying the quality of generic products. Examples may include a cohort study investigating clinical outcomes from generics over several years, in comparison with those by original products, which would be more likely to be accepted by doctors who are familiar with such research frames.

Rational policy may also be impeded by complex factors such as improper policy environments, robust industry, and international trade power. The issues and prescriptions over some of these subjects seem closely linked to those concerning evidence, such as the shortage of available evidence, immature infrastructures, the presence of other influences, or the lack of resources and organising capacity. One notable point in this respect was that there was surprisingly little pragmatic discussion regarding setting societal priority, although this is particularly urgent in South Korea,

given pervasive anxiety across the whole society. In some sense, developing a sound healthcare system starts with setting an agreed priority in the use of limited resources. This can soothe tensions among stakeholders and show an easier method of finding a point of agreement when interests clash. Presumably, this is caused by the tradition of government-led development in modern Korea. In the past, society has been used to following what the decision of the authorities. Nowadays, setting societal priority is undertaken largely in a vacuum, as the government's authority has weakened and various decentralised powers are becoming stronger.

Relatively less attention was paid to measures tailored to the industry. Many participants expressed the difficulties of in-depth discussion on this subject because of a lack of understanding of industrial mechanisms. Participants perception of the generic industry was largely in line with the findings in the empirical study of this thesis (Chapter 10). Central to discussion was concern about a price bubble in generics, even with the existence of a long-lasting price regulation.

Participants invariably called for building a competitive condition in the generic market. On this issue, some writers argued that abolishing direct price control would be helpful in constructing a more competitive market in the US (Danzon and Chao, 2000; Danzon and Furukawa, 2003). Others suggested that direct price control could provide incentive to companies to develop 'me-too' products with little innovation but higher prices, or to encourage moral hazard through heavy marketing (Guillen and Cabiedes, 2003; Jacobzone, 2000). In contrast to these, Korean policy-makers rarely think that the abolition of price control is helpful to enhance competition in the Korean market. They were deeply concerned about corrupt transactions in the current market, which could distort competition under the absence of direct price controls. Their opinion is that the current pricing system for generics requesting only a small price cut from that of brand counterparts should be changed and prices should undergo a considerable reduction.

Regarding the original industry, although there was profound awareness among participants of the need to develop multi-faceted strategies towards the original industry, actual discussions were rarely noted. It was agreed that few methods would be effective to curb such a strongly profit-oriented business within a single nation. The Korean situation appears especially difficult, because the Korean economy is mainly

dependent upon international trade (Lee and Kim, 2005). Many domestic drug policies have not only been opposed by private companies, but have also undergone considerable pressure for trade talks with their home governments (Lee, 2004). A recent example is the Free Trade Agreement with the US, which offered a clear objection to the PERP (DongA Ilbo, 2006).

Participants acknowledged that social inequity was augmented by insufficient insurance benefits and high private payments. However, none of them thought copayment useless. They argued for the importance of controlling patients' extravagant behaviour on one hand while channelling the savings for the vulnerable on the other. For this purpose, participants were unanimous concerning the need for a differential copayment scheme. But, as presented in the systematic reviews, a differential system also has a weakness of reducing access to medications if it designs drug categorisation inappropriately.

12.5.3 Obstacles to evidence-based policy-making

To recap the themes, four dominating ideas were specified as obstacles to evidence-based policy-making in this particular setting: *shortage of resources; absence of systematic arrangement; lack of trust* ; and *nature of policy-making.*

The first concern was the shortage of resources. Resources ranged from a qualified workforce with training, experience or analytic techniques necessary to discern optimal strategies, to a network of individuals, organisations and relevant information (for instance, epidemiological studies on local population). These may be directly associated with the lack in quality and quantity of evidence.

Second, there was the absence of a systematic arrangement for both planning and evaluation frameworks. Since resources for a robust system as stated above cannot be established in a short time, it seems essential to organise the different activities and individuals or organisations involved in the system to work together in the long term. However, in South Korea, the conventional milieu has made policy changes that are sudden and rash. The consistency of a policy has often been ignored. The demand for policy change has been formed in a top-down manner, irrespective of evidence and then, evidence seems to have been used to justify decisions already made. Within this

environment, it may be hard to implement a systematic plan for constructing an evidence-based tradition, or set an agreed priority for resource allocation. These situations are presumably brought about by a lack of transparency and accountability in the policy cycle. Reciprocally, the transparent process can hardly be instituted without careful systematic planning.

Third, it has been brought up in all discussions that the Korean pharmaceutical arena has suffered from a significant lack of trust. The belief that illegitimate activities have distorted the market order and, consequently, there has been little adequate response from pharmaceutical policies so far was universal among participants. Doubts were raised between different professional groups, professionals and the authorities, the government and manufacturers, or policy-makers and researchers.

For instance, on the subject of doctors' resistance, the participants remarked on doctors' distrust over pharmacists, quality control of generic products and policy itself as underlying causes on one hand. On the other, they voiced their own doubts about professionals, expressing the perception that undisclosed interests were a source of policy resistance. While it is inconclusive in the present study how significantly such doubts can be supported on scientific grounds, it becomes clear that distrust is linked with the transparent process of policy-making.

The final idea participants kept returning to in all themes was to the nature of policy-making. To some degree, they acknowledged that it was unavoidable that policy decisions could be made differently from what the evidence suggested. As stated several times throughout this thesis, policy-making is an activity influenced by many internal and external factors that comprise political, social, cultural and economic aspects. Hence, it is thought that the central trait of policy-making is to find a way to balance interests and influences from a variety of perspectives, which may not always be rational. This means that scientific evidence is part of the decision but not the whole – and worse, is often less robust than other factors. Even though this was admitted in full, it was invariably testified in discussions that other considerations beyond scientific evidence were stronger than necessary in South Korea. Possibly this severely reduces a general perception about the significance of evidence-based policy-making, as well as sound research. Consequently, there seems to be a gap where bias from outside can enter the policy process.

These premises largely overlap with findings in an earlier study that systematically reviewed barriers to the use of evidence by policy-makers (Innvaer *et al.*, 2002). The authors argued that barriers were "the lack of timeliness or relevance of research", "mutual mistrust", "power and budget struggles", "poor quality of research", and "political instability or high turnover of policy-making staff". The idea of systematic arrangements in this study indicates the breadth of the concept – ranging from policy-making to evaluating, while "political instability or high turnover of policy-making staff" focused more on policy-making. Dialogue about personal contact between researchers and policy-makers was not apparent in this study, unlike other articles (Choi *et al.*, 2005a; Innvaer *et al.*, 2002; Sharpe, 2004; Soumerai *et al.*, 1997; Wilson *et al.*, 2007). This may partly be due to the absence of evidence; any available body of knowledge may be still weak and insufficient to notice whether the policy-makers and scientists disagreed.

Unfortunately, in Korea, the milieu for 'evidence-based' policy may not be easy to realise in the short term, since the underlying causes of the current situation are largely the result of a long-lasting and stubbornly held tradition. In order to diminish the tradition, and to build a positive atmosphere for evidence-based policy-making, live debate should be encouraged more often, in order to raise social interest in this area.

12.6 Study limitations

There are some limitations to the study. Firstly, it was designed with a small, selective sample of policy-makers from a limited number of organisations and mostly with a background in pharmacy. This was, in part, a consequence of the snowballing sampling technique used. Participants identified by this technique were necessarily within personal connection networks and more likely to have homogeneous characteristics. This certainly limits the generalisability of the study. However, the present sample is regarded as typical of policy-makers involved with pharmacy policy, given the culture for allotting duties in government bodies in Korea – a person with a background in pharmacy is more likely to be involved in pharmaceutical affairs. Moreover, there was little evidence in the data that their academic background circumscribed their views to any degree. Rather, they expressed a wide range of opinions, giving the researchers a much better understanding of the process from the themes that emerged from the

data.

Secondly, the participants tended to have a range of perspectives based on their experiences. Some spoke distinctly personally, others appeared to see themselves as spokespersons for others in a similar situation or in their organisation. Some addressed topics, frequently reflecting back to their own experiences, while others took a more abstract view and dealt with questions from a theoretical standpoint. Many participants appeared cautious about making comments on record that would end up in the public domain, which potentially made their comments more abstract.

Thirdly, the questionnaire employed for this study created some further issues. It was certainly helpful in reducing the time spent on interviewing by quickly getting to the point of the discussion. However, it put up certain limits to discussion, even though it was used solely for the purpose of initiating dialogue in this study. For example, it sometimes impeded participants from discussing issues more deeply and in an extensive context beyond the examples displayed in the questionnaires in issues concerning potential influences or possible future policies. In addition, some differences arose from vague understanding of the intrinsic purpose of inquiries in the questionnaire.

To the best of my knowledge, this is the first study to investigate Korean pharmaceutical policy-making in a qualitative manner. This exploratory study has identified many of the issues involved in pharmacy policy decision-making for those individuals who occupy these roles in Korea. The issues identified here could serve as a platform for future research – both qualitative and quantitative, that could explore any of these themes in greater depth and across different policy-making contexts.

Given one of the advantages of mixed methods that a qualitative research is a useful tool to explore the reasons behind the quantitative findings, this thesis would benefit from addressing what caused patients to reduce their utilisation of antihyperlipidemics after the copayment increase (Chapter 10). The limitation of time and relevant data identifying proper interviewees for this aim did not permit this in the current study. Further qualitative exploration is recommended to address these questions.

12.7 Summary

Through in-depth interviews with eight policy-makers involved in the pharmaceutical arena, this study found four potential factors hampering evidence-based policy-making in the South Korean context: the shortage of resources; the absence of systematic arrangements; the lack of trust; and the nature of policy-making. The key challenge may be the apparent lack of available evidence. This has been caused by several features, such as a scarcity of qualified researchers and background knowledge, or the absence of coordinator. Some strong influential factors arising from the study confirmed the presence of policy-based research environments in Korea. There were also some concerns about the quality of evidence currently available, since most of them remained at the stage of theoretical or superficial information. Discussion on the impact of current policies confirmed that evidence investigating policy consequences has certainly been neglected, creating some bias in the perception of policy-makers.

The awareness of the need to move towards an information-based and outcome-oriented strategy is increasing among Korean drug policy-makers, as policy decisions have been affected by more decentralised powers. The role of the central government was claimed to set the tradition of evidence-based policy-making by arranging policy planning and evaluating in a systematic manner. So far, interests over building up the store of reliable information or setting priorities for policy decisions have been weak across the whole society. Stimulating social debates in this field seems crucial to improve the current situation. Good research can, of course, stimulate this debate. Thus, the need to produce high-quality evidence is ongoing, and is expected to continue in South Korea.

PART 4 CONCLUSIONS AND PROSPECTS FOR THE FUTURE

CHAPTER 13: CONCLUSIONS AND FUTURE RESEARCH OPPORTUNITIES

13.1 Introduction

This thesis began with three questions:

- What is known internationally about the impact of policy interventions in the pharmaceutical market?
- What has been the effect of Korean pharmaceutical policy interventions?
- What are the contextual factors creating gaps between evidence and practice, and the challenges of evidence-based policy-making in the Korean pharmaceutical market?

To find answers to these questions, the study has been accompanied by three core concepts – mechanism, context and outcome, suggested by Pawson and Tilley (1997) for 'realistic' policy evaluation.

Chapters 1 and 2 were devoted to shaping the research agenda, which presented a general background of 'mechanism' and 'context' of interest in this thesis. The first chapter briefly introduced evidence and the causes of market failure in the pharmaceutical sector from a welfare economics perspective. This demonstrated that the prime reason for pharmaceutical policy is to control the factors that make the pharmaceutical market fail. This was followed by a general introduction to public regulations which strive for cost control, efficient and equitable allocation of resources in this market.

Chapter 2 first outlined the salient environments that are seen in South Korea, and the perception that policy impact is contingent on nation-specific conditions. This led to a related argument that there is a pressing need for evidence-based policy-making in each setting to lessen uncertainties originating from divergences in contextual factors. In order to build sound scientific grounds for policy-making, it is essential to evaluate policy outcomes with empirical data from individual settings, accompanied by study of international experience. In this regard, Chapter 2 also explored scientific tools for

policy evaluation in general, and specifically those relevant to this thesis.

From Chapters 3 to 7, the effects of international pharmaceutical policies were explored in systematic reviews of published studies. In conducting this review, it was important to acknowledge the set of general mechanisms through which pharmaceutical polices work across nations, to understand the original contexts in which policy mechanisms were successful or failed, and to learn lessons for Korea and for this thesis.

Based upon findings from the systematic reviews, empirical investigations were conducted in the third part of the thesis, from Chapters 8 to 12. Firstly, Korean pharmaceutical claims were investigated in a quantitative way to examine the actual impact and consequences of two recent policies. This gave an opportunity to discuss similarities and differences between policy outcomes in the Korean context and from the results of the systematic reviews.

Finally, in-depth interviews were conducted with Korean experts who are closely involved in the pharmaceutical policy cycle to explore potential contextual factors that result in gaps between evidence and practice. A primary focus was on revealing contextual challenges in evidence-based policy-making in the Korean pharmaceutical market, in order to improve future decision-making.

In this concluding chapter, the following issues are discussed:

- reflection of the methods used in this project;
- key findings and implications from the main chapters;
- strengths and weaknesses of this project;
- recommendations for Korean pharmaceutical policy;
- knowledge gaps for future research;
- concluding remarks.

13.2 Reflection of the methods used in this project

In this section, the methods used in this thesis are discussed critically with a focus on the types of problems that other researchers in the field of pharmaceutical policy research may encounter when conducting similar evaluations.

The systematic reviews provided a good foundation for the empirical research conducted. However, by only selecting three robust study designs this may have lost information that was more relevant to the local study setting of the empirical exploration. Within the systematic reviews, the synthesis of information from such diverse studies was challenging due to the heterogeneity between studies, not only in policy environments but also in measurement units and concepts of each study.

Policies are often introduced without thought to how they could be evaluated, and interrupted time series analyses are often employed to evaluate such interventions retrospectively. The main challenge with this approach is obtaining sufficient numbers of observations for analysis. Insufficient observations create a number of problems, especially for analytical techniques. As the researcher is often unable to control when a policy is introduced, or indeed when the next policy is introduced, then it is not always possible to obtain a large enough sample to provide robust results.

Within this thesis an autoregressive integrated moving average (ARIMA) technique could not be used as the primary analysis due to a shortage of time points after the interventions, but the number of data points did allow use of segmented regression. Although segmented regression is used often in pharmaceutical policy studies, it has one important limitation relating to the assumption of independent error terms. Hence it is important to test and correct, if necessary, for autocorrelation. The Durbin-Watson d-statistic, is one such test that is used to detect autocorrelation, however, there is no consensus on the most appropriate technique to address autocorrelation. One approach to correct for autocorrelation is to use a generalised least squares estimator, such as the Prais-Winsten estimator. The Prais-Winsten estimator, used in this thesis, is a method used to correct for first order autocorrelation. Whilst first order autocorrelation is the most frequently occurring type it is possible that higher order autocorrelation may have been present in the data and this may have led to misspecification of the model. Although it is worth noting that while other possible scenarios of autocorrelation (e.g. higher order autoregressive structures) could potentially arise, they are much less likely to occur when using real world data.

With these potential limitations of segmented regression, within this thesis, the ARIMA approach was chosen as a sensitivity analysis to check the robustness of the results

and conclusions drawn. ARIMA was chosen as it was the one of the most commonly used techniques in pharmaceutical policy studies, as highlighted in the systematic reviews. The experience gained from undertaking the ARIMA analysis identified that the best fitting models from the overall diagnostic results still produced spurious appearances in some of the residual analysis graphs, which required a close examination of competing models to determine the intervention effect. Although the coefficients from the models varied somewhat, the direction and significance of the results remained robust across closely competing models, which provided more confidence in the outcomes from the segmented regression analyses.

When comparing the two techniques, segmented regression was more useful than ARIMA given the complexities involved in specifying the ARIMA models and in interpreting the results. Upon reflection, since both methods of analyses gave similar results it may have been sufficient to only undertake segmented regression analysis. However, the experience gained from undertaking both segmented regression and ARIMA analyses would lead me to conclude that both techniques were required for the datasets used in this thesis. No method could be completely advocated but undertaking both analyses led to more confidence in the results. This approach is recommended to other researchers in the field facing similar data issues.

Qualitative methods were used as a contrasting, but complementary, approach to penetrate the subject of evidence-based policy-making in this thesis. It tackled the contextual issues surrounding pharmaceutical policy in South Korea, which is a subject that has been addressed rarely by quantitative or qualitative exploration in a comprehensive way.

The questionnaire that was undertaken prior to the qualitative analysis was useful in a number of ways. Firstly, it was helpful in distinguishing between potential interviewees. For example, eligible information-rich personnel could be distinguished from administrative personnel or those who held less relevant roles in the policy cycle. Secondly, it assisted the researcher to have pragmatic information about individual participants and to build interview questions that were more pertinent to each participant. Thirdly, it led participants to have a greater understanding of the purpose and scope of the study. This may have limited the scope of discussion and if probed deeper on other subjects may have led to different insights. Upon reflection, the

qualitative research was worthwhile undertaking and provided a greater understanding context of pharmaceutical policy-making, which could not have been gained through using quantitative methods alone.

13.3 Summary of findings and implications

13.3.1 Evidence of policy impact across nations

Following a thorough electronic search strategy, 176 studies were identified and reviewed systematically. Structured assessment of drug policy studies raises complex issues regarding the validity, generalisability and transferability of specific research findings.

Throughout, common challenges have been found across studies. All findings were subject to the limitations of available data and largely restricted to short-term and aggregate values. Although the reviews included only robust randomised controlled trials (RCT) and quasi-experimental designs to increase the validity of results, studies generally had much room for improvement. For instance, in RCT studies it was often unclear whether randomisation had been done properly; controlled before and after (CBA) studies occasionally failed to offer appropriate information about their study and control groups; and interrupted time series (ITS) studies had been limited by the quality of data sources. The quality of studies were slightly better in RCT studies and more varied in ITS studies, but the differences were not great and, in general, studies were of moderate quality. Studies concerning cost-sharing/ reimbursement restrictions were in particular of mixed quality; those concerning educational interventions/ tiered formularies/ reference-pricing schemes were generally rated as moderate quality; those addressing incentives were rated as moderate to low quality. Overall, the included studies were of very mixed quality, with little apparent association between quality rating and direction or strength of results.

The three systematic reviews, focusing on policies targeting patients, prescribers and industry, highlighted that existing rigorous evidence is also limited in quantity. The paucity of evidence was discerned in three aspects: intervention; setting; and outcome measure. The reviews found that existing robust evidence about the impact of pharmaceutical policies is directed to a small range of interventions: cost-sharing

programmes; educational approaches; North American reimbursement restrictions; British fundholding; and reference-pricing schemes. Most evidence was produced within limited settings. Strikingly, 78% of included studies came from five countries – Canada, Spain, Sweden, the UK and the US. Almost no studies came from countries comparable with South Korea. Two studies exploring the Korean separation of prescribing and dispensing (SPD) were excluded as a result of unreliable methodology. Outcome measures of interest concentrated on the effects on drug utilisation and public expenditure after policy changes. Evidence about policy consequences on drug accessibility, private expenditure and other service utilisation occasionally appeared. Very few studies examined health outcomes, and of those that did, most employed surrogate outcomes. Thus, the causal relationship between pharmaceutical policies and health remains unanswered.

Another factor limiting the generalisability of findings was that even a single policy has a range of different structures across settings. Consequently, a large divergence was found in policy outcomes. A number of factors influencing drug policy appeared repeatedly, including therapeutic classes, intensity of the policy changes, patient-specific situations, market surroundings, characteristics of providers, concurrent policies, and some methodological factors. Additionally, a large number of underlying factors influence policy details, for example, determinants of clustering in reference-pricing, but extracted data from included studies did not allow these to be distinguished.

Thus, it is difficult to interpret policy impact without ambiguity for most settings. Nevertheless, some regularity about pharmaceutical policies was seen, which offered implications for this project and for South Korea.

Firstly, policies focusing mainly on restricting patient demand may be harmful to equity and health. Although some are carefully structured to reduce unnecessary utilisation or to facilitate less costly utilisation, they can still be a threat to socially disadvantaged populations who generally show greater price elasticity of demand in response to increases in out-of-pocket payments.

Secondly, policies aimed at improving prescribing behaviour seem to have an impact on improving efficiency in prescribing profile without compromising equity or health, if

they are supported by providers and well-designed information with good grounds. However, improved prescribing profiles may control total expenditure to only a limited degree.

Thirdly, price control alone is rarely linked to success in cost containment. Jacobzone (2000) viewed this as the result of direct price control encouraging firms to seek "bypass" strategies such as 'me-too' innovation or increasing the volume of sales. Reference-pricing, as an indirect way of drug pricing, has been increasingly implemented to reduce costs by fostering price competition. However, it is unclear whether reference-pricing schemes achieve the intended objective in existing studies. Rather, they appear to produce similar outcomes and consequences to cost-sharing programmes.

Fourthly, therefore, greater attention has been paid to the promotion of cost-effective use of drugs. In this respect, policies encouraging the use of generics have been attempted in a variety of areas. However, it has become obvious that generics can be a 'cost-effective' option only if they have clinically interchangeable quality, sizable market share and lower prices.

Lastly, careful consideration of the possible consequences followed by complementary policies may improve policy results by reducing adverse effects. Here, 'possible consequences' vary considerably by local factors. It seems vital for a better future to make a careful exploration of potential local influences before policy change and to examine the actual outcomes after their introduction.

13.3.2 Evidence of policy impact in a local setting

To explore the actual effects and consequences of Korean pharmaceutical policies, 66 months of Korean pharmaceutical claims were investigated. Two recent policies, the Pharmaceutical Expenditure Rationalisation Plan (PERP) and the new cost-sharing programme, were examined using an ITS design in Chapters 8 to 11. While the PERP is a comprehensive policy package including four different sets of measures, a price control measure was mainly explored owing to the delayed implementation of other measures. Quantitative investigation was followed by a qualitative study that explored contextual barriers to evidence-based policy-making in a local setting. Semi-structured

in-depth interviews were conducted with eight core personnel who were either policy-makers or influential experts affecting policy-makers. During the interviews, participants discussed how and why pharmaceutical policy studies have remained a neglected field in South Korea.

The empirical research supported and clarified the messages from the systematic reviews. Quantitative investigation revealed that the new cost-sharing scheme might achieve the objective of cost containment to a limited degree, while the price cut did not appear to achieve any of its intended effects. In response to rising private expense, Korean patients were likely to reduce drug use not as a result of clinical need, but out of financial anxiety. Little evidence was apparent that supported the cost-conscious behaviour of patients owing to the copayment increase. The copayment increase was likely to have achieved only a marginal policy effect, while increasing social inequity by discouraging patients from access to essential medication in some conditions. For example, copayments apparently had little effect on patients' access to antihypertensives. By contrast, copayments were associated with a reduction in patients' access to antihyperlipidemics, that are generally more expensive than antihypertensives in the Korean market. This raises concerns not only for long-term health consequences, but also in long-term prospects for healthcare spending.

The sensitivity of demand to price increases shown in the antihyperlipidemics market was unexpectedly large in Korea. Utilisation trends fluctuated according to policies – use went up after the price cut and down after the copayment increase. Further sub-analyses demonstrated that patients with generic antihyperlipidemics might present an instant response to copayment changes, in comparison with the prescribed brand-named products, which showed a gradual effect. The most plausible explanation of the responses may be financial worries among patients who might be in the less privileged strata of society. International experience suggests that copayment increases show little direct influence in patients with chronic conditions except in those from the socially disadvantaged group. Given the conditions of pre-existing high levels of copayment in Korea, in this regard, Korean patients under financial pressure have been more likely to feel the burden of needing costly long-term medications, to take generic products and, thus, to be influenced more by cost changes. In addition, misconception about the new cost-sharing programme might in part influence a fall in use.

Another important feature uncovered in this thesis was that the gap between value and volume of generic share has been maintained at around 10 per cent in two chronic medication markets in Korea over more than 5 years. Two explanations were suggested by Korean policy-makers in the qualitative exploration. First, the level of generic prices has been determined generously just slightly below than that of brand-named counterparts in the Korean market. Second, among generics, expensive branded-generics have been more likely to be used.

These might produce excessive profits for generic businesses and foster manufacturers concentrating on maintaining their generic market share by commercial marketing activity or me-too innovation. Two recent studies similarly demonstrated that direct price control might reduce generic competition and maintain generic prices at a higher level than would result in a competitive market (Huh *et al.*, 2006; Shin and Choi, 2008). One branch manager of an international pharmaceutical company pointed out that original manufacturers often did not cut their prices even after going off patent in the Korean market because their products were still competitive with their generic counterparts (DailyPharm, 2005b). This finding implies that savings from generic utilisation may not be considerable in the Korean market in spite of a sizable volume share of around 30~50%. In the successive qualitative investigation, Korean policy-makers have generally confirmed the weaknesses of existing policies suggested by the empirical analyses of this project.

13.3.3 Contextual issues and challenges of evidence-based policy-making

So far in Korea, not only the two policy interventions examined in this thesis, but also other major pharmaceutical policies (including the Best Prescribing Project or pharmacist incentives for generic substitution) have shown few of their intended effects. Many policy efforts (such as generic prescribing, reference-pricing, or incentives for saving prescribing costs) have hardly progressed beyond theoretical debates or pilot trials. The qualitative investigation showed that a complex set of local factors has challenged the development of optimal policies. Most of all, government policy has not been supported by medical providers, and has often faced severe resistance from them. The situation has been aggravated by a weak political will as well as by poor science to support policy change.

Korean policy-makers discussed the possible causes of the lack of success and suggested the following as the major weaknesses of the current system:

- lack of scientific grounds, expertise, experience, or resources for policy decisions and implementation;
- lack of measures to amend prescribing behaviour;
- defects in the Korean generic market;
- a weak position of Korea within the global pharmaceutical market;
- insufficient policy attention to patients' welfare.

From the policy-makers arguments, four main themes emerged that might explain the gap between evidence and policy in this particular setting despite the clear awareness of the shortcomings among policy-makers. They were *the shortage of resources, the absence of systematic arrangements, the lack of trust* and *the nature of policy-making*.

In the background, I argued that the shortage of evidence has been a hurdle to the decision-making process in South Korea. This thesis has demonstrated that the lack of knowledge in Korea not only reflects a shortage of scientific knowledge from research, but also suggests the absence of a knowledge-building system. Relevant resources are lacking, which include tangible and intangible elements such as human resources, experience and expertise, a systematic network amongst people and/or institutions, and appropriate information support and dissemination systems.

In the last decade, resource constraints have been apparent in the Korean healthcare system. Faced with similar concerns to those of rich nations, Korean pharmaceutical policies are evolving rapidly, and tend to follow international trends. Unfortunately, efforts as well as time have been lacking to create a social consensus in crucial issues such as priority of healthcare resource allocation. This weakens the authority to introduce policy interventions or implement them properly after introduction.

Without the development of a supporting social system and knowledge base, hasty policy change has apparently raised social distrust and tension between the authorities and professionals. Rowe and Calnan (2006; p390) suggest that the lack of trust renders people to have a "belief that others might harm us", which requires constant

monitoring, prescriptive regulations, intensive supervision, and/or risk aversion. The policy cycle inevitably becomes unhealthy in these social environments. On one hand, widespread distrust and policy resistance has impeded the introduction of some interventions controlling prescribing behaviour. This keeps Korean policies controlling patient demand or drug prices, which potentially results in deteriorating social equity and market competition. On the other hand, they undermine the development of a fundamental atmosphere for evidence-based policy-making, coupled with the knowledge deficit.

13.4 Strengths and limitations

This project has several strengths. By including three robust research designs, the reliability of outcomes from systematic reviews was improved. In quantitative analyses, credibility was much improved in two aspects: 1) by crosschecking analysis results through two statistical tools; and 2) by constructing long-term time series compared with the former Korean studies. In addition, two-layer analyses – overall and therapeutic subgroups – provided a unique chance to obtain insight into Korean market conditions. The strength of this research is most evident in the multidisciplinary and applied nature of the research, using both quantitative and qualitative investigations to focus on a single project. It is increasingly recognised that both quantitative and qualitative studies have clear limitations on their own, but are able to corroborate one another through compensating for the weaknesses (Denscombe, 2007b; Pope and Mays, 2006). Two heterogenic methods found several well-matched issues, which definitely enhanced the validity of the findings. Moreover, in-depth interviews expanded the subjects beyond those able to be addressed with quantitative data. Furthermore, they formulated good grounds for the researcher's arguments, which was troublesome owing to the lack of existing relevant studies.

However, this research also has some limitations. Most of them have been already discussed at the end of each study. The important issues are recapped here for the purpose of summarising, along with those of the whole project.

The systematic reviews have shortcomings as follows. Firstly, they were conducted by one reviewer, so could be viewed as subjective in some quarters. This was reduced as much as possible by setting all criteria clearly in advance. Secondly, it included only

two electronic databases, which might not be sufficient to identify all relevant studies. To lessen the loss of potential studies, a comprehensive hand-search was carried out with references from relevant reviews. Thirdly, potentially worthwhile studies could be excluded by the inclusion criteria that limited to well-controlled studies.

The empirical analyses have the following limitations. First, they employed pharmacy claims, which made it impossible to investigate patient-level changes after policy interventions. At the beginning of the project, the plan was to analyse patient-level data taken by hospitals, but data was not made available to permit this. Second, exploring the long-term results of the SPD was also planned but this was not possible as data before 2003 was unavailable. Third, all findings need to be qualified with a longer-term examination. Fourth, caution is required regarding the generalisability of findings for two chronic medications to other therapeutic classes. Finally, caution is needed to generalise qualitative findings beyond the study population, although participants were thought a typical group closely involved in Korean pharmaceutical policy-making.

13.5 Recommendations for Korean pharmaceutical policy

First, policies limiting patient demand such as cost-sharing seem to sacrifice equity for only a marginal reduction in pharmaceutical costs in Korean society. The intention that the copayment increase based on prescription costs might mainly affect patients with less-essential drugs was not realised. In this regard, prescription costs as an indirect indicator of discretionary utilisation may not be appropriate. Explicit guidelines are helpful to achieve the policy aim. For example:

- Providing a clear list of the limited drugs such as that in differential copayments programmes (including reference-price systems), prior-authorisations or step-therapy approaches is worth considering because it can achieve selective reduction in less essential consumption, compared to a fixed rate of copayment.
- Providing accessible information directly to patients can be another option. One interesting and practical suggestion from previous research is worthy of introducing here. Yoon (2008) proposed the indication of differences between a prescribed product and a possible lower-priced alternative in prescription (or dispensing) receipt to alerting price consciousness.

Second, the importance of generics needs to be augmented given that new and expensive drugs lead the growth of expenditure inflation. In South Korea, however, before going further to a fully-fledged generic policy, the generic market must be revisited to ensure that a policy change results in containing costs effectively without compromising quality and equity.

- There is an urgent need to clarify the definition of generics, to set up classification parameters and to develop a database capturing the market performance of generics.
- It is problematic to maintain the small price gap between generics and brand-named drugs. Cutting generic prices substantially and restoring price competition are two prerequisites for improving the performance of generic policies. One previous study found that the price variation within a single active ingredient is significantly large, between 40 and 70 per cent and suggested the removal of price differences by cutting generic prices equal to the least priced product unless it sacrifices quality (Yoon, 2008).
- A breakthrough reform is required in the current bio-equivalence validation programme (BVP) toward reducing the rate of dependence on data from manufacturers and strengthening the watchdog system after passing through the BVP. In the local market, the most fundamental issue for reducing generic policy resistance is definitely interchangeability of generic products from the clinical point of view. One study reported that cheaper generics occupy a smaller market share in the Korean market (Shin and Choi, 2008), reflecting a social view on generic products in some quarters, i.e. the lack of confidence about the quality of 'cheap' generic products. This is in line with the finding of this study suggesting the tendency to increase the use of expensive medications after decreasing prices. Some local clinics advertise themselves as giving high quality pharmaceutical care by quoting the results from the authority assessing them as a high spender.
- Alternatively, first-line therapies can be effective options in achieving cost containment as well as quality of care. For example, adhering to evidence-based guidelines may achieve considerable savings in the treatment of high blood pressure that has well-established prescribing guidelines (Bradford *et al.*, 1999; Fischer and Avorn, 2004a).

Third, it requires steady as well as urgent building of a knowledge base. The empirical findings from both quantitative and qualitative studies continuously exhibited the paucity of available local evidence in South Korea. To extend knowledge, the following needs have to be noted.

- Fundamentally, a qualified workforce needs to be developed. However, developing a qualified workforce will take time and so must be accompanied by efforts to seek the most cost-effective way of utilising present human resources. Examples may include networking academic institutions. This can facilitate sharing of expertise among professionals and integration of inter-professional teams and in so doing, be the basis of multi-disciplinary approaches, which are increasingly valuable in social sciences.
- The existing data on pharmaceuticals should be expanded to a store of basic information (such as local epidemiological data and cost-effectiveness data). In addition, variables reflecting real diagnoses, case-mix adjustment and biological measures of morbidity (e.g. blood pressure, cholesterol level, and/or side effects) must be developed.
- The objectives of research require diversification to explore the negative aspects of policy interventions. For example, the quantitative investigation of this thesis demonstrated potential policy consequences in therapeutic subgroup analyses, but not in analyses with overall pharmaceuticals.

Fourth, to overcome the weaknesses of the current system uncovered by the qualitative investigation, greater efforts should be made to reach a consensus on 'trade-off' between efficiency and equity, costs and quality, or health and wealth. It is also necessary to make an agreement about the objectives and the desired outcomes of interventions prior to policy change. Without a shared view on public resources among the members of society, any good interventions can be overwhelmed by 'bypass' strategies striving for private profits in the market. Making a consensus can be facilitated by the following:

- Open discussion is required to set social priority in resource allocation, which is lacking even among policy-makers engaged in the interview. Recently, cost-effectiveness is increasingly stressed as a priority by the Korean authorities, though this is challenged significantly by the lack of credible economic evidence (Choi,

2008; Lee *et al.*, 2005). Without the support of credible economic evidence, the result may be inferior quality of care or the augmentation of overall costs if cost-effective items are restricted merely owing to expensive prices. On this issue, the establishment of the National Evidence-based Healthcare Collaborating Agency (NECA) offers the prospect of a more systematic discussion of priority issues at a national level. Hopefully, this will play a vital role in developing principles for assessing the cost-effectiveness of new drugs and treatment. Additionally, it would be beneficial to expand its scope to explore policy cost-effectiveness in the not-too-distant future.

- Communal values need to be disseminated to the members of society. In particular, medical students (including other professional students) and trainee doctors need more opportunities to understand the complex issues and dilemmas of the healthcare arena (such as finite resources, prioritisation, and cost-effectiveness) given that most professionals practice privately after graduation. It may therefore be worth developing policy options to alter prescribing practices striving for cost-effective medications in major teaching hospitals, because Korean doctors are likely to establish their prescribing behaviour in the residency period (Kim, 2005). It is also important to provide patients with information about a resource-limited world because enlightened patients can create an important new source of legitimacy in formulating social consensus on healthcare issues.
- Although there are limitations in making policies solely based on evidence, the importance of scientific evidence must not be undermined. A body of evidence provides standards for the decision-making process, through which the process becomes more transparent by being able to show explicit reasons for decisions (Daniels and Sabin, 1997). This can strengthen decision-making, weaken the top-down tradition, and minimise policy consequences. Fair decision-making will improve the credibility of the system and be a good way of restoring social trust.

13.6 Future research opportunities

The systematic reviews highlighted a large knowledge gap in pharmaceutical policy evaluation studies. Overall, most policy interventions have been under-researched, except for a small range of interventions described above. Except in a handful of settings, most nations have neglected evaluation of their pharmaceutical interventions. Long-term outcomes of policy interventions are generally unknown. There is a lack of

focus on the negative effects of policies, which should all be listed and publicised. Above all, studying the association between pharmaceutical policies and individual patient outcomes appears warranted.

Few researchers appear to be interested in the possible different clinical effectiveness between original and generic products, while interests in generic policies are increasing. It may be interesting to explore outcomes from brand versus generic drugs with long-term cohort studies. Cost-effectiveness studies of policy changes are thought valuable in programmes with high administrative costs. Further exploration into the relationship between the characteristics of prescribers and outcomes of budgetary constraints would be extremely useful.

Empirical studies of Korean pharmaceutical policies raised a number of issues that warrant further exploration. Causes and longer-term effects of reducing essential drug use should be tackled at the individual level. A closer investigation into why the utilisation of antihyperlipidemics was more susceptible to policy changes, and who actually reduces drug use in socially disadvantaged groups, appears urgent. Studying other therapeutic sub-classes is recommended. Given the objectives of the new cost-sharing scheme, it may be interesting to examine if the policy influence in symptom-relief and chronic medications operates differently. Further analyses employing market price data deserve attention to verify the real impact of the new pricing programme. Lastly, qualitative investigation must be expanded and balanced by addressing other perspectives, for instance, those of prescribers, industry and the general population.

Future research should strive to improve methodologies including the development of standards in the realms of outcome variables. Relating to this issue, the credibility of Korean databases needs to be quantified.

13.7 Concluding remarks

Confronting mounting financial pressure on healthcare budgets, multifaceted strategies are increasingly adopted in the pharmaceutical arena in particular by the developed world. Throughout this thesis, it becomes clear that there is no 'holy grail' of pharmaceutical strategy for any local setting. Often, interventions have not produced equivalent effects in different settings. The policy cycle is influenced by a variety of

factors and policy effects are the results of interactions of those factors. There will always be dilemmas in balancing the needs from various stakeholders and viewpoints that may show a considerable divergence according to local environments. Policy-making is often about political decisions concerning affordability and appropriateness and, thus, a political value at the time of formulation is frequently a primary determinant of policy change. Scientific evidence is not the prime force of policy changes even though the significance of evidence is increasingly argued in the recent decade.

Reviews of international experience demonstrate that the concept of evidence-based policy-making sounds hollow in this arena; some policies tend to be employed continuously regardless of poor (sometimes adverse) evidence, while others seem under-used even though promising evidence exists. Thus, generalisation of international experience is certainly limited in a local setting. Ironically, the reality that de-emphasises evidence augments the significance of rigorous policy evaluation in each local setting to reduce policy uncertainties and produce better prospects in this field. Nevertheless, pharmaceutical policy evaluation is one of the most under-researched scopes in less-developed countries.

A good example of this was revealed by the empirical exploration of Korean policies in this thesis. It was seen that Korea is still left with suboptimal strategies and has faced considerable resistance to moving towards strategies that may be more effective. So far, suboptimal measures have disrupted equity objectives with only minimal improvements in efficiency and costs in Korean society. Despite aggressively seeking improvement at all times, actual changes appeared faint and slow. Regulating pharmaceuticals is challenged by lack of available information, widespread distrust, resource constraints, and strong professionals. Korean policy-makers generally support the international trend of cost-effectiveness and evidence-based policy-making as the prospect of the local policy direction. Unfortunately, however, these subjects remain mostly at a superficial level of debate in Korea. Therefore, the awareness seems to need more rigid and wide social acknowledgement to produce effective changes in this arena and must be the subject of continuing debate.

Hence, despite the clear limitations in generalisability and transferability, International experience has been valuable as a learning tool for policy-makers and as an important

initiative of policy reform for some considerable time in this setting. Therefore, it is important to remember that drug policies are often derived from a complex mix of constrained evidence, sometimes irrational judgments and wishful thinking, perhaps focusing on benefits and ignoring the potential negative consequences. The predictions made based upon such imperfect grounds could easily collapse with the failure of engagement with contextual specificities. These drawbacks are real but could be minimised by the careful development of policy. It may be necessary to start by being cautious in generalisation of the policy impact exhibited in foreign settings amid Korean policy environments where there is a paucity of local evidence. At the same time, it is necessary to develop policy-making capacity in the face of an immature evidence base. Efforts that build research capacity and seek local evidence are essential to strengthen such capacity as well as to be an ultimate solution to the absence of a knowledge base.

List of acronyms

AAP	Actual Acquisition Price system
ACEI	angiotensin-converting enzyme inhibitors
ACF	autocorrelation function
ADHD	Attention-Deficit Hyperactivity Disorder
AIDS	Acquired immune deficiency syndrome
ARB	angiotensin II receptor blockers
ARIMA	autoregressive integrated moving average
ATC	Anatomic Therapeutic Chemical
BPP	Better Prescribing Project
BVP	Bio-equivalence Validation Programme
CA	copayment adjustment
CBA	controlled before and after study
CCB	calcium channel blocker
CERM	Committee on Evaluation of the Reimbursement of Medicines
COX_2I	Cox 2 selective inhibitor
CRD	Centre for Reviews and Dissemination
CRRM	Committee on Reconcilliation of the Reimbursement of Medicines
DDD	defined daily dose
DTC	direct-to-consumer
DUR	drug utilisation review
DW	Durbin–Watson *d* statistic
EBM	evidence based medicine
EBP	evidence based policy-making
EGLS	estimated generalised least squares
EMEA	European Medicines Agency
EPOC	Cochrane Effectiveness Practice and Organisation of Care collaborative review group
FDA	Food & Drug Administration
FFS	fee-for-service
GDP	gross domestic product
GNI	gross national income
GSL	general sales list
H_2RA	histamine type 2 receptor antagonists
HIRA	Health Insurance Review & Assessment Service
HMG CoA	3-hydroxy-3-methyl-glutaryl-CoA
ITS	interrupted time series
KFDA	Korea Food & Drug Administration
KRW	Korean Won

MAC	Maximum Allowable Cost
MAP	Medical Aid Programme
MOHW	Ministry Of Heaith and Welfare
MRI	Magnetic resonance imaging
NCE	new chemical entity
NFMI	National Federation of Medical Insurance
NHI	National Health Insurance
NHIC	National Health Insurance Corporation
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NL	negative list
NSA	non-sedating antihistamines
NSAID	non-steroidal anti-inflammatory drug
OECD	Organisation for Economic Co-operation and Development
OLS	ordinary least-squares
OTC	*over-the-counter*
PACF	partial autocorrelation function
PACT	prescribing analysis and cost
PDL	Preferred Drug List
PERP	Pharmaceutical Expenditure Rationalisation Plan
PET	positron emission tomography
POM	prescription only medicine
PPI	proton pump inhibitor
PPP	purchasing power parity
PPRS	*Pharmaceutical Price Regulation Scheme*
QOF	Quality and Outcomes Framework
R&D	Research and Development
RCT	randomised controlled trial
RFID	radio frequency identification
SNRI	serotonin–norepinephrine reuptake inhibitor
SPD	Separation of Prescribing and Dispensing of drugs
SSRI	selective serotonin reuptake inhibitor
TNC	transnational corporation
TRP	triennial re-pricing
UK	United Kingdom
US	United States
USA	United States of America
WHO	World Health Organization
WTO	World Trade Organization

ANNEX

Annex 1: OECD raw data

a) Social expenditure
Total social expenditure
Public, % gross domestic product

Countries	1980	1985	1990	1995	2000	2003
Australia	11	13.1	14.1	17.1	17.9	17.8
Austria	22.6	23.9	23.7	26.6	25.3	26.1
Belgium	23.5	26.1	25	26.4	25.3	26.5
Canada	14.5	17.3	18.2	19.1	16.6	17.3
Czech Republic	n/a	n/a	16	18.2	20	21
Denmark	25.2	24.1	25.5	28.9	25.8	27.7
Finland	18.2	22.7	24.3	27.4	21.1	22.1
France	20.8	26	25.2	28.4	27.6	28.5
Germany	22.4	22.9	21.9	26.6	26.3	27.2
Greece	10.2	16	16.6	17.2	19	19.2
Hungary	n/a	n/a	n/a	n/a	20.2	22.3
Iceland	n/a	n/a	13.7	15.2	15	18
Ireland	16.8	21.8	15.5	16.3	13.6	15.9
Italy	18	20.8	19.9	19.8	23.2	24.2
Japan	10.6	11.4	11.5	14.1	16.3	18.1
Korea	n/a	n/a	3	3.5	5.1	5.7
Luxembourg	20.7	20.2	19.2	20.8	19.8	20.7
Mexico	n/a	1.9	3.6	4.7	5.8	6.8
Netherlands	24.8	25	25.4	23.5	19.4	20.6
New Zealand	17.2	17.9	21.8	18.9	19.1	17.9
Norway	16.8	17.8	22.3	23.4	22.1	24.8
Poland	n/a	n/a	14.8	22.6	20.6	22.2
Portugal	10.2	10.4	13	17.2	19.1	22.1
Slovak Republic	n/a	n/a	n/a	18.6	17.9	17.2
Spain	15.5	17.8	20	21.5	20.4	20.2
Sweden	28.3	29.4	30.2	32.1	28.3	30.6
Switzerland	13.6	14.5	13.4	17.5	17.8	20.4
Turkey	4.4	4.2	7.6	7.5	n/a	n/a
United Kingdom	16.9	19.9	17.3	20.5	19.2	20.7
United States	13	12.7	13.2	15.2	14.4	16

Source: OECD HEALTH DATA 2008, June 08

b) Total expenditure on health
Public expenditure on health
% gross domestic product

Countries	1980	1985	1990	1995	2000	2003
Australia	3.9 d	4.6 d	4.6 d	4.9 d	5.5 d	5.7 d
Austria	5.1	4.9	6.1 b	7	7.5	7.7
Belgium	n/a	n/a	n/a	6.5	n/a	n/a
Canada	5.3	6.1	6.6	6.4 b	6.2	6.9
Czech Republic	n/a	n/a	4.6	6.4	5.9 b	6.7 b
Denmark	7.9	7.3	6.9	6.7	6.8	n/a b
Finland	5	5.6	6.2	5.7 b	5.1	5.9
France	5.6	6.3	6.4	7.7 b	7.5	8.7 b
Germany	6.6	6.8	6.3	8.2	8.2	8.5
Greece	3.3	n/a	3.5	4.5	4.7 b	5.4
Hungary	n/a	n/a	n/a	6.1	4.9	6
Iceland	5.5	6.3	6.8	6.9	7.7	8.5
Ireland	6.8	5.7	4.4 b	4.8	4.6	5.6
Italy	n/a	n/a	6.1	5.1	5.8	6.2
Japan	4.7	4.8	4.6	5.7 b	6.2	6.6
Korea	0.8	1.1	1.6	1.5	2.2	2.8
Luxembourg	4.8	4.6	5	5.1 b	5.2	6.8 b
Mexico	n/a	n/a	2	2.4	2.6	2.8
Netherlands	5.1	5.2	5.4	5.9	5	n/a
New Zealand	5.2	4.4	5.7	5.5	6	6.3
Norway	5.9	5.6	6.3	6.6	6.9	8.4
Poland	n/a	n/a	4.4	4	3.9	4.4
Portugal	3.4	3.1	3.8	4.9 b	6.4 b	7.1
Slovak Republic	n/a	n/a	n/a	n/a	4.9	5.2
Spain	4.2	4.3	5.1	5.4	5.2	5.7 b
Sweden	8.2	7.7	7.4	6.9	7	7.8
Switzerland	n/a	3.9	4.3	5.2	5.7	6.7
Turkey	1	1.1	2.2	2.4	3.1	4.3
United Kingdom	5	5	5	5.8	5.8	6.6 b
United States	3.6	4	4.7	6	5.8	6.7

Source: OECD HEALTH DATA 2008, June 08

c) Pharmaceuticals and other medical non-durables
Pub. exp. on pharmaceuticals & other medic.non-durables
% gross domestic product

Countries	1980	1985	1990	1995	2000	2003
Australia	0.2	0.3	0.3	0.5	0.7	0.7
Austria	n/a	n/a	0.4 b	0.5	0.8	0.9
Belgium	0.6	0.6	0.5	0.6	n/a	0.9
Canada	0.1	0.2	0.3	0.4	0.5	0.6
Czech Republic	n/a	n/a	0.9	1.5	1.2 b	1.4
Denmark	0.3	0.3	0.2	0.4	0.4	0.5 b
Finland	0.3	0.3	0.3	0.5 b	0.5	0.6
France	0.7	0.9	0.9	1.0 b	1.2	1.3 b
Germany	0.8	0.9	0.9	0.9	1	1.2
Greece	0.7	n/a	0.5	1	0.9 b	1.2
Hungary	n/a	n/a	n/a	1.2	1.2	1.4
Iceland	0.5	0.7	0.9	0.9	0.8	0.9
Ireland	n/a	n/a	n/a	n/a	n/a	n/a
Italy	n/a	n/a	0.9	0.6	0.8	0.9
Japan	n/a	0.7	0.8	1.0 b	0.9	1.1
Korea	0.1	0.1	0.2	0.2	0.4	0.7
Luxembourg	0.7	0.7	0.7	0.5 b	0.5	0.6 b
Mexico	n/a	n/a	n/a	n/a	0.0 d	0.1
Netherlands	0.4	0.4	0.5	0.8	0.5	n/a
New Zealand	0.6	0.5	0.7	0.7	n/a	n/a
Norway	0.3	0.3	0.4	n/a	0.5	0.5
Poland	n/a	n/a	n/a	0.8	0.6	0.8
Portugal	0.7	0.9	0.9	1.2	1.1 b	1.2
Slovak Republic	n/a	n/a	n/a	n/a	1.5	1.9
Spain	0.7	0.7	0.8	1	1.1	1.4 b
Sweden	0.4	0.4	0.5	0.7	0.8	0.8
Switzerland	n/a	n/a	n/a	0.5	0.7	0.8
Turkey	n/a	0.3	0.7	n/a	0.8	n/a
United Kingdom	0.5	0.5	0.5	0.7	n/a	n/a
United States	0.1	0.1	0.1	0.2	0.3	0.4

Source: OECD HEALTH DATA 2008, June 08

b: Break in series
d: Differences in methodology
n/a: Data not available

Annex 2: Searching strategy for policies influencing patients

1. Drug Polic$/ or Drug Regulation?/ or Health Polic$/ or Pharmaceutical Regulation?/ or Pharmaceutical Polic$/ or Managed Care?/ or Prescribing/
2. ((regulat$ or restrict$ or pay$ or drug? or pharmaceutic$ or medicine? or medicament? or medicat$ or generic?) adj5 (coverage or utili?ation or polic$ or system? or program$ or schedule or prescri$ or expenditure?)).tw.
3. 1 or 2
4. (patient? or consumer? or beneficiar$ or user? or medi$ population? or household?).ab,tw.
5. (cost-sharing or (cost? adj3 (sharing or share))).ti,ab,tw.
6. (out-of-pocket or (out of pocket? adj3 pay$)).ti,ab,tw.
7. (copay$ or co pay$).ti,ab,tw.
8. ((prescrib$ or prescription? or pharmaceutic$ or pharmacy or pharmacies or dispens$ or user or user$ or patient or patient$) adj3 (charg$ or fee?)).ti,ab,tw.
9. ((charg$ or fee?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
10. ((coinsurance or deductible?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
11. or/5-10
12. DTC/ or OTC/
13. (direct-to-consumer? or (direct? adj3 consumer?) or over-the-counter? or (over? Adj3 counter?)).ti,ab,tw.
14. 12 or 13
15. (formulary or formularies or positive list? or negative list?).ti,ab,tw.
16. ((drug? or pharmaceutic$ or medicine? or medica$ or prefer$) adj3 (list? or cover$)).ti,ab,tw.
17. ((reimburse$ or insur$ or (third party adj1 pay$) or benefit plan? or withdraw$) adj4 (drug or drugs or pharmaceutic$ or pharmacy or pharmacies or medicines or medicament? or medicat$)).ti,ab,tw.
18. ((pay$ or reimburse$) adj3 (cess$ or restrict$ or polic$)).ab,tw.
19. (reference$ adj3 (price? or pricing)).ti,ab,tw.
20. (index$ adj3 (price? or pricing)).tw.
21. ((prescib$ or prescription? or benefit) adj3 (limit$ or cap$)).ti,ab,tw.
22. ((step therapy or tiered benefit) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
23. or/15-22
24. *Drug Information Services/ and (patient? or consumer?).tw.
25. *Patient Education/
26. ((educat$ or inform$) adj3 (patient? or consumer?)).tw.
27. or/24-26
28. 11 or 14 or 23 or 27
29. (((health or patient$) adj1 outcome?) or readmission?).tw.
30. ((control$ or containment or curtailment or reduc$ or save or saving) adj3 cost?).tw.
31. ((drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescib$ or prescription? or reimburs$) adj3 (use$ or cost? or expenditure? or expense?)).ab,tw.
32. *Adverse Drug Reaction/ or (safe$ adj1 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
33. (drug use$ or drug utili?ation or ((medical care or healthcare or health care or resource) adj1 (us$ or utili?tion)) or institutionali$ or hospitali$).ab,tw.
34. ((prescrib$ or prescrip$) adj2 (attitude or variation? or behavior or behaviour or pattern? or practice? or habit? or accurate or trend? or cost? or change? or shift$ or rational? or reduc$ or influenc$ or expenditure?)).ab,tw.
35. or/29-34
36. randomized controlled trial.pt.
37. ((control or comparison) adj1 (group? or participant?)).ab.
38. ((time adj series) or time-series).ti,ab,tw.
39. (pre-post or ((pre test or pretest) adj4 (posttest or post test))).ab,tw.

40. (before-after or (before adj2 after)).ab,tw.
41. or/36-40
42. 3 and 4 and 28 and 35 and 41
43. (opioid or abuse or alcohol or smok$ or captopril or addiction or virus or antibody or energy).ti,ab.
44. ((pharmac$ or nurse?) adj2 (led or based or manage$ or delivered or service? or collaboration? or counsel$)).ti,ab.
45. (discharg$ or placebo or depression or hip or asthma or homeopath$ or dementia or rhinitis or COPD or radiography or satisfaction or heart or transplant$).ti.
46. (cost-effectiveness or cost-minimi?ation or (economic adj1 (analys$ or stud$ or evaluation?))).ti.
47. or/43-46
48. editorial.pt.
49. letter.pt.
50. comment.pt.
51. or/48-50
52. animals/
53. humans/
54. 52 not 53
55. 47 or 51 or 54
56. 42 not 55

Annex 3: Searching strategy for policies influencing providers

1. Drug Polic$/ or Drug Regulation?/ or Health Polic$/ or Pharmaceutical Regulation?/ or Pharmaceutical Polic$/ or Managed Care?/
2. ((regulat$ or restrict$ or pay$ or drug? or pharmaceutic$ or medicine? or medica$ or generic?) adj5 (coverage or utili?ation or polic$ or system? or program$ or schedule or prescri$ or expenditure?)).tw.
3. 1 or 2
4. *Nurses/ or *Nurse Clinicians/ or *Nurse Practitioners/ or *Pharmacists/ or *Pharmacies/ or *Pharmacy/ or *Hospitals/
5. (physician$ or GP? or doctor? or prescriber? or group pract$ or institutional pract$ or partnership pract$ or family pract$ or general pract$ or office pract$ or private pract$ or primary pract$ or nurse? or pharmac$ or hospital?).tw.
6. 4 or 5
7. (formulary or formularies or positive list? or negative list?).ti,ab,tw.
8. ((drug? or pharmaceutic$ or medicine? or medica$ or prefer$) adj3 (list? or cover$)).ti,ab,tw.
9. ((reimburse$ or insur$ or (third party adj1 pay$) or benefit plan? or withdraw$) adj4 (drug or drugs or pharmaceutic$ or pharmacy or pharmacies or medicines or medicament? or medicat$)).ti,ab,tw.
10. ((pay$ or reimburse$) adj3 (cess$ or restrict$ or polic$)).ab,tw.
11. (reference$ adj3 (price? or pricing)).ti,ab,tw.
12. (index$ adj3 (price? or pricing)).tw.
13. ((prescib$ or prescription? or benefit) adj3 (limit$ or cap$)).ti,ab,tw.
14. ((step therapy or tiered benefit) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
15. ((pre-authori#ation? or preauthori#ation? or prior authori#ation?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
16. *"Pharmacy and Therapeutics Committee"/ or ((drug? or formulary or pharmac$) adj3 committee?).tw.
17. or/7-16
18. ((drug? or pharmaceutic$ or prescrib$ or prescrip$) adj1 budget?).ti,ab,tw.
19. (((local$ or global$) adj3 budget$) and (general pract$ or GP? or physician? or doctor?)).tw.
20. (fundhold$ adj3 (general pract$ or GP? or physician? or doctor?)).tw.
21. (incentive? adj1 (plan? or money$ or financ$ or payment? or reimburs$)).tw.
22. (capitation or salaries or salary or income? or wages or fringe benefit? or benchmarking).tw.
23. or/18-22
24. ((information or reminder? or feedback or monitor$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescri$)).tw.
25. *Guidelines/ or *Practice Guidelines/
26. ((guideline? or recommendation? or protocol) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
27. ((prescrib$ or prescip$) adj1 scheme?).tw.
28. or/24-27
29. (generic adj3 (price? or pricing or substitut$ or foster$)).ti,ab,tw.
30. (generic$ adj3 (prescri$ or drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
31. 29 or 30
32. (((academi$ or group) adj1 detail$) or outreach or out-reach or visit? or letter? or mail$ or telephon$ or phon$).tw.
33. (advert$ or promot$ or market$).tw.
34. (quality adj3 (framework or pay$)).ti,ab,tw.
35. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).tw.
36. (32 or 33 or 34) and 35
37. 17 or 23 or 28 or 31 or 36
38. (((health or patient$) adj1 outcome?) or readmission?).tw.
39. ((control$ or containment or curtailment or reduc$ or save or saving) adj3 cost?).tw.

40. ((drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescib$ or prescription? or reimburs$) adj3 (use$ or cost? or expenditure? or expense?)).ab,tw.
41. *Adverse Drug Reaction/ or (safe$ adj1 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
42. (drug use$ or drug utili?ation or ((medical care or healthcare or resource) adj1 utili?tion) or institutionali$ or hospitali$).ab,tw.
43. ((prescrib$ or prescrip$) adj2 (attitude or variation? or behavior or behaviour or pattern? or practice? or habit? or accurate or trend? or cost? or change? or shift$ or rational? or reduc$ or influenc$ or expenditure? or adherence)).ab,tw.
44. or/38-43
45. randomized controlled trial.pt.
46. (randomi$ or ((control or comparison) adj1 (group? or participant?))).ab.
47. ((time adj series) or time-series).ti,ab,tw.
48. (pre-post or ((pre test or pretest) adj4 (posttest or post test))).ab,tw.
49. (before-after or (before adj2 after)).ab,tw.
50. or/45-49
51. 3 and 6 and 37 and 44 and 50
52. (opioid or abuse or alcohol or smok$ or captopril or addiction or virus or antibody or energy or syringe or detoxification or BDRs or bypass or knee or PET or stent or skin).ti,ab.
53. (((cost or burden) adj2 illness) or (neurological adj1 disorder?) or (medica$ adj1 error?) or ((behavioral or behavioural) adj1 disorder?) or (residen$ adj2 program$) or case-control).ti,ab.
54. ((pharmac$ or nurse?) adj2 (led or based or menage$ or delivered or service? or collaboration? or counsel$)).ti,ab.
55. (discharg$ or placebo or depression or hip or asthma or homeopath$ or dementia or rhinitis or COPD or radio$ or satisfaction or heart or transplant$ or prevent$ or fracture or rehabilitation or misclassification or indigent or epidemiology).ti.
56. (cost-effectiveness or cost-minimi?ation or (economic adj1 (analys$ or stud$ or evaluation?))).ti.
57. (incremental adj1 cost adj1 effective adj1 ratio?).tw.
58. or/52-57
59. editorial.pt.
60. letter.pt.
61. comment.pt.
62. or/59-61
63. animals/
64. humans/
65. 63 not 64
66. 58 or 62 or 65
67. 51 not 66

Annex 4: Searching strategy for policies influencing industry

1. Drug Polic$/ or Drug Regulation?/ or Health Polic$/ or Pharmaceutical Regulation?/ or Pharmaceutical Polic$/ or Managed Care?/ or Health Care/ or Madicaid/
2. ((drug? or pharmaceutic$ or medicine? or medica$) adj5 (regulat$ or restrict$ or polic$ or system? or program$ or schedule or expenditure? or scheme or plan$)).tw.
3. 1 or 2
4. ((reference$ or least or maximum or allow$) adj3 (price? or pricing or cost)).ti,ab,tw.
5. ((index$ or reimburs$ or list$) adj3 (price? or pricing or cost)).tw.
6. ((control$ or reduc$ or cut$ or regular$ or negotiat$ or fix$ or polic$) adj3 (price? or pricing or volume)).tw.
7. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or compet$)).tw.
8. (patent adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
9. (profit? adj3 (control$ or reduc$ or regulat$ or fix$ or restrict$ or return)).tw.
10. or/4-9
11. *Drug Approval/ or (approv$ adj3 (drug or durgs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
12. *Marketing/ or *Marketing of Health Services/ or *Advertising/ or *Licensure/ or *Drug Labeling/
13. ((licens$ or registrat$ or label$ or authori$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or market)).tw.
14. or/11-13
15. (generic adj3 (price? or pricing)).tw.
16. (generic$ adj3 (market or compet$)).tw.
17. 15 or 16
18. 10 or 14 or 17
19. (((health or patient$) adj1 outcome?) or readmission?).tw.
20. ((control$ or containment or curtailment or reduc$ or sav$ or cut$ or down$) adj3 (cost? or pric$)).tw.
21. (market adj2 shar$).tw.
22. ((drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescib$ or prescription? or reimburs$) adj3 (use$ or cost? or expenditure? or expense?)).ab,tw.
23. *Adverse Drug Reaction/ or (safe$ adj1 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
24. (drug use$ or drug utili?ation or ((medical care or healthcare or resource) adj1 utili?tion) or institutionali$ or hospitali$).ab,tw.
25. ((prescrib$ or prescrip$) adj2 (attitude or variation? or behavior or behaviour or pattern? or practice? or habit? or accurate or trend? or cost? or change? or shift$ or rational? or reduc$ or influenc$ or expenditure? or adherence)).ab,tw.
26. or/19-25
27. randomized controlled trial.pt.
28. (randomi$ or ((control or comparison) adj1 (group? or participant?))).ab.
29. ((time adj series) or time-series).ti,ab,tw.
30. (regression or extrapol$ or (generali?ed adj1 estimating adj1 equation?) or (longitudinal adj1 data) or (repeated adj1 measures) or (least adj1 squares) or (smoothing adj2 model?) or autocorrelation).ti,ab,tw.
31. (pre-post or (pre adj2 post)).ab,tw.
32. (before-after or (before adj2 after)).ab,tw.
33. or/27-32
34. 3 and 18 and 33
35. (opioid or placebo or reflumilast or exenatide or ectomy or athlete? or sport? or lactation or acupucture or inject$ or (clinical adj2 trial?)).ti,ab.
36. (pharmacokinetic? or radio$ or tumor or tobacco or cigarette or vaccine? or alcohol or rat or mice or mouse or rabbit? or pig? or gene).ti,ab.
37. editorial.pt.
38. letter.pt.
39. comment.pt.
40. or/35-39
41. animals/
42. humans/
43. 41 not 42
44. 40 or 43
45. 34 not 44

Annex 5: Quality criteria for systematic review

a) Controlled before and after designs

Score	Baseline measurement	Characteristics for control	Reliable primary outcome measure(s)	Attrition rate	Reasons for drop-out participants	Blinded assessment	Protection against contamination
clear	prior measurement performed, a) absolute difference between the groups less than 10% b) analysis take into consideration the baseline imbalance (for example, analysis of co-variance or analysis by change scores between groups)	characteristics for study and control group reported and similar	outcomes obtained from some automated system, from those maintained at organisational level	< 20%	state explicitly	state explicitly, outcome variables are objective e.g. length of hospital stay	allocation performed by community, institution, or practice and unlikely that the control group received the intervention
unclear	not provide enough information to judge	characteristics are mentioned in the text but no data are presented	not reported reliability for outcome measures that were obtained by chart extraction or collected by an individual; not specified in the paper	not provide enough information to judge	state partly	not provide enough information to judge	subjects allocated within a clinic or practice and communication between study and control group likely occurred
none	not met above conditions	not reported or inequal	any discrepancies occurred in the paper; irrelavant outcomes measured	> 20%	not reported	not assessed blindly	likely that the control group received the intervention

b) Interrupted time series designs

Protection against secular changes

model	high	medium	low
ARIMA	≥ 50 data points before and after	20 ≤ data points < 50 before and after	not meet any criteria
segmented regression	≥ 12 data points before and after including 4 seasons	4 ≤ data points < 12 before and after including 4 seasons	

Score	Appropriate data analysis	Reasons for the number of points	Shape of the intervention effect prespecified	Same methods of data collection	Blinded assessment	Completeness of data set	Reliable primary outcome measure(s)
clear	(a) If at least twenty points are recorded before the intervention AND the authors have done ARIMA analysis OR (b) If at least 12 months are recorded pre and post intervention AND the authors have done a segmented time series analysis with formal tests verifying the absence of autocorrelation	rationale for the number of points stated or sample size calculation performed	clear study objectives and hypotheses provided	sources and methods of data collection were the same before and after the intervention	stated explicitly; outcome variables are objective e.g. length of hospital stay	< 20%	outcomes obtained from some automated system; from those maintained at organisational level
unclear	not provide enough information about data analysis	not provide enough information, but many enough to assume appropriateness	not provide enough information to judge	not provide enough information to judge	not provide enough information to judge	not provide enough information to judge	not reported reliability for outcome measures that were obtained by chart extraction or collected by an individual
none	not met above conditions	not met above conditions	not met above conditions	any change in source or method of data collection reported	not assessed blindly	> 20%	any discrepancies occurred in the paper; irrelavant outcomes measured

c) Randomised controlled trial designs

Score	Concealment of allocation	Blinded assessment	Baseline measurement	Reliable primary outcome measure(s)	Intention-to-treat analysis	Attrition rate	Reasons for drop-out participants
clear	allocation sequence adequately generated and allocation adequately concealed	stated explicitly; outcome variables are objective e.g. length of hospital stay	prior measurement performed, a) absolute difference between the groups less than 10% b) analysis take into consideration the baseline imbalance (for example, analysis of co-variance or analysis by change scores between groups)	outcomes obtained from some automated system; from those maintained at organisational level	stated explicitly and confirmed by tables and contexts	< 20%	stated explicitly
unclear	not provide enough information to judge	not provide enough information to judge	not provide enough information to judge	not reported reliability for outcome measures that were obtained by chart extraction or collected by an individual	not provide enough information to judge	not provide enough information to judge	stated partly
none	cleary broke the concealment	not assessed blindly	not met above conditions	any discrepancies occurred in the paper; irrelavant outcomes measured	not performed an intenion-to-treat analysis	> 20%	not reported

Annex 6: Characteristics of excluded studies and references

a) Pharmaceutical policies influencing patients

Study	Cause for exclusion	Intervention	Setting
Balkrishnan *et al.* 2001	before and after study	cost-sharing	USA
Birch 1986	before and after study	cost-sharing	UK
Chalker 1995	post-test only control group design	cost-sharing	Nepal
Cunningham 2005	before and after study	cost-sharing	USA
Delate and Henderson 2005	less than 6 months	educational approach	USA
Huang and Tung 2006	before and after study	cost-sharing	Taiwan
Krol *et al.* 2004	less than 6 months	educational approach	Netherlands
Parsons *et al.* 2004	less than 6 months	educational approach	UK
Pilote *et al.* 2002	before and after study	cost-sharing	Canada
Rector *et al.* 2003	post-test only control group design	tiered formulary	USA
Trygstad *et al.* 2006	before and after study	OTC switch reimbursement coverage	USA
Tseng *et al.* 2004	post-test only control group design	annual cap	USA

b) Pharmaceutical policies influencing providers

Study	Cause for exclusion	Intervention	Setting
Adair and Holmgren 2005	single institution	distribution of samples	USA
Albañil-Ballesteros *et al.* 2002	before and after study	educational approach	Spain
Angunawela *et al.* 1991	less than 6 months	educational approach	Sri Lanka
Babington *et al.* 1983	before and after study	educational approach	USA
Balkrishnan *et al.* 2001	before and after study	reimbursement restriction	USA
Bernstein *et al.* 2005	before and after study	educational approach	USA
Bjornson *et al.* 1990	less than 6 months	educational approach	USA
Bloom and Jacobs 1985	before and after study	reimbursement restriction	USA
Carey *et al.* 1992	before and after study	educational approach	Australia
Cunningham 2005	before and after study	reimbursement restriction	USA
Denig *et al.* 1990	less than 6 months	educational approach	Netherlands
Dormuth *et al.* 2004	less than 6 months	educational approach	Canada
Duborija-Kovacevic 2006	before and after study	educational approach	Montenegro
Elkharrat *et al.* 1998	before and after study	educational approach	France
Fagundes *et al.* 2007	qualitative study	educational approach	Portugal
Fick *et al.* 2004	no interpretable data presented	educational approach	USA

(continued)

Pharmaceutical policies influencing providers (continued)

Study	Cause for exclusion	Intervention	Setting
Fontaine *et al.* 2006	less than 6 months	educational approach	France
Frighetto *et al.* 1992	before and after study	reimbursement restriction	Canada
Fudge *et al.* 1993	before and after study	educational approach	USA
Gehlbach *et al.* 1984	single institution	educational approach	USA
Gleason *et al.* 2004	improper comparison group chosen (CBA)	educational approach	USA
Gleason *et al.* 2005	before and after study	reimbursement restriction	USA
Goldfarb *et al.* 1999	before and after study	reimbursement restriction	USA
Guo *et al.* 1995	before and after study	educational approach	USA
Hadiyono *et al.* 1996	less than 6 months	educational approach	Indonesia
Hall 1990	before and after study	educational approach	UK
Headen *et al.* 2006	less than 6 months	reimbursement restriction	USA
Kersemakers *et al.* 2000	before and after study	educational approach	Netherlands
Knight *et al.* 2000	before and after study	educational approach	USA
Kotzan *et al.* 1996	post-test only control group design	reimbursement restriction	USA
Kozma *et al.* 1990	before and after study	reimbursement restriction	USA
Kreling *et al.* 1989	before and after study	reimbursement restriction	USA
Latour-Perez *et al.* 2000	less than 6 months	educational approach	Spain
Layton *et al.* 2006	before and after study	reimbursement restriction	Thailand
Lee and Malone 2003	before and after study	SPD	South Korea
Limpanasithikul *et al.* 2002	less than 6 months	reimbursement restriction	Thailand
Mallet *et al.* 2001	before and after study	educational approach	Kenya
Martens *et al.* 2006	no interpretable data presented	educational approach	Netherlands
McCaig *et al.* 1999	before and after study	educational approach	UK
McCombs *et al.* 2002	before and after study	reimbursement restriction	USA
McElnay *et al.* 1995	before and after study	educational approach	UK
McManus *et al.* 2001	before and after study	generic substitution	Australia
McMullin *et al.* 1999	before and after study	educational approach	USA
Momani *et al.* 2002	less than 6 months	reimbursement restriction	USA
Murray *et al.* 2005	before and after study	educational approach	UK
Ozkurt *et al.* 2005	before and after study	reimbursement restriction	Turkey
Park *et al.* 2005	before and after study	SPD	South Korea
Parsons *et al.* 2004	less than 6 months	educational approach	UK

(continued)

Pharmaceutical policies influencing providers (continued)

Study	Cause for exclusion	Intervention	Setting
Philips *et al.* 2001	before and after study	incentives	UK
Raisch and Sleath 1999	less than 6 months	educational approach	USA
Risser *et al.* 2005	post-test only control group design	reimbursement restriction	USA
Rolle *et al.* 1995	before and after study	reimbursement restriction	Italy
Rosich *et al.* 2005	before and after study	educational approach	Spain
Roth *et al.* 2001	before and after study	educational approach	USA
Schmidt *et al.* 1998	single institution	educational approach	Sweden
Schöffski and Graf von der Schulenburg 1997	before and after study	incentives	Germany
Scoble *et al.* 2003	post-test only control group design	educational approach	UK
Shankar *et al.* 2007	before and after study	educational approach	Nepal
Sharma *et al.* 2003	before and after study	educational approach	India
Sketris *et al.* 2005	before and after study	educational approach	Canada
Smith *et al.* 1998	less than 6 months	educational approach	USA
Strikwerda *et al.* 1994	less than 6 months	educational approach	Netherlands
Tseng *et al.* 2006	before and after study	reimbursement restriction	USA
Walley *et al.* 2000	before and after study	incentives	Ireland
Walton *et al.* 1997	less than 6 months	educational approach	UK
Wang and Pauly 2005	before and after study	reimbursement restriction	USA
Wathen and Dean 2004	before and after study	educational approach	UK
Watkins *et al.* 2004	qualitative study	educational approach	UK
Welch *et al.* 2000	before and after study	educational approach	Australia
Wilson *et al.* 2005	before and after study	reimbursement restriction	USA
Wu and Gray 1990	before and after study	educational approach	USA
Wyatt *et al.* 1992	before and after study	reimbursement restriction	UK
Yakabowich *et al.* 1994	before and after study	reimbursement restriction	Canada
Yeo *et al.* 1994	qualitative study	educational approach	Australia

c) Pharmaceutical policies influencing industry

Study	Cause for exclusion	Intervention	Setting
Anis	before and after study	price control	Canada
Costa-Font and Kanavos 2007	unclear when intervention occurred	parallel importing	Germany, Netherlands, UK
Gill *et al.* 2000	before and after study	reference-pricing	Canada
Jiang *et al.* 2004	before and after study	price control	China
Martini *et al.* 1996	before and after study	price control	Italia
McManus *et al.* 2001	before and after study	price control	Australia
Meng *et al.* 2005	before and after study	price control	China
Okunade 2001	cross-sectional study	profit control	USA
Spooner *et al.* 2007	one group posttest-only design	AMCP[1)] format dossier requests	USA
Stargardt *et al.* 2005	descriptive study	reference-pricing	Germany
Stargardt *et al.* 2007	before and after study	market deregulation	Germany

1) Academy of Managed Care Pharmacy

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Annex 7: Characteristics of included studies exploring cost-sharing programmes

a) Studies from Western Europe

Study	Setting	Population	Study drugs	Study design	Intervention		Control intervention	Data sources	Follow-up[1)]
					before	after			
Introduction of cost-sharing programme in Western Europe									
Starmans *et al.* 1994	Nether-lands	General	Essential	ITS (no control)	free	fixed copayment	N	state-level aggregated claims data	M
Increased cost-sharing in Western Europe									
Andersson *et al.* 2006	Sweden	General	Overall	ITS (no control)	fixed copayment	stepwise coinsurance	N	national aggregated claims data	M
Almarsdottir *et al.* 2000	Iceland	General	Overall	ITS (no control)	user charges	increase	N	national aggregated claims data	M
Hughes and McGuire 1995	UK	General	Overall	ITS (no control)	fixed user charges	continuous increase of user charges	N	national aggregated claims data	L
Lavers 1989	UK	General	Overall	ITS (no control)	fixed user charges	continuous increase of user charges	N	national aggregated claims data	L
O'Brien 1989	UK	General	Overall	ITS (no control)	fixed user charges	continuous increase of user charges	N	national aggregated claims data	L
Ong *et al.* 2003	Sweden	General	antidepressants, anxiolytics, sedatives	ITS (no control)	a stepwise copayment	increase	N	commercial aggregated claims data	M
Ryan and Birch 1991	UK	General	Overall	ITS (no control)	fixed user charges	continuous increase of user charges	N	national aggregated claims data	L
Winkelmann 2004	Germany	General	Overall	CBA	fixed copayment	increase	Y (exempted)	national annual survey	M
Decreased cost-sharing in Western Europe									
Martikainen *et al.* 2007	Finland	General	Essential	ITS (no control)	fixed copayment	decrease	N	national aggregated claims data	M

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

b) Studies from North America

Study	Setting	Population	Study drugs	Study design	Intervention		Control intervention	Data sources	Follow-up[1)]
					before	after			
Introduction of cost-sharing programme in North America									
Blais *et al.* 2003	Canada	Poor	Essential	ITS (control)	free	25%coinsurance	Y (coinsurance)	state-level aggregated claims data	S
Foxman *et al.* 1987	USA	Non-elderly	Less-essential	RCT	free	25,50,95%coinsurance	Y (free)	academic pharmacy data	S
Harris *et al.* 1990	USA	Non-elderly	Overall/Essential/ Less-essential	CBA	free	continuous increse of a fixed copayment	Y (free)	health plan aggregated claims	M
Kephart *et al.* 2007	Canada	Elderly	Essential/ Less-essential	ITS (no control)	free	a fixed copayment and increase to	N	state-level aggregated claims data	M
Leibowitz *et al.* 1985	USA	Non-elderly	Overall	RCT	free	25,50,95%coinsurance and deductibles	Y (free)	academic pharmacy data	S
Nelson *et al.* 1984	USA	Poor	Overall	ITS (control)	free	fixed copayment	Y (free)	state-level aggregated claims data	M
Reeder and Nelson 1985	USA	Poor	10 categories	ITS (no control)	free	fixed copayment	N	state-level aggregated claims data	M
Increased cost-sharing in North America									
Blais *et al.* 2001	Canada	Elderly	Essential/ Less-essential	ITS (no control)	fixed copayment	25%coinsurance	N	state-level aggregated claims data	M
Gibson *et al.* 2006	USA	Non-children	Essential	ITS (control)	copayment change		Y (new/contining user, vice versa)	commercial aggregated claims	M
Gurwitz *et al.* 1995	USA	Women, non-children	Less-essential	ITS (no control)	fixed copayment	increase	N	health plan aggregated claims	M
Kozyrskyj *et al.* 2001	Canada	Children	Essential	CBA	fixed deductible and coinsurance	income-based deductibe	Y (no change)	state-level aggregated claims data	M
Klepser *et al.* 2007	USA	Non-children	Overall/ Essential	CBA	3-tier copayment	4-tier coinsurance	Y (no change)	health plan aggregated claims	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

(continued)

Studies from North America (continued)

Study	Setting	Population	Study drugs	Study design	Intervention		Control intervention	Data sources	Follow-up[1)]
					before	after			
Increased cost-sharing in North America (continued)									
Johnson *et al.* 1997	USA	Elderly	Overall	CBA	fixed copayment	increase	Y (coinsurance)	health plan aggregated claims data	M
					50%coinsurance	70%coinsurance	Y (fixed copayment)		
Roblin *et al.* 2005	USA	Non-children	Essential	ITS (control)	fixed copayment	increase	Y (no change)	health plan aggregated claims	S
Sun and Lee 2007	USA	Elderly	Overall	CBA	not reported	drug coverage gap	Y (not change)	state-level aggregated claims data	S
Tamblyn *et al.* 2001	Canada	Elderly, Poor	Overall/Essential/ Less-essential	ITS (no control)	free (poor elderly) or fixed copayment	deductible and 25%coinsurance	N	state-level aggregated claims data	M

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

c) Studies from other settings

Study	Setting	Population	Study drugs	Study design	Intervention		Control intervention	Data sources	Follow-up[1)]
					before	after			
Cost-sharing changes in other settings									
Holloway *et al.* 2001	Nepal	General	Overall	CBA	fee/prescription	fee/item	Y (fee/prescription)	individual pharmacy data	S
McManus *et al.* 1996	Australia	General	Essential/ Less-essential	ITS (no control)	fixed copayment	increase	N	national aggregated claims data	M
		Elderly			free	fixed copayment			
Lee *et al.* 2006	Taiwan	General	Overall	ITS (no control)	free	copayment	N	national aggregated claims data	S
Liu and Romeis 2004	Taiwan	Elderly	Overall/Essential/ Less-essential	CBA	free	a stepwise copayment	Y (exempted)	national aggregated claims data	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

Annex 8: Differential effects of cost-sharing by drug classes

Class	Study	Population	Effects
increase copay			
antibiotics	Foxman *et al*. 1987	non-elderly	decrease (-46%)
anticoagulants	Blais *et al*. 2001	elderly	NS
anticonvulsants	Blais *et al*. 2003	poor	NS (temporal decrease)
antidepressants	Ong *et al*. 2003	general	NS in men, decrease in women
antigout preparations	Andersson *et al*. 2006	general	decrease after 1997 reform
antihypertensives	Blais *et al*. 2001	elderly	NS (temporal decrease)
	Klepser *et al*. 2007	non-children	decrease (-5%)
	Starmans *et al*. 1994	general	NS
asthma drugs	Kozyrskyj *et al*. 2001	children	decrease (-15%)
anxiolytics	Ong *et al*. 2003	general	NS
benzodiazepines	Blais *et al*. 2001	elderly	NS (temporal decrease)
bronchodilators	Andersson *et al*. 2006	general	decrease after 1997 reform
inhaled corticosteroids	Blais *et al*. 2003	poor	decrease (-37%)
neuroleptics	Blais *et al*. 2003	poor	NS (temporal decrease)
nitrates	Blais *et al*. 2001	elderly	NS (temporal decrease)
NSAIDs*	Andersson *et al*. 2006	general	decrease after 1997 reform
oral hypoglycemics	Roblin *et al*. 2005	non-children	decrease in >$10 increase of copay
sedatives	Ong *et al*. 2003	general	NS
SSRIs*	Andersson *et al*. 2006	general	down shift in level after 1997 reform
SSRIs/SNRIs*	Klepser *et al*. 2007	non-children	decrease (-6%)
statins	Klepser *et al*. 2007	non-children	decrease (-4%)
vaginal antifungal products	Gurwitz *et al*. 1995	women	NS
relieve copay			
antiglaucoma drugs	Martikainen *et al*. 2007	general	increase (+21% ~ +109%)

* NSAIDs; nonsteroidal anti-inflammatory agent, SSRIs; selective serotonin reuptake inhibitor, SNRI; serotonin/norepinephrine reuptake inhibitor

Annex 9: Characteristics of included studies exploring tiered formularies

Study	Setting	Population	Study drugs	Study design	Intervention		Control intervention	Data sources	Follow -up[1)]
					before	after			
Fairman *et al*. 2003	USA	General	Overall	CBA	2-tier (generic/brand)	3-tier (generic/formulary/nonformulary)	Y (2-tier)	health plan aggregated claims data	M
Gibson *et al*. 2005	USA	General	Overall	CBA	1-tier	2-tier (generic/brand)	Y (2-tier)	commercial aggregated claims data	M
Huskamp *et al*. 2003a	USA	General	Essential	CBA	1-tier	3-tier (generic/formulary/nonformulary)	Y (2-tier)	health plan aggregated claims data	M
					2-tier (generic/brand)	3-tier (generic/formulary/nonformulary)	Y (2-tier)		
Huskamp *et al*. 2005	USA	Children	ADHD[2)] medications	CBA	1-tier	3-tier (generic/formulary/nonformulary)	Y (2-tier)	commercial aggregated claims data	M
Landon *et al*. 2007	USA	Non-elderly	Overall	CBA	1-tier or 2-tier	3-tier (generic/formulary/nonformulary)	Y (1- or 2-tier)	health plan aggregated claims data	S
Landsman *et al*. 2005	USA	General	Essential/ Less-essential	CBA	2-tier (generic/brand)	3-tier (generic/formulary/nonformulary)	Y (2-tier)	health plan aggregated claims data	M
Motheral and Fairman 2001	USA	Non-children	Overall	ITS (control)	2-tier (generic/brand)	3-tier (generic/formulary/nonformulary)	Y (2-tier)	health plan aggregated claims data	S
Motheral and Henderson 1999b	USA	General	Overall	CBA	2-tier (generic/brand)	2-tier, increase copay	Y (2-tier)	health plan aggregated claims data	S
Nair *et al*. 2003	USA	Sicker	Overall	CBA	2-tier (generic/brand)	3-tier (generic/formulary/nonformulary)	Y (2- or 3-tier)	health plan aggregated claims data	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 13 months.

2) Attention-deficit hyperactivity disorder

Annex 10: Characteristics of included studies exploring prescription caps

Study	Setting	Population	Study drugs	Study design	Intervention		Control intervention	Data sources	Follow-up[1)]
					before	after			
Martin and McMillan 1996	USA	Poor	Overall	ITS (no control)	six reimbursable prescriptions/month	five reimbursable prescriptions/month	N	state-level aggregated claims data	S
Soumerai *et al*. 1987	USA	Poor	Overall	ITS (control)	no limit	limit of three paid prescriptions per month	Y (no cap)	state-level aggregated claims data	S
Soumerai *et al*. 1994	USA	Poor elderly	Essential	ITS (control)	no limit	limit of three paid prescriptions/month	Y (no cap)	state-level aggregated claims data	S
Soumerai *et al*. 1991	USA	Poor elderly	Overall/ Essential	ITS (control)	no limit	limit of three paid prescriptions/month	Y (no cap)	state-level aggregated claims data	S
Starmans *et al.* 1994	Netherlands	General	Essential	ITS (no control)	no limit	maximum of 30 days dosages/prescription item	N	state-level aggregated claims data	M

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

Annex 11: Characteristics of included studies exploring an educational approach to patient and OTC switch

Study	Setting	Population	Study drugs	Study design	Intervention		Control interventio	Data sources	Follow-up[1)]
					before	after			
Valles *et al.* 2003	Spain	General	Overall	RCT	Usual care	Verval and written information encouraging generic use	Y (usual care)	institutional pharmacy data	S
Gurwitz *et al.* 1995	USA	Women, non-children	Less-essential	ITS (no control)	Prescription drugs only	OTC products available	N	health plan aggregated claims data	M

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

Annex 12: Characteristics of included studies exploring educational approaches to providers

a) Guideline-like information

Study	Setting	Population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
guideline-like information, passive contacts								
Jones *et al*. 1996	USA	2 hospitals and 2 primary care clinics	non steroidal anti-inflammatory drugs	CBA	conveying a stepped-care prescribing protocol encouraging the use of less expensive NSAIDs first	Y (computer cost-prompt) Y (no intervention)	institutional pharmacy data	M
Martens *et al*. 2006	Netherlands	107 GPs	antibiotics, asthma medications	CBA	posting prescribing guidelines on study drugs	Y (no intervention)	health plan aggregated claims data	M
O'Malley *et al*. 2006	USA	31,576 physicians (intervention)	generics	CBA	delivering campaigns to encourage generic use by member mailings and advertising in Michigan	Y (out of Michigan)	health plan aggregated claims data	M
Sheldon *et al*. 2004	UK	no information	taxanes, Alzheimer drugs, Orlistat	ITS (no control)	delivering NICE guidance for study drugs	N	national aggregated claims data	M
Tu *et al*. 2002	Canada	no information	antihypertensives in elderly	ITS (control)	disseminating hypertension guidelines for elderly patients (recommend diuretic agents and beta-blockers as first-line therapy)	Y (mean of British Columbia)	state-level aggregated claims data	M
guideline-like information, group detailing								
Avorn and Soumerai 1983 Soumerai and Avorn 1986,1987	USA	432 physicians	propoxyphene, vasodilators, cephalexin	RCT	distributing printed-materials discourating the excessive use of study drugs by post twice two visits with printed-materials by pharmaceutical educators with the same aim	Y (usual care)	state-level aggregated claims data	S
Bernal-Delgado *et al*. 2002	Spain	158 GPs/ 24 primary healthcare teams	non steroidal anti-inflammatory drugs	RCT	a group educational outreach session conveying printed information based on a systematic review	Y (conventinal educational meeting) Y (no intervention)	state-level aggregated claims data	S

(continued)

Study	Setting	Population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
guideline-like information, group detailing (continued)								
Bexell *et al.* 1996	Zambia	16 generic health centres	essential drugs, antibiotics	RCT	three 2-days group seminars using standard treatment guidelines for common conditions seen in primary care	Y (no intervention)	institutional pharmacy data	S
Chazan *et al.* 2007	Israel	16 clinics	antibiotics	RCT	providing monthly educational campaign for 2 years through group education meeting and a massive educational campaign before two consecutive winters	Y (seasonal campaign)	health plan aggregated claims data	M
Coen 1998	9 European countries[2)]	453 GPs	overall	RCT	European Formulary and a session of group presentation during two hours	Y (no intervention)	individual pharmacy data	S
Diwan *et al.* 1995	Sweden	116 community health centres	antihyperlipidemics	RCT	group detailing of 4 sessions for encouraging lipid-lower drugs use according to guidelines	Y (no intervention)	individual pharmacy data	M
Fessler *et al.*, 2006	Germany	90 doctors (intervention)	antihyperlipidemics antidiabetics cardiovascular drugs	CBA	providing face-to-face small group discussions with educational printed materials	Y (mean of the area)	state-level aggregated claims data	M
Hagen *et al.* 2005	Canada	24 long-term care facilities	psychotropic drugs	CBA	offering a 30-minute academic detailing session and laminated copies of the algorithm of appropriate prescribing	Y (no intervention)	institutional pharmacy data	S
Knowlton and Knapp 1994	USA	18 community pharmacies	overall	RCT	providing one-day group workshop to initiate changes in medication prescriptions to contain costs, to enhance communication with patients and prescribers, and to intervene in drug-related problems, followed reminding mails	Y (no intervention)	health plan aggregated claims data	S
				CBA		Y (no intervention in a different region)		
Maclure *et al.* 1998	Canada	teleconference-282; workshop-192; letters-499 physicians	antihypertensives in elderly	CBA	implementing three sets of educatory interventions of teleconference, small group workshop, newsletter	Y (no intervention)	state-level aggregated claims data	M
Midlov *et al.* 2006	Sweden	15 practicies/ 54 doctors	benzodiazepines, antipsychotics in elderly	RCT	providing 2 group-educational visits to convey information concerning drug treatments that may cause confusion in the elderly	Y (no intervention)	commercial aggregated claims data	S

(continued)

Study	Setting	Population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
guideline-like information, group detailing (continued)								
Mohagheghi *et al*. 2005	Iran	80 GPs	antibiotics, injections	RCT	providing a group educational programme	Y (no intervention)	academic pharmacy data	S
guideline-like information, individual detailing								
Freemantle *et al*. 2002 Mason *et al*. 2001	UK	69 practices/ 162GPs	antiplatelets, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, antidepressants	RCT	providing clinical practice guidelines of study drugs and pharmacists outreach visits	Y (non-targeted guidelines)	institutional pharmacy data	S
Jackson *et al*. 2004	Australia	272 GPs (intervention)	antithrombotic drugs	CBA	posting locally produced guidelines on stroke risk stratification and recommendations antithrombotic drug use in atrial fibrillation, followed by an individual visit with general educational materials	Y (no intervention)	national aggregated claims data	S
Pit *et al*. 2007	Australia	16 practices/ 20 GPs	non steroidal anti-inflammatory drugs, low-dose thiazides, benzodiazepines in elderly	RCT	providing individual visits educating how to conduct medication reviews with educatory materials, feedback from patients and remunaration for time	Y (no intervention)	individual pharmacy data	S
Shuval *et al*. 2007	Israel	90 primary care doctors	thiazides, statins	RCT	providing 3 times evidence-based medication education and 6 times individual academic detailing visits	Y (no intervention)	health plan aggregated claims data	M
Simon *et al*. 2005	USA	9 practicies/ 781 prescribers	diuretics, beta-blockers	RCT	delivering a physician-educator meeting individually with clinicians to address barriers to prescribing guideline-recommended medications	Y (mailing prescribing guidelines)	health plan aggregated claims data	M
					group academic detailing			
Weatherby *et al*. 2001	USA	no information	cisapride	ITS (no control)	sending two times 'Dear Doctor' letters, followed by face-to-face information about labelling changes	N	health plan aggregated claims data	M

(continued)

Study	Setting	Population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
guideline-like information, computerised devices								
Filippi *et al*. 2003	Italy	300 GPs	antiplatelet drugs in high risk diabetic patients	RCT	offering automated electronic reminder alerting the need of study drugs with a educational letter	Y (letter-only)	data from medical association	S
Martens *et al*. 2007a	Netherlands	14 practices/ 53 GPs	antibiotics, asthma medications	RCT	applying a computer guideline real-time automated reminder system for study drugs	Y (same intervention for cholesterol prescribing)	individual pharmacy data	S
McMullin *et al*. 2004	USA	38 prescribers	overall	CBA	offering evidence-based decision support integrated into an electronic prescribing module	Y (no intervention)	health plan aggregated claims data	S
Murray *et al*. 2004	USA	no information	antihypertensives	RCT	providing computerised individual treatment suggestions based on patients' medical history to physicians to pharmacists to physicians and pharmacists	Y (no intervention)	institutional pharmacy data	S
Tamblyn *et al*. 2003	Canada	107 physicians	inappropriate prescribings	RCT	offering automated alerts for potential prescribing problems such as drug-disease contraindication, drug-age contraindication, excessive duration of therapy, therapeutic duplication, and drug interaction	Y (no intervention)	state-level aggregated claims data	M
Vedsted *et al*. 1997	Denmark	20 practices/ 28 GPs (intervention)	overall	ITS (control)	applying cost comparison information software delevering information about prescribing the cheapest varieties in a semiautomatic way	Y (another computer system) Y (no computer)	state-level aggregated claims data	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.
2) Belgium, England, Ireland, Italia, North Ireland, Portugal, Scotland, Spain

b) Prescribing feedback

Study	Setting	Population	Study drugs[1)]	Study design	Intervention	Control intervention	Data sources	Follow-up[2)]
group-level prescribing feedback, group detailing								
Bradley *et al*. 2000	UK	21 practices	gastrointestinal, cardiovascular, respiratory, central nervous, musculoskeletal medications, antibiotics	CBA	giving a group presentation of practice-specific prescribing information and advices for study drugs by educator	Y (no intervention)	national aggregated claims data	M
Braybrook and Walker 1996	UK	66 practicies	antibiotics	RCT	giving a group-level prescribing discussion visit with practice-specific prescribing analysis workbooks	Y (printed-material only)	national aggregated claims data	M
Braybrook and Walker 2000	UK	66 practicies	NSAIDs	RCT	giving a group-level prescribing discussion visit with practice-specific prescribing analysis workbooks	Y (printed-material only)	national aggregated claims data	S
Calvo Alcantara and Inesta Garcia 1999	Spain	10 general practices/ 48 physicians	generic drugs	CBA	conveying monthly educational seminars encouraging generic drugs use and prescribing feedback at group-level	Y (no intervention)	national aggregated claims data	S
Horn *et al*. 2007	Australia	a third of GPs (numbers given)	antihypertensives	ITS (no control)	mailing newsletter and general prescribing feedback followed by a small group educational detailing to encourage the first-line therapy	N	national aggregated claims data	M
Lassen and Kristensen 1992	Denmark	108 practices	overall	CBA	mailing a group prescribing feedback and encouraging to join local peer group discussions	Y (no intervention)	national aggregated claims data	S

(continued)

Study	Setting	Population	Study drugs[1)]	Study design	Intervention	Control intervention	Data sources	Follow-up[2)]
group-level prescribing feedback, group detailing (continued)								
von Ferber *et al*. 1999	Germany	89 GPs (on intervention)	antirheumatics, herbal prokinetics, enzymes, digestives, benzodiazepines, NSAIDs, H_2RAs, opioids, PPIs, varicose vein drugs, peripheral vasodilators	CBA	providing face-to-face small group discussions (8 meets) about poor quality prescribing over about 18 months with educational printed materials	Y (mean of the area)	state-level aggregated claims data	S
Wilson *et al*. 2003	Australia	40 GPs	antibiotics	RCT	providing educational materials (guidelines, disease-specific information sheets, prescription pad, poster), followed by a group meeting with prescribing feedback	Y (guideline only)	national or state-level aggregated claims data	M
Witt *et al*. 2004	Denmark	84 practices	asthma drugs	RCT	offering a outreach visit to discuss guideline recommending more inhaled steroids and less $ß_2$ agonists, and a practice-level prescription profile	Y (mailing the same information)	national aggregated claims data	S
group-level prescribing feedback, individual detailing								
Perez Rodriguez *et al*. 1996	Spain	16 GPs	overall	CBA	conducting face-to-face individual interviews with general prescribing profile	Y (no intervention)	state-level aggregated claims data	S
Sicras Mainar *et al*. 2004	Spain	107 nursing homes	antiulcers, antidepressants, antihypertensives, antiasthmatics, antibacterials, NSAIDs in elderly	CBA	providing face-to-face interview with educatory information, followed by prescribing monitoring and group-level feedback with personal follow-up interviews	Y (no intervention)	institutional pharmacy data	S
Sicras Mainar and Pelaez de Lono 2005	Spain	107 nursing homes		CBA		Y (no intervention)	institutional pharmacy data	M
Sicras Mainar *et al*. 2007	Spain	195 nursing homes		CBA		Y (no intervention)	institutional pharmacy data	M
individual-level prescribing feedback, passive								
Hux *et al*. 1999	Canada	251 primary care physicians	antibiotics	RCT	mailing confidential prescribing feedbacks and targeted educational bulletins in every 2 months for 6 months	Y (no intervention)	state-level aggregated claims data	S

(continued)

Study	Setting	Population	Study drugs[1)]	Study design	Intervention	Control intervention	Data sources	Follow-up[2)]
individual-level prescribing feedback, passive (continued)								
O'Connell *et al*. 1999	Australia	2440 physicians	overall	RCT	mailing two sets of graphical displays of individual prescribing rates with educational newsletters	Y (no intervention)	national aggregated claims data	S
Pimlott *et al*. 2003	Canada	374 physicians	benzodiazepines	RCT	mailing feedback report every 2 months for 6 months (3 times), including confidential profiles of benzodiazepines prescription use and evidence-based educational bulletines	Y (same intervention about antihypertensives)	state-level aggregated claims data	S
individual-level prescribing feedback, group detailing								
Finkelstein *et al*. 2001	USA	12 practices/ 157 prescribers	antibiotics in infants	RCT	2 small group meetings with a physician peer leader with CDC-endorsed summaries plus reinforcement visit with feedback on individual-, group-level prescribing practices, mailing to parents	Y (no intervention)	health plan aggregated claims data	S
Madridejos-Mora *et al*. 2004	Spain	282 family physicians	antibiotics, NSAIDs, antiulcerative agents	RCT	providing group detailing of goup-level performance, followed by informing individualised prescribing data and prescribing recommendations	Y (feedback of group prescribing data)	state-level aggregated claims data	S
Nilsson *et al*. 2001	Sweden	120 GPs	antihypertensives, antiulcers, antidepressants	RCT	providing feedback on individual prescribing rates and interative group educational visits	Y (no intervention)	institutional pharmacy data	S
Wensing *et al*. 2004	Germany	177 doctors	overall	CBA	providing written feedback on individual practice patterns, followed by group discussions comprising 11 sessions and repeated educational feedback on prescribing	Y (no intervention)	health plan aggregated claims data	M
individual-level prescribing feedback, individual contacts								
Raebel *et al*. 2007	USA	59,680 elderly patients	inappropriate prescribings in elderly	RCT	when newly prescribed a potentially inappropriate medication, not allowing the prescription label to print until the pharmacist actively intervened	Y (no intervention)	health plan aggregated claims data	S

1) H_2RAs; histamine-2-receptor antiagonists, NSAIDs; non steroidal anti-inflammatory drugs, PPIs; proton pump inhibiors

2) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

c) Drug utilisation review

Study	Setting	Population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
drug utilisation review, passive								
Allard *et al*. 2001	Canada	no information	various potential inappropriate prescribings	RCT	after a case conference and a telephone conversation, mailing individual recommendations to patients' physicians	Y (usual care)	individual pharmacy data	S
Atthobari *et al*. 2004	Netherlands	no information	antihypertensives, antihyperlipidemics	CBA	advising to use study drugs by post, sent both patients and their GPs	Y (mean of InterAction	academic pharmacy data	S
Collins *et al*. 1997	USA	no information	dipyridamole	CBA	sending the patients' dipyridamole drug use histories (DUR letter) with advising discontinuation to physician, or to pharmacist, or both physician and pharmacist	Y (no intervention)	state-level aggregated claims data	S
Rascati *et al*. 1996	USA	no information	anti-ulcer medications	CBA	sending letters to physicians about patients profiles that indicate possible inappropriate use of medicines	Y (no intervention)	state-level aggregated claims data	S
drug utilisation review, group detailing								
Fretheim *et al*. 2006a, 2006b	Norway	139 practices/ 501 physicians	antihypertensives, antihyperlipidemics	RCT	offering educational and feedback outreach visit, each Patient's information, computerised reminders, audit, feedback, printed guideline	Y (guidelines-only)	institutional pharmacy data	S
drug utilisation review, individual contacts								
Culbertson *et al*. 1999	USA	no information	atiulcer medications	CBA	mailing individual patients' DUR profiles to physicians and pharmacists, and phone call to pharmacists	Y (mailing to physicians only) Y (mailing to physicians and pharmacists)	state-level aggregated claims data	S

(continued)

Study	Setting	Population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
drug utilisation review, individual contacts (continued)								
Goldstein *et al*. 2005	USA	36 clinicians	antihypertensives	RCT	providing recommendations of patient's antihypertensive drug regimen at each visit of a study patient and individual physician's prescribing rates alongside with general intervention (group educational detailing)	Y (group educational detailing)	institutional pharmacy data	S
Gregoire *et al*. 2006	Canada	3 hospitals	cisapride	ITS (control)	providing concurrent drug utilisation reviews (DUR) over cisapride prescriptions after distributing prescribing criteria	Y (no intervention)	institutional pharmacy data	M
					providing retrospective drug utilisation reviews (DUR) over cisapride prescriptions after distributing prescribing criteria			
Samore *et al*. 2005	USA	12 communities	antibiotics	RCT	providing computerised decision support tolls on the basis of patient-specific information plus group-level educatory programmes (educational lectures, small group meetings, feedback on community-level antimicrobial prescribing data) and limited remuneration for time	Y (group-level feedback)	commercial market sales data	M
		18 communities		CBA		Y (no intervention)		

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

Annex 13: Characteristics of included studies exploring reimbursement restrictions

a) Delisting

Study	Setting	Patient population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
Breen *et al*. 2004	Australia	General	temazepam capsule	ITS (no control)	delist of temazepam capsules from benefit list to restrain the injection of temazepam capsules	N	national aggregated claims data	S
Campbell *et al*. 2003	Canada	Elderly	topical corticosteroid products	ITS (no control)	all but 2 combination topical corticosteroid products removed from the Nova Scotia Seniors' PharmaCare Program benefit list	N	state-level aggregated claims data	S
Soumerai *et al*. 1990	USA	Poor	various[2)]	ITS (no control)	delist of ineffective 12categories of drugs in New Jersey Medicaid programme	N	health plan aggregated claims data	M
Zechnich *et al*. 1998	USA	Poor	OTC drugs[3)]	ITS (no control)	eliminating universal coverage for OTC (with exceptions of family planning products, insulin, diabetic supplies)	N	state-level aggregated claims data	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

2) vasodilators, asthma and sedative combinations, gastrointestinal antispasmodics with sedatives, analgesic combinations, combination steroid-antibiotic creams and ointments, ineffective antiemetics, anagesic and sedative combinations, phenylbutazone-antiacid combinations, nitrate and meprobamate combinations, diuretic and potassium combinations, cerebral stimulants, antibiotic combinations

3) antiulcer and gastrointestinal preparations, antidiarrheals, laxatives, antihistamines, antitussives-expectorants, cough and cold preperations, multivitamins hematinics fungicides

b) Formularies or Preferred Drug Lists

Study	Setting	Patient population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
Abdelgawad and Egbuonu-Davis 2006	USA	Poor	statins	CBA	restrictions on prescribing cholesterol-lowering statins (Alabama, Texas, Virginia)	Y (no restrictions in New Jersey, North Carolina, Pennsylvania)	health plan aggregated claims data	S
Christian-Herman *et al*. 2004	USA	General	overall	CBA	generic-only drug coverage	Y (no restrictions)	state-level aggregated claims data	S

(continued)

Formularies or Preferred Drug Lists (continued)

Study	Setting	Patient population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
Huskamp *et al*. 2003b	USA	Elderly, disabled	various[2)]	ITS (no control)	National closed formulary in the Veterans Health Administration (VHA)	N	commercial market sales data	M
Kephart *et al*. 2005	Canada	Elderly	respiratory drugs	ITS (no control)	a criteria-based reimbursement on the use of respiratory drugs (portable inhaler preferable practice guideline rather than wet nebulisation therapy)	N	state-level aggregated claims data	M
Lichtenberg 2005a	USA	Poor	various[3)]	CBA	access restrictions (PDLs or PAs)	Y (non-Medicaid prescription claims)	state-level aggregated claims data	M
Motheral and Henderson 1999a	USA	General	overall	CBA	change from a open formulary to a closed formulary	Y (no closed formulary)	health plan aggregated claims data	S
Murawski and Abdelgawad 2005	USA	Poor	antihypertensives	CBA	Medicaid PDL with a prior authorisation requirements	Y (non Medicaid)	state-level aggregated claims data	S
Ridley and Axelsen 2006	USA	Poor	statins	CBA	PDL restricting access to certain branded medications and imposed a monthly prescription limit in Alabama Medicaid programme	Y (North Carolina)	commercial aggregated claims data	S
Virabhak and Shinogle 2005	USA	Poor	cardiovascular medications	ITS (control)	PDLs for the study drugs with a prior authorisation requirements for unpreferred drugs in Illinois, Louisiana Medicaid programmes	Y (no PDLs in New York, Mississippi)	health plan aggregated claims data	S
Wang *et al*. 2003	USA	Poor	proton-pump inhibitors	CBA	enacting a restrictive drug formulary for the study drugs with pantoprazole as the only preferred drug in Maine Medicaid programme	Y (no restrictions in New Hampshire, Vermont)	commercial market sales data	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months
2) angiotensin-converting enzyme inhibitors, statins, proton-pump inhibitors, histamine-2-receptor antagonist, alpha blockers, calcium-channel
3) antidepressants, antihypertensives, cholesterol-lowering drugs, diabetic drugs, osteoporosis/menopause drugs, pain management medications

c) Prior-authorisations

Study	Setting	Patient population	Study drugs[1)]	Study design	Intervention	Control intervention	Data sources	Follow-up[2)]
Carroll *et al.* 2006	USA	Poor	Cox_2 inhibitors	CBA	introducing a computerised programme for prior authorisation criteria (Missouri)	Y (no PA in eastern state)	state-level aggregated claims data	S
Delate *et al.* 2005	USA	Poor	proton-pump inhibitors	ITS (no control)	introducing prior authorisation for PPIs according to diagnosis- and risk-based clinical criteria	N	state-level aggregated claims data	S
Fischer *et al.* 2004	USA	Poor	Cox_2 inhibitors	ITS (control)	require physicians' clinical indications (high risk user) for prescribing Coxibs (22 states)	Y (no PA in 28 states)	state-level aggregated claims data	M
Hartung *et al.* 2004	USA	Poor	celecoxib	ITS (control)	requiring prescribing clinician to contact the pharmacy benefits company and to provide documentation verifying that the patients met the established criteria	Y (no PA)	state-level aggregated claims data	S
Kotzan *et al.* 1993a	USA	Poor	H_2RIs	ITS (no control)	limit Medicaid recipients requiring acute dosages of H_2 antagonist therapy to a 90-day supply, a prior-authorisation needed for extendsion the prescribing period	N	state-level aggregated claims data	S
Kotzan *et al.* 1993b	USA	Poor	NSAIDs	ITS (no control)	requiring a prior-authorisation for singlesource NSAIDs	N	state-level aggregated claims data	S
Marshall *et al.* 2007	Canada	Elderly	Cox_2 inhibitors	ITS (control)	need physicians' clinical indications for prescribing Coxibs in Ontario (limited use), prior authorisation in British Columbia	Y (no restrictions in Quebec)	health plan aggregated claims data	M
Roughead *et al.* 2006	USA	Poor	Cox_2 inhibitors	ITS (control)	need to get authorisation for prescribing Coxibs (19 states)	Y (17 states without restrictions)	state-level aggregated claims data	M
Smalley *et al.* 1995	USA	Poor	NSAIDs, other analgesics, psychotropics	ITS (no control)	requring mandatory advance approval for the use of nongenerics for NSAIDs in Tennessee Medicaid	N	state-level aggregated claims data	M
Yokoyama *et al.* 2007	USA	General	ACEIs, ARBs	CBA	introducing ACEIs first restrictions and prior authorisation needed for ARBs prescribed as an initial therapy	Y (no restrictions)	health plan aggregated claims data	S

1) ARBs; angiotensin-receptor blockers, Cox_2 inhibitors; cyclooxygenase inhibitors, H_2RAs; histamine-2-receptor antagonists, NSAIDs; nonsteroidal anti-inflammatory drugs
2) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

d) Step-therapies or limited-uses

Study	Setting	Patient population	Study drugs[1)]	Study design	Intervention	Control intervention	Data sources	Follow-up[2)]
Dunn *et al*., 2006	USA	General	antidepressants	CBA	a brand-name antidepressant was covered only after trial with a generic antidepressants, excluding TCAs, no medical exception or prior authorisation allowed	Y (pharmacy claims without interventions)	health plan aggregated claims data	S
Fretheim *et al*. 2007	Norway	General	antihypertensives	ITS (no control)	applying a new reimbursement rule for antihypertensives (starts with thiazides if not, require a medical reason in the medical record), no penalties for non-adherence	N	institutional pharmacy data	S
MacCara *et al*. 2001	Canada	Elderly	fluoroquinolones	ITS (no control)	imposing reimbursement guideline requiring a physician-completed Request for Exception Status Drug Form to receive a fluoroquinolone (ciprofloxacin, ofloxacin, norfloxacin) as a benefit	N	state-level aggregated claims data	S
Mamdani *et al*. 2007	Canada	Elderly	fluoroquinolones	ITS (no control)	ciprofloxacin, ofloxacin on the limited use list as a second-line therapy, required that prescribers indicate the reason for use	N	state-level aggregated claims data	S
Marshall *et al*. 2006	Canada	Elderly	fluoroquinolones	ITS (no control)	ciprofloxacin, ofloxacin on the limited use list as a second-line therapy	N	state-level aggregated claims data	M
Motheral *et al*. 2004	USA	General	PPIs, SSRIs, NSAIDs	ITS (control)	generic first step-therapy	Y (no restrictions)	health plan aggregated claims data	S
Schneeweiss *et al*. 2004	Canada	Elderly	ineffective asthma medications	RCT	limiting reimbursement for study drugs with exception of appropriate clinical reasons given by doctors	Y (exempted patients)	state-level aggregated claims data	S
Schneeweiss et al. 2006	Canada	Elderly	proton-pump inhibitors	ITS (no control)	restricting benefit coverage to rabeprazole in case of the failure in treatment with H2 blockers, and to other PPIs with doctors' exemption request	N	state-level aggregated claims data	S
Sun *et al*. 2007	USA	General	non-sedating antihistamines (NSAs)	CBA	moving NSAs to non-preferred status (**F**ormulary change only group)	Y (prefered status with original copayments)	health plan aggregated claims data	S
					implementing the NSA step care programme requiring the utilisation of an efficacious first-line agent before alternative therapies (**S**tep therapy only group)			
					introducing both (**F&S**)			

1) NSAIDs; nonsteroidal anti-inflammatory drugs, NSAs; non-sedating antihistamines, PPIs; proton-pump inhibitors, SSRIs; selective serotonin reuptake inhibitors

2) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.

Annex 14: Characteristics of included studies exploring incentives

a) UK fundholding

Study	Intervention population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
Baines *et al*. 1997	41 fundhloders	overall	CBA	1st wave of fundholding in Lincolnshire and Devon	Y (192 non-fundholders)	national aggregated claims data	M
Bradlow and Coulter 1993	5 non-dispensing fundhold practices / 3 dispensing fundlhold practices	overall	CBA	1st wave of fundholding in Oxford region	Y (7 non-fundholding practices)	national aggregated claims data	S
Corney and Kerrison 1997	19 fundholding practices	overall	CBA	1st/2nd wave of fundholding in the South Thames Region	Y (4 non-fundholding practices	national aggregated claims data	M
Harris and Scrivener 1996	2649 fundholders	overall	CBA	1st~5th wave of fundholding in England	Y (non-fundholding practices)	national aggregated claims data	M
Rafferty *et al*. 1997	66 fundolders	overall	CBA	1st~3rd wave of fundholding in Northern Ireland	Y (268 non-fundholding practices)	national aggregated claims data	M
Whynes *et al*. 1995	19 fundholders	overall	CBA	1st~3rd wave of fundholding in Lincolnshire	Y (86 non-fundholding practices)	national aggregated claims data	M
Whynes *et al*. 1997	23 fundholders	overall	CBA	4th wave of fundholding in Lincolnshire	Y (19 1st~3rd fundholders) / Y (63 non-fundholders)	national aggregated claims data	S
Wilson *et al.* 1995	100 fundholders	overall	CBA	1st~3rd wave of fundholding in former Mersey Regional Health Authority	Y (all non-fundholders)	national aggregated claims data	S
Wilson *et al*. 1999	52 fundholding practicies	overall	CBA	3rd/4th wave of fundholding in the Northwest Region	Y (52 non-fundholding practices)	national aggregated claims data	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

b) Global budgets and others

Study	Setting	Intervention population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
global budget								
Etter and Perneger 1998	Swizerland	no information	overall	CBA	introducing a global budget on a capitation basis	Y (fee-for-service)	health plan aggregated claims data	S
Granlund *et al.* 2006	Sweden	no information	overall	CBA	introducing fixed pharmaceutical budgets	Y (open-ended budgets)	state-level aggregated claims data	S
Lee *et al.* 2006	Taiwan	no information	overall	ITS (no control)	introducing a flat rate of payment for pharmaceuticals per day	N	national aggregated claims data	M
Yip and Eggleston 2004	China	14 hospitals	expensive drugs	ITS (control)	introducing a prepayment sheme, 90% of the amount of budget reimbursed for a given month the previous year with offering a set of cost reduction incentives	Y (fee-for-service)	institutional pharmacy data	S
others								
Elhayany *et al.* 2001	Israel	9 primary care practices	overall	CBA	offering an itemized budget, no penalties were imposed on practices where expenditure exceeded budget	Y (expenditure in the district as a whole)	health plan aggregated claims data	M
Law and Wu 2003	Canada	1 pharmacy/ 11 physicians	various[2)]	ITS (control)	sharing the savings with pharmacist and insurer through recommendation by pharmacist to make a substitution of a lower-priced therapy	Y (other physicians without pharmacists' intervention)	state-level aggregated claims data	S
Martens *et al.* 2007b	Netherlands	237 GPs	antibiotics, gastric medicines	CBA	offering performance independent one-off bonus	Y (no bonus in other region)	health plan aggregated claims data	S
O'Malley *et al.* 2006	USA	2,107 physicians	various[3)]	CBA	offering reward payments for generic prescribing	Y (no intervention)	health plan aggregated claims data	M

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

2) lipid-lowering drugs, angiotensin-converting enzyme inhibitors, antiasthmatics (inhalants, glucocorticoids)

3) angiotensin-converting enzyme inhibitors, α-blockers, calcium channel blockers, oral hypoglycemics, proton-pump inhibitors, selective norepinephrine reuptake inhibitors, selective serotonine reuptake inhibitors

Annex 15: Characteristics of included studies exploring other interventions influencing providers

Study	Setting	Population	Study drugs	Study design	Intervention	Control intervention	Data sources	Follow-up[1)]
distribution of samples								
Mukamal *et al.* 2002	USA	10 primary care practices/ 44 physicians	various[2)]	ITS (control)	removal non-formulary drugs from sample closets	Y (no intervention)	health plan aggregated claims data	S
O'Malley *et al.* 2006	USA	289 physicians (on intervention)	various[3)]	CBA	providing free generic sampling	Y (no intervention)	health plan aggregated claims data	M
Scott *et al.* 2007	USA	1,014 physicians (on intervention)	various[4)]	CBA	an automated generic drug sampling system, provide sample bottles of generics in the physician's office at the point of care with complementing academic detailing	Y (all other physicians without intervention in the region)	health plan aggregated claims data	M
mandatory generic substitution								
Andersson *et al.* 2007	Sweden		overall	ITS (no control)	pharmacists should dispense the cheapest substitutable products on the list	N	commercial aggregated claims data	M
repeat prescribing								
Bond *et al.* 2000	UK	19 general practice/ 71GPs	overall	RCT	after instalment, the prescriptions were kept by a pharmacist	Y (usual care)	institutional pharmacy data	S
separation of prescribing and dispensing drugs								
Chou *et al.* 2003	Taiwan	1610 clinics	overall	CBA	SPD in primary care clinics with allowing on-site pharmacy, no changes in hospitals (Kaohsung, Taipei)	Y (no change in Hsin-Chu, Tainan)	national aggregated claims data	S

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

2) antihypertensives, antihyperlipidemics, antibiotics, histamine-2-receptor antagonists, nonsteroidal anti-inflammatory drugs

3) angiotensin-converting enzyme inhibitors, α-blockers, calcium channel blockers, oral hypoglycemics, proton-pump inhibitors, selective norepinephrine reuptake inhibitors, selective serotonine reuptake inhibitors

4) angiotensin-converting enzyme inhibitors, antihypertensions, antibiotics, antilipidemics, histamine-2-receptor antagonists, nonsteroidal anti-inflammatory drugs, hypoglycemics, topical corticosteroids, selective serotonine reuptake inhibitors

Annex 16: Characteristics of included studies exploring reference-pricing schemes

Study	Setting	Population	Study drugs[1)]	Study design	Date of change	Clustering				Set price	Control intervention[2)]	Data sources	Follow-up[3)]
						same active ingredient	therapeutic class	therapeutic effect	including patents				
Andersson *et al.* 2006	Sweden	General	Overall	ITS (no control)	JAN. 1993	Y			N[4)]	Lowest+10 % mark up[5)]	N	national aggregated claims data	M
Bergman and Rudholm 2003	Sweden	General	18 drug ingrediants facing patent expiry[6)]	ITS (no control)	JAN. 1993	Y			N[4)]	Lowest+10 % mark up	N	national aggregated claims data	M
Grootendorst and Stewart 2006	Canada	Elderly	ACEIs, CCBs	ITS (control)	JAN. 1997		Y		N[7)]	Lowest daily cost[8)]	Y (no RP)	state-level aggregated claims data	M
Grootendorst *et al.* 2001	Canada	Elderly	nitrates, CCBs	ITS (no control)	NOV. 1995 (nitrates)		Y		N[7)]	Lowest daily cost	N	state-level aggregated claims data	M
					JAN. 1997 (CCBs)		Y						
Grootendorst *et al.* 2005	Canada	Elderly	NSAIDs	ITS (no control)	APR. 1994	Y			N[7)]	Lowest daily cost	N	state-level aggregated claims data	L
					NOV. 1995		Y						
Hazlet and Blough 2002	Canada	Elderly	H_2RAs (PPIs)	ITS (control)	OCT. 1995		Y		N[7)]	Lowest daily cost	Y (no RP)	state-level aggregated claims data	S
Mabasa and Ma 2006	Canada	General	PPIs	CBA	JUN. 2003		Y		Not available	Lowest daily cost	Y (no MAC)	state-level aggregated claims data	M
Marshall *et al.* 2002	Canada	Elderly	H_2RAs (PPIs)	ITS (no control)	OCT. 1995		Y		N[7)]	Lowest daily cost	N	state-level aggregated claims data	M

(continued)

Study	Setting	Population	Study drugs[1)]	Study design	Date of change	Clustering				Set price	Control intervention[2)]	Data sources	Follow-up[3)]
						same active ingredient	therapeutic class	therapeutic effect	Including patents				
Pavenik 2002	Germany	General	oral antidiabetics, antiulcerants	ITS (no control)	1989 (antidiabetics)	Y (1989)	Y (1991)	Y (1992)	Y[9)] (until 1996)	Middle[10)]	N	commercial market sales data	L
					1992 (antiulcerant)			Y (1992)					
Puig-Junoy 2007	Spain	General	statins	ITS (control)	MAY. 2002 (lovastatin)	Y			N	Average of the three lowest	Y (other price policy)	commercial market sales data	M
					JAN. 2004 (simvastatin)	Y							
Schneeweiss *et al*. 2002b	Canada	Elderly	ACEIs	ITS (no control)	JAN. 1997		Y		N[7)]	Lowest daily cost[8)]	N	state-level aggregated claims data	S
Schneeweiss *et al*. 2002c	Canada	Elderly	ACEIs	CBA	JAN. 1997		Y		N[7)]	Lowest daily cost[8)]	Y (non-switchers)	state-level aggregated claims data	S
Schneeweiss *et al*. 2003	Canada	Elderly	dihydropyridine CCBs	ITS (no control)	JAN. 1997		Y		N[7)]	Lowest daily cost[8)]	partly Y (non-switchers)	state-level aggregated claims data	M
				CBA									S

1) ACEIs; angiotensin converting enzyme inhibitors, CCBs; calcium channel blockers, H_2RAs; histamine-2-receptor antagonists, NSAIDs;nonsteroidal anti-inflammatory agents,
2) RP refer to reference pricing; MAC refer to therapeutic maximum allowable cost.
3) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months.
4) Mrazek 2002
5) Bergman and Rudholm 2003
6) cimetidine, sucralfate, etacrynic acid, atenolol, pindolol, azapropazone, dicrofenac, naproxen, piroxicam, sulindac, lorazepam, oxazepam, clomipramine, lofepramine, maprotiline, mianserine, protriptyline and dipivefrin
7) Lopez-Casasnovas and Puig-Junoy 2000
8) Grootendorst *et al*. 2001
9) Danzon and Ketcham 2003
10) below the price of the most expensive brand but above the prices of the generics

Annex 17: Characteristics of included studies exploring other price controls

Study	Setting	Population	Study drugs	Study design	Intervention	Data sources	Follow -up[1)]
Almarsdottir *et al.* 2000	Iceland	General	Overall	ITS (no control)	deregulation of OTC price set and pharmacy ownership liberalisation	national aggregated claims data	M
Lee *et al.* 2006	Taiwan	General	Overall	ITS (no control)	6 times price adjustments	national aggregated claims data	L
Sawyer 1983	USA	Poor	Overall	ITS (no control)	Maximum Allowable Cost (MAC) programme setting upper limit of reimbursement of prescribed drugs	state-level aggregated claims data	M

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

Annex 18: Characteristics of included studies exploring other interventions regulating industry

Study	Setting	Population	Study drugs	Study design	Data sources	Follow-up[1)]
formal quest for cost-effectiveness information in market authorisation						
Lundkvist *et al*. 2006	Finland, Sweden	General	242 new chemical entity drugs	ITS (no control)	data from the regulatory authorities	M
patent regulation						
Boersma *et al.* 2005	Netherlands	General	18 pharmaceuticals facing patent expiry[2)]	ITS (no control)	academic pharmacy data	M
profit control						
Borrell 1999	UK	Poor	various[3)]	ITS (no control)	national price index	L

1) L refer to longer than 60 months; M the period between longer than 12 months and 60 months; S equal or less than 12 months

2) products for enalapril, fluoxetine and ranitidine

3) central nervous system medicines, cardiovascular medicines, respiratory system medicines, antiulcerants, mscular and skeletal system preparations, dermatologics, antiinfectives

Annex 19: Follow-up period by intervention

Intervention	Follow-up period			No. of studies
	≤ 12 months	> 12 months & ≤ 60 months	> 60 months	
Total (%[1])	**99 (54)**	**79 (43)**	**7 (4)**	**185[2] (100)**
patients				*46*
cost-sharing	9	18	3	30
prescription caps	4	1		5
tiered formulary	4	5		9
educational approach	1			1
OTC switch		1		1
providers				*119*
educational approaches	41	22		63
reimbursement restrictions	24	9		33
incentives	9	8		17
distribution of samples	1	2		3
mandatory generic substitution		1		1
repeat prescribing	1			1
SPD[3]	1			1
industry				*20*
price control - reference pricing	4	8	2	14
price control - others		2	1	3
market authorisation		1		1
patent regulation		1		1
profit control			1	1

1) rounded

2) number of included studies by intervention; Schneeweiss *et al*. 2002 is included twice

3) Separation of Prescribing and Dispensing of drugs

Annex 20: Outcome variables by intervention

Intervention	*No. of studies*	Utilisation	Expenditure	Out-of-pocket	Other services use	Heath outcomes
patients	***46***	***42***	***23***	***9***	***9***	***0***
cost-sharing	*30*	26	12	2	4	
prescription caps	*5*	5	2		2	
tiered formulary	*9*	9	8	7	2	
educational approach	*1*	1	1			
OTC switch	*1*	1			1	
providers	***119***	***84***	***54***	***4***	***16***	***6***
educational approaches	*63*	42	18		4	5
reimbursement restrictions	*33*	28	20	3	10	1
incentives	*17*	9	14			
distribution of samples	*3*	3				
mandatory generic substitution	*1*		1	1		
repeat prescribing	*1*	1			1	
SPD[1)]	*1*	1	1		1	
industry	***19***	***11***	***12***	***4***	***3***	***1***
price control - reference pricing	*13*	11	9	4	3	1
price control - others	*3*		3			
market authorisation	*1*					
patent regulation	*1*					
profit control	*1*					

1) Separation of prescribing and dispensing of drugs

Annex 21: Example of the categorisation of brand and generic drugs for amlodipine derivatives

active ingredient	market name		producers or marketer		insured code	Korean bioequivalent reference list	hospital pharmacy database	FDA or EMEA	news or firm
	Korean	English	Korean	English					
brand drugs									
amlodipine besylate 5mg	노바스크정5mg	Novasc	한국화이자	Pfizer Korea	A03102361	YES	YES	YES	YES
amlodipine besylate 5mg	노바스크정5mg	Novasc	한국화이자	Pfizer Korea	E01890381	YES	YES	YES	YES
valsartan 160mg/amlodipine besylate 5mg	엑스포지정 5/160mg	Exforge	한국노바티스	Novartis Korea	E01631481		YES	YES	YES
valsartan 80mg/amlodipine besylate 5mg	엑스포지정 5/80mg	Exforge	한국노바티스	Novartis Korea	E01631491		YES	YES	YES
valsartan 160mg/amlodipine besylate 10mg	엑스포지정 10/160mg	Exforge	한국노바티스	Novartis Korea	E01631501		YES	YES	YES
generic drugs									
amlodipine besylate 5mg	국제암로디핀정5mg	Kukje amlodipine	국제약품공업	Kukje Pharm. Co.	A03006261				
			and 1 product						
amlodipine maleate 5mg	에이엠정	AM	코오롱제약	Kolon Pharmaceuticals, Inc.	A04705321				
			and 58 products						
amlodipine maleate 2.5mg	암로핀캡슐2.5mg	Amlopin	유한양행	Yuhan corporation	A04506691				
amlodipine camsylate 5mg	아모디핀정	Amodipin	한미약품	Hanmi Pharmaceutical Co., Ltd.	A21404061			YES	
amlodipine adipate 5mg	암로디아정5mg	Amrodia	한일약품공업	Hanil Pharmaceuticals.	A01050671				
			and 1 product						
amlodipine maleate monohydrate 5mg	암로맥스정5mg	Amlomax	근화제약	KunWha Pharmaceutical Co., Ltd.	A07208521	YES			
amlodipine maleate monohydrate 10mg	암로맥스정10mg	Amlomax	근화제약	KunWha Pharmaceutical Co., Ltd.	A07208531				
amlodipine orotate 5mg	오로디핀정	Orodipine	동아제약	Dong-A pharmaceutical	A01508491	YES		YES	
amlodipine nicotinate 5mg	암로텐정	Amloten	일동제약	IlDong pharmaceutical Co., Ltd.	A03452091				
			and 2 products						
s-amlodipine besylate 2.5mg	암로에스정2.5mg	Amlo-S	대한뉴팜	Daehan New Pharm Corporation	A60657251				
			and 3 products						
s-amlodipine nicotinate 2.5mg	하이탑핀정	Hytoppin	신풍제약	Shin Poong Pharm. Co., Ltd.	A00306981				
			and 1 product						

Annex 22: Autoregressive integrated moving average (ARIMA) modelling and an empirical example

ARIMA model

An ARIMA model is a model of the stochastic process which generated the observed time series. ARIMA modelling is an iterative process involving several steps; 1) Identification, 2) Estimation and 3) Diagnosis (McCain and McCleary, 1979).

1) Identification

At the identification step, correlogram, the autocorrelation function (ACF) and partial autocorrelation function (PACF) computed from the time series observations is used to select a tentative ARIMA model for the series. If the series is nonstationary, it needs to be turned into a stationary series (McCain and McCleary, 1979). A stationary series is one that has no secular trend in its mean and variance. A nonstationary time series can be made stationary by differencing and in such a case a time series is technically said to be nonstationary in the homogeneous sense. Differencing can be performed regularly or seasonally. Autoregressive processes, moving average processes, seasonal autoregressive processes, seasonal moving average processes, or mixed processes of them can be specified on the basis of correlogram (McCain and McCleary, 1979).

2) Estimation

After a tentative ARIMA model has been identified, the values of parameters, say the Φ and θ, of the model are estimated (McCain and McCleary, 1979). Two basic criteria in estimating parameters should be satisfied (McDowall *et al.*, 1980). First, the estimated autoregressive and moving average parameters should be statistically significant. Second, the estimated parameters must lie within the bounds of stationarity and invertibility (stationarity-invertibility conditions). The bounds of stationarity for the parameters is

$$-1 < \Phi_p < +1.$$

The bounds of invertibility is

$$-1 < \theta_p < +1.$$

If p is more than one (i.e. ARIMA models in a higher order autoregressive or moving average process) then the sum of Φs or sum of θs should be less than unity.

3) Diagnosis

If a tentative model is statistically adequate, its residuals would satisfy two diagnostic criteria (McCain and McCleary, 1979). First, there are no spikes at lag 1 and the seasonal lags of the ACF and PACF. Second, these residuals must be white noise. The Box-Ljung Q statistic is often employed in practice to test this hypothesis. If either criterion is not met in the Estimation or Diagnosis step, then the whole process of identification, estimation, and diagnosis is repeated to select a new model.

Impact Assessment Model

An interrupted time series analysis aims to explore whether the intervention had any impact at the specific time point the intervention occurred (Shadish *et al.*, 2002c). The underlying concept is to establish whether the intervention component adds significantly to predicting the behaviour of a time series over and above the prediction that is offered through an understanding of the regular and seasonal components of the noise. In other word, the impact of an intervention can be assessed after controlling a noise component (trend, seasonality and so forth) using an ARIMA model. Representing the ARIMA model as N_t, the impact assessment model may be written as

$$Y_t = f(I_t) + N_t$$

where Y_t is a dependent variable of interest; N_t denotes a noise component; and $f(I_t)$ denotes an intervention component (McCleary *et al.*, 1980a).

Impact assessment begins with identifying an ARIMA model for the time series, which describes the stochastic behaviour of the time series process. An intervention component is then added to the identified ARIMA model (McDowall *et al.*, 1980). At this step, there are several distinct functions of $f(I_t)$ which correspond to several distinct types of impact. Among them three transfer functions are generally explored in empirical research, which reflect 1) an abrupt, permanent change, 2) a gradual, permanent change, and 3) an abrupt, temporary change (McCain and McCleary, 1979).

1) Abrupt, permanent change

An abrupt, permanent change is where the time series immediately changes its level at the time of the intervention and the change persists over time. The transfer function model for this intervention effect is written as:

$$Y_t = \omega I_t + N_t$$

where ω is a parameter interpreted as the magnitude of the abrupt, permanent change and where N_t is an ARIMA model. The independent variable I_t is a dummy variable such that:

$I_t = 0$ before the intervention, $t < /$

$= 1$ after the intervention, $t \geq /$

where / is the time of the intervention (McCain and McCleary, 1979).

Thus, the intervention hypothesis test for this transfer function is a test of significance for the ω parameter which is the magnitude of the shift.

2) Gradual, permanent change

A gradual, permanent change can be characterised as beginning gradually at the introduction point rather than abruptly and the treatment effect persists for a long period, eroding slowly. The transfer function model for this intervention effect is written as:

$$Y_t = \delta Y_{t-1} + \omega I_t + N_t$$

where ω is a parameter interpreted as the magnitude of changes at the moment of intervention and where δ is a parameter to be estimated from the data, determining how gradually the series will change from time to time. Again, N_t refers an ARIMA model for noise and the independent variable I_t is a dummy variable (McCain and McCleary, 1979). The intervention hypothesis test for this transfer function is a test of significance for both ω and δ. When δ is very small, for example δ=0.1 or smaller, the impact can be interpreted abrupt and permanent rather than gradual (McCain and McCleary, 1979).

3) Abrupt, temporary change

The last transfer function model describes an abrupt but temporary intervention effect. That is:

$$Y_t = \delta Y_{t-1} + \omega I_t + N_t$$

where I_t is defined a pulse function such that

$I_t = 0$ before the intervention, $t < /$

$= 1$ at the moment of intervention, $t = /$

$= 0$ thereafter, $t > /$

where / is the time of the intervention (McCain and McCleary, 1979).

The intervention causes a profound change in level at the time of introduction and the magnitude of change is ω. However, after the temporary spike, the series has returned

to its pre-intervention level. The parameter δ is interpreted as the momentary rate of decay of the spike. When δ is large, for example δ=0.9 or larger, the treatment effect erodes slowly, indicating a permanent change (McCain and McCleary, 1979).

Specifying the Transfer Function

The transfer function should be determined a priori. If there is a reasonable priori notion relating to the nature of the hypothesised effect, then a transfer function can be selected accordingly. However, in practice, it may be uncertain which transfer function may be more adequate.

So, instead of making a priori choice of which transfer function to use, analyses often start with a transfer function for an abrupt, temporary change:

$$Y_t = \delta Y_{t-1} + \omega I_t$$

where I_t is defined as a pulse function as discussed above. The δ parameter is a greater than zero but less than unity, that is:

$$0 < \delta < +1.$$

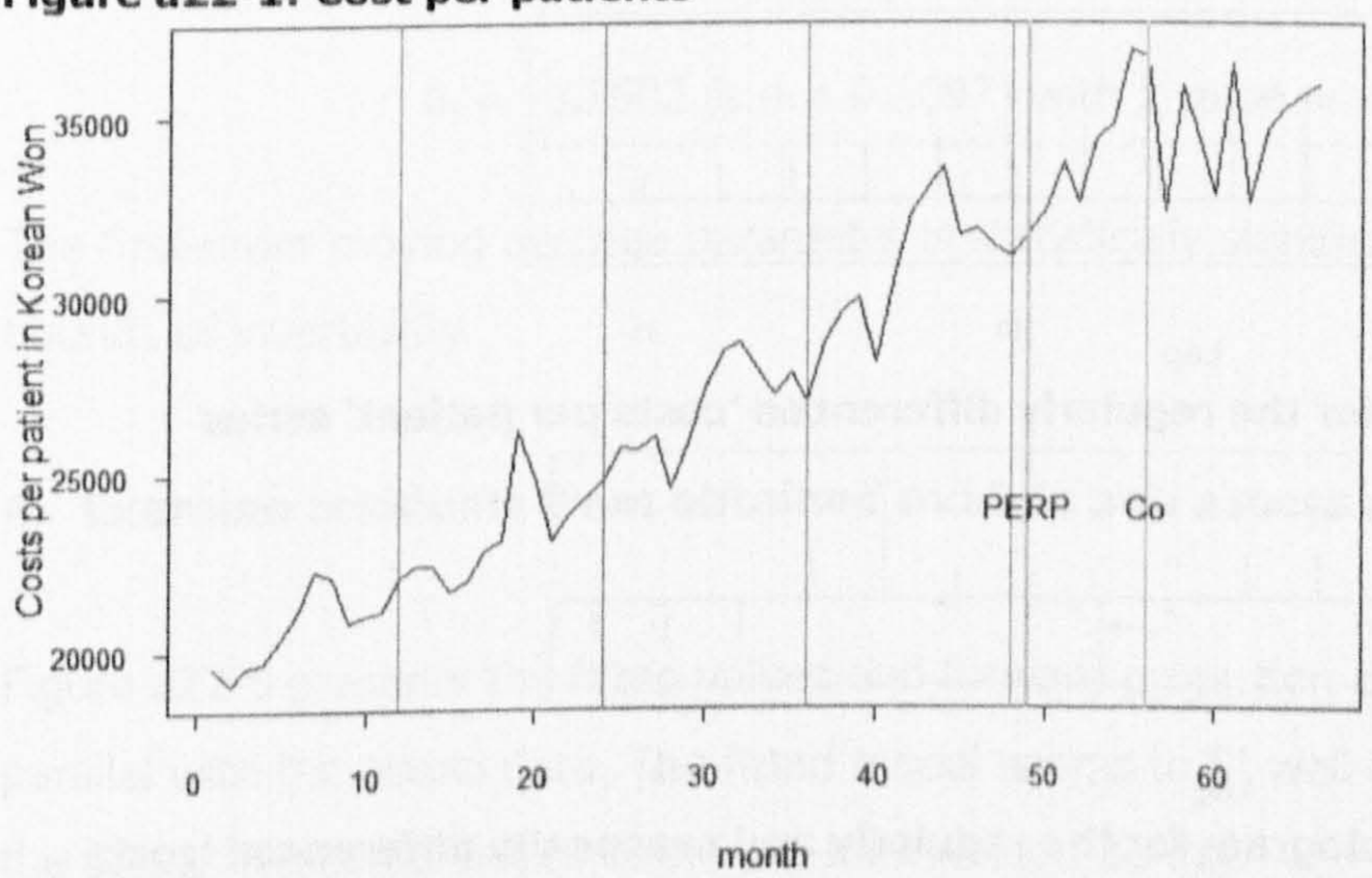
These constraints on the δ parameter are called the bounds of system stability (McDowall *et al.*, 1980). If the δ parameter is not constrained to these bounds, then the time series system is unstable, indicating nonstationary. If the estimated value of δ is relatively large, say δ = 0.9 or larger, then this could be considered as evidence of a permanent effect. Then, the analysis is replicated using a transfer function for a gradual, permanent change (i.e. the same equation as above but with I_t defined as a dummy variable). At this step if the estimated value of δ is relatively small, say δ = 0.1 or smaller, then this could be considered as evidence that the effect is both permanent and abrupt. Then, the analysis is replicated using a transfer function for an abrupt, permanent change (McCain and McCleary, 1979). Analyses in the present study followed the same principles unless there was a clear a priori notion as to the nature of the hypothesised intervention effect.

Empirical example

1. Visual examination of the time plot of the data series of interest

The first step in the analysis is to plot observations against time to scrutinise any irregular variations or patterns of the series such as trend, seasonality, outliers and discontinuities. Figure a22-1 presents a time series graph of the 'costs per patient' each month in South Korea from January 2003 to June 2008. Two study policies to contain pharmaceutical expenditure were introduced at the 49th (PERP) and 56th (Co) time points.

Figure a22-1: Cost per patients



1) Stationarity

The plot shows a clear upward trend over time, indicating a nonstationary time series. Hence, visual examination of this time series data suggests differencing the raw data to make it stationary.

2) Seasonality

The plot also shows the seasonal periodicity. Individual drug costs rise in summer and fall in spring and autumn. This pattern repeats every year and the length of the cycle seems to be almost 12 months. Therefore, multiplicative ARIMA seasonal models would be considered if there is clear evidence in the residual analysis.

3) Outlier and intervention impact from the visual examination

There are neither prominent outliers in the data nor is there an abrupt drop or rise

demonstrated in the post-intervention data. It is seen that the underlying data structure appears to be altered after the second policy.

2. Examination of correlogram to identify a 'noise' model

In specifying a tentative noise model, a time series data structure in the pre-intervention region is used. An ACF and PACF are estimated to investigate autocorrelations. The ACF shows an obvious trend in the data, suggesting differencing (Figure a22-2). Figure a22-3 shows the ACF estimated from the differenced data. A large spike is seen at lag-12 in the ACF, indicating seasonal periodicity.

Figure a22-2: The ACF for the raw 'costs per patient' series

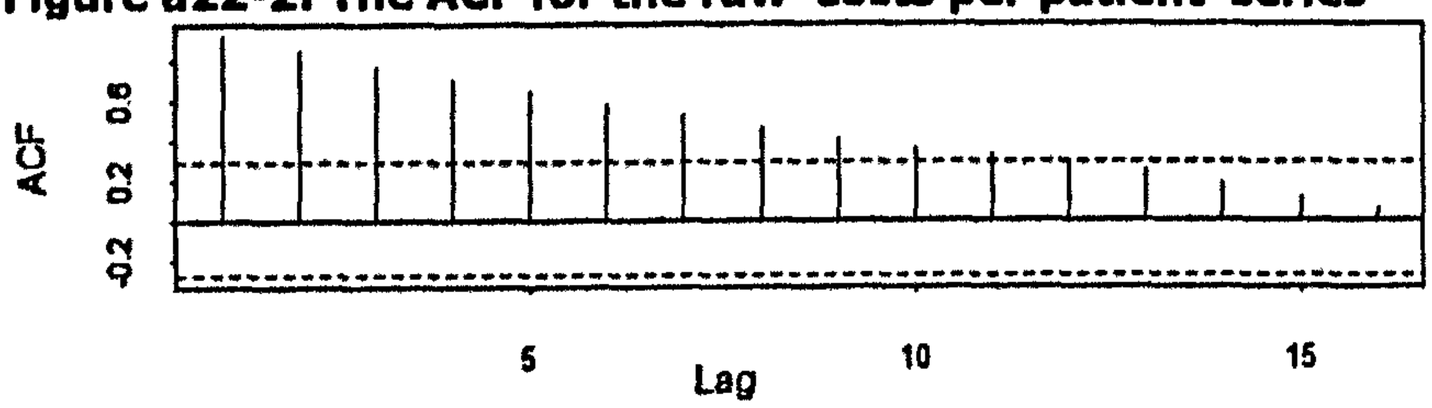


Figure a22-3: The ACF for the regularly differenced 'costs per patient' series

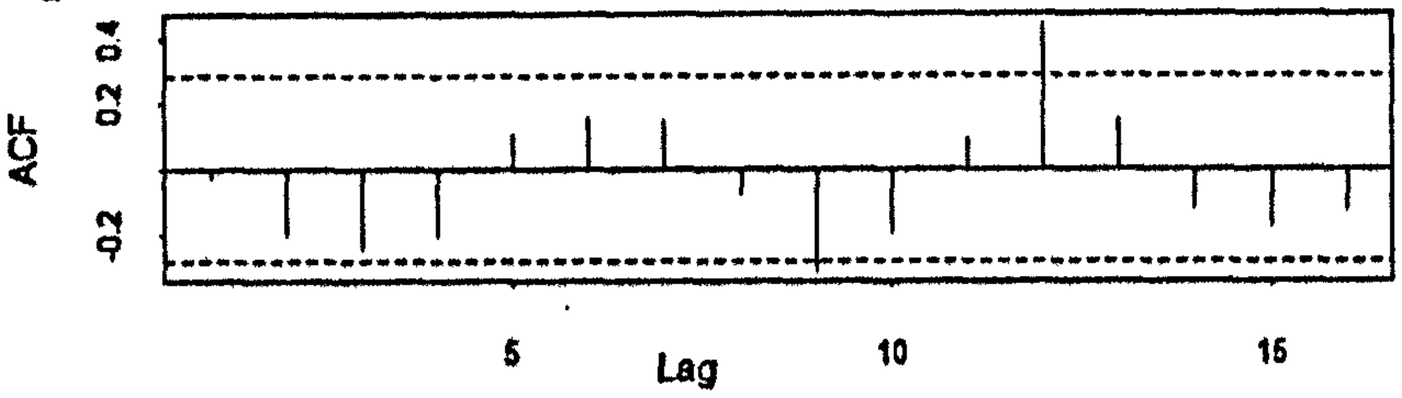
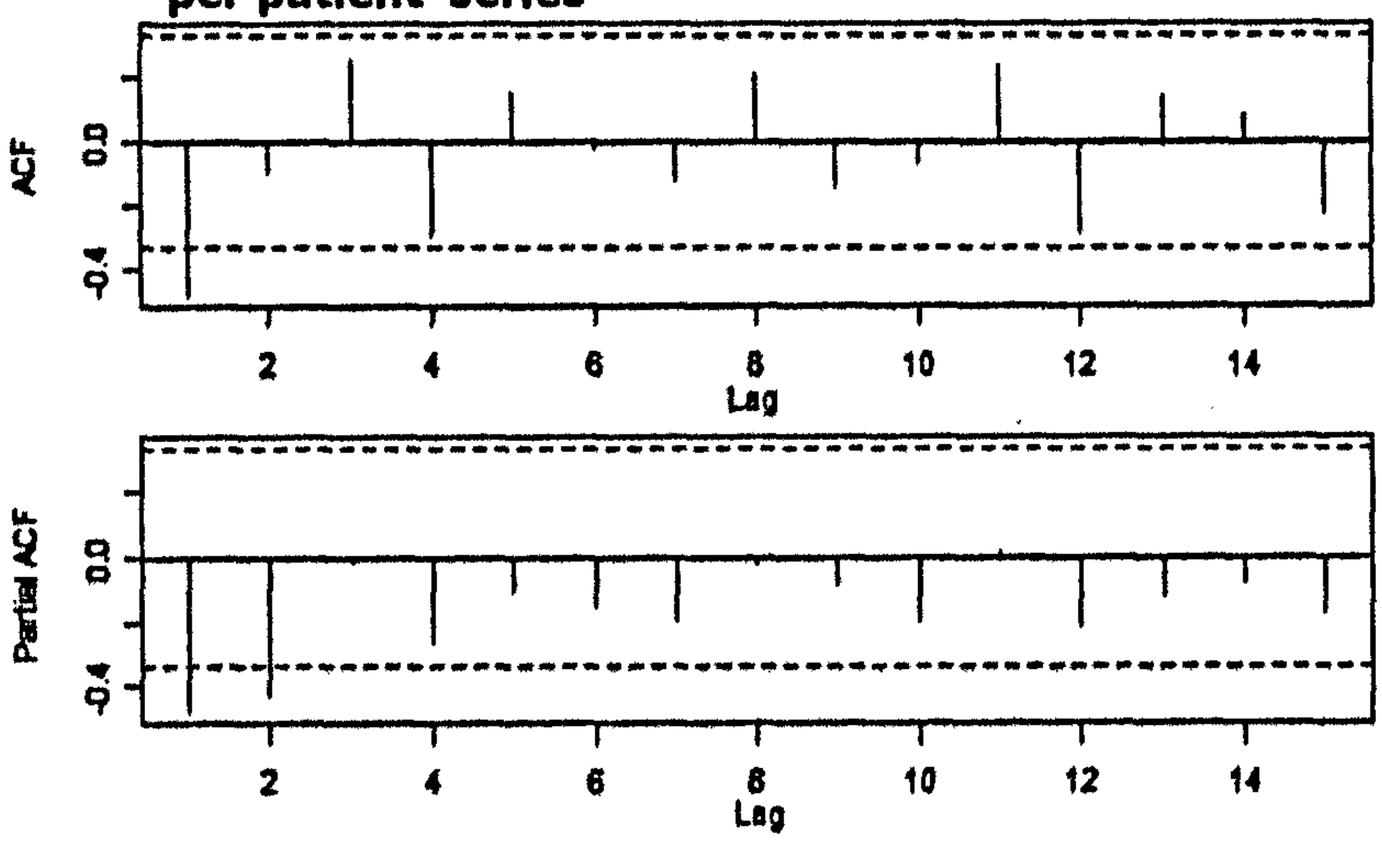


Figure a22-4: The correlogram for the regularly and seasonally differenced 'costs per patient' series



To deal with the apparent seasonal periodicity, the series differenced seasonally as well as regularly is inspected. The seasonally differenced model looks like the most useful data structure to consider. The correlogram presented in Figure a22-4 strongly

suggests at least one moving average term and indicates some autoregressive terms, possibly two.

From the simplest model which is MA(1) on the differenced series, i.e. ARIMA(0,1,1)(0,1,0) $_{12}$, several models with parameters slightly different from the ones in the simplest model are explored. The AIC values are used to choose a best model among them. From this point of view, the model given above produces the smallest AIC values and appears to be the most appropriate for the data.

3. Estimation of parameters and check them within basic criteria

Parameter estimates for an ARIMA $(0,1,1)(0,1,0)_{12}$ are:

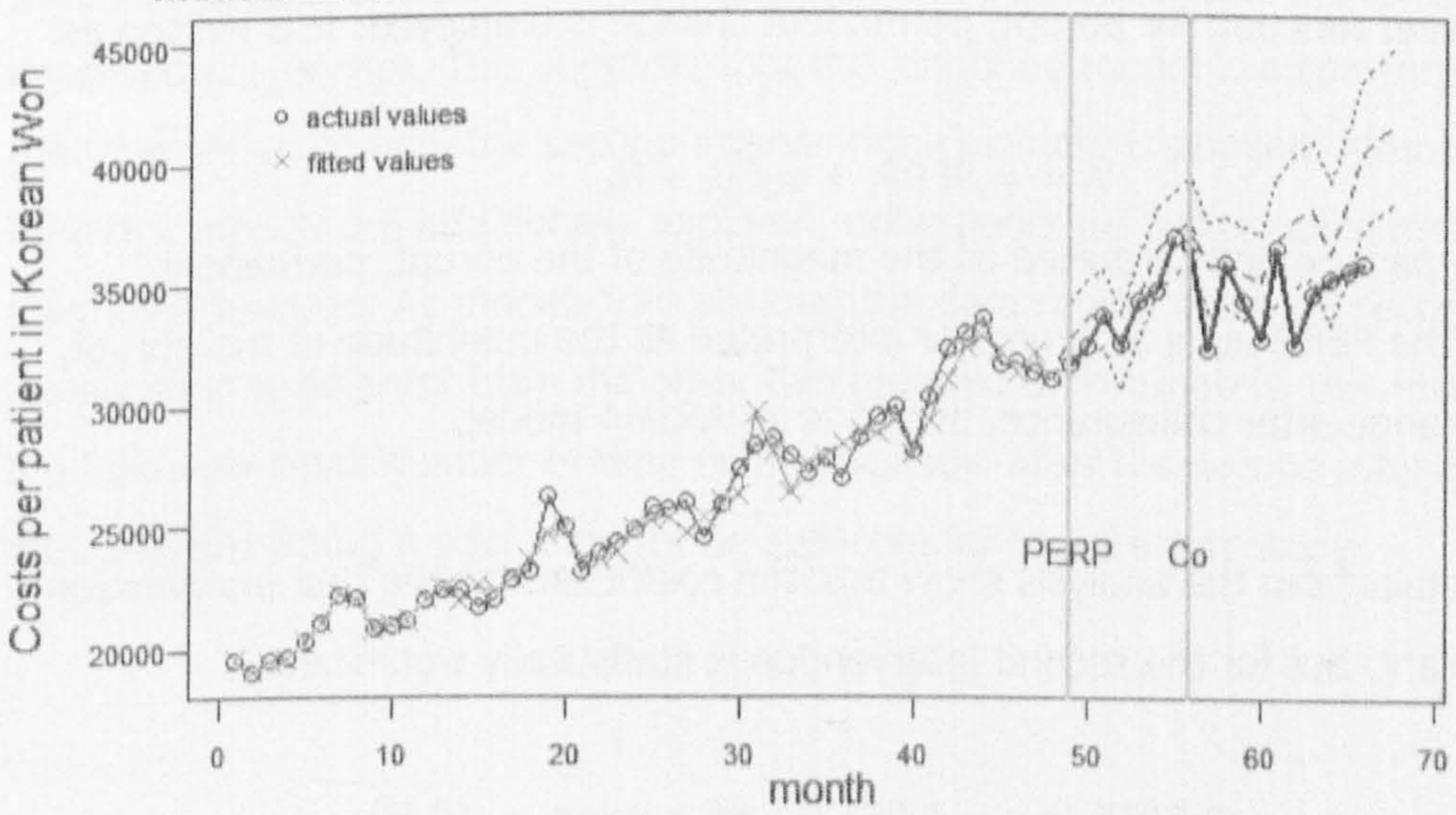
$$\theta_1 = -0.7502 \text{ (s.e.= 0.1097) with z value = -6.84}$$

The first-order moving average parameter is statistically significant and within the bounds of invertibility.

4. Examine residuals from obtained models and assess adequacy

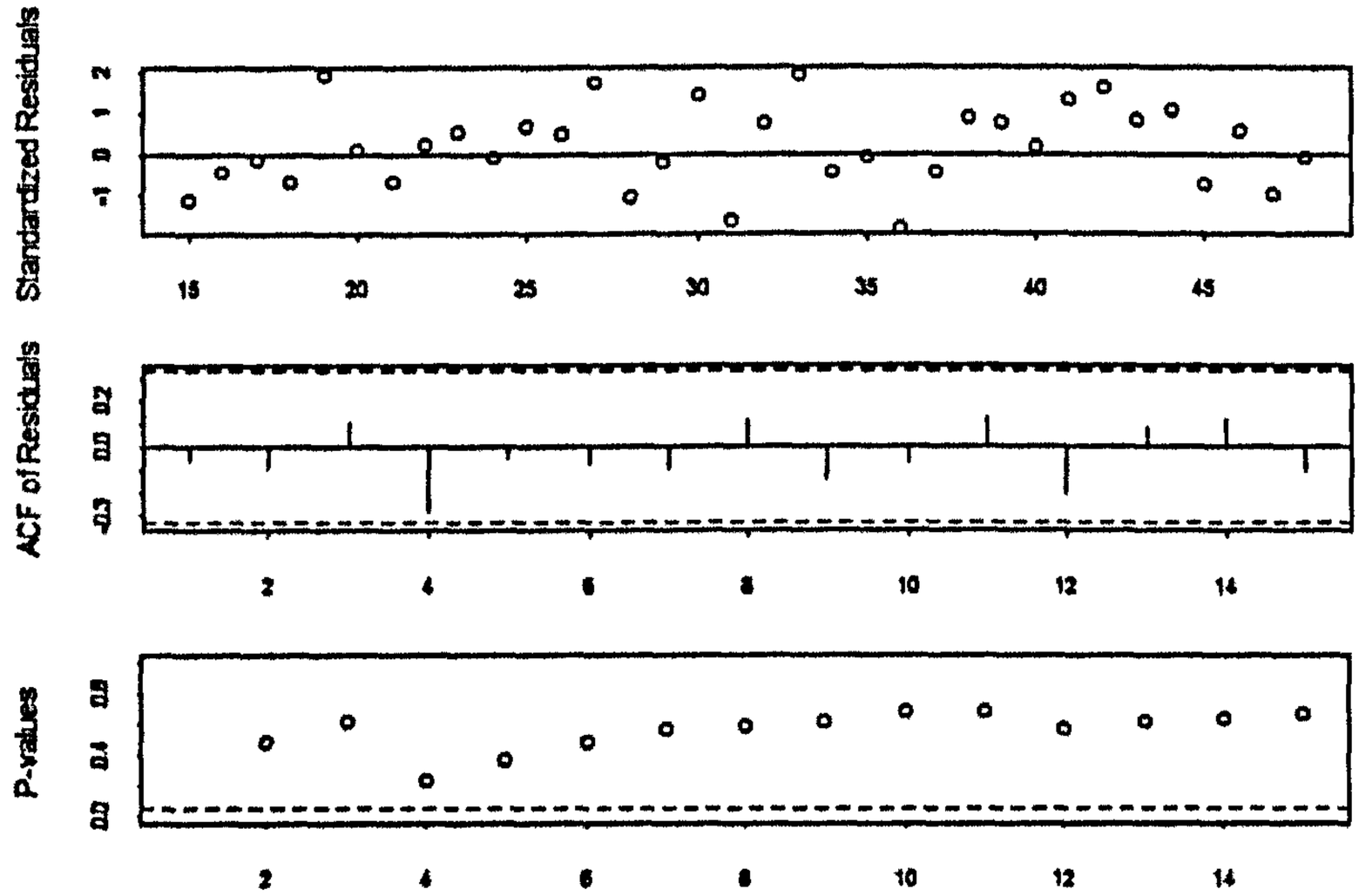
Figure a22-5 presents the fitted values and forward projection of the tentative model in parallel with the actual data. The fitted model seems to fit well with the superimposed the actual measured values in the pre-intervention period.

Figure a22-5: The forward projection of the indentified model with the actual measured values



The projection looks consistent with the second period. However, in the third period after the second intervention, it looks as though the data may be different. To diagnose the identified model, residual analysis is performed. The Q statistic is not significant (p=0.680), indicating that the residuals from this tentative model are white noise. The overall diagnostic tests shown in Figure a22-6 confirm that this is a reasonable model.

Figure a22-6: Residual analysis of ARIMA(0,1,1)(0,1,0)$_{12}$ model



5. Fit the intervention component to the identified 'noise' model

At the next step, an intervention component is added to the ARIMA model identified in the stochastic process. From the primary segmented regression analysis, it is discerned that drug expenditure may be lowered significantly after the second intervention. Hence, a transfer function for abrupt, permanent change is employed. It is written as:

$$Y_t = \omega_1 PERP_t + \omega_2 Co_t + N_t$$

where ω_1 is a parameter interpreted as the magnitude of the abrupt, permanent change after the PERP, ω_2 is a parameter interpreted as the magnitude of the abrupt, permanent change after coinsurance, and N_t is an ARIMA model.

The model details from the analysis show that the coefficient for the first intervention is non-significant, but for the second intervention is statistically significant.

$$\theta_1 = -0.8536 \text{ (s.e.= 0.0813) with z value = -10.50}$$

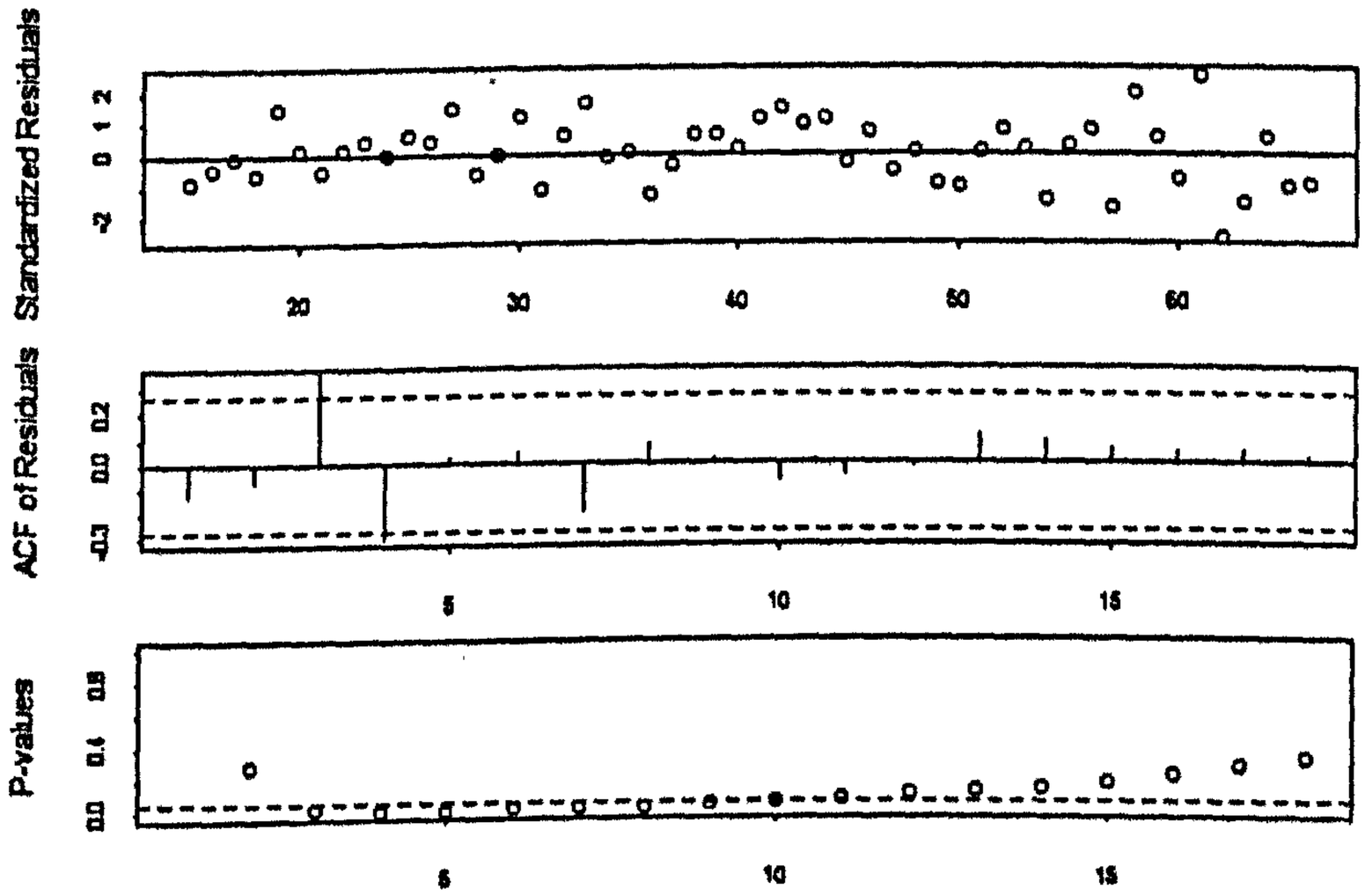
ω_1 = -40.20 (s.e.= 415.36) with z value = 0.92

ω_2 = -1447.86 (s.e.= 532.80) with z value = -2.72

6. Diagnosis for the residuals of the full impact assessment model

Although the Q statistic is non-significant (p=0.3136), the overall diagnostics for the model are less good (Figure a22-7).

Figure a22-7: Residual analysis of the full impact model



When setting up the specified model with time series data for the period before the second intervention and ignoring the first intervention as it appears non-significant, it produces coefficients that are consistent with the previous model and provide much improved diagnostics. This suggests that the identified model is a convincing model for the time series up until the second intervention covariate is applied. Although several tentative models are additionally explored, none generate better outcome in the diagnostic analysis. All models indicate that the data region after the second intervention is different from the other two regions. Unfortunately, this may be due to the relatively small number of time points available after the second intervention and thus a better fitting model may not be available for the present study.

Annex 23: Topic guide

THE UNIVERSITY of York

— DEPARTMENT OF —

HEALTH SCIENCES

Topic Guide for Participants

Policy-makers' Views on Pharmaceutical policies in Korean Context

1. Your background

- Your current and recent roles and responsibilities

2. Your views on policy evidence available in Korea

- Current source of evidence employed in policy-making in Korea
- Plans for improving the quality of evidence

3. Your experience in the pharmaceutical policy-making

- Your views on policy outcomes and of which supporting evidence you have
- Other potential factors that influence the policy decisions

4. Opinions of the potential policies available to policy-makers

- Causes of increasing drug spending
- Current concerns to be tackled
- Potential policies you suggest
- Barriers, feasibility, implications of the potential policies in Korean context

5. Any other thoughts

Annex 24: Semi-structured questionnaire

THE UNIVERSITY *of York*

— DEPARTMENT OF —
HEALTH SCIENCES

Semi-structured questionnaire

Evidence-based pharmaceutical policy-making in the Korean Context

This research is being carried out as part of a Doctorate in Health Policy Research. It has been reviewed and approved by the Department of Health Sciences Research Governance Committee, University of York.

SECTION 1. About You:

1. What is your background? (check √ ***all*** relevant items)

1) Administration ( )
2) Economics ( )
3) Medicine ( )
4) Nursing ( )
5) Pharmacy ( )
6) Health Sciences/Health service research ( )
7) Other ( )

2. What is your current or recent role(s) in pharmaceutical regulation for the recent 10 years? (check √ ***all*** relevant items)

1) Policy-maker ( )
2) Policy implementor ( )
3) Policy adviser ( )
4) Researcher ( )
5) Other ( )

3. How long have you been engaged in pharmaceutical regulations?

1) less than 5 years ( ) 2) between 5 and 10 years ( ) 3) more than 10 years ( )

SECTION 2. Your views on Evidence-based policy-making in Korea:

4. Please circle the number that most closely matches your opinion in each row about *how often* each of following evidence is used in the pharmaceutical policy-making process in Korea.

	Never use				Always use
Studies investigating Korean pharmaceutical regulations	1	2	3	4	5
Studies investigating overseas' pharmaceutical regulations	1	2	3	4	5
Comparative studies of pharmaceutical regulations	1	2	3	4	5
Economic evaluation studies	1	2	3	4	5
Reports after a business trip to foreign countries by governmental officers	1	2	3	4	5
Experts' opinion	1	2	3	4	5
Clinical research	1	2	3	4	5
Other1 ( )	1	2	3	4	5
Other2 ( )	1	2	3	4	5

5. Please circle the number that most closely matches your opinion in each row about *the quality of each of following evidence* employed in the pharmaceutical policy-making process in Korea.

	Low quality				High quality
Studies investigating Korean pharmaceutical regulations	1	2	3	4	5
Studies investigating overseas' pharmaceutical regulations	1	2	3	4	5
Comparative studies of pharmaceutical regulations	1	2	3	4	5
Economic evaluation studies	1	2	3	4	5
Reports after a business trip to foreign countries by governmental officers	1	2	3	4	5
Experts' opinion	1	2	3	4	5
Clinical research	1	2	3	4	5
Other1 ( )	1	2	3	4	5
Other2 ( )	1	2	3	4	5

6. Would you be satisfied with the sources of and quality of evidence employed in the pharmaceutical policy-making process in Korea?

1) Very satisfied ( )

2) Satisfied ( )
3) Neutral ( )
4) Unsatisfied ( )
5) Very unsatisfied ( )

7. Which of following strategies do you think are in an essential need to improve Korean stance in Evidence-Based policy-making? Please answer if you choose *Neutral*, *Unsatisfied*, or *Very unsatisfied* in Question 5? (make ***three choices*** and check √ them in parentheses)

1) Constructing a proper database ( )
2) Aggressive involvement of government body(ies) in Developing/Evaluating/Disseminating body of evidence ( )
3) Funding for research ( )
4) Government/university/industry cooperation ( )
5) Improving ability to use existing resources
6) Making easier access to available data ( )
7) Nurturing potential researchers ( )
8) Other ( )

SECTION 3. Your views on current pharmaceutical regulations in Korea:

8. **From the following list of potential factors affecting the policy-making process of pharmaceutical regulations arrange them in order of importance that you think influences greater in Korean policy-making process.** (you can ***suggest other factors not on the following list*** or ***remove some of factors on the list*** and arrange them in order together with the following list)

Scientific evidence (**A**)/
Social norm (**B**)/
Consumers' groups (**C**)/
Effects and consequences on pharmaceutical industry (**D**)/
Opinion leaders' perspective (**E**)/
Conventional precedents (**F**)/
Interest groups (professionals, manufacturers, wholesalers, etc.) (**G**)/
Political context (**H**)/
Impact on other resource use (**I**)/
Overseas' experience (**J**)/
Other ( )

9. **Which countries do you think are often benchmarked in the pharmaceutical policy-making process in Korea?** (list ***more than three countries*** with no limitation)

10. **Would you have involved in the pharmaceutical policy-making process** (including planning/development/decision-making/advisory/implementation/evaluation) **of the following regulations recently introduced in Korea?** (check ***all*** relevant items; you can ***suggest other regulations*** in which you have involved on 'Other#' with no limitations)

1) Expanding 30% coinsurance for prescription drugs ( )
2) Best Prescribing Project ( )
3) Pharmaceutical Expenditure Rationalisation Plan
4) Other1 ( )
5) Other2 ( )

11. Choose the option that most closely matches your opinion on the following statement: (check √ only one in each of regulation)

The impact of each of following regulations are in accord with the policy aims and expected effects in the stage of policy development.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Expanding 30% coinsurance for prescription drugs					
Best Prescribing Project					
PERP*- price control					
PERP*- positive list/formal request of economic evaluation in listing					
Other1 ( )					
Other2 ( )					

* PERP refers to Pharmaceutical Expenditure Rationalisation Plan

12. Please answer if you have any single regulation on which you choose *Disagree* or *Strongly disagree* in Question 10. What do you think cause such differences in the regulation you choose *Disagree* or *Strongly disagree* in Question 10?

Expanding 30% coinsurance for prescription drugs:

Best Prescribing Project:

PERP – price control:

PERP – positive list/formal request of economic evaluation in listing:

Other1 ( ):

Other2 ( ):

13. Choose the option that most closely matches your opinion on the following statement: (check √ only one in each of regulation)

The each of following regulation brought unwanted consequences after implementation.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Expanding 30% coinsurance for prescription drugs					
Best Prescribing Project					
PERP*- price control					
PERP*- positive list/formal request of economic evaluation in listing					
Other1 ( )					
Other2 ( )					

* PERP refers to Pharmaceutical Expenditure Rationalisation Plan

14. Please answer if you have any single regulation on which you choose *Agree* or *Strongly agree* in Question 11. What do you think are unwanted consequences in each regulation you choose *Agree* or *Strongly agree* in Question 11?

Expanding 30% coinsurance for prescription drugs:

Best Prescribing Project:

PERP – price control:

PERP – positive list/formal request of economic evaluation in listing:

Other1 ( ):

Other2 ( ):

15. **The following list of pharmaceutical policies displays regulations have been attempted but failed to introduction or just piloted so far during the recent decade in Korea. In your opinion, to tackle current challenges in Korean pharmaceutical sector each of regulation is:** (you can ***suggest other regulations*** that were attempted but failed to introduce on 'Other#' with no limitations)

	Very useful	Useful	Neutral	Unuseful	Very unuseful
Reference pricing programme					
Prescribing budget					
Diagnosis-related group					
Generic name prescribing					
Other1 ( )					
Other2 ( )					

16. **Please answer if you have any single regulation on which you choose *Useful* or *Very useful* in Question 14. What would you think causes the failure of introduction of the regulation you choose *Useful* or *Very useful* in Question 14?**

Reference pricing programme:

Prescribing budget:

Diagnosis-related group:

Generic name prescribing:

Other1 ( ):

Other2 ( ):

SECTION 4. Your views on future pharmaceutical regulations in Korea:

17. Which one of the following do you think has caused an increase of pharmaceutical expenditure the most afterward in Korea? (rank them by writing the numbers 1, 2 and 3 (or 4 if you suggest other option in 'Other') in parentheses: ***Most = 1***)

1) Price ( )
2) Volume ( )
3) Non cost-effective drug utilisation ( )
4) Other
( )

18. What do you think is the most serious issue to be considered in the process of Korean pharmaceutical policy-making? (make ***three choices*** and check √)

1) Cost control ( )
2) Improving organisational efficiency including government bodies, medical institutions, industry etc. ( )
3) Rational use of medicines ( )
4) Equity and affordable access across various social groups ( )
5) Consumers' right ( )
6) Accountability and transparency ( )
7) Priority setting in resources allocation ( )
8) Competitive pharmaceutical industry ( )
9) Other ( )

19. Who do you think should be the first target of policy in coping with the issue you suggest in the Question 17? (make ***more than one and no more than three choices*** and check √)

1) Authorities ( ) *go to Question 19*
2) Consumers ( ) *go to Question 20*
3) Prescribers or Dispensers ( ) *go to Question 21*
4) Domestic manufacturers ( ) *go to Question 22*
5) Global manufacturers ( ) *go to Question 23*
6) Wholesalers ( ) *go to Question 24*
7) Other ( ) *go to Question 25*

►19~25◄ Questions from 19 through 25 are about your suggestion on potential pharmaceutical policies in Korean context.

Please suggest regulation(s) you think is effective to cope with the issues you suggest in Question 17 with targeting to each group who you choose in Question 18. (each question has the list of relevant pharmaceutical regulations that are only ***for your convenience*** and this does not aim at guiding or limiting your opinion at all; you can ***freely alter*** one or some of them and also ***suggest other regulations*** not on the list in your own view)

20. If you choose *Authorities* in Question 18 please suggest regulation(s):

For example;
• Enhancing monosopny power
• Enhancing transparency in policy-making process
• Establishment of quality control of generic products
• Extending privatisation domain in the pharmaceutical sector
• Improving accountability reports to the public or the industry
• Making, evaluating, and disseminating of appropriate information
• Raising fund through beneficieries' contribution
• Raising fund through public resources
• Raising public subsidy to disadvantaged groups

21. If you choose *Consumers* in Question 18 please suggest regulation(s):

For example;
• Increasing copayment
• Encouraging self-medication
• Enlightening the cost-effective utilisation of drugs
• Premium charge on costly drugs (eg. reference pricing, etc.)
• Prescription caps

22. If you choose *Prescribers or Dispensers* in Question 18 please suggest regulation(s):

For example;
• Establishing curricular in medical/pharmacy schools to improve understanding about public health care/drug policies • Financial incentives on prescribing (or dispensing) less-costly drugs • Mandatory generic name prescribing (substitution) • Prescribing audit (Prescribing feedback, Drug utilization review, etc.) • Prescribing budget limit • Providing continuing medical education programmes to encourage cost-effective prescribing (dispensing) • Reimbursement restriction *ante facto* (eg. prior authorisation, formulary, positive/negative list, preferred list, step therapy, reference pricing scheme etc.) • Reimbursement restriction *ex post facto*

23. If you choose *Domestic manufacturers* in Question 18 please suggest regulation(s):

For example;
• Direct price control (Price freezing, Price cut, Maximum allowance price, Actual acquisition price, etc.) • Making no doubt about the bioequivalent test of generic products • Market transparency • Profit control • Reducing drug patent period • Regulating Direct-to-Consumer advertising • Reimbursement restriction *ante facto* (eg. prior authorisation, formulary, positive/negative list, preferred list, step therapy, reference pricing scheme etc.) • Request economic evidence in the process of reimbursement decision

24. If you choose *Global manufacturers* in Question 18 please suggest regulation(s):

For example;
• Direct price control (Price freezing, Price cut, Maximum allowance price, Actual acquisition price, etc.) • Making no doubt about the bioequivalent test of generic products • Market transparency • Profit control • Reducing drug patent period • Regulating Direct-to-Consumer advertising • Reimbursement restriction *ante facto* (eg. prior authorisation, formulary, positive/negative list, preferred list, step therapy, reference pricing scheme etc.) • Request economic evidence in the process of reimbursement decision

25. If you choose *Wholesalers* in Question 18 please suggest regulation(s):

For example;
• Direct price control (eg. margin control, etc.) • Elevating the level of approval standard • Expanding bidding system in drug contract • Improving market transparency by central information body

26. If you choose *Others* in Question 18 please suggest regulation(s):

Thank you for your participation.

–The End–

Annex 25: Original languages of quotations

p006

(p006:4) 정책 개선요구가 급작스럽게 오고 빠른 시일 내에 개선안을 내고 시행하는 경우가 많다 :

There are often sudden requests for policy reform, then, [policy-makers] have to come up with the request and carry it out in a very limited amount of time.

(p006:4) 아무래도 정책을 만드는 그 시점에서 이미 연구가 완료된, 시장에 나와있는 연구자료 그런 것들을 활용하게 되고 대부분 또 그렇게 보면 아무래도 전문가의 의견을 많이 의존할 수 밖에 없는 상황입니다. : So when it comes to policy-making process, we end up using research materials or data that are either already done by someone else, or already on the market. I just don't think we really have any choice but to rely on experts' opinions.

(p006:6) 통상 연구용역 결과를 보면 너무 거시적인 것만 터치를 하고 뭐라 그럴까 좀 막연한, 좀 일반적인 내용으로 결론이 많이 나는 경우가 있어요. : If you look at the outcomes of most evidence produced in Korea, they usually tend to cover just the general aspects of it and leave out all the details.

(p006:20) 굉장히 권력남용적인 그렇게 협상이 진행되는 경우가 있다는 그런 얘기를 들었습니다. : I've heard that there have been some cases where certain negotiations were made under such monopsony.

(p006:22) 우리나라의 현재 제도의 문제점이 뭐냐면 가격은 어쨌든 계속 낮추고 가격위주의 통제정책을 지금 하고 있습니다. 그게 한계가 좀 있거든요 그런데 좀 부족한 게 뭐냐면, ... 같은 약 중에서도 싼 약, 어떤 성분 중에서도 좀 싼 성분, 저렴한 약의 사용을 유도할 수 있는 정책이 좀 부족해요. : The problem with South Korea's current policies is that they're price-centred, controlled ones, so they keep on lowering the price anyway. But there's a limit to that. We need policies that can encourage us to use drugs, or ingredients that are not as expensive.

(p006:24) 건강보험 제도권내에서의 어떤 순수한 효율적인 의료이용 이런 쟁점이 아니라 의사의 어떤 동의가 필요하다는 거죠. : The main issue is not about the efficiency of medical services in a healthcare system, but about getting the approval of doctors'.

(p006:26) 아무래도 그런 정보를 독점하고 있는 제약회사들의 논리가 먹혀 들어갈 수 밖에 없고 : It's no surprise that pharmaceutical companies dominating that type of information draw people into their circles with their logic and reason.

(p006:32) 이건 아주 공자님 같은 얘긴데, ... 논리적인 합리성이라든가 투명성을 제고할 수 있도록 계속 노력을 해야 된다는 거구요. : though this may sound a very theoretical and like one of those "Confucius sayings.."...the government should continuously make an effort to enhance logical solutions, rationality, or clarity when carrying out policies.

(p006:40) 평가에 대한 노하우도 부족하고 ... 다음에 이걸 이렇게 평가하고 그 다음에 이걸 제도화하는 데에 대한 경험도 부족하고 그런 상황이어서요 : We just don't really have much experience with all of these policy evaluations... like how to evaluate and systematise them...

p014

(p014:4) 시행한 제도 자체의 장점만 부각 시켜서 발표한 경우가 많은 것 같아요. : there were many cases where those evaluations have been made public mainly focused on the 'good aspects' of them.

(p014:4) 평가가 장기적으로 되어야 되는데요 상당히 단편적으로 이루어지고 있어요. : the short-term and fragmented policy evaluation

(p014:4) [외국의 제도들을] 보고 오셔서 그냥 단편적으로 좋아 보이더라 하면 그 체계하고는 상관없이 그때부터 고민에 들어가긴 하는데 이미 약간 그런 외국의 정책들에 많이 이미 마음이 끌려서 오시는 거죠. : They basically already liked what they saw in that short period of time, so they don't really seem to care too much about fully comprehending foreign policies or the systems that they're interested in as long as they like [the foreign systems].

(p014:8) 제도고찰 그런 쪽으로 많이 하다 보니까 약간 우리나라에서 제대로 적합하게 맞아 떨어지고 있느냐 없느냐 뭐 그런 것까지 평가할 여건이 안되다 보니까 아쉬운 점이 상당히 많거든요. : Since the policy monograph is mostly focused on a system itself, it's too bad that there isn't really any chance to evaluate whether that system would work or not for South Korea.

(p014:8) 말씀하신 evidence가 될만한 어떤 제도 평가라든가 정책 평가라든가 그런 연구를 좀 많이 하고 싶은데요, 인력 풀이 적다 보니까 거까지는 또 안되고 정책이 하도 많이 계속 변하다 보니까 원하는 충분한 심층적인 연구가 이루어지지 않는 경우가 또 많거든요. : I'd like to do more about the evidence you mentioned before, such as evidence on a certain policy evaluation or a system evaluation that we could use in the future. But it's not easy for us to pursue in-depth research because policies continue to change, and also there aren't enough networks for us to reach out to those who might be able to help.

(p014:12) 직접적으로 부딪힐 일은 없었거든요. 여기서 말씀하시는 이익집단이 제가 만약 공단이나 심평원에 있었다면 상당히 크게 느껴졌을 것 같아요. : I didn't really have to face it directly. However, if I had been involved in either the NHIC or in the HIRA, then I would've understood the importance of it.

(p014:36) 결국은 예전에 약으로 인한 리베이트 받아서 계속 신약이나 뭐 계속 처방을 바꾸던 분들이 있잖아요. 이런 분들에게 일반명 써라 하는 게 갑자기 먹히지는 않을 것 같고, : I don't think doctors who had previously been getting illegitimate financial benefits by giving out new drugs or keeping changing prescriptions would change to generic prescriptions suddenly because of a policy.

(p014:36) 생동성 시험 자체를 안 믿더라구요 의사들이. 그러면 뭐 자기들이 들었던 과학적 기준에 대한 의대 교육은 맞고 생동성 시험은 말도 안되고 그런 건 또 아니잖아요. : Doctors don't really believe in bio-equivalence test itself. But the thing is, you can't say that all bio-equivalence tests are completely absurd, and the scientific facts they've learned in medical school are absolutely right.

(p014:39) 그니까 얼개는 있는데 제대로 구체적으로 못한다 뿐이지, 근데 거기서 보면 제일 중요한 컵처,

의사의 컬쳐가 가장 중요한데 그 부분은 못 건드리고 있더라구요. : So basically, there is already a structure for this, but just not in a more concrete way. Also, they can't really do anything when it comes to the cultural aspect of medical professionals, which I think is the most vital part.

p017

(p017:20) 정책을 추진할 때 의사들의 수용성도 굉장히 중요하다는 생각이 들고 : I think gaining the acceptance of doctors is crucial when it comes to carrying out a policy,

(p017:42) 단기적으로 이것[처방예산제]을 과연 시행해 낼 수 있을지는 자신이 없거든요. 준비가 좀 안되어 있는 것 같아요, 예산을 어떻게 책정을 해야 되는지 그런 기준에 대한 연구도 별로 안되어 있고, : I'm not sure if we are going to be able to carry this [prescribing budget] out in a short period of time. We don't really have any ideas or previous research on how to allocate the budget... I just don't think we're ready yet.

(p017:64) 우리나라 제네릭 약가를 높게 해 준 게 국내 산업을 유지를 시키고 그런 측면이 있었잖아요. : Our country has, in some ways, intended to maintain the domestic industry by setting generous prices for generics.

(p017:64) 제네릭 약가가 높기 때문에 그거 가지고 R&D를 하는 거 보다는 제네릭을 계속하는 게 당연한 거잖아요. 기업으로 볼 때는. : since generics are relatively at a premium price, the manufacturers continue to be in generic business for profit rather than to invest that money towards researching and developing new drugs, it's natural from the manufacturers' perspective.

p019

(p019:8) 경제성 평가와 관련해서 비용 : costs data in relation to an economic evaluation

(p019:8) social sciences에 대한 훈련이 없는 교수님들이 평가하는 경우도 왕왕 있고 그러다 보니까 조금 인제 약간 외국에 대한 제도 비교 라던지 한국에 대한 어떤 굉장히 피상적인 평가, 이렇게 하는 경우도 있고 해서 : There are times when researchers who aren't really specialists in the social science field get involved in the evaluating process, and because of this, they simply make comparison with foreign policies or evaluate Korean policies tend to be too generalised...

(p019:24) [처방예산제를 논의하기 위해서는] 예산을 어떻게 배분 해야 할 지 배분에 대한 evidence들 : evidence on how to allocate the budget [to discuss a prescribing budget]

(p019:24) 약가가 높게는 안가는데 그 우리나라의 가장 큰 문제 중에 하나가 상대적으로 가격이 높은 약을 많이 써요. 그 이유는 약가가 높은 약은 마진이 많아서 이익이 많아서 리베이트를 줄 수 있는 여력이 생기는 거죠. : I don't think the drug itself is very pricy. However, one of our country's biggest problems is that we tend to use drugs that are relatively high in price. This is because expensive drugs have more surpluses, which can cause illegal financial rebates in the end.

(p019:36) 지금도 독점적인 품목 같은 경우에는 우리나라가 휘둘리죠 한국에 안주겠다 이럴 수도 있고 :

South Korea still doesn't have much control when it comes to certain leading products, and there's a chance that international companies might even refuse to offer their products to us.

(p019:40) 일단 듣는 open-mind된 상태에서 가장 합리적인 점을 찾아가야 되는데 그 중심에는 국민들이 있으면 될 것 같거든요. : I think it's important for people to be open-minded and try to find what's best for our nation people.

p028

(p028:14) 대게 연구자들이 정부측의 정책방향에 대한 이해가 부족한 경우가 많아서 정책보고서는 보통 우리가 요구를 할 때 우리랑 디스커션을 많이 하면서 리포트를 쓰이 분야를 우리가 이렇게 조사하고 있는지 확인해 보십시오 이런 식의 리퀘스트를 계속 해가면서 보고서를 쓰게 만들어요. : Most researchers don't understand very well about the policy direction. So, whenever we ask them to write out policy reports to researchers, we normally request them to focus and verify the topics we mostly discuss and write about.

(p028:18) 나는 이런 데에 우선 순위를 두고 일을 한다라는 거거든요. 그런데 이걸 객관화된 순서를 매기십시오 이러면 이익집단의 영향이 상당히 위로 올라올 거예요. : It's like saying this is one of my top priorities. But if I had to rate this objectively, then it would be much more influenced by interest groups.

(p028:22) 정책의 성패에 대한 평가는 일정기간이 지난 후 후세에 이루어지는 것: The evaluation for that would be the successor's responsibilities

(p028:24) 보통 3년 내지 5년 정도 실시를 해봐야 그것이 잘 돌아가고 있는지 안 돌아가고 있는지가 나오는데요. 보통 3 내지 5년쯤 되면 정책입안자들이 대개 바껴요. : It normally takes about three to five years to figure out if policies are really working or not, but policy-makers usually end up being replaced after that amount of time.

(p028:40) 미국은 다보험이니까 내가 브랜드네임을 안 써도 다른 누군가는 쓰겠지 라고 해서 얘네들은 제네릭 장려정책을 막 쓰는데 우리는 [단일보험자기 때문에] 만약에 제네릭 장려정책을 쓰면 국내 산업 보호정책으로 오해를 받게 되요. : Since America has plural insurers, they tend to implement generic policies easily with thinking in the way that someone else will eventually use the brand name anyway. However, [we have a single central insurer so] if we use generic policies, then it would end up being misunderstood as protective trade policies.

(p028:60) [사전승인] 꼭 써야 되는 사람이나 아닌 사람이나에 대한 [판단기준] : [for prior authorisation] [a standard of judgment] on whether this person really needs this or not

p030

(p030:8) 객관적으로 나온 자료라 하더라도 또 우리나라 제도랑 외국이랑 또 차이가 많아가지고 실제적으로 그걸 그대로 적용하거나 하는 그런 부분에서 어려운 측면이 있고 : ...even if the evidence were objective, it's hard to apply it simply because of the difference between Korean system and other countries' systems, and ...

(p030:10) 어떤 성분 관련한 역학이라든지 역학조사라든지 : epidemiology relating to chemical substances or epidemiologic researches [on local population]

(p030:10) 약물에도 head-to-head 자료 : head-to-head data on drugs

(p030:10) 네트워크처럼 구성을 해서 ...조금 더 활발히 이루어져야 된다 : needs a live, close network among research institutions

(p030:16) 소비자가 진정 이렇게 저렇게 했을 때 문제가 없나 하는 부분에서 한번 정도 더 짚어질 수 있는 그런 최종의 그런 요소이기는 해야 된다 그런 측면에서 : I think it should be the final factor that we carry out this or that which doesn't harm in consumers.

(p030:35) 원칙적으로 의/약사 쪽을 제제하거나 관리하는 게 가장 우선적인 문제이기는 한데 결국 현재 우리나라에서는 그 일이 쉽지 않은 부분인 거고 또 그러다 보니까 바로 영향 받는 게 소비자이니까 : Technically, the most important thing to do is to place both doctors and pharmacists under control, but that's easier said than done. So consumers would be the ones who would be directly affected by it....

(p030:57) 조금의 서로간에 환자가 되었든 의/약사가 되었든 인지를 통해서 조금만 더 자기의 이익이라든지 집단의 이익이라든지 이런 것들을 많이 좀 줄이고 양보할 수 있다면 : Whether you're a doctor or a pharmacist or a consumer, I just hope they all can at least try to understand each other instead of focusing on either their own personal benefit, or their group...

(p030:58) 너무 급한 마음에 어떻게 보면 별로 우리나라랑 맞지 않아도 미국 거나 유럽 거를 자꾸 들여다가 이렇게 더하기 하듯이 그렇게 제도들이 시행이 되니까 : since we are usually pressured for time, we try to introduce all these American and European policies, just add to, even if they are not necessarily the best ones for our country

p047

(p047:4) 기본적으로 다음의 어떤 의사결정을 할 때 활용할 수 있을 만큼 이전의 다른 정책에 대해서 평가한 어떤 연구들이 많지가 않기 때문에 사실 사용이 안되고 있는 부분이 좀 있구요. : It's also not being used because, so far, there basically hasn't been enough evidence available on other previous policy-making processes for us to learn from and use as an example whenever we have to make certain future decisions.

(p047:4) 그런 것들을 할려면 민간에서 알아서 되지는 않으니까 정부가, ...근거자료의 형성/평가/보급 부분에서 정부기관이 양적으로 많이 해야된다 뿐만이 아니라 좀더 체계화, 체계적으로 할 필요가 있다고 생각을 합니다. : I think it's important for the government to focus not only on the quantity aspect of establishing, evaluating, and promoting the policy evidence, but also on processing it in a more systematic way.

(p047:6) 처음에는 사실 오피니언 리더들의 입에서, 그리고 어떤 소비자 단체들이라든지 여러 사람들의 입에서 이게 문제다 개선해야 된다는 목소리가 일단은 먼저 나오구요, 그런데 그러고 나면 실제 이게 정책으로 집행되는 과정에서는 사실 어떤 외국의 사례라든지 기존의 평가라든지 이런 부분들이 많이 고려를 하게 되는 부분이고, 일단 그 단계로 넘어가면 다른 사례라든지 근거라든지 이런 부분이 좀더 중요하게 작용을 하긴 하구요.... 그 다음에 이걸 어느 정도의 강도로 시행을 할 것인가 라고 하는

부분들에 있어서는 사실은 제약산업이라든지 이런 데의 여러 가지 작용 같은 것은 있을 것 같기도 하구요, : At first, opinion leaders and other people, such as a group of consumers, would announce something like 'these are the problems in a policy, and it should be reformed.' However, when it comes to the process of carrying out the policy, cases from other countries or pre-existing evaluations are taken into consideration. In the next step, other example cases and evidence grounds may play an important role, and then, the pharmaceutical industry or some interest groups would play a part in deciding how strongly they enact...

(p047:6) 제약회사 영향과 같은 경우에는 사실 표면적으로 드러나지는 않으니까 : Since the influence of a pharmaceutical company is not explicit in outside...

(p047:14) 워낙에 국내에서 의사와 약사가 대립하고 있는 정도가 심하기 때문에 괜히 어느 한 편 들어서 불지를 필요는 없다고 생각을 합니다. : Since there's already too much conflict between doctors and pharmacists, I think it's best to stay neutral rather than firing them by favouring one side over another.

(p047:16) : 품질이 동등하다 그리고 거의 동등하다 라고 하는 것이 좀 이제 동의가 되어야 가능한데 우리나라에서는 의료제공자들 속에서 이게 동의가 별로 안 되는 상황이라서 사실은 굉장히 유용할 수 있는 여러 정책들을 펴는데 되게 장애가 있거든요 : I don't think people in our country, especially the service providers, still believe that the quality of generics is just good as other brand-named drugs. I think this is what is holding us back from enforcing all these useful policies that are out there.

(p047:22) 특허 만료 후에는 그야말로 가격경쟁이 조금 더 활발할 필요가 있고, 소비자가 굳이 연구개발 활동에 투자를 하지도 않은 제품들에 대해서 생산, 그야말로 마지날 코스트보다 훨씬 더 높은 가격을 지불하고 그 제품을 어느 특정한 산업들을 유지하기 위한 대가로 계속 저는 유지할 필요가 있을까 하는 생각은 들구요, 언제까지 그런 식으로 보호될 수 없다는 생각을 하고 : After patents expire, I think the price competition should be more in force. I also think -- consumers pay much more than a marginal cost on the products not resulted from the R&D just in order that such extra expenses can help maintain a certain industry--is really unnecessary.

p048

(p048:4) 모든 어떤 정책들을 평가하기 전에 벌써 다른 것 하고 있고: doing another before evaluating a policy introduced ahead

(p048:6) 그런 외국의 논문이나 다른 working paper같은 경우에도 좀 다양한 방식으로 평가를 하는 것 같은데 우리나라는 상대적으로 그런 것들이 별로 없죠. : If you take a look at other working papers or essays from other countries, you can see how there are various evaluative procedures, we [South Korea] rarely do like that.

(p048:6) 그런 정책연구 용역을 줄만한 기관들의 경우에는 특별히 그런 분석적인 방법론을 원하지는 않아요. 원하지 않고, 대부분 descriptive한 것을 원하고, 그냥 descriptive한 수준에서 자기들이 원하는 방향대로 해석을 해주기를 원하거든요. : Either the government or other organisations in

South Korea that would recruit researchers for policy research prefer more descriptive methods than in-depth analytic ones, they just want things to be explained descriptively and in certain ways they want them to be explained.

(p048:42) 실제로 우리가 보험이 된다고는 하지만, 그리고 병원에 쉽게는 갈 수 있지만, 막상 큰 질병이 생겼을 때는 못 가는 경우도 또 상당수 있잖아요. : Even though we are covered by insurance and can go to a hospital whenever we have to, still there are many cases when you can't even go if you're in extremely critical condition.

(p048:46) 조직이기주의가 많아가지고, 특히 약가정책 가지고 이렇게 나눠먹기식으로 하는 게 상당히 있어요 : There are a number of those [government bodies] who are mainly focused on their group-interest, well, especially with drug pricing policies

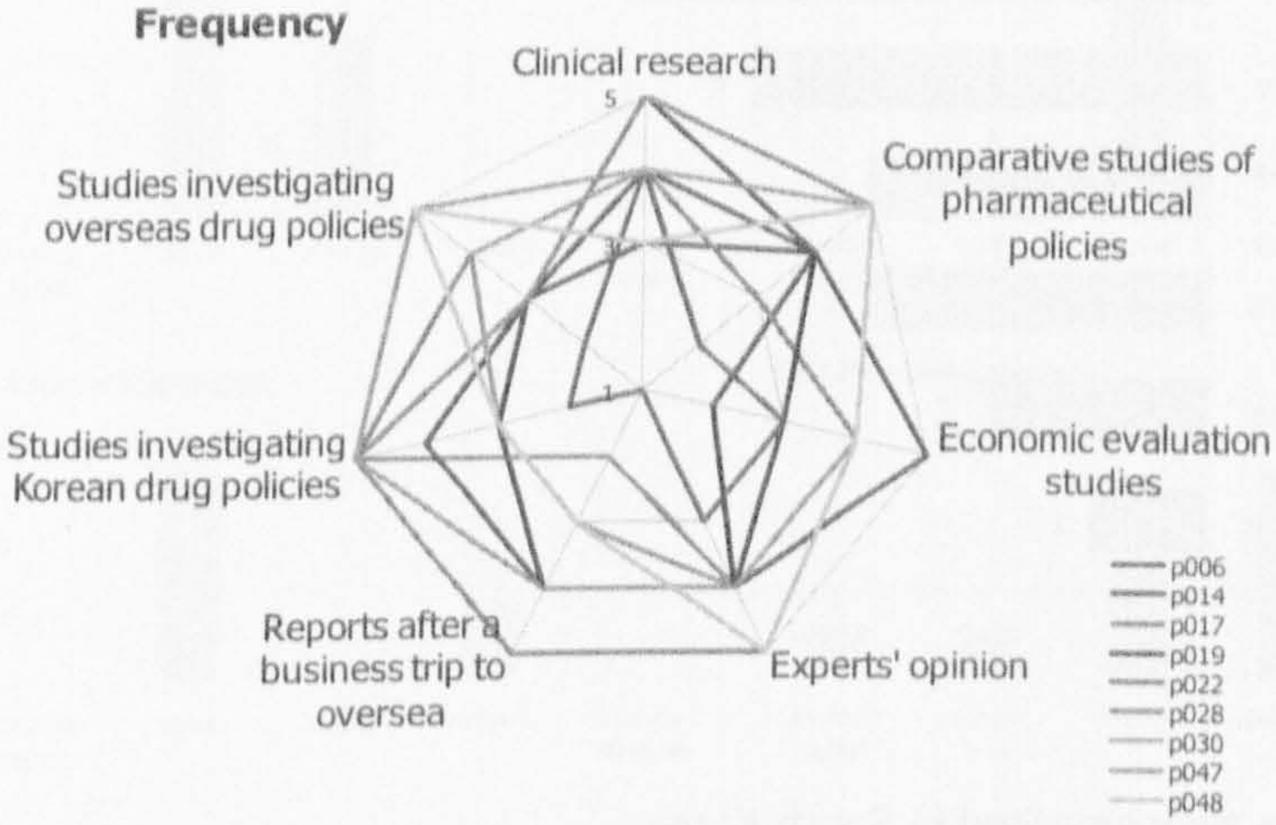
(p048:52) 가장 큰 어려움은 처방으로 인해서 경제적 이득이 있기 때문에 안 되는 게 많죠. : The biggest problem is that doctors prescribe certain drugs because they have an economic interest in doing so.

(p048:58) 지금 우리가 얘기한 그런 음성적인 여러 가지 이상한 거래들을 다 없애지 않고서는 가격경쟁을 붙일 수 있는 방법이 잘 안 떠오르더라구요 : I can't really think of a good way to ensure this price competition unless we get rid of all the illegal trading we discussed so far.

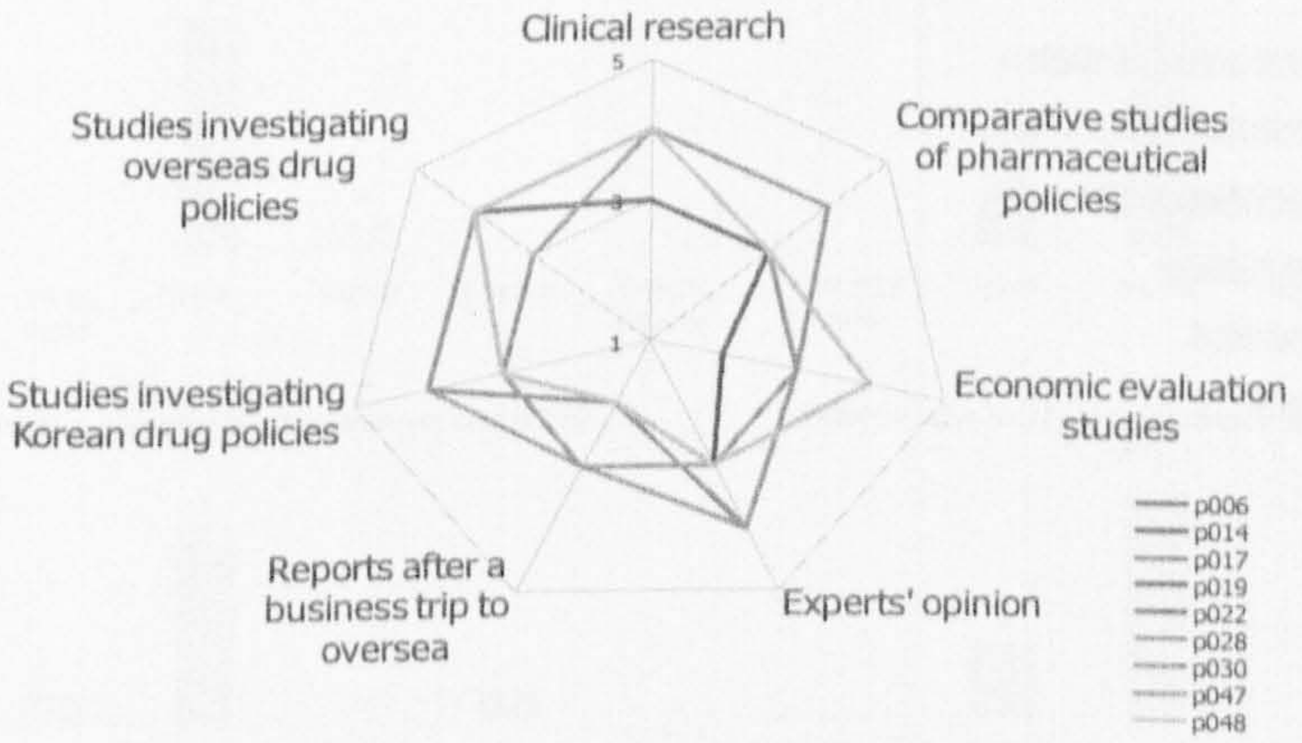
Annex 26: Summary of questionnaire responses

a) Question 4 and 5: Rating in frequency and quality of evidence employed in the current pharmaceutical policy-making process (5=highest, 1=lowest)

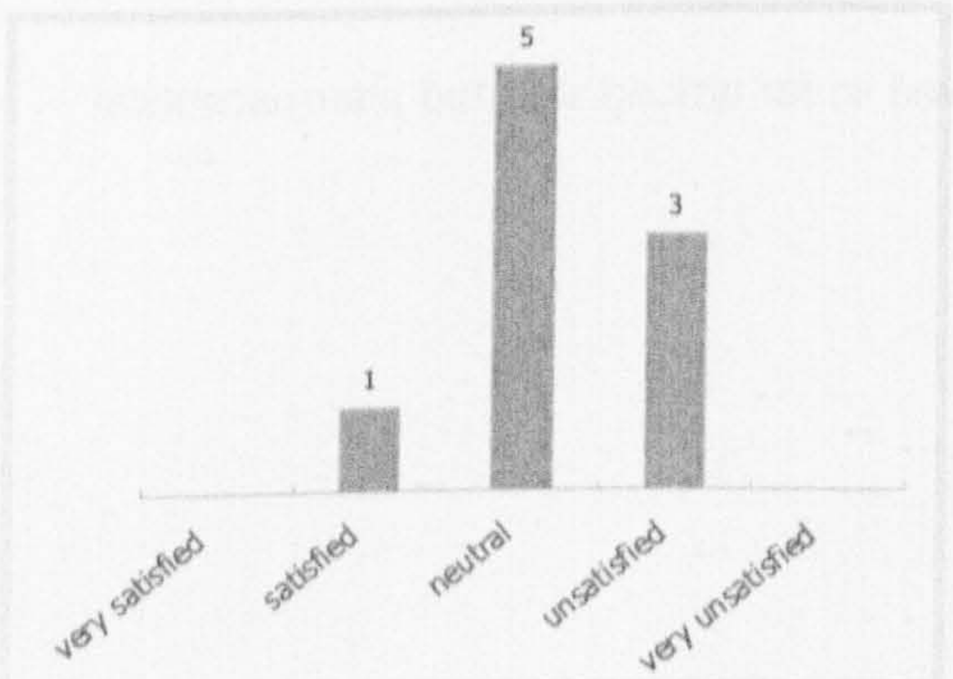
Frequency



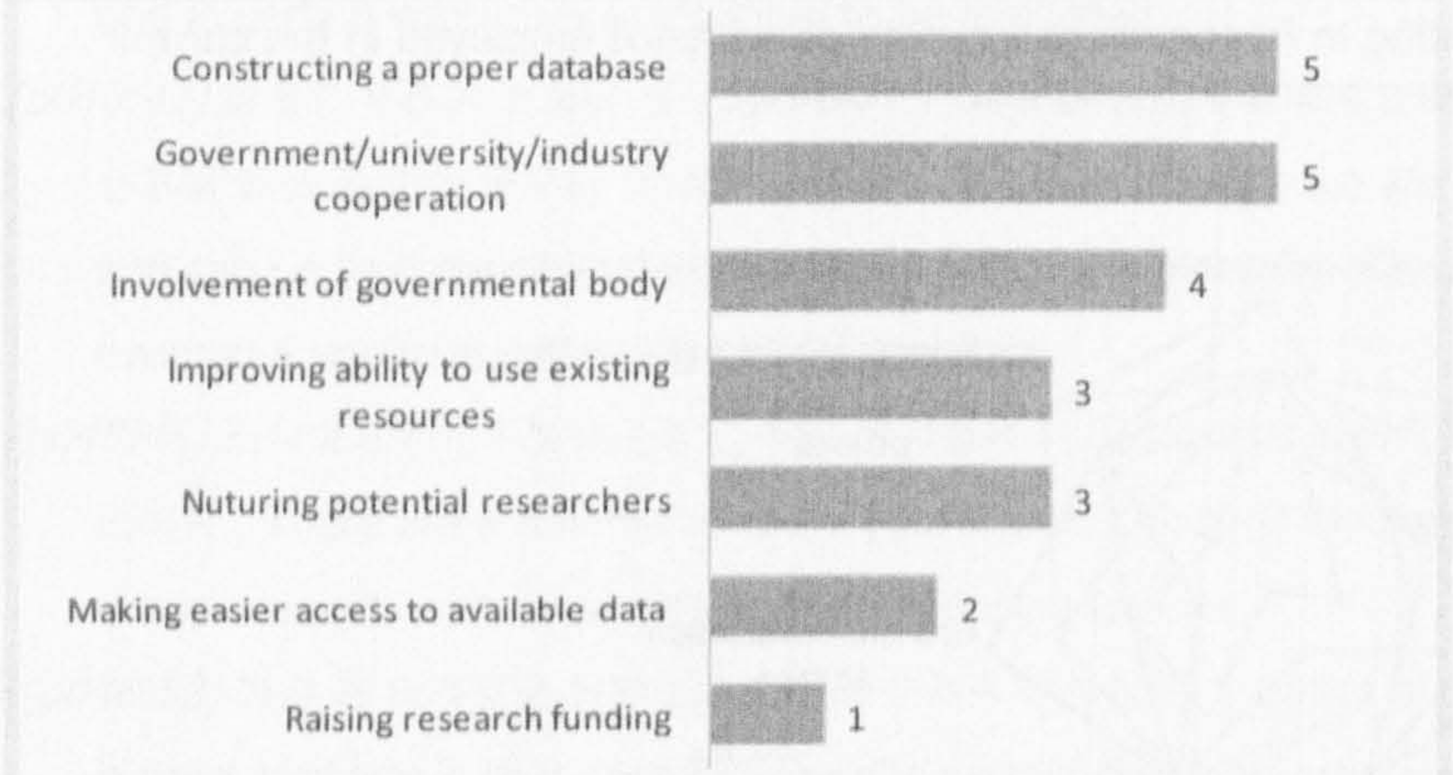
Quality



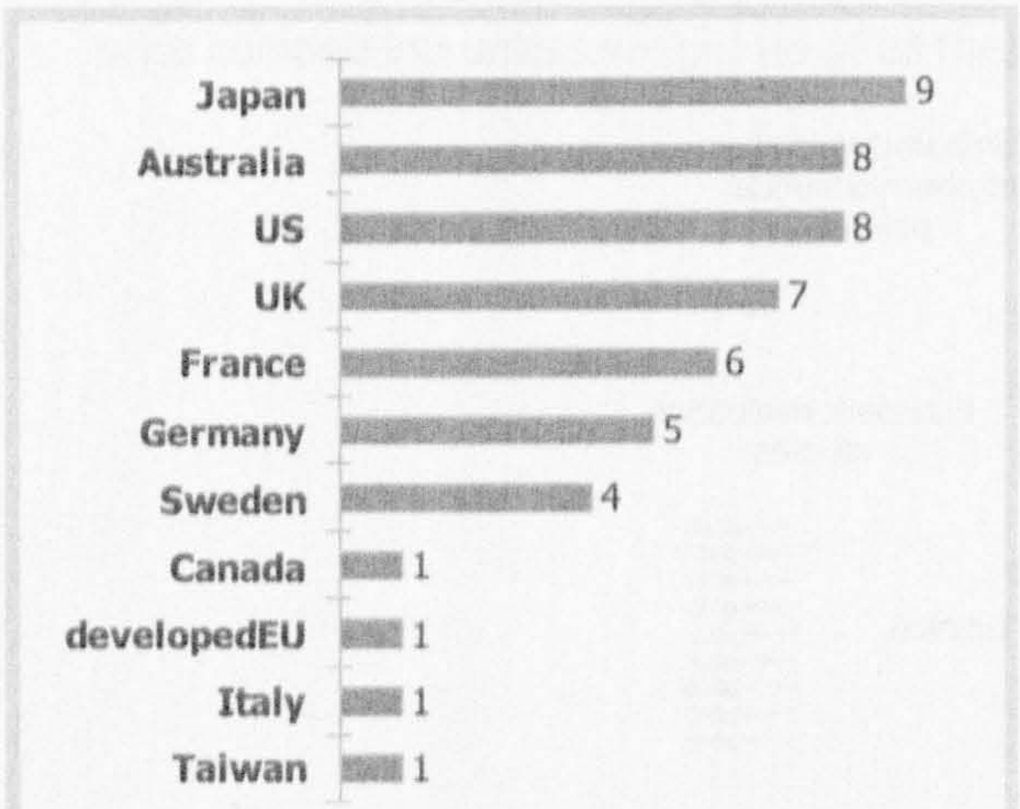
b) Question 6: General satisfaction with existing evidence



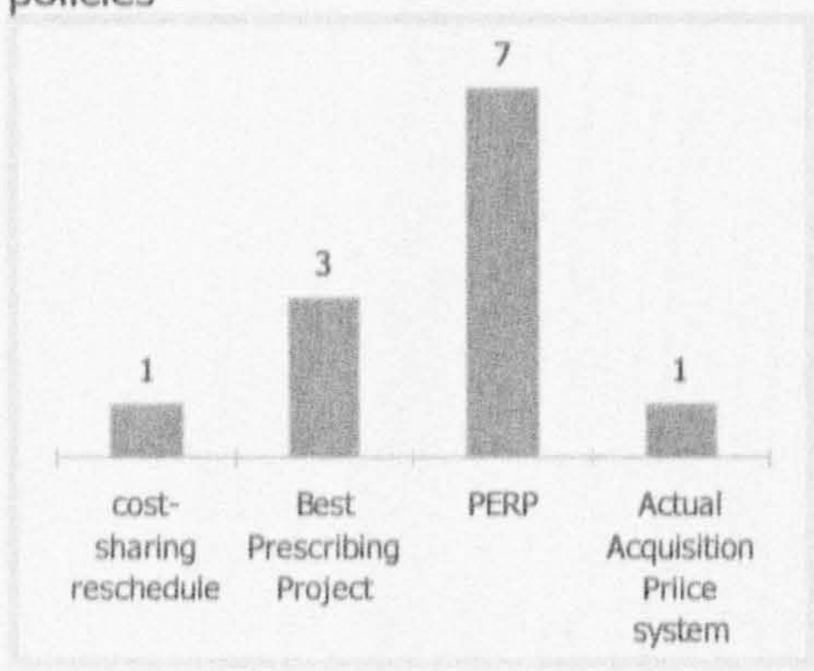
c) Question 7: Primary requisites for good evidence



d) Question 9: Countries often benchmarked in South Korea



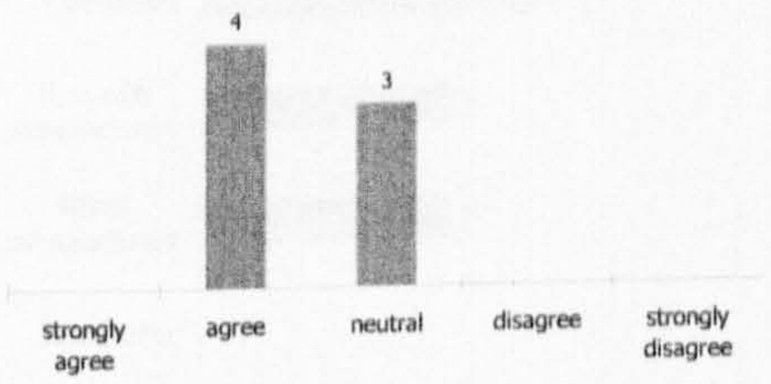
e) Question 10: Policies participants having involved so far among selected pharmaceutical policies



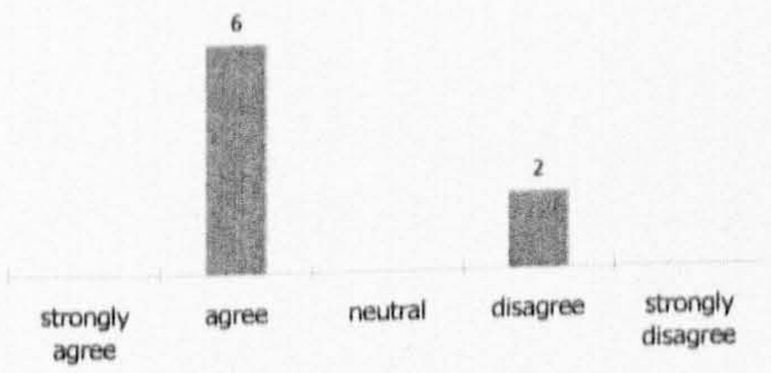
f) Question 11 and 13: Positive and negative effects of four current policies

The impacts of each of following policy are **in accord with the policy aims and expected effects** in the stage of policy development.

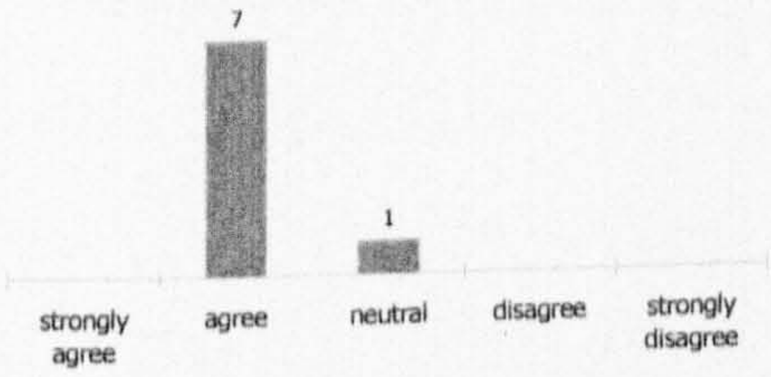
Cost-sharing reschedule



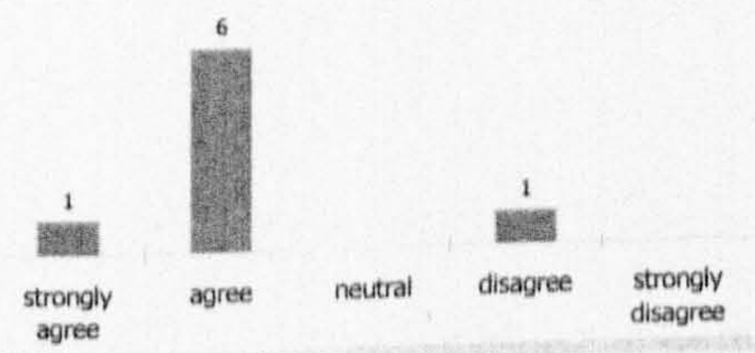
Best Prescribing Project



PERP-price cut/agreement

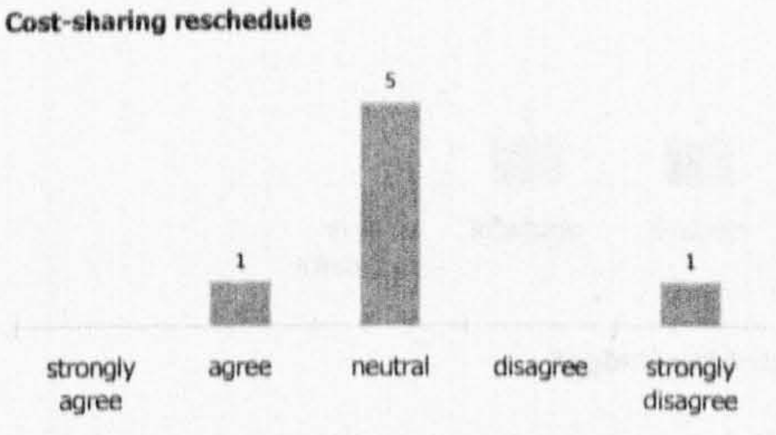


PERP-positive list/formal economic evaluation

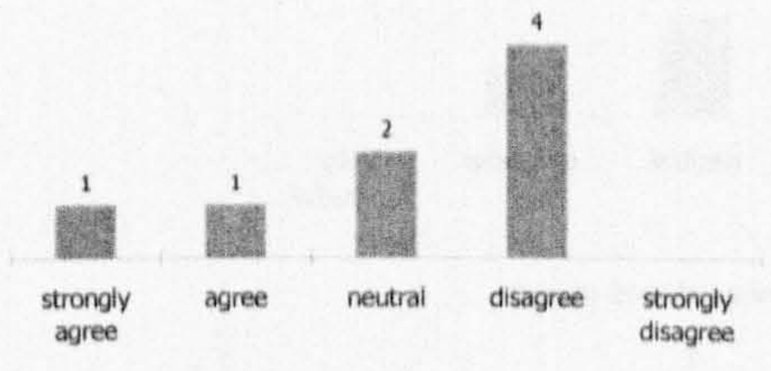


The each of following policy brought **unwanted consequences** after implementation.

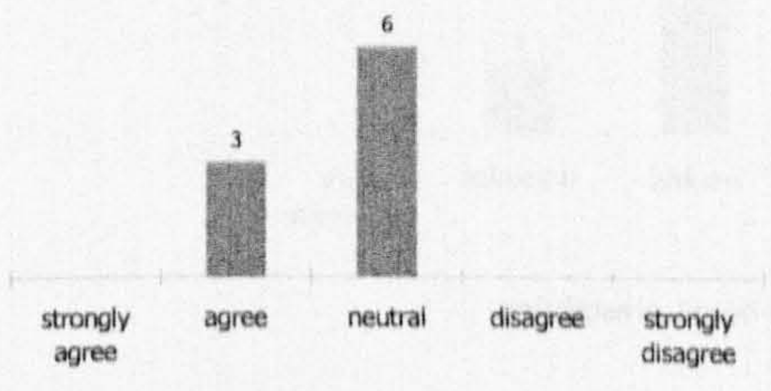
Cost-sharing reschedule



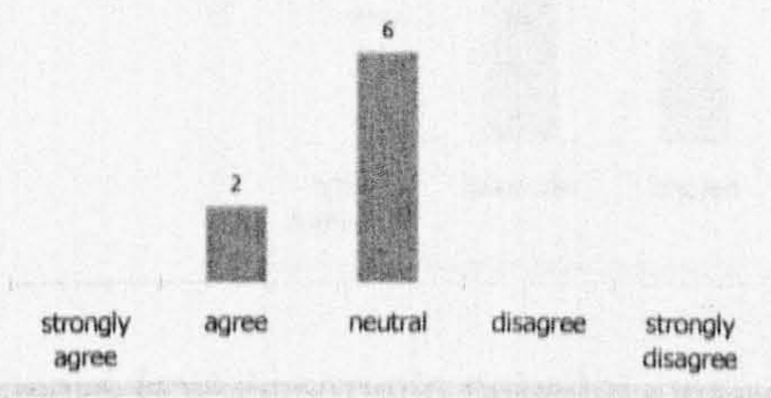
Best Prescribing Project



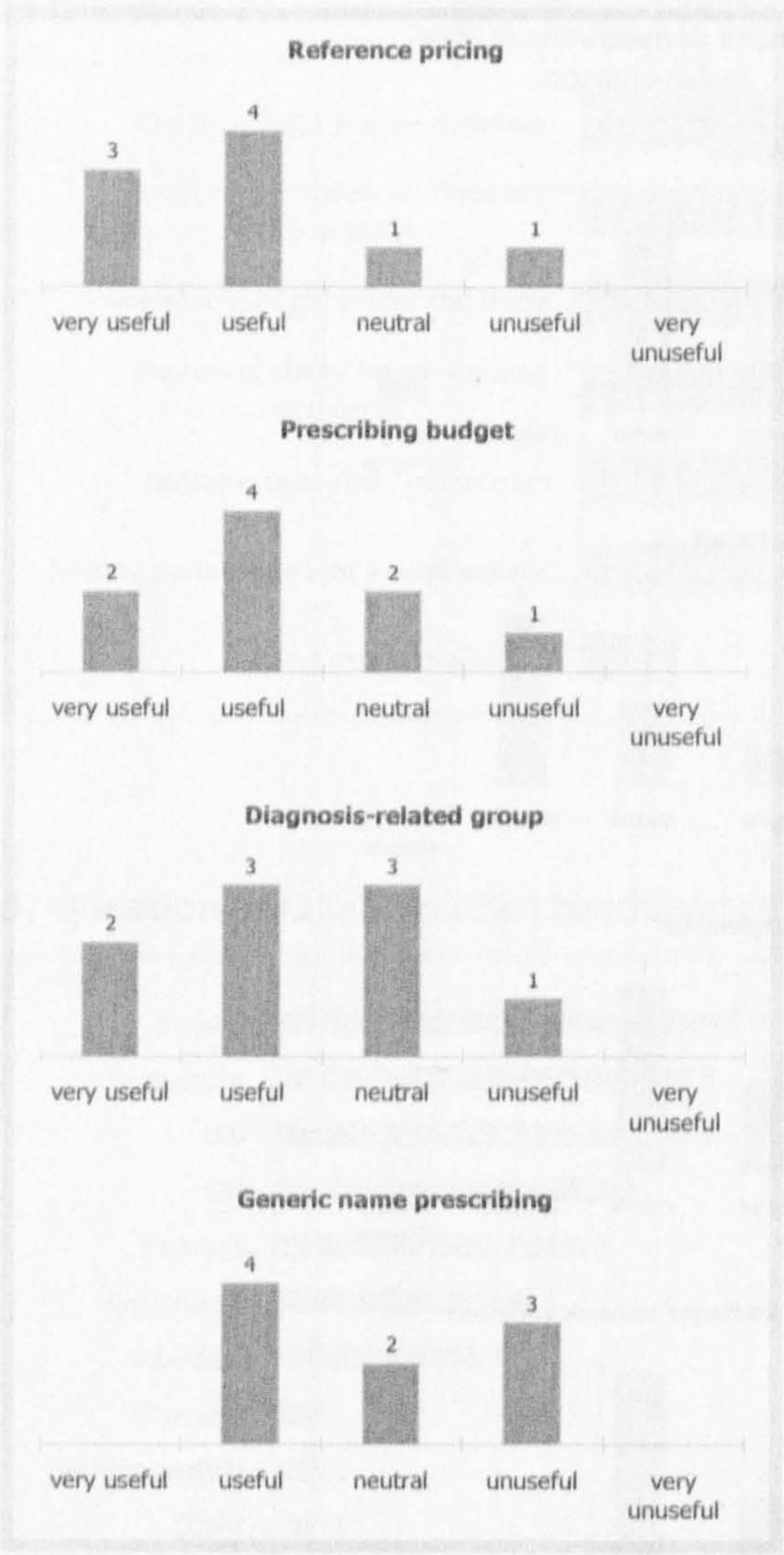
PERP-price cut/agreement



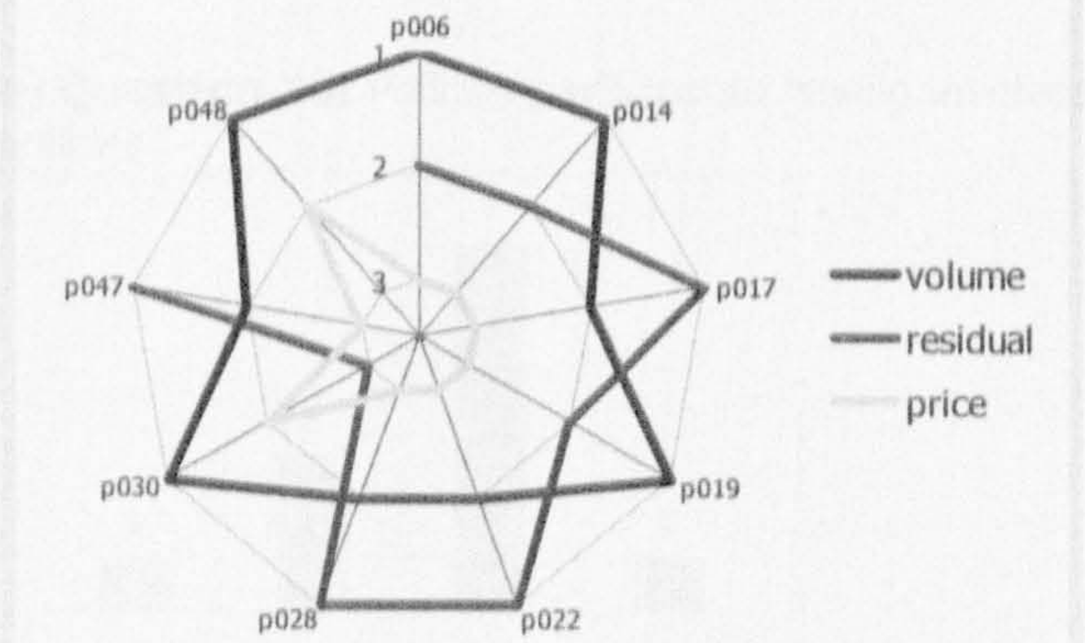
PERP-positive list/formal economic evaluation



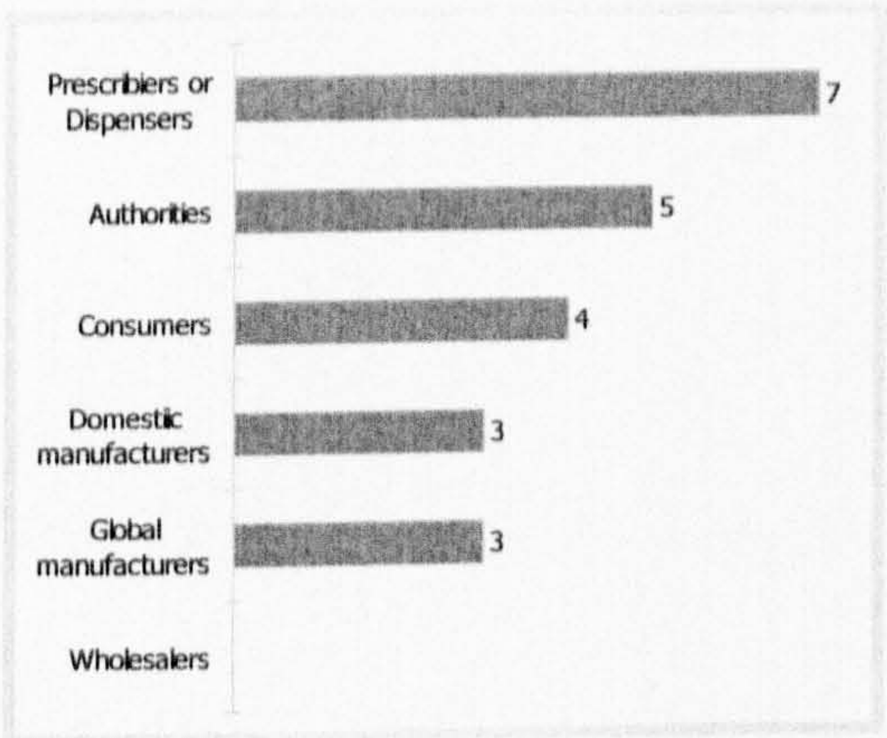
g) Question 15: Opinions on some of potential policies



h) Question 17: Factors inflating pharmaceutical expenditure in South Korea (1=most influential, 3=least influential)



i) Question 19: stakeholders under control in priority


Prescribers or Dispensers
7
Authorities
5
Consumers
4
Domestic manufacturers
3
Global manufacturers
3
Wholesalers

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