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Pharmaceutical Pricing and Reimbursement:

An Irish Perspective

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A thesis submitted for the degree of Doctor in Philosophy

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&

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2005

'Be not the first by whom the New are try'd,

Nor yet the last to lay the Old aside'

From 'An Essay on Criticism', Alexander Pope

DECLARATION

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SUMMARY

There has been a five-fold increase in state expenditure on medicines under the Community Drug Schemes in Ireland over the last decade (1994 to 2004). As a result of this marked increase in pharmaceutical expenditure, the issue of obtaining value for money from the drugs budget arises. The research presented in this thesis was undertaken in response to the issues of concern to the Department of Health and Children (DoHC) in relation to pricing and reimbursement of pharmaceuticals in Ireland. The aim of this thesis is to determine the potential impact of implementing various pharmaceutical cost-containment measures in the Irish healthcare system.

Similar increases in state expenditure on medicines have occurred across other European Union (EU) Member States, and various policies have been adopted by decision makers to contain this rise in pharmaceutical expenditure, including price controls, restriction of publicly reimbursed drugs by positive or negative lists, promotion of generic markets, prescribing budgets and patient co-payments. It is difficult to establish which of the different cost-containment strategies is most effective as they are rarely applied in isolation and it is often difficult to determine the influence of each in an overall effect. Therefore, before any cost-containment strategy can be introduced, a full assessment of the potential impact is necessary.

Currently, the price of medicines in Ireland reflects a Northern European price, which is generally higher than the European average. An international price comparison study was undertaken to compare the prices of reimbursed prescription medicines in Ireland to those in Denmark (which were linked to an average European price at the time of the study) and the UK (which is reported to have one of the highest prices for medicines in the EU) to determine potential cost savings on the largest Community Drug Scheme (the General Medical Services (GMS) Scheme) if an alternative pricing mechanism were adopted. The analysis covered a sample of 39 drugs (44.8% of the total ingredient cost of medicines on the GMS Scheme) selected from the top 70 drugs in order of total ingredient cost. Potential cost savings ranged from €20.7 million if a Danish price were adopted to €6.8 million for the UK price. This study demonstrated the high ex-wholesale price of prescription medicines in Ireland.

It is generally accepted that the prescribing of less expensive generic drugs is cost-effective. The potential savings that could be made if a system of generic substitution was introduced under the two main Community Drug Schemes (General Medical Services (GMS) and Drugs Payment (DP) Schemes) in Ireland were determined. In 2003, 21% of prescription items on the GMS Scheme and 23% of items on the DP Scheme were dispensed as a proprietary preparation when a generic equivalent was available. Substitution of the cheapest generic equivalent preparations of the top 30 drugs by expenditure would result in estimated annual savings of €12.7 million on the GMS and €9.1 million on the DP Scheme. Potential savings if the most expensive generic drug were dispensed would be in the region of €9.0 million on the GMS and €6.4 million on the DP Scheme. This evaluation demonstrates the potential for savings to be made from introducing a system of generic substitution in Ireland.

Finally, the use of the GMS prescription database to monitor utilisation of and expenditure on pharmaceuticals, using Nicotine Replacement Therapy (NRT) as an example, was investigated. Prescribing trends for therapies for nicotine dependence from September 2000 to December 2004 were analysed. The impact of including NRT on the list of reimbursable items for the GMS Scheme in April 2001 and the introduction of the ban on smoking in all workplaces in March 2004 on the rate of prescribing of therapies for nicotine dependence was demonstrated. The strength, formulation and duration of therapy, as well as the demographic characteristics of patients prescribed NRT, were determined. This analysis suggests high quality prescribing of therapies for nicotine dependence in accordance with current clinical and cost-effectiveness evidence. The dose and duration of therapy was in keeping with guidance from the National Institute for Health and Clinical Excellence (NICE) in the UK, indicating that expenditure of €2,709,954 on NRT in 2002 should provide value for money.

The results of this thesis highlight the potential impact of introducing policies to control the rising drug expenditures in the Irish healthcare setting and the use of the GMS prescription database to monitor utilisation of and expenditure on reimbursed medicines in primary care.

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ABPI	Association of the British Pharmaceutical Industry
ACE	Angiotensin-Converting Enzyme
AEP	Average European Price
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
CHD	Coronary Heart Disease
CI	Confidence Interval
DDD	Defined Daily Dose
DG	Directorate-General
DMA	Drugs and Medical Appliances
DP	Drugs Payment
DoHC	Department of Health and Children
EEA	European Economic Area
EFPIA	European Federation of the Pharmaceutical Industries and Associations
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GMS	General Medical Services
GNP	Gross National Product
GPs	General Practitioners
GTN	Glyceryl trinitrate
HBSC	Health Behaviour in School-aged Children
HIQA	Health Information and Quality Authority
HSE	Health Service Executive

HTA	Health Technology Assessment
HTD	High Tech Drugs
ICER	Incremental Cost Effectiveness Ratio
IDTS	Indicative Drug Target Scheme
IHD	Ischaemic Heart Disease
IMB	Irish Medicines Board
IMS	Intercontinental Marketing Services
INN	International Non-proprietary Name
IPHA	Irish Pharmaceutical Healthcare Association
IQR	Inter Quartile Range
LTI	Long Term Illness
MRP	Mutual Recognition Procedure
NCPE	National Centre for Pharmacoeconomics
NHO	National Hospitals Office
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMIC	National Medicines Information Centre
NRT	Nicotine Replacement Therapy
NSSC	National Shared Services Centre
OAD	Obstructive Airways Disease
OECD	Organisation for Economic Co-operation and Development
ONS	Oral Nutritional Supplements
OR	Odds Ratio
OTC	Over-The-Counter
PA	Product Authorisation
PACT	Prescribing Analysis and Cost

PCRS	Primary Care Reimbursement Service
PCTs	Primary Care Trusts
POM	Prescription Only Medicine
PPI	Proton Pump Inhibitor
PPP	Purchasing Power Parity
PPRI	Pharmaceutical Pricing and Reimbursement Information
PPRS	Pharmaceutical Price Regulation Scheme
QALY	Quality Adjusted Life Year
R&D	Research and Development
RP	Reference Pricing
SLÁN	Survey of Lifestyles, Attitudes and Nutrition
SPC	Supplementary Protection Certificate
SR	Sustained release
VAT	Value Added Tax
WHO	World Health Organisation

Chapter 1

Pharmaceutical Pricing and Reimbursement Policies in Ireland

Table of Contents for Chapter 1

1.1 Introduction

In many countries expenditure on medicines has risen at a faster rate than total healthcare spending. Total pharmaceutical expenditure is a function of the quantity of drugs dispensed, multiplied by price [which includes distribution margins and Value Added Tax (VAT)]. The growth in pharmaceutical expenditure is driven by a number of factors, including population growth and ageing, rising healthcare expectations, an increase in the incidence and duration of chronic diseases, improved treatment and technological progress and the introduction of new, more effective and more expensive drugs[1, 2]. However, there is a limit to what modern societies can afford to pay for better health.

The objectives of pharmaceutical policies are multidimensional and must take into consideration the conflicting demands to contain rising costs, improve health, support industrial growth and remain within the EU legislative framework[3, 4]. Every country is attempting to reconcile these objectives through a combination of policy tools[5]. A key target for pharmaceutical cost-containment within European healthcare systems, is the variety of mechanisms for the pricing and reimbursement of medicines.

Ireland has experienced similar increases in expenditure on medicines to other EU Member States. The rising drugs budget has been identified as an area, which would benefit from rigorous evaluation to optimise value for money[6]. The research presented in this thesis was undertaken in response to the issues of concern to the Department of Health and Children (DoHC) in relation to pricing and reimbursement of pharmaceuticals in Ireland.

The overall aim of this thesis is to describe the pharmaceutical pricing and reimbursement systems in Ireland and in the other EU Member States and to determine the potential impact of implementing various pharmaceutical pricing and reimbursement policies in the Irish healthcare system.

A description of pharmaceutical pricing and reimbursement policies in Ireland is presented in this chapter.

1.2 The Irish Healthcare System

1.2.1 Organisation and Structure of the Irish Healthcare System

In Ireland healthcare policy and expenditure is governed by the DoHC and, until recently, was administered through 10 regional Health Boards. However, this structure was designed over 30 years ago when the scale of activity and the number of services provided were considerably smaller. More effective ways of organising the healthcare system are now required to meet the demand and expectations of the twenty-first century. Therefore the structure of the health services in Ireland is currently undergoing a process of reform.

1.2.2 The Health Service Reform Program

In June 2003 the government announced the Health Service Reform Programme initiating an unprecedented change for the Irish healthcare system. The programme emerged from the recommendations of two key reports (see section 1.2.8):

1. The Audit of Structures and Functions in the Health System ("*The Prospectus Report*" 2003)[7].
2. The Report of the Commission on Financial Management and Control Systems in the Health Service *("The Brennan Report" 2003)*[8].

Key elements of the Reform Programme include[9]:

- A major rationalisation of the existing health service agencies to reduce fragmentation. This includes abolition of the existing Health Board structures;
- Reorganisation of the DoHC to ensure improved policy development;
- Establishment of a Health Service Executive (HSE) to manage the health service as a single national entity;
- The establishment of a Health Information and Quality Authority (HIQA) to ensure that quality of care is promoted throughout the system.

There are three main organisations within the restructured health service (Figure 1.1):

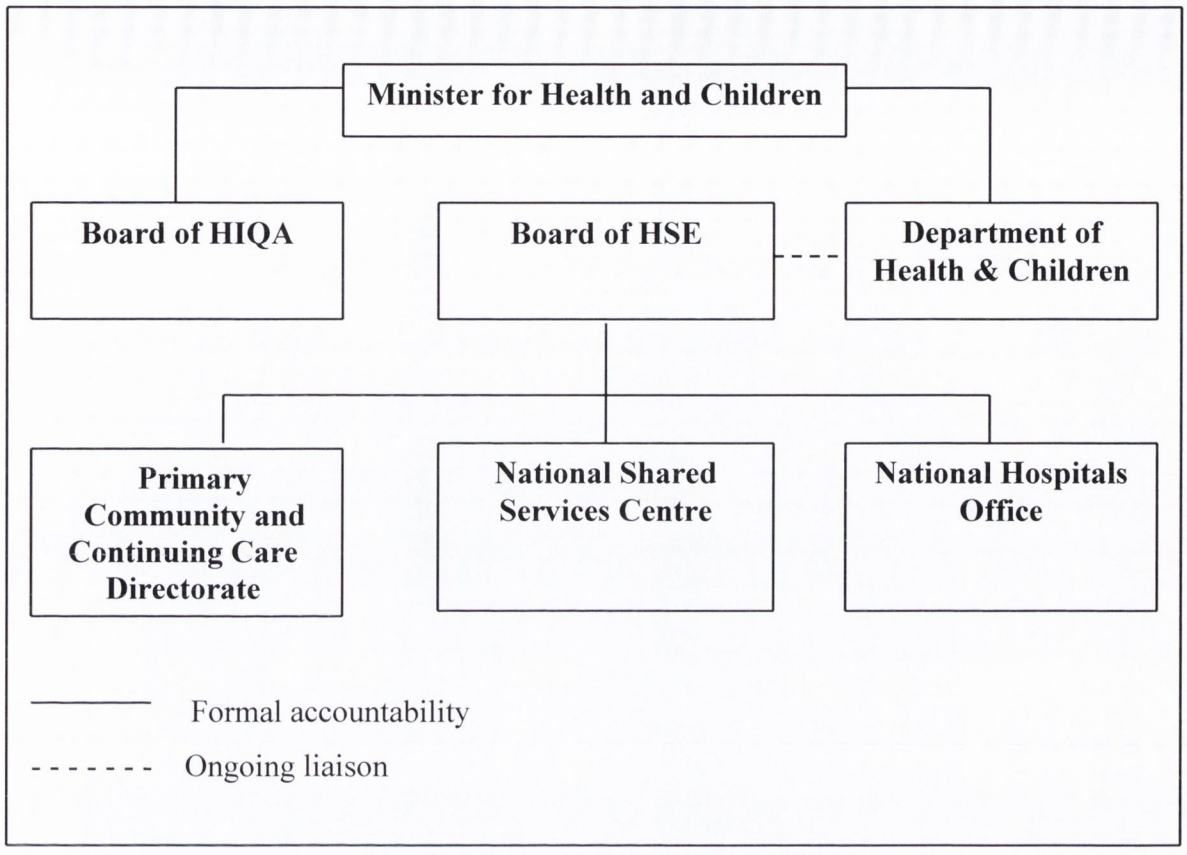
a. ***The Department of Health and Children (DoHC):*** The DoHC has a dual role within the new structure, which includes focusing on strategic and policy issues and having ultimate responsibility for holding the service delivery system to account for its performance.

b. ***Health Service Executive (HSE):*** The HSE functions as a national agency that delivers services, specified by the DoHC, within budget. There are three main bodies within the HSE:

- The National Hospitals Office (NHO) which is responsible for the management and co-ordination of the acute hospital sector nationally;
- The Primary, Community and Continuing Care Directorate which is responsible for the management and delivery of non-hospital services.
- The National Shared Services Centre (NSSC) which is responsible for provision of shared services across the wider health system and promotion of a "single" standard of health service delivery.

c. **Health Information and Quality Authority (HIQA):** The HIQA was established to ensure that high quality information is available to the healthcare system and to facilitate delivery of the key policy aim of the National Health Strategy 2001 (see section 1.2.8) i.e. to deliver high quality services that are based on evidence-supported best practice. The HIQA will be responsible for developing health information, promoting and implementing quality assurance programmes nationally and overseeing Health Technology Assessment (HTA).

Figure 1.1 The Restructured Health Service.



1.2.3 The Role of the National Shared Services Primary Care Reimbursement Service (PCRS)

The National Shared Services Primary Care Reimbursement Service (PCRS) (formerly the General Medical Services (Payments) Board) provides capitation funding to general practitioners, direct payments to pharmaceutical wholesalers for high cost medicines dispensed under the High Tech Drugs (HTD) Scheme and payment to pharmacists for the acquisition cost and dispensing fees for medicines dispensed under the various Community Drug Schemes.

The role of the PCRS is to calculate, verify and make payments under the various schemes and to compile statistical data. As part of the reform of the health service the PCRS now reports into the newly formed NSSC of the HSE.

The National Centre for Pharmacoeconomics (NCPE) receives the drug pricing, utilisation and expenditure data for the Community Drug Schemes from the PCRS on a regular basis. In this thesis the PCRS is referred to as the GMS (Payments) Board, as the analysis of the

GMS prescription database was undertaken prior to the transition of the GMS (Payments) Board to the PCRS.

1.2.4 Healthcare Funding and Expenditure

Healthcare funding is mainly derived from taxation (75%) with private funding via insurance agents accounting for 11% and patient co-payment the remainder[10]. The overall funding level for the health services is determined in negotiations between the Department of Finance and the DoHC[10].

In recent years, coincident with increased economic prosperity, public expenditure on healthcare in Ireland has increased considerably from €3.7 billion in 1997 to €8.3 billion in 2002 and an estimated €11 billion in 2005[11, 12]. Ireland has had the highest average growth in total expenditure on health between 1998 and 2003 of all the EU-15 Member States[13].

In the international context, over the last 20 years, Ireland has commonly been at the lower end of the Organisation for Economic Co-operation and Development (OECD) league tables for expenditure on healthcare[13]. Since 1995, Luxembourg was the only one of all EU-15 Member States to spend a smaller proportion of Gross Domestic Product (GDP) on healthcare than Ireland[13]. However, it has been highlighted that real increases in health expenditure in Ireland in recent years have commanded a smaller share of GDP, due to a high rate of growth in the economy in general[10].

1.2.5 Pharmaceutical Expenditure

State expenditure on medicines reimbursed under the Community Drug Schemes exceeded €1.2 billion in 2004, an 18% increase on the previous year[14, 15]. OECD Health Data 2005 highlights that, apart from Denmark, Ireland has the lowest expenditure on pharmaceuticals as a percentage of total expenditure on health across the EU-15 Member States[13]. However, there has been a marked increase in pharmaceutical expenditure in Ireland over the last decade.

Total pharmaceutical expenditure under the Community Drugs Schemes (i.e. payment to pharmacies for the cost of medicines and dispensing fees, plus payments to wholesalers under the HTD Scheme) has increased from €228 million in 1994 to €1,234 million in 2004, a five-fold increase[15, 16].

Prior to 1997 the annual increase in payments ranged from 8% to 11%. In recent years this has increased significantly from approximately 15% between 1997 and 1998, to a peak of 27% between 2000 and 2001 (Table 1.1).

Table 1.1 The annual increase in public pharmaceutical expenditure under the Community Drug Schemes (1993-2004).

	Public pharmaceutical expenditure under the Community Drug Schemes	Annual percentage increase
1993	€ 211m	
1994	€ 228m	8.1%
1995	€ 252m	10.5%
1996	€ 279m	10.7%
1997	€ 333m	19.4%
1998	€ 384m	15.3%
1999	€ 459m	19.5%
2000	€ 580m	26.4%
2001	€ 736m	26.9%
2002	€ 898m	22.0%
2003	€ 1,047m	16.6%
2004	€ 1,234m	17.9%

Source: *GMS (Payments) Board Annual Reports 1993-2004.*

1.2.6 Eligibility for Healthcare

There are two categories of entitlement to healthcare in Ireland[17]:

Category I: Below an income threshold all inpatient and outpatient services, including drug therapy, are free under the General Medical Services (GMS) Scheme. The GMS Scheme is also known as the medical card scheme and covers approximately 30% of the Irish population.

Category II: The rest of the population receives free inpatient treatment with a levy but they are not entitled to free GP services or prescribed medicines. Drug expenditure is reimbursed above a threshold of €85 under the Drug Payments (DP) Scheme.

Therefore the entire population is entitled to a core publicly funded service, including hospital in-patient services. In addition, the Health Boards have traditionally had discretion to provide services free of charge in cases of hardship to people who are not normally eligible for particular services[17]. There is, however, a mix of public and private care in the system, which is reflected in the fact that voluntary private insurance is an established part of arrangements used to meet the cost of hospital services.

1.2.7 Public/Private Mix

Approximately 45% of the Irish population hold private medical insurance, despite universal access to the public healthcare system[18]. The number of insured persons has been rising, principally, it seems, because of the speed and certainty of access to care, as well as quality of care, which the holding of insurance is perceived to provide[19]. Private insurance does not cover the cost of medicines under the Community Drug Schemes.

The majority of GPs and hospital consultants provide services to both public and private patients; pharmacists serve the public and private sectors; and in the major public hospitals approximately one-fifth of the beds are private[20]. Half of the private beds in the country are provided in public hospitals[21]. Therefore, those with private insurance generally receive private care in private or semi-private rooms, and choose their own consultant, but much of this care is delivered in public hospitals[19]. It has been highlighted that it is potentially problematic that the same providers face different incentives when they respond to the needs of public and of private patients[20]. According to the Brennan Report (see section 1.2.8) "*the existing arrangements for mixing public and private treatments are inherently unsatisfactory from a management and control perspective*"[8].

1.2.8 Healthcare Policies in Relation to Pharmaceuticals

Over the last five years, prior to the restructuring of the Irish healthcare system, a number of health policy documents have been commissioned by the DoHC. Although individual pharmaceutical policies have not been produced, pharmaceutical policy tends to fall within overall health policy. The key policy documents and their influence on pharmaceutical policy are described below.

a. The National Health Strategy 2001. *Quality and Fairness: A health system for you*[22].

The National Health Strategy 2001, which outlines the programme of investment and reform for the time period 2001 to 2011, was published in 2001. This document was preceded by the National Health Strategy 1994 (*Shaping a Healthier Future*), which strove to develop a strategic planning process for the Irish healthcare system[23].

The four principles of the National Health Strategy 2001 are equity and fairness, a people centred service, quality of care and clear accountability. The National Health Strategy 2001 builds on the policy objectives outlined in previous documents, such as the Cancer Strategy, the Cardiovascular Strategy and the Primary Care Strategy, and includes promotion of preventative healthcare as a crucial tool in improving population health[24-26]. General Practitioners (GPs), for example, are encouraged to prescribe preventative pharmacological strategies, such as, statins for the prevention of cardiovascular disease and nicotine replacement therapy for the prevention of cardiovascular disease and cancer.

The expansion of entitlement criteria for the GMS Scheme is an objective of the National Health Strategy 2001. There is considerable political pressure to further increase the income threshold for the GMS Scheme to the minimum wage level. This will increase the number of claimants and consequently the level of pharmaceutical expenditure on the GMS Scheme.

Part of the organisational reform associated with the National Health Strategy 2001 includes the setting up of the Health Information and Quality Authority (HIQA) to ensure delivery of high quality services that are based on evidence supported best practice. The HIQA will *"oversee HTA to ensure that the most modern appropriate care and treatments are used in a way that maximises health gain and achieves value for money"*[22].

The National Health Strategy 2001 promotes equity of access to healthcare. Access to medicines across Health Boards is for the most part uniform as the public pharmaceutical budget is administered centrally by the PCRS and a single positive list of drugs applies nationwide. Therefore, "postcode prescribing" to keep within regional pharmaceutical budgets and the resultant geographical inequities of access to medicines, which has been a feature of the UK National Health Service (NHS), is not a characteristic of the Irish healthcare system. However, there is some evidence of inequities in prescribing of

pharmaceuticals across Ireland. Inequality in the uptake of proven technologies e.g. Angiotensin-Converting Enzyme (ACE) inhibitors, beta blockers, aspirin and statins for secondary prevention of ischaemic heart disease (IHD) has been demonstrated. Using GMS prescription data (representing 70% of all prescribing in primary care), Bennett *et al.* demonstrated a two-fold variation in prescribing of ACE inhibitors and a 1.6-fold variation in the prescribing of statin medications as secondary preventive therapy for IHD, between the Health Board regions in Ireland[27]. Men were most likely to be prescribed these therapies whilst the elderly were least likely. The authors concluded that access to secondary preventative therapy is not equitable across regions, gender and age in Ireland. The wide variability may be due to failure to adhere to guidelines on prescribing secondary preventative therapies and/or variability in clinical need between the regions.

b. The Value for Money Audit of the Irish Healthcare System 2001[6].

The significant increase in public health expenditure since the 1990s raised the question of whether the healthcare system was delivering value for money. This report highlighted the scarcity of routine and systematic evaluation of value for money in the health services and the focus on cost-containment rather than cost-effectiveness[6]. Pharmaceutical policies have focused mainly on cost-containment endeavours (e.g. increasing the patient co-payment level) combined with some incentives to improve the quality of prescribing in particular the promotion of cost-effective prevention strategies, such as nicotine replacement and statin therapy.

c. The Prospectus Report 2003: *Audit of Structures and Functions in the Health System*[7]**.**

The Prospectus Report provided an independent audit of structures and functions in the health system. The central theme of this report was the need to consolidate fragmented structures and functions to enable the health system deliver sustained VFM and a high quality service that supports implementation of the National Health Strategy. The main change proposed in this Report was the reorganisation of existing agencies and their functions by replacing the Health Board structure with a single national Health Services Executive.

d. ***The Brennan Report 2003.*** *Commission on Financial Management and Control Systems in the Health Service*[8].

The Brennan Report evaluated the financial systems, practices and procedures throughout the health services. This report also identified major structural weaknesses in the health system including a fragmented structure, a lack of incentives to manage costs effectively, insufficient evaluation of existing programmes and associated expenditure and inadequate investment in information and management systems.

The report highlighted that under the DP Scheme there is no incentive comparable to the GMS Scheme [i.e. the Indicative Drug Target Scheme (IDTS); see section 1.9.1] to encourage GPs to consider costs when prescribing. In addition, where a doctor prescribes the more expensive product under the DP and Long Term Illness (LTI) Schemes (see section 1.4.2), profits of the community pharmacies are increased. The Commission recommended a review of the Community Drug Schemes, focusing on the following issues:

1. Creating incentives for positive prescribing behaviour;
2. Minimising inappropriate prescribing;
3. Maximising the prescription and dispensing of generic products;
4. Negotiating cost competitive drug prices at national level;
5. Implementing common hospital/primary care drug formularies;
6. Introducing a flat-fee basis for reimbursement of drug costs across all national drug schemes and reimbursing at the rate of the lowest cost for therapeutically equivalent products in all schemes;
7. Evaluating the clinical and cost-effectiveness of the publicly funded drug reimbursement schemes.

e. ***Health Information.*** *A National Strategy 2004*[28].

The main aim of this strategy is to rectify present deficiencies in health information systems and to put in place the frameworks to ensure optimal development and utilisation of health information. HIQA will play a pivotal role in the implementation of the Health Information Strategy. Delivery on health information will be an essential prerequisite to the development of HTA and economic evaluation of pharmaceuticals in the Irish setting.

f. The G10 Medicines Report

The G10 Medicines Report was published by the European Commission's High Level Group on Innovation and Provision of Medicines in 2002 (see chapter 2)[29]. This report makes recommendations on how to foster the competitiveness of the European pharmaceutical industry while meeting important public and social objectives. The G10 recommendations that may impact specifically on pharmaceutical policy in Ireland include:

- Fostering HTA including the economic evaluation of drugs prior to reimbursement;
- Ensuring fast access for patients to innovative medicines by encouraging rapid and transparent licensing and reimbursement procedures;
- Promoting generic penetration;
- Promoting the self-medication market.

The G10 recommendations are considered by the DoHC in formulating pharmaceutical policy.

1.2.9 Importance of the Pharmaceutical Industry

Ireland's pharmaceutical industry is the world's largest net exporter of medicines, with net exports now exceeding €13.3 billion annually[30]. In addition, the industry employs 21,000 people in Ireland. There has been major investment in the Irish economy by US companies in recent years, with eight of the top ten US pharmaceutical companies having manufacturing facilities in Ireland. Therefore, the pharmaceutical manufacturing and related industries are now amongst the most important contributors to the Irish economy. It has been suggested that the political decision to allow high drug costs in Ireland may be linked to the major contribution of the pharmaceutical industry to the national economy[31].

The Irish Pharmaceutical Healthcare Association (IPHA) represents innovator pharmaceutical companies in Ireland and makes regular representations to the DoHC on a range of healthcare policy issues. IPHA suggests that maintaining a positive sales environment is crucial to the continuing investment by international pharmaceutical manufacturers in the Irish economy. However, given the relatively small size of the Irish market, it is likely that the tax-break incentives and the highly educated workforce are more important considerations in investment decisions[32].

The Irish government acts as both the regulator and supporter of the pharmaceutical industry, restraining its profits by ensuring drugs are reasonably priced for the Irish

healthcare system, while promoting the pharmaceutical industry for the benefit of the Irish economy.

1.3 Pricing of Medicines in Ireland

1.3.1 The Irish Pharmaceutical Healthcare Association (IPHA) - Department of Health and Children (DoHC) Agreement

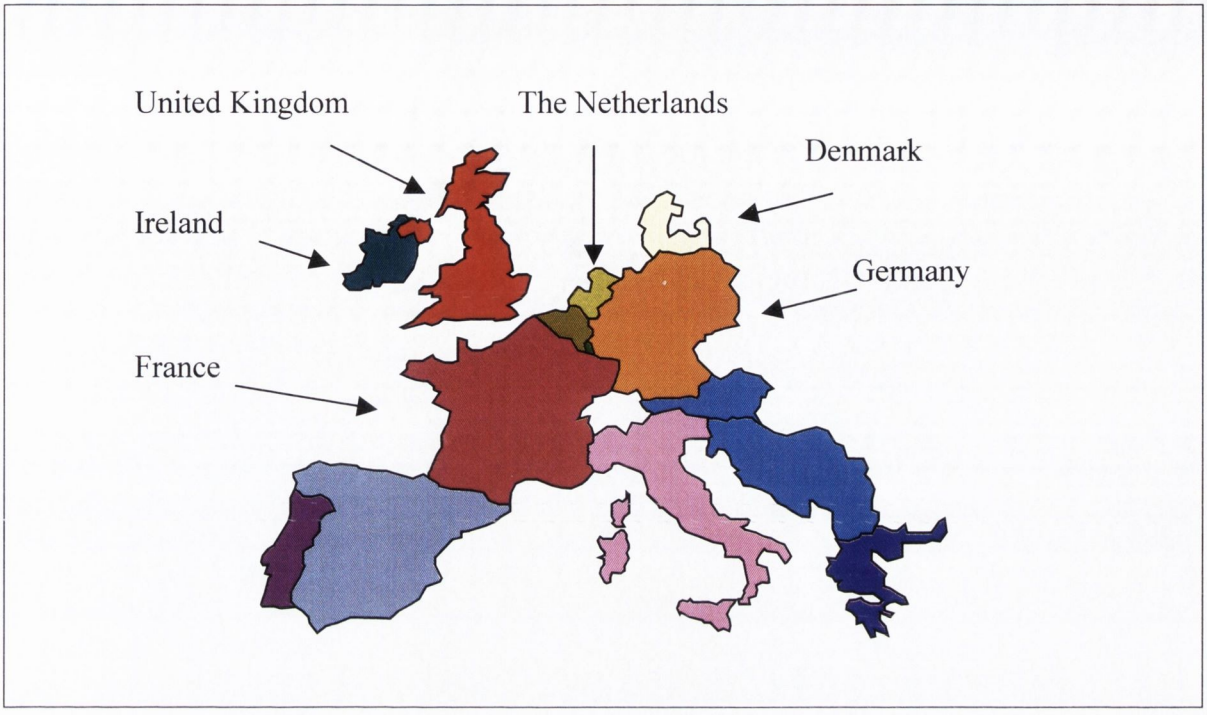
The Agreement between the IPHA and DoHC (IPHA-DoHC Agreement) outlines the supply terms, conditions and pricing of medicines supplied to the health service in Ireland (see Appendix 1). The current Agreement commenced in 1993, was renewed in 1997 and extended in 2001 until 2005. The Agreement covers all medicines prescribable and reimbursable in the Community Drug Schemes and all medicines supplied to hospitals and Health Boards.

1.3.2 Regulation of Prices of Medicines

Under the current IPHA-DoHC Agreement, Ireland links the price of medicines by formula to those of five other EU Member States. The price to the wholesaler of any medicine will not exceed the lesser of the currency adjusted wholesale price in the UK or the average of wholesale prices in Denmark, France, Germany, the Netherlands and the UK (Figure 1.2)[33]. This Agreement reflects the government's support for the pharmaceutical industry in Ireland. High prices are tolerated because gains from the presence of industry far exceed costs to the State of reimbursement[34]. The IPHA-DoHC Agreement is currently being renegotiated[35].

A pharmaceutical company wishing to launch a new medicine is required to submit an application to the DoHC with the ex-manufacturer prices in each of the reference states where it is available. If a product is not available in any of the reference countries the Irish ex-manufacturer price is agreed between the DoHC and the manufacturer or importer.
The maximum price at which medicines can be supplied by manufacturers or importers to hospitals or Health Boards is the Irish ex-wholesale price less a discount of 15% on orders over €634.87, but hospitals are at liberty to negotiate additional discounts[33].

Figure 1.2 Ireland links its drug price by formula to those of five other EU Member States.



1.3.3 Price Freeze

There has been a price freeze on all prescription medicines since 1993. If the average currency adjusted increase or decrease in the ex-manufacturer price in the 5 basket countries exceeds 10%, the price freeze may be reviewed. However, although there is a price freeze on medicines, pharmaceutical expenditure continues to increase dramatically due to the introduction of new and more expensive medicines and the growth in the volume of items dispensed.

1.3.4 Price Modulation

Price modulation of some products is permitted under the agreement on an 'exceptional' basis and on condition that any such modulation will be demonstrably cost-neutral in each year of the agreement[33]. The DoHC may require audited documentation of any price modulation and has the sole discretion to accept, reject or seek variation in any modulation application. The NCPE evaluates price modulation requests for the DoHC using the prescription data from the GMS prescription database.

1.3.5 Industry Payback Arrangements

Each month pharmaceutical manufacturers and importers must rebate to the GMS (Payments) Board 3% of the value, at trade price level, of all medicines dispensed under the GMS Scheme[33].

1.3.6 Pharmacy Retail Prices Under the Community Drug Schemes

Pharmacy retail prices for medicines vary depending on the eligibility of the patient and the formulation of the medicine prescribed:

- **GMS Scheme:** The pharmacy retail price is determined from the ex-wholesale price + dispensing fee per item (€2.98).
- **DP / LTI Scheme:** The pharmacy retail price comprises the ex-wholesale price + 50% mark-up + dispensing fee per item (€2.59).

- **HTD Scheme**: The ex-wholesale price minus 5% is paid to wholesalers directly. In addition, a set patient care fee of €49.64 per patient per month is paid by the GMS (Payments) Board to the pharmacy to cover dispensing costs.

Consequently payment to pharmacists is much greater under the DP and LTI Schemes as compared with the GMS Scheme (Table 1.2).

Table 1.2 The price of pravastatin 20mg daily on the GMS, DP and LTI Schemes.

GMS Scheme	**DP / LTI Schemes**
Ingredient cost of 28 tablets: ***€43.44***	Ingredient cost of 28 tablets: ***€43.44*** + 50% mark-up: ***€21.72***
Dispensing fee: ***€2.98***	Dispensing fee: ***€2.59***
Oral formulation – no VAT	Oral formulation – no VAT
Total payment to pharmacy: *€46.42*	**Total payment to pharmacy: *€67.75***

The wholesale margin on all medicines, other than to hospitals, is 15% of the ex-wholesale (pharmacy purchase) price[34, 36]; for high-tech medicines the margin is 10%[36]. However, it appears that a substantial portion of the wholesale margin is passed onto pharmacists as discounts.

A rate of VAT at 21% is charged on non-oral formulations including topical preparations and injections[37].

1.4 Reimbursement of Medicines in Ireland

1.4.1 The Positive List

Prior to reimbursement under the Community Drug Schemes a medicine must be included in the GMS code book or positive list. The list of reimbursable medicines is applicable to all of the Community Drug Schemes. The IPHA-DoHC Agreement provides that all newly introduced products will be reimbursed, provided that they conform to the general requirements regarding pricing, advertising and prescription status. In order to qualify for reimbursement, a product must conform to the list of criteria published by the Minister for Health and Children pursuant to the EU Transparency Directive (Council Directive 89/105/EEC, 1989) (see Appendix 2)[38]. Consequently, following the receipt of market authorisation there is a short time delay to reimbursement.

In addition to this positive list, certain extemporaneous medicines and unlicensed medicines are also prescribable and reimbursable on the Community Drug Schemes[34]. Exclusions to the positive list are mainly OTC medicines.

1.4.2 The Community Drug Schemes

The majority of drug expenditure under the Community Drugs Schemes (€1,234.11 million in 2004) are related to claims processed under the General Medical Services (GMS), the Drugs Payment (DP), Long Term Illness (LTI), European Economic Area (EEA) and the High Tech Drugs (HTD) Schemes. The number of prescription items, cost, eligibility criteria and patient co-payment for each of these schemes is shown in Table 1.3.

Table 1.3 Number of prescription items, cost, eligibility criteria and patient co-payment for each of the Community Drug Schemes in 2004.

Community Drug Scheme	Number of prescription items (millions)	Payment to pharmacies: drug cost + dispensing fee (€ million)	Eligibility	Patient co-payment
GMS	35.03	763.32	All below income threshold & all over 70 years	None
DP	9.93	226.83	All who are not eligible for GMS or LTI schemes	€85 per month
LTI	1.67	85.55	Fifteen specific chronic conditions (see Table 1.4)	None
EEA	0.08	1.79	Residents of an EU/EEA country or Switzerland	None
HTD	0.18	6.80*	All patients for selected high cost drugs	None if GMS eligible otherwise €85 per month
Other**	0.29	8.40		
Total	**47.18**	**1,092.69**		

*Payment to wholesalers under the HTD Scheme = €141.41 million

**Other = Methadone Treatment Scheme & Dental Treatment Services.

Source: *GMS (Payments) Board Report for the year ended December 2004.*

a. General Medical Service (GMS) Scheme

Those who are unable without undue hardship to arrange GP medical and surgical services for themselves and their dependants are eligible to receive a free general medical service and are issued with medical cards[37]. In addition, since July 1st 2001, all residents over the age of 70 years are entitled to a medical card regardless of means. Medical card holders are entitled to free GP medical and surgical services and free prescription drugs, medicines and appliances through their local participating pharmacist. The issuing of medical cards is

means tested and dependant upon factors such as age, marital status, living alone or with family and allowances e.g. for children under sixteen years.

The number of eligible persons under the GMS Scheme at the end of the year 2004 was 1,148,914 i.e. 28.41% of the population. Over 96% of eligible persons availed of the scheme in 2004[15].

b. Drugs Payment (DP) Scheme

The DP Scheme, introduced on 1/7/1999, applies to Irish residents who do not have a medical card[37]. Under the DP Scheme no individual or family is required to pay more than €85 in any calendar month for approved prescribed medicines for use by that person or his/her family in that month. Family expenditure covers the nominated adult, his/her spouse and children less than 18 years – persons over 18 years and less than 23 years who are in full time education may be included as dependents.

The number of persons registered under the DP Scheme at the end of the year 2004 was 1,469,251 i.e. 36.33% of the population. Approximately 34% of those eligible availed of the scheme in 2004 and the cost of medicines under the DP Scheme was €226.8 million that year. Patient co-payment under the DP Scheme is not covered by private health insurance. Patient co–payment under this scheme was €127.2 million in 2004[39].

It has been suggested that the basis of remunerating pharmacists under the DP Scheme should be changed, from the current system whereby a 50% mark-up is added to the ingredient cost, to a fee for service basis.

c. Long Term Illness (LTI) Scheme

The LTI Scheme entitles patients suffering from any one of fifteen specified chronic conditions to full drug reimbursement, for the management of these conditions, irrespective of income (Table 1.4)[37]. There has been considerable effort by patient advocacy groups to have other high cost chronic illnesses such as asthma included on the LTI Scheme.

Table 1.4 Chronic illnesses covered by the LTI Scheme.

Mental Illness for persons <16yrs	Cystic Fibrosis	Cerebral Palsy	Multiple Sclerosis
Mental Handicap	Spina Bifida	Epilepsy	Acute Leukaemia
Haemophilia	Hydrocephalus	Diabetes Mellitus	Parkinsonism
Phenylketonuria	Muscular Dystrophies	Diabetes Insipidus	

At the end of December 2004 there were 93,504 persons registered under the LTI Scheme (2.31% of the population) and expenditure on medicines under this scheme was €85.55 million for that year[15]. Therefore almost one third (30.7%) of the population of Ireland are eligible to receive free medicines under the GMS and LTI Schemes. This one third of the population accounts for approximately two thirds of total drug expenditure. The remaining two thirds of the population have to contribute towards the cost of their medication.

The LTI operates essentially as a GMS Scheme, in that it does not operate on a threshold basis like the DP Scheme. However, pharmacists still receive the benefit of the 50% mark-up on the ingredient cost as in the DP Scheme. On this basis, it has been recommended that the more efficient approach would be to incorporate the LTI into the GMS Scheme[40].

d. High Tech Drugs (HTD) Scheme

The HTD Scheme, introduced in November 1996, facilitated the supply by community pharmacies of certain high cost medicines e.g. those used in conjunction with chemotherapy, beta-interferon etc. which had previously been supplied primarily in the hospital setting[37]. The cost of medicines dispensed under the HTD Scheme is paid directly to the wholesalers and pharmacists are paid a standard patient care fee of €49.64 per month to cover dispensing. In 2004 payment to wholesalers under the HTD Scheme was €141.41 million and payment to pharmacies to cover dispensing fees was €6.8 million[15].

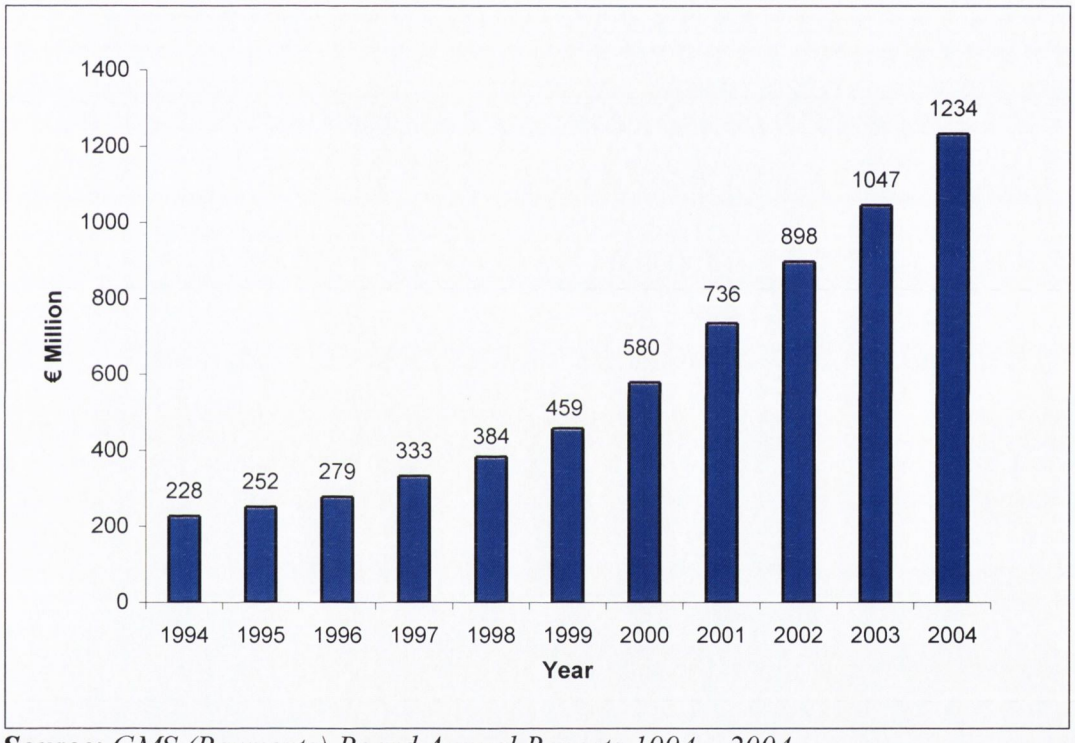
e. European Economic Area (EEA) Scheme

On production of a European Health Insurance Card, the EEA Scheme provides visitors from other EU/EEA countries and Switzerland with emergency GP services while on a temporary visit to Ireland. In 2004, prescription items dispensed under the EEA Scheme cost €1.8 million[15].

1.4.3 Factors Contributing to Increased Drug Expenditure on the Community Drug Schemes

Total pharmaceutical expenditure under the Community Drug Schemes (i.e. payment to pharmacies for cost of medicines and dispensing fees plus payments to wholesalers under the HTD Scheme) has increased from €228 million in 1994 to €1,234 million in 2004 (Figure 1.3)[15, 16].

Figure 1.3 Public expenditure on medicines in Ireland (Community Drug Schemes 1994-2004).



Source: *GMS (Payments) Board Annual Reports 1994 – 2004.*

The two main factors contributing to the increased expenditure on medicines include the "product mix" i.e. the prescribing of new and more expensive medicines and the "volume effect" i.e. growth in the number of prescription items dispensed.

Despite the price freeze on medications since 1993, the influence of product mix is seen as the average ingredient cost per item prescribed on the GMS Scheme increased over two-fold, from €7.67 in 1994 to €16.70 per item in 2004[15, 16]. Furthermore, the influence of the volume effect is demonstrated by analysis of the GMS Scheme where the number of eligible patients has fallen by 10.7% over the last decade, from 1,286,632 persons in 1994 to 1,148,914 persons in 2004 (Table 1.5). However the 35.0 million items prescribed on

the GMS Scheme in 2004 represents a 96% increase over the 10 year period. There was an average of 2.05 items dispensed per prescription in 1994 compared to an average of 2.74 items per prescription in 2004[15, 16].

Table 1.5 Overview of prescription volume and costs on the GMS Scheme over the period 1994-2004.

Year	Eligible Persons (million)	Total ingredient cost (€ million)	Dispensing fees (€ million)	Number of items (000's)	Ingredient cost per item (€)
1994	1.287	137	37	17,906	7.67
1995	1.277	149	40	18,879	7.91
1996	1.252	159	42	19,131	8.32
1997	1.219	173	46	19,944	8.66
1998	1.184	195	49	20,696	9.41
1999	1.164	223	53	21,679	10.30
2000	1.148	263	59	22,882	11.49
2001	1.199	330	85	25,521	12.91
2002	1.169	423	105	29,500	14.35
2003	1.158	504	121	32,241	15.62
2004	1.149	585	149	35,030	16.70

Source: *GMS (Payments) Board Annual Reports 1994-2004.*

It is evident from the trends outlined in Table 1.5 that, while the number of eligible persons has fallen over this period, a significant increase has occurred in both the number of items prescribed and the average ingredient cost per item. The number of eligible persons increased in 2001 following the introduction of the New Over 70's Agreement that year. The increase in ingredient costs has been particularly pronounced since 1998, with a more than doubling of the total ingredient costs in the five-year period from 2000 to 2004. The introduction of the DP Scheme in 1999 and the inclusion of all citizens of 70 years of age and over on the GMS Scheme are likely to have contributed to the increase in expenditure on the Community Drug Schemes over the last decade.

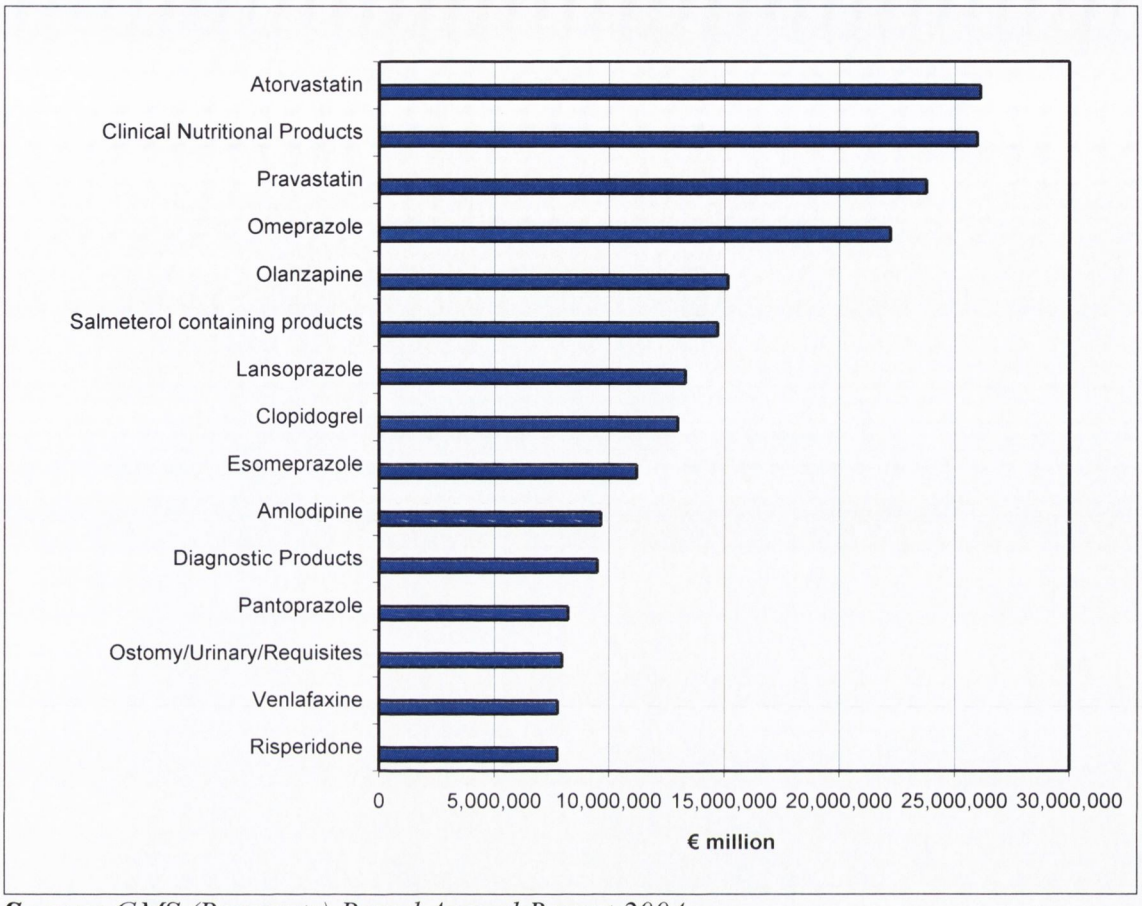
The Community Drug Schemes have grown considerably since their inception and a review of the schemes by Deloitte & Touche (published in 2005) highlight the following issues[40]:

- The need to involve GPs and other service providers in budget holding to improve financial management and accountability.
- The requirement to assess whether the LTI Scheme should be merged into the GMS Scheme, thus removing the 50% pharmacy mark-up from the LTI Scheme.
- The requirement to amend the basis of remunerating pharmacists under the DP and LTI Schemes to a fee for service basis and not a mark-up on the ingredient costs.
- The requirement to establish protocols for prescribing, and to monitor prescription data at GP level to ensure appropriate and effective prescribing patterns.
- The requirement for HTA on an ongoing basis.

Analysis of the 4 drugs accounting for the highest expenditure on the GMS Scheme.

Two classes of drugs, the proton pump inhibitors (PPIs) and the statins, accounted for 9.87% and 9.90% of the total ingredient cost of medicines in 2004 respectively (Figure 1.4). Atorvastatin was the product of highest cost to the GMS Scheme in 2004, followed by oral nutritional supplements which accounted for 4.35% of the total ingredient cost of medicines on the GMS Scheme.

Figure 1.4 Top 15 products of highest cost in order of their ingredient cost under the GMS Scheme in 2004.



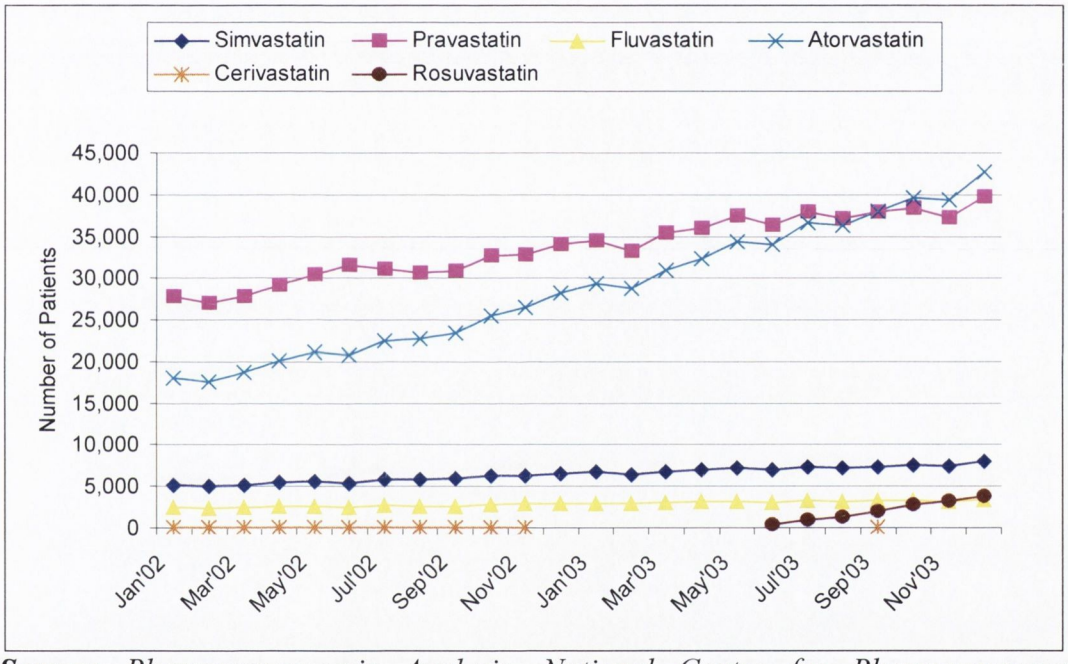
Source: *GMS (Payments) Board Annual Report 2004.*

1. Atorvastatin and Pravastatin

The efficacy and safety of statin medications in reducing the morbidity and mortality of coronary heart disease (CHD) is well established. As a result of widespread use of these medicines expenditure under the GMS Scheme, on the 3 most widely prescribed statins (atorvastatin, pravastatin and simvastatin), has increased from €14.43 million in 2001 to €54.29 million in 2004 – a 3.8 fold increase over a 3 year period[41]. The cost-effectiveness of statin therapy for the secondary prevention of CHD in the Irish healthcare setting, using economic modelling techniques, was determined in 2001. All of the statins available at that time were found to be cost-effective with the incremental cost per Quality Adjusted Life Year (QALY) ranging from €1,172 for atorvastatin to €3,900 for pravastatin[42]. This study suggests that atorvastatin is the most cost-effective statin therapy for the secondary prevention of CHD in Ireland. However, the most widely prescribed statin in Ireland was pravastatin, until 2004 when expenditure on atorvastatin surpassed pravastatin (Figure 1.5).

A more recent study, undertaken in 2005, on the use of statins for primary prevention of CHD in the Irish healthcare setting reported cost per QALY ranges from €26,439 (atorvastatin 10mg daily) to €50,087 (pravastatin 40mg daily)[43]. Rosuvastatin (the least expensive branded statin) and the cheapest generics available for both simvastatin and pravastatin fell between these ranges. Therefore atorvastatin is considered the most cost-effective statin for the primary and secondary prevention of CHD in Ireland and is now the most widely prescribed statin on the GMS Scheme.

Figure 1.5 Total number of patients prescribed statins on the GMS Scheme between 2002 and 2003.



Source: *Pharmacoeconomic Analysis. National Centre for Pharmacoeconomics* (http://www.ncpe.ie).

2. Oral Nutritional Supplements

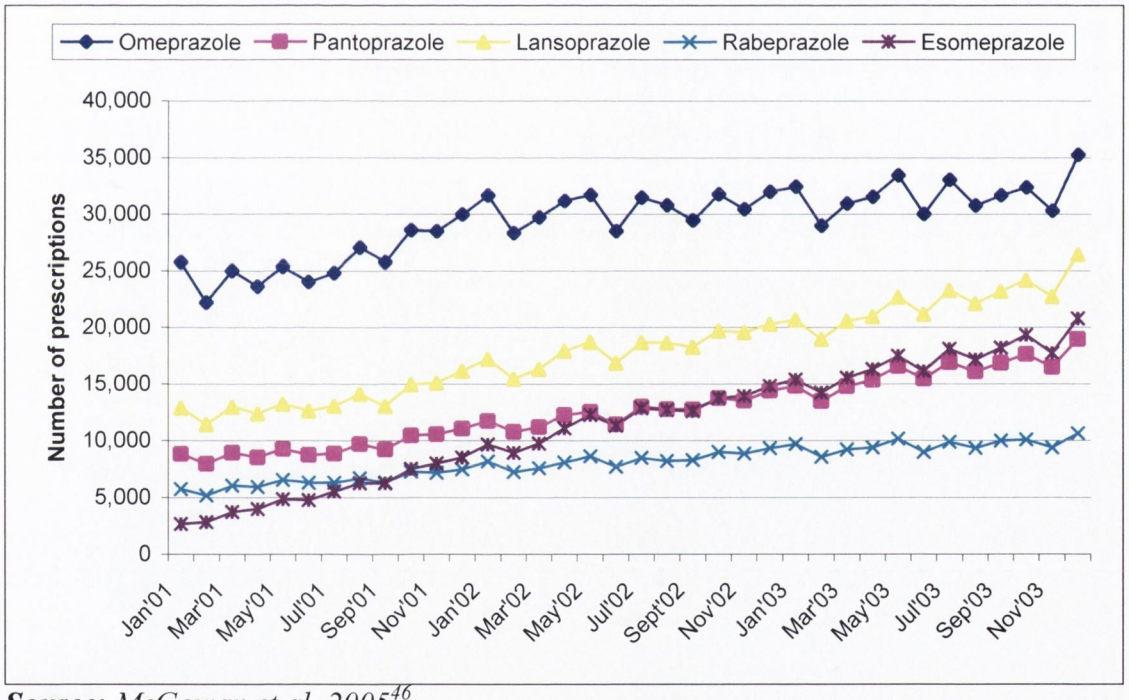
The clinical use of oral nutritional supplements (ONS) has increased greatly over the last decade and they were the products of highest cost in 2003 and the products of second highest cost to the GMS Scheme in 2004. In 2004 ONS accounted for 4.35% of the total ingredient cost of medicines (i.e. € 26.0 million) and 1.01% of prescriptions dispensed (0.35 million prescription items) on the GMS Scheme. A bulletin produced by the National Medicines Information Centre (NMIC) in Ireland in 2004 highlighted that the evidence base for their usage is poor[44]. In addition, audits suggest that up to 50% of prescribed ONS may not be consumed by patients. The NMIC guidelines are circulated to all GPs in the country and they recommend that *"in the absence of evidence-based guidelines, the*

potential benefit of ONS in primary care should be critically assessed on an individual basis and closely monitored throughout use".

3. *Omeprazole*

The PPIs are one of the classes of drugs of highest cost to the GMS Scheme and omeprazole has been the drug accounting for the greatest expenditure on the GMS Scheme from 1994 to 2002[16, 45]. Omeprazole is the most widely prescribed and most expensive of the PPIs (Figure 1.6).

Figure 1.6 The number of prescriptions for PPIs on the GMS Scheme between 2001 and 2003.



Source: *McGowan et al, 2005*[46].

The National Institute for Health and Clinical Excellence (NICE) in the UK issued guidance on prescribing of PPIs in 2000 and concluded that the efficacy of individual PPIs did not differ significantly and the choice of agent should be based on licensed indication and cost[47]. These recommendations have subsequently been updated by, and incorporated into, the clinical guideline on managing dyspepsia in adults in primary care[48]. Nevertheless, the guidance still recommends that doctors should prescribe the least expensive PPI that is appropriate for the patient's condition; the aim being to reduce the dose or even stop the medicine where it is appropriate. A study carried out at the NCPE using the prescribing data from the GMS Scheme in 2003, determined the potential cost

savings to the GMS Scheme should the prescribing of PPIs follow published clinical and cost-effectiveness guidelines[46]. Substitution, in accordance with therapeutic indication, of the PPI with the highest ingredient cost i.e. omeprazole (Losec MUPS®) with any of the alternative agents, particularly the generic omeprazole preparations (Ulcid® and Lopraz®) would be expected to produce significant cost savings (Table 1.6).

Table 1.6 Estimated annual savings following the substitution of omeprazole (Losec MUPS®) with alternative PPIs during maintenance therapy according to current prescribing practices in the GMS Scheme.

Drug (Trade Name)	Strength	Percentage of prescriptions dispensed at given strength	Estimated savings when omeprazole (Losec MUPS®) is substituted with an alternative PPI
Generic Omeprazole (Losamel®)	20mg	100%	€3,135,971
Esomeprazole (Nexium®)	20mg 40mg	52% 48%	€3,355,926
Lansoprazole (Zoton®)	15mg 30mg	28% 72%	€4,233,020
Pantoprazole (Protium®)	20mg 40mg	34% 66%	€5,728,656
Generic Omeprazole (Ulcid®)	20mg	100%	€6,419,600
Rabeprazole (Pariet®)	10mg 20mg	19% 81%	€6,829,631
Generic Omeprazole (Lopraz®)	20mg	100%	€6,843,294
Note: Not all PPIs are indicated for maintenance therapy of peptic ulcer disease or NSAID induced ulceration. All are indicated for maintenance therapy of gastro oesophageal reflux disease.			

Source: *McGowan et al, 2005*[46].

1.5 Patient Co-Payments

Medicines prescribed for patients covered by the GMS Scheme are fully reimbursed. In addition, there is no patient co-payment for medicines prescribed for the management of the chronic illnesses covered by the LTI Scheme. When the DP Scheme was introduced in July 1999 no individual or family was required to pay more than €53.33 per calendar month. From the 1st August 2002 the co-payment was increased to €65 per month. In December 2002 there was a further increase in the patient co-payment to €70 per month. This was followed by a further increase to €78 per month[15]. The recent budget (December 2004) resulted in an increase in the patient co-payment to €85 per month. Patients are incentivised to curb their own pharmaceutical expenditure below the threshold. Above the patient co-payment threshold no further incentive to curb consumption exists.

1.6 Economic Evaluation: The National Centre for Pharmacoeconomics (NCPE)

The NCPE was established in Ireland in 1998 and is funded by the DoHC. The aim of the centre is to promote expertise in Ireland for the advancement of the discipline of pharmacoeconomics through practice, research and education. The centre has negotiated a framework for economic evaluation with IPHA i.e. Irish Healthcare Technology Assessment Guidelines 2000 (Available at http://www.ncpe.ie). HTA is seen as a significant element of future health policy in Ireland[17].

A demonstration of cost-effectiveness is not a pre-requisite for reimbursement in Ireland. However the current IPHA-DoHC Agreement (see Appendix 1) indicates that the DoHC has "*the right to seek cost benefit studies for any new chemical entity introduced after 1997 and to raise these in discussions with the IPHA*"[33]. In practice this right is rarely exercised, however an example relates to the introduction of the phosphodiesterase inhibitor sildenafil for the treatment of erectile dysfunction in 1998. In this case reimbursement was limited to 4 tablets per month[37]. Prescribing of sildenafil for other indications (e.g. pulmonary arterial hypertension) is restricted to medical specialists and a protocol has been compiled outlining the diagnostic criteria which must be met prior to reimbursement. Other expensive agents e.g. betaferon must be prescribed initially by a consultant physician before being reimbursed on the HTD Scheme.

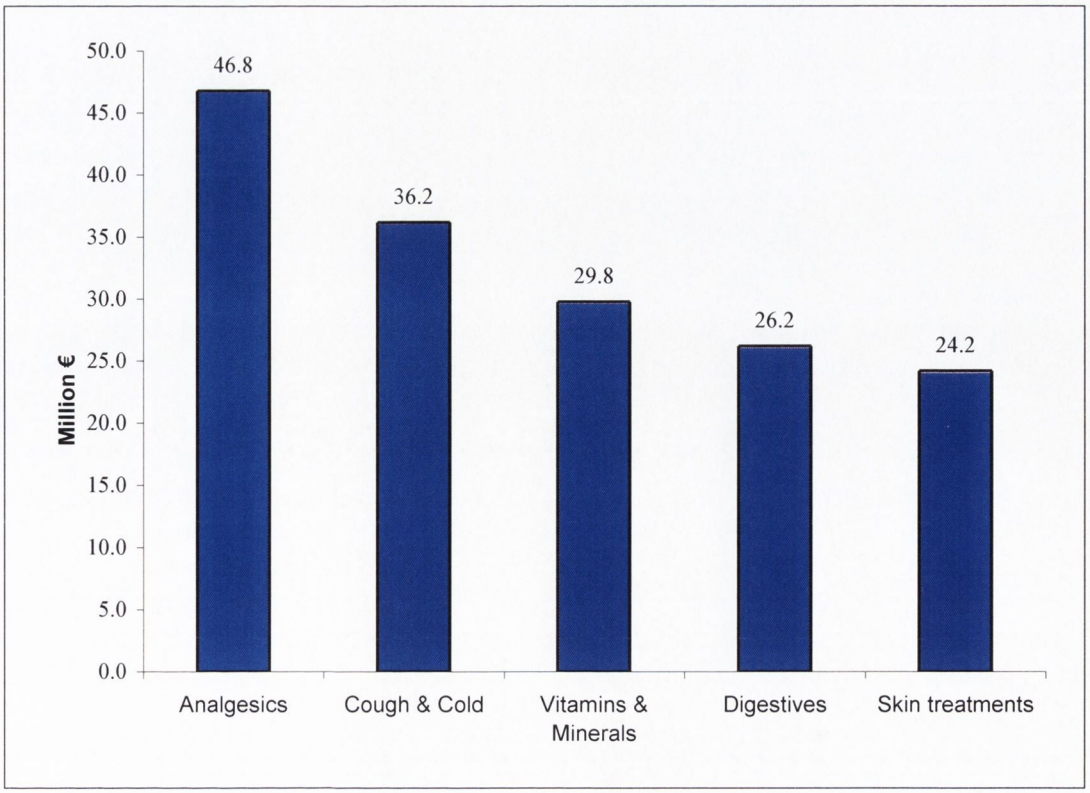
1.7 Generics

Ireland has traditionally had a low rate of generic drug utilisation, despite the fact that the DoHC has a policy of encouraging generic prescribing. Approximately 19% of prescription items on the GMS Scheme were dispensed generically [branded generics (15.2%) and unbranded generics (3.9%)] for the year 2003. Only 7% of the total ingredient cost of drugs dispensed in 2003 was spent on generic drugs. Over 21% of prescription items were dispensed as proprietary preparations when a generic equivalent was available (Chapter 4)[49]. The Irish system tends to encourage branded generic prescribing. In Ireland, if a drug is prescribed generically the pharmacist chooses which product to dispense and will be reimbursed for the cost of that particular brand. Currently, in the Irish system, automatic generic substitution is not allowed by pharmacists when a drug is prescribed by the brand name.

1.8 Over-the-Counter (OTC) Medicines

Sales of all medicines legally available without a prescription for 2003 were €219.2 million (16.6% of the total pharmaceutical market)[50]. OTC medicines can be priced freely and traditionally pharmacists charge a 50% mark-up on their own purchase price (Figure 1.7).

Figure 1.7 Leading self-medication markets in Ireland in 2003 (by value).



1.9 Policies Towards Prescribers

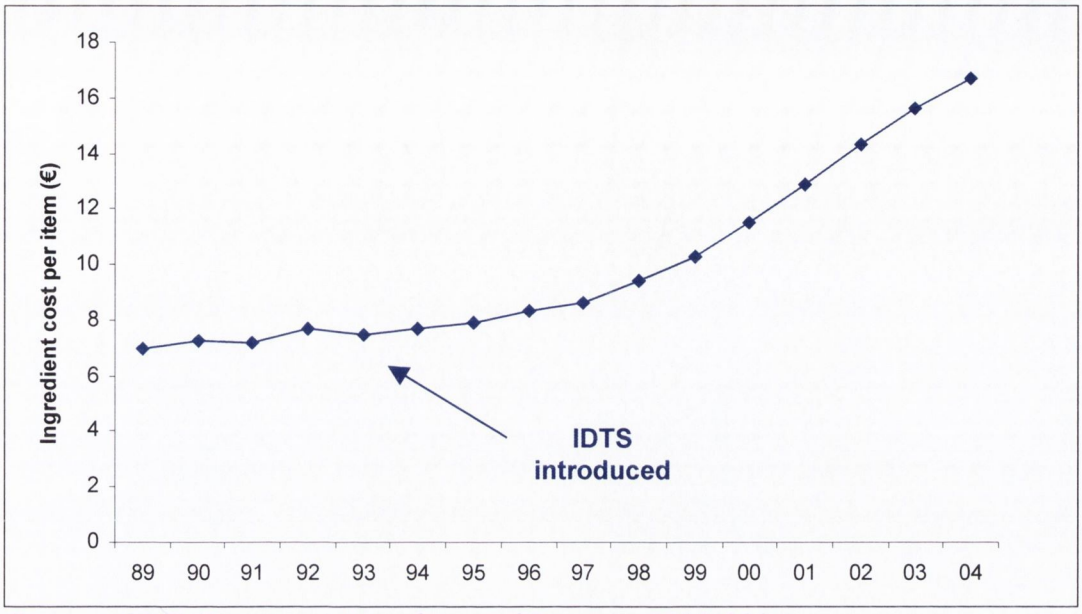
According to the IPHA-DoHC Agreement doctors are free to prescribe the medicines of their choice from a list of medicines available under the GMS or DP Schemes. The DoHC reserves the right to influence the prescribing habits of doctors. The DoHC has taken a number of steps to improve the quality of prescribing by promoting cost-effective strategies e.g. statin therapy is promoted by making it budget neutral above a specified threshold.

1.9.1 Prescribing Budgets

In response to rising costs of prescribing to GMS patients, the Irish government introduced a financial incentive scheme, the Indicative Drug Target Scheme (IDTS), on the 1st of January 1993. The aim of the IDTS was to encourage more rational and economic prescribing. Individual indicative budgets for GP prescribing and associated pharmacy fees were set. Any savings achieved were divided between the GP concerned and the local Health Board, to be used for the development of primary care services[51]. Information on prescribing patterns and costs, relative to the national average performance and taking account of age and gender of the patient panel, is provided to doctors on a regular basis, to enable them to keep within their budgets and improve their performance.

The indicative budgets are thought to be responsible for the lower growth rate of drug expenditure in the GMS compared with the private sector. It was estimated that IR£13.5 million (approximately €17 million) was saved in the first year of the scheme and a trend towards increased generic prescribing was reported[52]. However, savings under the IDTS were mainly generated in the early years following its introduction. Initially the level of prescribing of symptomatic therapies e.g. NSAIDs and H_2 antagonists decreased and the level of generic prescribing increased but the budgetary effect was shortlived[53]. Five per cent of the GPs who were continuously in the scheme over the first 4 year period achieved savings each year, whereas 27% of GPs did not achieve savings in any year. In fact, the only year that the ingredient cost per item dispensed on the GMS Scheme fell was 1993, the year the IDTS was introduced (Figure 1.8)[39, 54-56]. This is similar to the effects of fundholding in the UK, where the relative reduction in costs, compared to non-fundholders, disappeared after the third year of fundholding[57]. In the UK the relative reduction was achieved by a fall in the average cost per item, which was thought to have been brought about by an increase in generic prescribing[57-59].

Figure 1.8 The ingredient cost per prescription item on the GMS Scheme from 1989 to 2004.



Source: *GMS (Payments) Board Annual Reports (1993-2004).*

In recent years the savings achieved on the IDTS have not matched expectations and it is felt that the Scheme, as currently structured, has reached its limit[40]. The operation of the IDTS is currently under review.

1.9.2 The National Medicines Information Centre (NMIC)

The National Medicines Information Centre (NMIC), which was established in September 1994, provides independent information and advice to healthcare professionals in primary and secondary care, particularly GPs and community pharmacists, on all aspects of the therapeutic use of medicines. Information is provided both in direct response to requests for assistance and also proactively in the form of bulletins and newsletters. The NCPE contributes advice on the cost-effectiveness of medicines to the NMIC publications.

1.10 Conclusion

In conclusion it may be worth considering the cautionary advice of the architects of the modern health service when considering future developments: *"our health services . . . must be planned so as to ensure the utmost efficiency and economy in their administration and so as to avoid expenditure on services not demonstrated to be reasonably necessary"* (Department of Health 1966)[10].

It is clear that pharmaceutical expenditure in Ireland will continue to grow in the future should current trends continue.

Having described the pricing and reimbursement system in Ireland, we now consider the situation in the other EU Member States.

Chapter 2

European Pharmaceutical Pricing and Reimbursement Strategies

Table of Contents for Chapter 2

2.1 Introduction: The European Pharmaceutical Market

Over the last 20 years pharmaceutical expenditure and total healthcare expenditure, have grown more rapidly than the gross national product (GNP) in all European countries[1].
Policies to control the rise in pharmaceutical expenditure vary between the EU Member States, but they all invariably impact both the supply (i.e. manufacturers, wholesalers and pharmacists) and the demand (i.e. prescribers and patients) for medicines.

The aims of this chapter are to illustrate the complexities of drug policy decision making and to review some of the existing pharmaceutical cost-containment policies in Europe.
This information was obtained from published literature, policy documents and personal communication with local contacts from the EURO-MED-STAT network and Pricing and Reimbursement Congresses. The main focus of this chapter is the EU Member States (excluding the Central and Eastern European countries which joined the EU in May 2004) and Norway. In order to compile this review an up-to-date, comprehensive analysis of the European pharmaceutical pricing and reimbursement strategies was undertaken[60].

2.1.1 Pharmaceutical Innovation

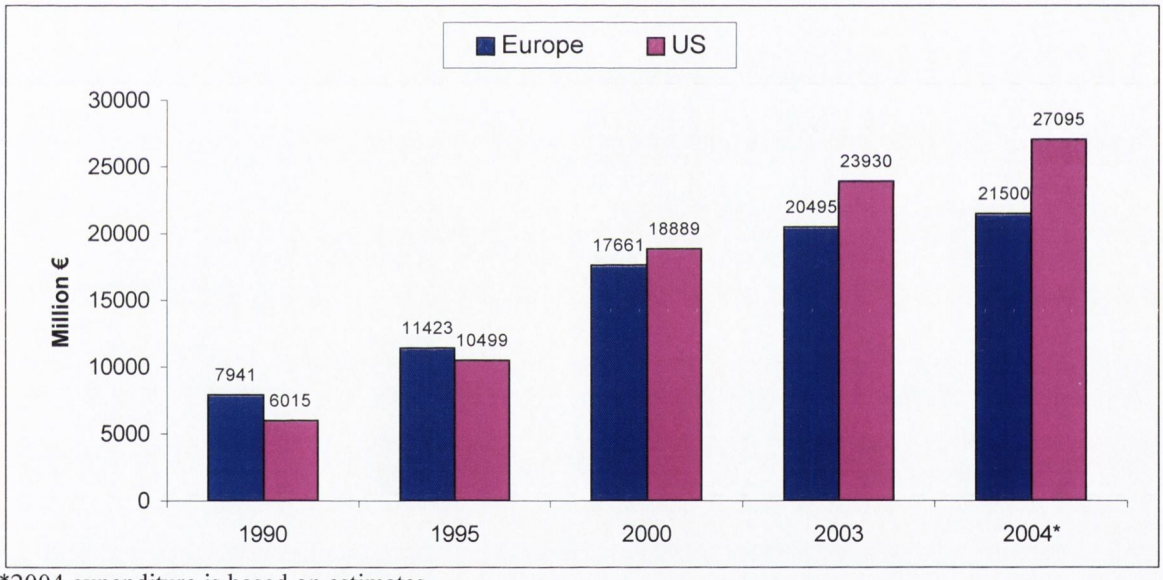
The world pharmaceutical market was worth an estimated €442 billion at ex-factory prices in 2004[61]. An increase in spending on medicines of more than 70% was reported in Australia, Canada, Finland, Ireland, Sweden and the US between 1990 and 2001[62]. However, despite this annual rise in pharmaceutical expenditure and the fact that the pharmaceutical industry remains one of the most profitable industries in the world, there are concerns that there is a crisis in innovation in the pharmaceutical sector[63, 64]. There has been a significant reduction in applications and authorisations of new active substances in Europe, the US and Japan over the last 3 years whilst the overall level of resources being invested has risen dramatically[63]. However, a report commissioned by the Enterprise Directorate-General (DG) of the European Commission in 2004, suggests that this recent downturn does not reflect a trend and that a gradual increase in marketing authorisations over the next couple of years may be expected[63].

It is well known that the global level of research and development (R&D) has increased dramatically over the last 20 years. There is also considerable evidence to demonstrate that the cost of researching and developing a pharmaceutical product has increased. One potential explanation for the rise in R&D costs is a shift towards developing more complex products e.g. gene therapy. In addition, the number and size of trials required to support a

new product has expanded over the last ten years. There is an increased requirement for comparative studies to support marketing authorisations, formulary negotiations and reimbursement decisions[63]. Furthermore, a number of high profile product withdrawals (e.g. rofecoxib in September 2004) has resulted in an increasing focus on drug safety and demonstration of a favourable risk-benefit profile[65].

The US supports the largest and fastest growing expenditure on pharmaceutical R&D (Figure 2.1)[61, 66]. There is a clear trend that a higher proportion of R&D expenditure is spent in the US compared to Europe and Japan[63]. Between 1990 and 2004, investment in the US increased 4.5-fold whereas in Europe it increased by a factor of 2.7[61]. There is now a perception that the US is subsidising drug development for the rest of the world[64].

Figure 2.1 Pharmaceutical R&D expenditure in Europe and the US (1990-2004)[61].



*2004 expenditure is based on estimates.

Source: *European Federation of the Pharmaceutical Industries and Associations (EFPIA).*

2.1.2 Pharmaceutical Pricing

The prices of original branded medicines in the US are often 4 to 10 times higher than in Europe[67]. Many European countries control drug prices or place caps on profits, whereas in the US drug prices are not fixed[68]. As a result, while the prices of patent protected drugs in the US have been rising steadily over the past several years, price increases in the EU have been constrained. However, in the US, as compared with Europe, there is greater generic competition on patent expiry where branded products can lose as much as 75% of their market share in the first 4 months after initial generic entry. Although, the definition of a generic is not always consistent between countries, generally generic drugs are produced

by manufacturers different from the inventor of the original product and are marketed when intellectual property protection rights have expired. The market share of generics is usually significantly lower in price-controlled environments than in non price-controlled ones[61].

2.1.3 The G10 High Level Group on Innovation and Provision of Medicines

In 2001 the Enterprise DG of the European Commission funded a study to investigate the decline in competitiveness of the EU based pharmaceutical industry since the early 1990s. The report, known as *"The Pammolli Report"*, identified lack of competitive national markets, fragmented research systems and low investment in R&D and in new technologies, as the primary causes of this problem[69].

Following on from this report, in 2001 the European Commission established The High Level Group on Innovation and the Provision of Medicines - the G10 Medicines Group. The aim of the group was to explore ways of improving industry competitiveness in Europe while encouraging high levels of health protection[29]. The G10 Medicines Group emphasised the importance of achieving the balance between encouraging and rewarding the development of innovative medicines, by providing sufficient intellectual property protection, and creating a genuine market in generic medicines. The G10 recommendations were published in May 2002 and ranged from the establishment of measures aimed at accelerating product availability (both marketing authorisation and pricing decision procedures) to increased information exchange between Member States and the European institutions on assessments of cost and clinical effectiveness[29].

In July 2003 the European Commission announced a response to the G10 medicines report. Part of this response included a recommendation to Member States to update regulatory structures, to accelerate drug authorisation procedures and to make pricing and reimbursement procedures faster and more transparent. Many of the G10 recommendations have already been taken into account in the 2004 review of the European pharmaceutical legislation[70].

2.1.4 Harmonisation of the European Pharmaceutical Market

The pharmaceutical markets in the EU have been harmonised in some areas and are uniform across EU Member States. The creation of the European Medicines Agency (EMEA) in 1995 and the development of centralised drug licensing in the EU may be

considered key steps towards harmonisation of the European pharmaceutical market. This follows from a system of individual national licensing agencies acting independently that has not entirely disappeared, but which is far less prominent than before[71]. In addition, intellectual property rights will also be harmonised over the next few years[70]. Furthermore, since 1989, the pricing of medicines in EU Member States has been loosely governed at EU level by the Transparency Directive (89/105/EEC)[38].

a. The European Marketing Authorisation Process

The same level of quality, safety and efficacy must be demonstrated for a medicine in all EU Member States in order to obtain a marketing authorisation[63]. Prior to implementation of the 2004 review of European pharmaceutical legislation, marketing authorisation for a pharmaceutical product in more than one country in the EU was applied for through one of two procedures[72]:

1. The Centralised Procedure: Since 1995, the European Community, through the EMEA, has the ability to approve medicines for Europe centrally, with one single licence[72]. This procedure is available to all new, innovative pharmaceuticals, and is mandatory for all new biotechnology products and orphan drugs (drugs for managing rare diseases)[73, 74]. It is open for generic applications from 2005, when the 10-year data exclusivity periods granted to originator products, authorised through this procedure, begin to expire[75].

2. The Mutual Recognition Procedure (MRP): Under this procedure a company applies for a national marketing authorisation in a Member State of their choice and the procedure operates by mutual recognition of the national marketing authorisation by other Member States[70]. Under the MRP, the assessment and marketing authorisation of the first Member State (the "Reference Member State") is then "mutually recognised" by the other countries in which the product is to be marketed i.e. "Concerned Member States"[73].

A third procedure, the Decentralised Procedure, will come into force with the revised EU Pharmaceutical Directive towards the end of 2005[70]. This new procedure will involve Concerned Member States at an earlier stage of the evaluation than the MRP, in order to facilitate the application for marketing authorisation in as many markets as possible[75]. The

Decentralised Procedure will apply to a product being authorised in the EU for the first time which is to be placed on a number of different markets at once.

"Abridged" or "abbreviated" applications for marketing authorisation are accepted for generic products. They are based on "essential similarity" and bioequivalence to existing products which have been authorised and marketed for a number of years[73, 76]. Bioequivalence, as defined by the US Food and Drug Administration (FDA), is the absence of a significant difference in the rate and extent to which the active ingredients become available at the site of drug action when two drugs are administered at the same dose under similar conditions in an appropriately designed study[77]. Therefore, it is not necessary to repeat pre-clinical and clinical trials for generic drugs[70].

b. Patent protection and data exclusivity in the EU

There are two different intellectual property legal frameworks, namely patent protection and data exclusivity, which are essentially independent. If an originator pharmaceutical product is covered by either, then a generically equivalent product cannot be developed. For most drugs, the period of data exclusivity usually expires before the patent protection. However, drugs which take a particularly long time in R&D benefit from the extra protection.

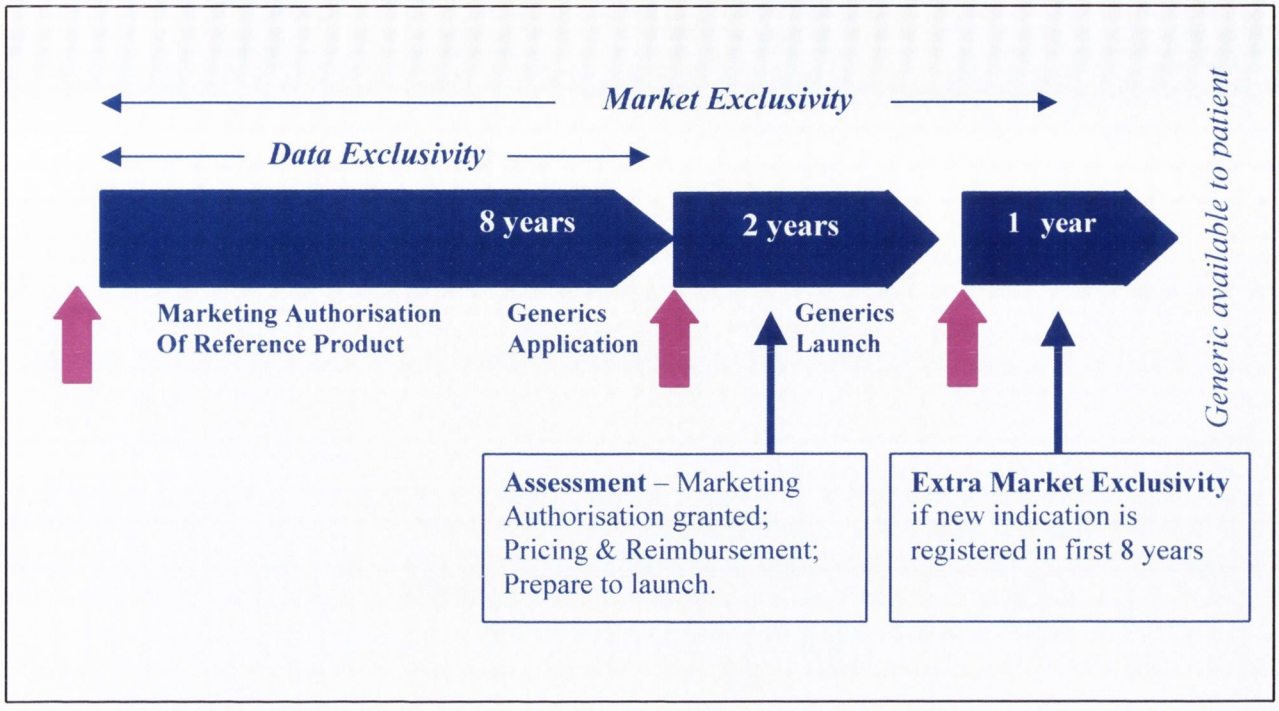
Patent protection grants it's holder the right to exclude others from making, using, selling or importing the patented product in the country where it is granted, without the holder's prior consent[76]. The patent protection commences at the beginning of the drug development process. In the EU, originator pharmaceutical products are protected by a 20-year pharmaceutical patent[75]. In addition, a Supplementary Protection Certificate (SPC) can be granted for up to 5 years to give a maximum effective patent life of 15 years from the date on which a product is authorised for first marketing in an EU Member State. The SPC was introduced in 1992 (Council Regulation EEC/1768/92) to compensate originator companies for the time and cost of developing registration data[78]. Leflunomide (Arava®), for example, took 17 years of trials to develop and, therefore, the costs of R&D would have had to be recouped in only 3 years without additional intellectual property protection[79]. In addition to this period of patent protection, further patents are regularly granted to pharmaceutical companies for new uses, indications, dosages and changes in formulation[75].

There is also a separate period of data exclusivity (also known as "data protection"), which prevents regulatory authorities from using pharmaceutical registration data from the manufacturer of the originator product to assess the safety and efficacy profile of a generic application for a period of time, beginning from the first marketing approval of the originator product. Under Directive 2001/83/EC, EU data exclusivity laws guaranteed market protection for originator medicines for either 6 years (Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain, Norway and Iceland) or 10 years (Belgium, France, Germany, Italy, Luxembourg, the Netherlands, Sweden and the UK) after the European marketing authorisation was granted[75, 78]. In addition to the 6 or 10 year period of data exclusivity, it took a further 1 to 3 years to register and market a generic medicine[75].

Intellectual property rights are being harmonised throughout the EU Member States and the revised EU Pharmaceutical Directive of 2004 has created a harmonised 8-year data exclusivity provision with an additional 2-year market exclusivity provision[70]. This 10-year market exclusivity can be extended by an additional one year maximum if, during the first 8 years of those 10 years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which are considered to have a significant clinical benefit in comparison with existing therapies[70]. This so called 8+2+1 (or (10-2) +1) formula applies to new active substances in all procedures and to all Member States (Figure 2.2). Therefore a generic application for marketing authorisation can be submitted after year 8, but the product cannot be marketed until after 10 years have elapsed from the initial authorisation of the originator product[75].

Another key change is that it will no longer be necessary for the reference originator product to be authorised in the Member State in which the generic is to be authorised. Instead it will suffice if the reference product is or has been authorised in another Member State.

Figure 2.2 8+2 (+1) Data Exclusivity Formula[75].



Source: *European Generic Medicines Association: The marketing authorisation process for generic medicines.*

Therefore, the new EU pharmaceutical legislation may simplify the registration of generics and promote increased manufacturing of generics in the EU. However, the implication of lengthening the exclusivity period will be to delay market entry of a generic to 10 years for all EU Member States. Nevertheless, as the last 2 years are market exclusivity only, this introduces a "Bolar-type" provision. The Bolar exemption is a policy that allows generic manufacturers to prepare production and regulatory procedures before patents expire, so that generics can enter the market as soon as the patent ends, rather than having to commence the lengthy preparatory process only after the patent period is over. This was not previously permitted under EU legislation[80]. Therefore, the new legislation will allow generics to enter the market immediately after patent expiry instead of only starting the development and testing work required to make an application at that time, which resulted in delays of up to approximately 2 years[76]. A Bolar provision has been in place in the US since the 1980s[76, 81].

c. Pricing of medicines in the EU: The European Union Transparency Directive (89/105/EEC).

Pricing of pharmaceuticals is a matter for individual Member States, rather than being harmonised at EU level. However, a perceived lack of clarity regarding how

pharmaceutical prices were determined in the EU Member States led to the introduction of the Price Transparency Directive (89/105/EEC) in 1989[38]. The Directive requires Member States to publish the procedures and criteria they use to approve or fix prices and profits[1]. The Directive establishes that authorities must make a price decision within 90 days of receipt of adequate information and that reimbursement decisions should take no longer than 180 days[38]. At least once a year, each EU Member State must publish a list of the medicinal products, the prices of which have been fixed during the relevant period, together with the prices which may be charged for such products. The same rules apply if an increase in the price of a medicine is requested.

The Directive also specifies that in the event of a price freeze imposed on all medicinal products, an annual review must be conducted to determine whether the macroeconomic conditions justify continuing the price freeze[38]. Furthermore, any direct or indirect mechanisms for controlling profits of those placing a medicine on the market need to be explicit, as must the decisions of including products on a positive list or excluding them from reimbursement by means of a negative list.

2.1.5 Fragmentation of the European Pharmaceutical Market

Pharmaceutical policy is primarily determined at the national level by individual EU Member States, although there is a considerable amount of EU legislation. The European Commission has no power to specify levels of national price controls or profit caps, but rather ensures that national procedures are transparent, efficient and fair[74].

Regulation of pharmaceutical markets varies between countries according to the balance between pursuing health policy versus industrial policy objectives[74]. Overall, objectives are similar but some countries are more willing to trade-off slightly higher pharmaceutical prices for a positive return from pharmaceutical companies in terms of R&D, employment and a positive trade balance.

Therefore, the pharmaceutical markets in the EU Member States remain fragmented in terms of:

- Pharmaceutical pricing and reimbursement systems (each of which is designed purely for domestic considerations);
- Availability of medicines;
- Therapeutic indications for medicines;

- Distribution costs i.e. pharmacy and wholesaler margins and VAT.

As a result, there are wide variations in drug prices, availability, utilisation and expenditure on medicines in the EU Member States[71, 82]. There are major differences between the optimal treatment and the actual treatment received by many patients[83]. Many older drugs are available in only one or some of the European countries and the doses and indications of drugs may also vary between countries[71]. Some of the most widely used medicines in some countries have even been withdrawn or were never licensed in others. There is rarely any scientific rationale for these discrepancies[71].

There are also many methodological difficulties in comparing data from different countries[82]. In addition, there are considerable variations in the launch dates of new medicines within the EU, due to significant differences in how medicines are priced and granted reimbursement. A study undertaken in the UK in 2000, discovered that there can be delays of up to 4 years (average 2 years) in patients accessing new drugs between Member States[4].

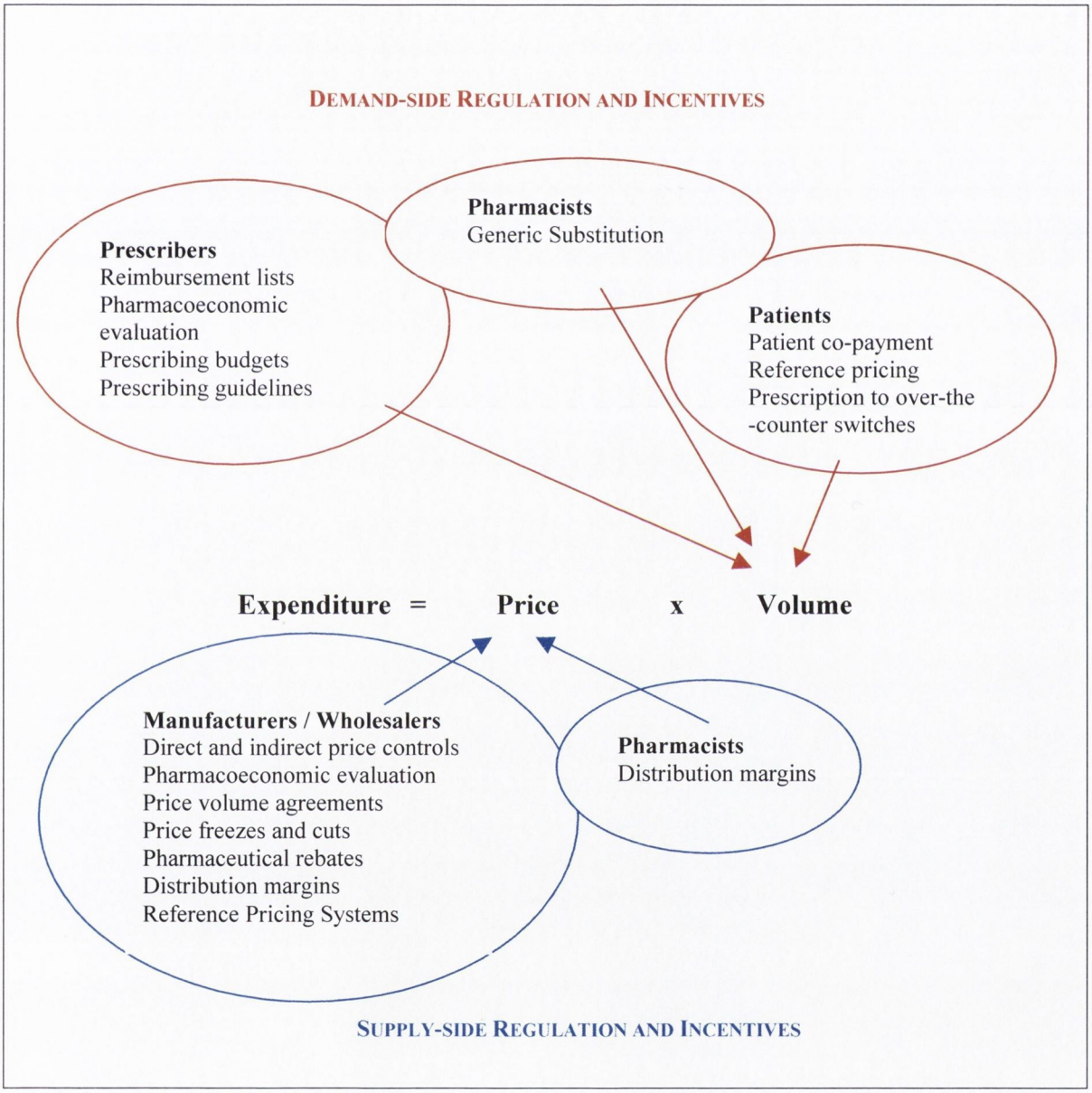
2.1.6 European Pharmaceutical Pricing and Reimbursement Strategies

Registration and market approval of a drug is based on quality, safety and efficacy data from clinical trials and other studies. However, registration is only the first entry barrier for a new drug, which is followed by hurdles due to pricing and reimbursement procedures[84]. Pharmaceutical pricing and reimbursement decisions in the EU are made within Member States, rather than centrally. A variety of systems for reimbursement and price control exist in different EU Member States and there is a complete lack of harmonisation between countries. In addition, developments in pricing and reimbursement policies across the EU occur at a very rapid pace[85].

All EU Member States have introduced various pricing and reimbursement policies in an attempt to contain pharmaceutical expenditure and influence prescribing towards a more cost-effective use of therapies. The strategies include price controls, restriction of publicly reimbursed drugs by positive or negative lists, promotion of generic markets, prescribing budgets and patient co-payments. Therefore, a range of measures have been employed to influence both the supply (price) and demand (volume) for pharmaceuticals (Figure 2.3). National policies to control the supply of medicines target manufacturers, wholesalers and pharmacists, whereas policies to control the demand for pharmaceuticals target prescribers,

patients and, in some countries, pharmacists. It is recognised that a combination of both methods may be needed to control the rate of growth of pharmaceutical expenditure. Overall, the success of these cost-containment measures is varied and pharmaceutical expenditure continues to rise in Europe.

Figure 2.3 National controls to influence the supply and demand for pharmaceuticals.



2.2 National Controls on Pharmaceutical Supply

Methods aimed at controlling the supply of pharmaceuticals include:

- Direct price controls;
- Indirect price controls;
- Price volume agreements;
- Price freezes and cuts;
- Pharmaceutical rebates;
- Fixed distribution margins;
- Reference Pricing (RP) systems.

It is generally considered easier to control the supply, for example with price controls, rather than the demand for medicines[86].

2.2.1 Direct Price Controls

A direct price control system is in operation in the majority of EU countries, except for the UK, Germany and Denmark (from April 2005)[86-88]. Strategies for price fixing vary but include the following criteria:

1. The therapeutic value of the drug: Methods used to determine this vary from country to country. Some countries (e.g. Finland, Italy and Sweden) require cost-effectiveness studies for decision making on pricing[86, 89, 90].

2. Reference to comparable products on the market: Several countries take into account the price of similar products already on the market (e.g. Spain, Finland)[91, 92].

3. Reference to international comparisons: Most countries take into account the price of the same product in other European countries (Table 2.1). In some countries, including Ireland, only the initial price is calculated this way. In other countries, for example, the Netherlands, the reference countries are monitored and the price is re-calculated periodically. Therefore, a change in the pricing system in one country can have an impact on the price of medicines throughout the EU i.e. these price comparisons may potentially be circular in derivation. Furthermore, there may be methodological problems in undertaking these comparisons: difficulties in selecting appropriate products for comparison as product availability varies from country to

country, obstacles in comparing prices across different formulations and pack sizes, or problems in converting comparator country prices into national currency.

4. Consideration of the overall cost of R&D, production costs and the price of raw materials (e.g. this is one of the criteria used for price setting in Spain[91]).

Most countries use a combination of these criteria for price setting. In France, for example, price setting takes into account the therapeutic value of the drug, expected sales, the research and marketing costs of the drug and the funds available for healthcare[87, 93]. In Italy, the price negotiation is based on therapeutic value and innovativeness, cost-effectiveness, prices in other countries, sales forecasts and consideration of the economic impact on the health sector and company commitments[86].

In many of the countries with fixed prices, there is no potential for competition below the maximum price, either because this is not allowed or because there is no incentive to do so.

Table 2.1 International price comparisons in the EU Member States and Norway[60].

Country	Reference Countries	Basis of Calculation	Prices re-calculated
Austria[94]	All EU countries (including the new Member States from July 2005)	Average price	Yes – revised regularly
Denmark[86] (until April 2005*)	10 EU countries and Norway, Iceland and Liechtenstein	Average	Yes – every 6 months
Greece[86]	All EU countries	Lowest price in Europe	Yes
Ireland[33]	Denmark, France, Germany, UK, the Netherlands	Lowest of the average of the 5 countries or the UK price	No
The Netherlands[87]	Germany, France, Belgium, the UK	Average	Yes – every 6 months
Norway[95, 96]	9 Northern European countries	Average	Yes - every 6 months for the first 2 years and then every year.
Portugal[87]	Spain, France, Italy	Lowest	Once a year but only the initial price is based on international comparisons
* In April 2005 a new pricing system was introduced in Denmark.			

Source: *Tilson L and Barry M. Pharmaceutical Pricing and Reimbursement Strategies, 2005.*

2.2.2 Indirect Price Controls

Some countries operate indirect price control systems. In the UK, for example, there is a system of profit control for branded medicines, whereby the prices are set to ensure that overall return on capital is within an authorised boundary of 21%[1, 86]. This system is called the Pharmaceutical Price Regulation Scheme (PPRS). It is a voluntary agreement between the Association of the British Pharmaceutical Industry (ABPI) and the Department of Health which is reviewed every few years. Since 1986, the scheme has covered only those drugs sold under brand names (including branded generics) and has excluded products sold under generic names[97]. The PPRS aims to secure the provision of safe and effective medicines to the NHS at reasonable prices whilst at the same time promoting a strong, profitable industry in the UK capable of sustained R&D expenditure[86]. The scheme is unique in the world's major pharmaceutical markets, as global profit rather than product price is controlled[98]. At the end of 2004, the PPRS was renegotiated for a 5-year period and a 7% price cut for branded prescription medicines was agreed with the ABPI. It is estimated that the price cut will deliver savings of £1.8 billion over the next five years (the total expected NHS drugs bill is £11 billion for 2005/2006). The PPRS provides a favourable and stable environment for the pharmaceutical industry in the UK.

In Spain, the aim of their price control system is to generate a return of approximately 12-18% on the company's investment. This bears a resemblance to the UK PPRS, however the fundamental difference is that the PPRS parameters are applied to companies total sales in the UK NHS, whereas the Spanish method applies to individual products[86].

2.2.3 Price Freezes and Cuts

Most European countries have negotiated a price freeze or price cut in the last few years. For example, in Ireland there has been a price freeze on all prescription medicines since 1993[33]. In some countries, a fixed percentage decrease has been applied to all products (e.g. Belgium, Italy and Spain)[86, 99-101]. Alternatively, pharmaceutical companies can modulate the price reduction among the products in their portfolio, as long as an overall reduction in cost is achieved (e.g. the 7% price cut for branded prescription medicines was agreed in the UK in 2004). This may be achieved by variable reductions to the prices of different products in a companies portfolio[102]. Price cuts usually result in a one-off and very short-lived decrease in pharmaceutical expenditure[74].

2.2.4 Price Volume Agreements

Price volume agreements stipulate the volume of a product that may be sold, based on forecast sales included in a drug application. The supplier is penalised, usually through a payback clause or by having the price of the product reduced, if the sales volume is exceeded[86]. This system aims to improve the likely reliability of forecasting the future costs of treatments. In Norway in 2003, for example, a price volume contract was proposed for some products under the national reimbursement scheme. Under this scheme, companies would sign a contract regarding how many patients are expected to use a particular drug, and agreeing to pay back any reimbursement costs beyond this figure. The rebates could be in the form of paybacks, sales taxes, price reductions or removal of the product from the reimbursement list[103]. In the past, the French system relied heavily on price volume agreements, which work at three levels: at the industry level, when overall sales exceed annual objectives of the public payer; at the company level when its sales exceed the overall sales number that is set through individual contracting; and at the level of a therapeutic class or individual drug[86, 104].

2.2.5 Pharmaceutical Rebates

A growing number of countries are sharing some of the risks associated with bringing innovative products to the market, by negotiating payback agreements with the pharmaceutical industry. Examples of payback agreements with the pharmaceutical industry include:

- Belgium: At the end of 2000 an agreement was reached, where if the annual pharmaceutical budget was exceeded the industry would pay back 65% of the extra spending[86].

- France: The Accord Cadre is the framework agreement with the pharmaceutical industry for the period from 2003 to 2006. According to this agreement prices should be in line with an average European price, but with rebates on sales to prevent any added costs to the social security[105].

- Germany: Under the healthcare reform of 2004, a rebate from manufacturers on non-reference priced drugs of 16% (6% for non-prescription medicines) was implemented[106]. The rebate was reduced to 6% in 2005[107].

- Ireland: Each month pharmaceutical manufacturers and importers must rebate to the GMS (Payments) Board 3% of the value, at trade price level, of all medicines dispensed under the GMS Scheme (see Chapter 1)[33].

- Italy: In 2003 a law was passed stating that annual pharmaceutical expenditure must not exceed 13% of total healthcare spending. By law, 60% of any additional spending would have to be covered by the pharmaceutical industry[108].

- Portugal: Ceilings on growth in pharmaceutical expenditure have been set (e.g. +6.5% in 2001, +5% in 2002 and +4% in 2003). If the growth targets were exceeded, the company had to pay back to the government 64.5% of the excess spending[86].

2.2.6 Distribution Margins

Distribution margins (i.e. wholesale margins, pharmacy margins and rates of VAT) on pharmaceuticals vary across Europe and this is one of the factors contributing to the variation in price of drugs[109]. Most governments have defined profit margins for wholesalers and pharmacists and this may facilitate the control of costs[1]. There are essentially three different models for determining the distribution margins: fixed margins, regressive margins and "loosely" regulated margins[109].

The simplest model is the fixed margin which can either be a fixed percentage of the ex-factory price or of the public price or, in the case of pharmacy margins, a flat rate dispensing fee [e.g. the UK and Ireland (GMS scheme)].

Regressive margins are the most common distribution margins and are based on the principle that the lower the price of the drug the higher the margin. Regressive margins can reduce the financial incentive to dispense more expensive medicines. There are a variety of formulas of differing complexities adopted to calculate these margins.

In some countries margins are loosely regulated, for example, the wholesaler margin is not fixed and is determined through individual negotiations between the wholesaler and the manufacturer (Table 2.2).

In addition, in some countries, margins are based on a combination of these models, such as, a fixed fee plus a regressive margin (e.g. pharmacy margins in Finland, Denmark and Norway). In an effort to promote the generics market, there may be different pharmacy margins depending on whether a generic or branded drug is dispensed (e.g. Belgium and Spain).

The rate of VAT on pharmaceuticals varies across European countries. Denmark, Germany and Norway have full rates of VAT on medicines, while in Sweden and the UK drugs are not subject to VAT at all[86, 87, 98]. In general, the greatest part of total pharmaceutical expenditure is publicly funded. Therefore taxes on reimbursed drugs increase their costs. In recognition of this, the rate of VAT on prescription drugs is reduced in many countries.

Table 2.2 Description of European wholesale and pharmacy margins[60].

Wholesale margins	Pharmacy margins
Fixed margins: Belgium, Greece, Ireland, Portugal, Spain, the UK.	***Fixed percentage margins:*** Belgium, Greece, Portugal.
Regressive margins: Austria, Italy, France.	***Fixed dispensing fees:*** Ireland (GMS Scheme), the Netherlands, the UK.
Loosely regulated margins: Denmark, Finland, the Netherlands, Norway, Sweden.	***Regressive margins:*** Austria, Italy, Spain, Sweden.
	Fixed fee plus a percentage margin: Germany, Ireland (DP and LTI Schemes).
	Fixed fee plus a regressive margin: Denmark, Finland, France, Norway.

Source: *Tilson L and Barry M. Pharmaceutical Pricing and Reimbursement Strategies, 2005.*

2.2.7 Reference Pricing Systems

Reference Pricing (RP) is a method used to indirectly set and control prices for categories of drugs and is restricted to areas of the drug market where several drugs exist without substantial evidence that any agent is superior. The principle of RP is to set a reimbursement price for a group of drugs that are considered to be interchangeable[110]. For each group of drugs a single price is set and if drugs are priced above the RP, the patient or supplementary private insurance, usually pays the difference between the reference price

and the actual price[111]. In theory, this creates an incentive for both prescribers and patients to consider drug prices in decision making.

RP implies a reimbursement limit, not a final market price[112]. Manufacturers remain free to set their prices but they may risk losing their market share to cheaper, fully reimbursed drugs. Therefore, manufacturers have a strong incentive to lower their prices to, but not below, the reference price[1].

There are three main approaches to grouping drugs in a RP system[110, 112]:

1. **Phase I** - Grouping drugs which have the same active ingredient (i.e. generic drug groups) e.g. Denmark, Norway, France and Spain. This is generally the most accepted and least controversial approach. All products included in Phase I RP are no longer protected by patent.

2. **Phase II** - Grouping related drug groups, for example, ACE inhibitors. This system is used for certain groups of drugs in Australia, Canada (British Colombia), Germany and Italy.

3. **Phase III** (therapeutic RP) - Grouping drugs by therapeutic indication, for example, antihypertensives. This is the most controversial approach, as criteria for defining therapeutic equivalence of drugs is not clear-cut or agreed. This approach is used for some groups of drugs in the Netherlands. For example, in the Netherlands, sumatriptan, a new drug for the treatment of migraine with a high acquisition cost, was categorised in the same class as ergotamine and dihydroergotamine, two older drugs with the same indication[1].

There are a number of different approaches to setting reference prices. In some countries, for example, the reference price is the minimum price of drugs in a group, whereas in others the average or the maximum price of drugs in a group is used (Table 2.3)[113, 114]. RP systems also vary between countries in terms of coverage, and whether they are inclusive or exclusive of patented medicines. RP only applies to off-patent medicines in most countries, with the exception of Germany, the Netherlands and Italy.

Germany was the first European country to introduce a RP system in 1989, followed by the Netherlands, Sweden and Denmark. Since the year 2000, a number of other EU Member States have implemented Phase I RP (Table 2.3). RP systems have also been developed in the US, Canada, New Zealand and Australia[111].

Table 2.3 Description of European Reference Pricing Systems[60].

Country	RP phase	Year introduced	Determinant of RP
Germany	Phase I Phase II Phase III	1989 1992 1993	Average price of drugs in a group
The Netherlands	Phase III	1991	Average price of drugs in a group
Sweden	Phase 1	1993	Lowest priced drug plus 10%
Denmark*	Phase I	1993	Lowest price of drugs in a group
Norway	Phase I	1993/2003	System abandoned in 2001 and reintroduced in 2003**
Spain	Phase I	2000	System revised in 2004 – average of 3 cheapest drugs in a group
Italy	Phase I Phase II	2001 2003	Lowest priced drug in a group
Portugal	Phase I	2003	Highest generic price in a group
France	Phase I	2003	Average price of drugs in a group
* A new pricing system was introduced in Denmark in April 2005. ** There are plans to drop the RP system again in Norway for some drugs in 2005.			

Source: *Tilson L and Barry M. Pharmaceutical Pricing and Reimbursement Strategies, 2005.*

The RP system has two primary functions:

1. To lower prices of drugs by inducing price competition and
2. To encourage greater use of generic drugs by making patients pay more for the higher price brand name product.

Introduction of a RP system may result in the manufacturers cutting the price of drugs priced above the reference price. In Sweden, for example, the introduction of Phase I RP resulted in manufacturers cutting the prices of drugs priced above the reference price in

anticipation of consumers not paying the higher price. Therefore, the price of brand name products fell close to that of the generics and the market share of original branded products increased[110]. Savings of approximately €44 million were achieved in the first year of implementation (1993) and approximately €5.5 million was saved in the second year. No further significant savings are expected with the current RP system in Sweden[110].

Phase II and III RP groups may or may not contain patented drugs. Initially, Germany included patented drugs, but in 1996 they were removed from the RP system[112]. In 2004 Phase II RP was re-introduced for patented drugs in Germany. There is now a concern that if pharmaceutical companies refuse to lower their prices in line with the reference price, the patient co-payments in Germany could increase significantly[63]. The effect Phase II RP of patented products will have on incentives to innovate will depend on how therapeutic groups are constructed, at what level reference prices are set and how so called "me-too" drugs are identified[63]. In the Netherlands, only drugs judged to be therapeutically "unique" and which are the first pharmacological option for a previously intractable condition, are exempt from the RP system[110]. As a result of these restrictions, only a few drugs are exempt from the RP system[111].

Italy introduced phase I RP (i.e. for products no longer protected by patent) in 2001 and Phase II RP for patented medicines in 2003. If the patented drug costs more than the reference price, it is not reimbursed at all; so there is a great pressure on companies to cut their prices[63].

There are three main advantages of RP systems[112]. Firstly, manufacturers remain free to set prices. Secondly, RP does not set legal limitations on the freedom of the doctor to prescribe drugs, unlike positive and negative lists. Thirdly, potential reductions in pharmaceutical expenditure may be achieved, by promoting cost-conscious drug consumption, without any compromise in effectiveness. A study undertaken in Canada in 2002, analysed the effect of reference pricing of ACE inhibitors on drug utilisation and expenditure and found that a sustained reduction in drug expenditure was achieved with no change in overall use of anti-hypertensive therapy[115].

The main argument against RP is its potential to act as a disincentive to pharmaceutical innovation. In particular, this applies to systems where new patented drugs are included in a RP group. In addition, the concept of interchangeability between drugs cannot always be

objectively defined, and as a result it varies from country to country. The issue of lack of equivalence between drugs included in the same group probably constitutes the most controversial issue in the literature on RP[112]. There are also administrative costs associated with operating a RP system. In addition, RP may fail to contain pharmaceutical spending. This can be explained by several factors[112]:

- RP may only be applied to a small proportion of the market and may not be applied to innovative drugs;
- RP stimulates the industry to make a major effort to promote drugs not included in the RP scheme (i.e. innovative drugs);
- RP only addresses the price component driving growth in pharmaceutical expenditure; growth in volume is not affected;
- RP may distort competition i.e. RP provides no incentive to price a product below the reference level.

RP is a cost-containment tool, designed to relieve the payer of some of the financial burden of drug reimbursement[111]. It has been reported that RP systems have been successful in achieving short-term cost savings. However, other factors influencing total pharmaceutical expenditure have often occurred simultaneously and make it difficult to isolate the specific effect of RP[110, 115]. Pharmaceutical expenditure has continued to rise in countries that have implemented RP but this does not mean that RP is not an effective cost-containment strategy. In fact, this is expected as RP influences only a part of the total cost of pharmaceutical expenditure. RP is currently a popular concept with governments searching for the means to control pharmaceutical expenditure.

2.3 National Controls on Pharmaceutical Demand

Methods aimed at controlling the demand for pharmaceuticals include:

- Reimbursement controls - positive and negative lists;
- Pharmacoeconomic evaluation;
- Prescribing guidelines;
- Prescribing budgets;
- Promotion of generic markets;
- Patient co-payments
- Prescription to over-the-counter (OTC) switches.

2.3.1 Reimbursement Controls – Positive and Negative Lists

One method of influencing prescribing is to restrict reimbursement by the use of positive and negative lists. All EU Member States operate restrictive lists, defining the drugs eligible for reimbursement. In some countries an inclusive system exists where drugs receiving marketing approval are, by default, reimbursed and those excluded from reimbursement are placed on a "negative list". The UK and Germany operate negative lists. In the UK, for example, some 3,000 drugs are listed in Schedule 10 of the Drug Tariff (the "Black List"). These drugs cannot be prescribed at the cost of the NHS, either because of lack of efficacy or because all clinical needs can be met less expensively without them[1, 116].

In other countries pharmaceutical companies have to apply for reimbursement status and if granted the drugs are placed on a "positive list". Most European countries operate a positive list. Drugs on a positive list are reimbursed to some extent, while drugs on a negative list must be paid for fully by the patient[84]. Therefore, there are few restrictions on what medicines may be prescribed, although not all medicines may be reimbursed.

The criteria for evaluating the reimbursement status of drugs vary between countries. Therapeutic benefit is usually the most important consideration; although requirements for cost-effectiveness data relative to similar products already reimbursed are increasing[86]. Many EU countries have sought to define the reimbursability of new, expensive drugs in such a way as to restrict reimbursement only to those patients who will benefit most from treatment[87]. When a drug loses its reimbursement status, its prescription sales fall and doctors often switch much of their prescribing to alternative, and sometimes more expensive, medications that are reimbursed[86].

2.3.2 Pharmacoeconomic Evaluation

The use of economic evaluation in decision making appears to have increased over the past few years[117]. Several countries have encouraged economic evaluation of new medicines to ensure that only medicines proven to be both clinically and cost-effective are reimbursed or made available on formularies. This approach is often referred to as "the fourth hurdle" and is seen as a barrier to market entry in addition to the requirements to demonstrate efficacy, safety and quality[117, 118]. Economic evaluations may either be formally required or submitted on a voluntary basis, for use in the decision making process.

Australia and the province of Ontario in Canada were the first places to formally include data on cost-effectiveness in decisions about reimbursement in 1993 and 1995, respectively[119, 120]. A growing number of EU countries have introduced a formal requirement for economic evidence as part of the pricing or reimbursement decision including Belgium, Finland, Norway, Portugal, Sweden and the Netherlands[86, 89, 95, 121]. Hungary has become one of the first Eastern European countries to consider the introduction of a formal requirement for economic evidence[118, 121]. In 2004, Germany established the Institute for Quality and Efficiency in the Health Service (Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen, IQWiG)[122, 123]. It is not clear whether the institute will have a role in economic evaluation. The main role of the institute is to evaluate benefits of medicines for reimbursement purposes, but it has been stated that cost will be an important part of the overall decision making process[124]. There is also some HTA at a regional level in Spain[121, 125]. In other countries pharmacoeconomic data is used in a less formalised way and may be considered when it is submitted on a voluntary basis e.g. Denmark, France and Italy[86, 121, 126, 127].

One of the most important developments in Europe has been the health technology appraisal programme of NICE in the UK. NICE was established in 1999 and one of its tasks is to evaluate new drugs and new technologies to determine whether they have a cost-effective role in the NHS in England and Wales[128]. The guidance issued by NICE indicates whether treatments should be routinely used in the NHS, restricted to certain categories of patients, used only in the context of clinical trials or not used in the NHS at all[129]. Although NICE develops and disseminates guidance to the NHS, it has no formal responsibility for implementation[130]. Studies commissioned by NICE and others suggest that uptake of the guidance is variable[131-133]. NICE has appointed an Implementation Systems Director to address these concerns[134].

A number of barriers to the use of economic evaluation have been suggested including mistrust, particularly by clinicians, and lack of understanding of the results of economic appraisals[117]. There are concerns that the development of reliable cost-effectiveness data will significantly increase the cost of product development[63]. In addition, the differing requirements for cost-effectiveness data between countries results in manufacturers having to invest in often substantially differing submissions for a new drug in order to meet local requirements[121]. Although variations in societal willingness to pay and decision making processes between countries are likely to continue, the development of a common

methodology in the EU for undertaking economic evaluations could help to create greater harmonisation[135].

2.3.3 Prescribing Guidelines

Influencing doctors' prescribing practices is seen as an important tool for controlling costs. In many countries, doctors are encouraged to prescribe clinically and cost-effective medicines. The main outcomes resulting from this are greater consistency in drug selection and duration of treatment for each condition, and reduction in the volume of drugs prescribed, as redundant or duplicate ones are eliminated. Rational prescribing also means that the cheapest drugs are selected from those that are medically interchangeable for a given condition[86]. Guidelines are seen as aids to, not substitutes for, clinical judgement[1]. However, concerns about using guidelines include the amount of time and effort required to produce and update them and the varying quality of existing guidelines[136]. In addition, there is a growing body of evidence to show that providing such information on its own will not lead to substantial changes in practice[137].

Monitoring of prescribing practice is increasing, both to assess how doctors apply prescribing guidelines and how their treatment costs compare to the average. The English Prescribing Analysis and Cost (PACT) scheme disseminates information about prescribing behaviour to GPs in the hope that it will increase their awareness of costs. Several countries have information feedback systems for prescribers similar to the PACT scheme. All these schemes are advisory and provide information on the volume and cost of prescribing, but in most cases diagnosis is not recorded and it is usually not possible to determine whether a patient was treated cost-effectively[86, 137].

2.3.4 Prescribing Budgets

In some countries doctors are allocated prescription budgets. The main reason for introducing prescription budgets is to encourage doctors to consider costs when selecting treatments, whilst allowing them the discretion of prescribing expensive treatments in individual cases. In most cases budgets are not absolute and prescribing does not cease when their limits are reached. However, to make budgets effective rewards can be used. In Ireland, for example, doctors contracted to the GMS are allocated indicative budgets which entitles prescribers to a proportion of any of the savings which can be used to fund improvements to services (see Chapter 1).

Budgets may be implemented at an individual or practice level, such as in the UK system, or collectively for whole regions, as in Germany until 2001. In Germany budgetary restrictions, that placed a limit on collective drug costs, were introduced in January 1993. This resulted in an immediate and pronounced drop in the number of prescriptions, from 795 million in 1992 to 712 million in 1993. This was accompanied by a change in the product mix of prescribed drugs, in particular a change to generic substitutes and older established drugs. Since then prescriptions have tended to increase back to the initial level, but it is claimed that the scheme realised savings of about 10% of the drugs budget[137]. This instrument was vigorously criticised by the physicians because, as a group, they did not want to be disadvantaged because some of them exceeded their limit. The collective medication budget was abolished in 2001 and in the following months drug expenditures rose by more than 10% compared with the previous year. Therefore it was considered by many as a serious mistake to remove one powerful regulatory instrument without instituting a new one[138].

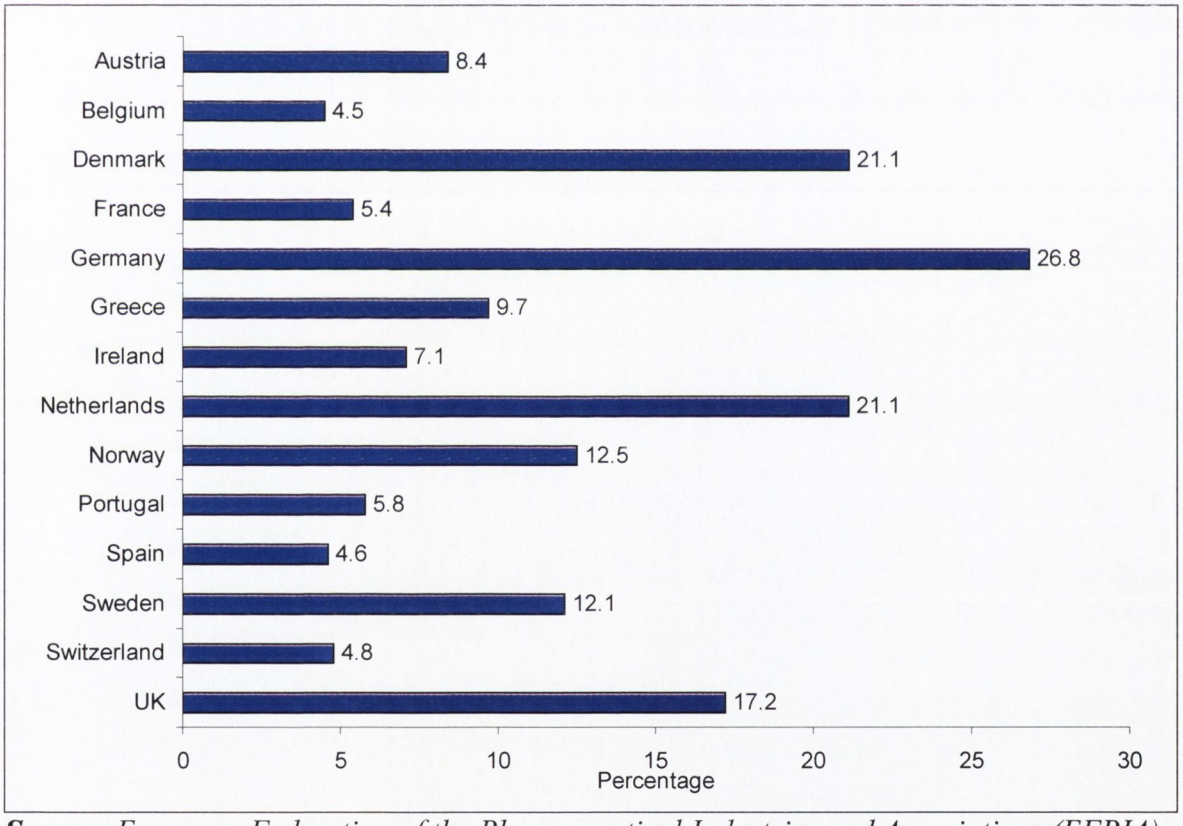
In the UK, between 1991 and 1999, general practice fundholders were given a drugs budget and the power to reinvest any savings that they could make in other services to their patients. It was found that prescribing costs of fundholders increased at a lower rate compared with that of non-fundholders[139]. This was often caused by switching to less expensive drugs[58]. The budget was generally based on the spending in the preceding year, rather than on the need of populations. Therefore, past inefficiencies were rewarded, whereas efficient behaviour in the preceding year was punished. This approach was therefore criticised for being inequitable and for possibly rewarding high-cost inefficient practices with more funds[140]. The GP fundholding system has been replaced by Primary Care Trusts (PCTs), which are responsible for regional spending on primary care, and have an annual budget that covers prescribing[98]. GPs receive visits from local health authority pharmaceutical and medical advisers, who discuss their prescribing patterns with them.

2.3.5 Promotion of Generic Markets

Once the patent on a pharmaceutical product expires, generic equivalents may come on the market. A generic equivalent is a substitute to the original brand and competes in price for market share. The generic product must demonstrate bioequivalence to the original branded product. Generic drugs potentially offer significant savings in pharmaceutical expenditure because of their low cost compared to the original brand; thus releasing funds to pay for innovative, patent protected products.

One of the recommendations of the G10 medicines report is to enhance the generics market in order to free up money for new and innovative drugs[29]. Most EU Member States are now encouraging greater generic competition after the patent of an innovative product expires[63]. The size of the generic markets in Europe vary considerably. Data from 2003 illustrate that Germany, Denmark, the Netherlands and the UK have the highest generic market shares, by value, in Europe; whereas Spain, France and Portugal have much smaller generic market shares (Figure 2.4)[61].

Figure 2.4 Percentage share of the pharmaceutical market held by generic medicines by sales value (at ex-factory prices), 2003[61].



Source: *European Federation of the Pharmaceutical Industries and Associations (EFPIA).*

EU Member States have different policies on generic prescribing and generic substitution. Incentives for physicians, pharmacists and consumers to use generic medicines also differ between countries. A number of European governments have clearly assisted the demand for generics, particularly Denmark, Germany, the Netherlands, the UK and more recently several southern European countries[86, 141].

There are a range of different policies which have been adopted in some countries to promote generic prescribing, including financial incentives aimed at encouraging cost awareness among prescribers (e.g. in the UK and Germany) (Table 2.4)[142].

Table 2.4 Policies to promote generic prescribing[60].

Country	Year	Description
Finland	1996	A voluntary system of generic prescribing was introduced. If a prescription was written generically, pharmacists were required to dispense the cheapest generic available. The system did not achieve the desired result of promoting the generic market.
France	1997	Financial incentive for prescribers to ensure a proportion of prescriptions are written generically. In 1997 prescribers received an annual fee per patient if 15% of prescriptions were for cheaper products, including 5% generics. Since 2002 doctors receive a fee increase if 25% of prescriptions are for a generic drug.
Germany		Generic prescribing rates have traditionally been high. Prescribing budgets were used in Germany between 1993 and 2001.
The Netherlands	1996	Project set up to encourage doctors to prescribe generically. In 1998 computer software was introduced to facilitate this.
Portugal	2002	A law was passed making it compulsory for doctors to prescribe by the International Non-proprietary Name (INN) when a generic is available.
Sweden	2004	Generic prescribing pilot project set up.
UK		Generic prescribing rates have traditionally been high. Prescribing budgets to promote economic prescribing.

Source: *Tilson L and Barry M. Pharmaceutical Pricing and Reimbursement Strategies, 2005.*

Many EU Member States have implemented policies to encourage pharmacists to dispense generic drugs, including generic substitution and margins that encourage generic dispensing.

Generic substitution is the process whereby pharmacists are either encouraged or obliged to dispense a generic product, where available, regardless of whether the prescription is written generically, or for a branded product[76]. An increasing number of European countries have implemented generic substitution policies as a cost-saving measure with varying levels of success (e.g. Norway, the Netherlands, Germany, Sweden, Finland and Denmark) (Table 2.5).

Table 2.5 Summary of generic substitution policies in the EU Member States[60].

Country	Date	Description
Denmark	1991	In 1991 pharmacists were allowed to substitute with the cheapest generic equivalent if the doctor marked the prescription with a "G". Since 1997 pharmacists dispense the cheapest equivalent generic unless the doctor explicitly forbids this. If the patient wants a more expensive brand they have to pay the difference in price.
Finland	2003	Cheapest generic equivalent dispensed unless forbidden by the prescriber or the patient.
France	1999	Generic substitution is permitted but doctors can override this right by writing 'no substitution' on the prescription and patients have the right to refuse the substitution offer. To encourage pharmacists to substitute generics for originators, the government modified their margin system.
Germany		Before 2002, generic substitution was only allowed with the permission of the prescriber. In 2002 pharmacists were obliged to substitute an equivalent generic product with a price below a certain threshold. In 2004, the substitution system was abolished for all reference priced products.
Italy	1999	Generic substitution has been possible in certain situations since 1999 (e.g. if a particular brand was not in stock). Since 2001 pharmacists are required to dispense the cheapest generic unless explicitly forbidden by the prescriber.
The Netherlands		Substitution of cheaper generic products by pharmacists must be permitted by the prescriber and patient.
Norway	2001	Pharmacists are required to dispense the cheapest generic equivalent unless the doctor indicates "no substitution" on the prescription.
Portugal		Generic substitution allowed with doctors agreement. New prescription forms were introduced in 2003 with 2 boxes for the doctor to either agree or disagree with substitution.
Spain	2000	Generic substitution is only applied if the price of a drug exceeds the reference price.
Sweden	2002	Cheapest generic equivalent dispensed unless the prescriber indicates "no substitution" on the prescription or the patient is willing to pay the difference in price between the branded and generic product.

Source: *Tilson L and Barry M. Pharmaceutical Pricing and Reimbursement Strategies, 2005.*

Finland introduced a generic substitution policy in April 2003 and is therefore the most recent EU Member State to implement such a system. The prescribed medicine is substituted in a pharmacy with the cheapest available generic alternative. Both the prescribing physician and the purchasing individual have the power to forbid the substitution[87]. Between April 2003 and March 2004, doctors forbade the substitution on

only 0.4% of prescriptions, while patients refused it in 10.7% of cases. The list of substitutable medicines is updated four times a year[143]. Figures for the first and second year of its implementation show the full effect of the introduction of generic substitution in Finland (Table 2.6). The amount saved approximated to 5.8% of the total cost of reimbursed medicines during the first year of introducing the scheme and the rate of growth in pharmaceutical sales was cut in half. The decline in growth was reported to be a result of price competition rather than of substitution itself[144]. The savings generated during the second year of generic substitution in Finland were substantially lower than the first year (1.7% of the total cost of reimbursed medicines). This can possibly be explained by the fall in the price of substitutable medicines at this time[145].

Table 2.6 The effects of generic substitution in Finland[145].

	1st Year (April 2003-March 2004)	**2nd Year (April 2004-March 2005)**
Prescriptions which generated substitution	12.6%	11.2%
Savings for the patient	€39.2 million	€12.6 million
Savings for the drug reimbursement payments	€49.1 million	€15.8 million
Total savings	**€88.3 million**	**€28.4 million**

However, there have also been examples of substitution schemes which have had a low impact due to a lack of incentives for doctors / pharmacists to substitute generics e.g. schemes in Spain and Germany[146-148]. In addition, an assessment of the generic substitution scheme in Sweden, during the first year of its implementation (2002), demonstrated that the actual savings achieved in practice were on average 60% of the total possible savings and were largely dependent on the extent to which the pharmacies kept the cheapest brand in stock[149].

Provision of financial incentives to pharmacists is another method that has been used by governments to help stimulate the sale of generic medicines. In the Netherlands, for example, the Drug Reimbursement Scheme (GVS) of 1991, enables pharmacists to keep one third of the savings made via the use of cheaper generic alternatives[98, 141]. In some countries, such as Denmark and Finland, there are regressive pharmacy margins (Table 2.2).

Patient co-payment levels are lower for generics in some countries. In Portugal, for example, the co-payment is 10% lower for generic drugs[150]. In addition, in some countries there is a requirement for the generic price to be a fixed percentage below the price of the original brand. For example, in Portugal generics are required to be priced 35% below the original brand[151].

2.3.6 Patient Co-payments

In all EU Member States, cost sharing for medicines has been introduced to try to control pharmaceutical expenditure and influence the demand for prescription drugs. Co-payments require patients to pay a proportion of the cost of a prescribed product or a fixed fee. There are four main mechanisms for patient co-payment:

- A fixed fee per item, per prescription or per pack size;
- A percentage of the value of the prescribed drug;
- A deductible up to a certain limit (this involves the individual paying the initial expense up to a specified amount);
- A combination of methods, such as a fixed fee plus a percentage of the value of the drug.

There may be certain exemptions to patient co-payments. Children, the elderly and disadvantaged social groups, for example, may be completely exempt from co-payment or there may be a greater percentage subsidy for serious or chronic illnesses. In the UK, almost 50% of the population is virtually exempt from co-payments on prescription drugs. In France almost 90% of the population has supplementary health insurance through health insurers or non-profit insurance companies (*Mutuelles*), which reimburses part or all of the co-payment. The majority of the population pays for less than 5% of retail prices out of pocket[152].

The direct effect of increasing patient co-payment levels is to shift the cost from one bearer to another. However, there are also indirect effects; for example, the demand for medicines may be reduced[153]. If this is the case, it raises the question of whether patients renounce only drugs that are unnecessary or does an increase in co-payment result in a fall in consumption of essential treatments? Overall this could potentially result in increased total

health expenditure in the future[83]. Therefore, the use of co-payments to control costs must be applied cautiously so as not to be counter-productive to the overall objective of a healthcare system.

Table 2.7 Patient co-payment for medicines in the EU Member States[60].

Country	Description	Exemptions
Austria	Fixed fee per item (€4.07 in 2002). Private prescriptions are subject to an additional 15% surcharge.	Approximately 18% of the population are exempt on social grounds.
Belgium	Varies depending on the severity of the illness e.g. 0% for serious illnesses. Reduced co-payment for generics.	Preferential rates for widows, the disabled, the elderly, orphans, unemployed (>50 years old).
Denmark	Varies depending on level of consumption. The patient pays the full price up to a threshold of €70, after which the patient pays different levels of co-payment (50%, 25%, 10%, 0%).	Full exemptions for the terminally ill. Reduced co-payments for the disabled, chronically ill.
Finland	Fixed deductible per purchase and a percentage co-payment which varies depending on the severity of illness (0%, 25% and 50%).	Those with chronic severe and life-threatening illnesses.
France	Varies depending on the therapeutic value of the product: 0% for drugs used in certain chronic or life-threatening illnesses; 35% for drugs to treat serious conditions and 65% for comfort drugs.	The co-payment is usually paid by supplementary health insurers.
Germany	Fixed fee of €4 and €5 per item (depending on pack size), subject to an annual cap of 2% of gross earnings. This is in addition to any amount payable above the reference price.	Children, pregnant women, the unemployed, those on low incomes.
Greece	25% co-payment rate.	Children, the elderly, and certain chronic illnesses.
Ireland	The patient pays the full price up to a threshold of €85 per month, after which there is no further co-payment that month (DP scheme (see Chapter 1)).	Those eligible for the GMS and LTI schemes (see Chapter 1).
Italy	Medicines are reimbursed up to the reference price. If the product dispensed is more expensive than the reference price, the patient pays the difference in price (for generics and non-patented brands) or the full price (for patented drugs).	Drugs not included in the RP system (i.e. innovative drugs) are free for the patient.
The Netherlands	The patient pays the difference between the reference price and the actual price of a drug.	Drugs not included in the RP system (i.e. innovative drugs) are free for the patient.
Norway	36% of the cost of medicines, up to a ceiling of €48 per prescription and €180 per year.	Medicines for chronic conditions, children (< 7 years) and the elderly (> 67 years).
Portugal	Varies depending on therapeutic indication. Patients pay either 0%, 30%, 60% or 80% towards the price of medicines. Co-payments are 10% lower for generic drugs.	Pensioners with an income lower than the minimum wage pay 15% less.
Spain	Two co-payment levels: 10% up to a maximum limit of €2.64 for drugs for chronic illnesses; and 40% for all other drugs. HIV/AIDS patients pay 10% less and certain other groups e.g. civil servants pay lower charges.	Pensioners and certain categories of patients e.g. the disabled (~20% of population are exempt).
Sweden	Varies depending on level of consumption. The patient pays the full price up to an annual threshold of €99, after which the patient pays different levels of co-payment (50%, 25%, 10% and 0%).	Insulin is the only drug exempt from co-payment.
UK	Fixed fee per item. Alternatively patients may buy a four monthly or annual pre-payment certificate.	<18 and > 60 year olds, pregnant women, mothers with children < 1 year, those on low incomes, some chronic illnesses and the oral contraceptive.

Source: *Tilson L and Barry M. Pharmaceutical Pricing and Reimbursement Strategies, 2005.*

2.3.7 Switching Prescription Drugs to Over-the-Counter Medicines

Increased numbers of prescription drugs are being made available over-the-counter (OTC) worldwide[154]. Recent high profile switches have included omeprazole in Sweden and simvastatin in the UK. The UK is the first country to allow a statin to be available on an OTC basis[155]. Switches are motivated by 3 main factors: the pharmaceutical industries desire to extend the viability of brand names since patent protection is frequently extended when such a switch is made (i.e. a profit motive); attempts by health care funders to contain costs; and the promotion of self care[154].

The number of drugs being switched from prescription to OTC is likely to rise. Manufacturers are likely to apply for switching before patents expire so that they can gain a foothold in an expanding OTC market. Healthcare funders are likely to support these applications in an effort to curb the growth in pharmaceutical expenditure[154]. For patients, the trend towards more switches will increase the level of self care for chronic conditions and preventive therapies and will avoid both the cost and the delays involved in visiting a prescribing physician. However, the impact of switching policies on public health should be an important consideration for decision makers, as the main grounds for restricting a medicine to Prescription Only Medicine (POM) status is safety[156]. Although switching to OTC status extends access to valuable medicines (e.g. at present moderate risk patients are not eligible for a statin prescription on the UK NHS[157]), there are a number of concerns with this policy. For example, when simvastatin was reclassified from POM to OTC status in the UK, in July 2004, a number of points were raised which include[155]:

- No trials have been conducted of OTC statins for primary prevention of heart disease;
- No data is available regarding patient compliance with OTC statins;
- The availability of OTC statins may lead to patients substituting drug use for life-style modification;
- The only strength available is the lowest strength of 10mg. Therefore, there may be a potential for some patients to take a sub-therapeutic dose.

There is a concern that the real reason behind the switch was that simvastatin lost its patent in the UK in May 2003. In addition, there is also a concern that such policies could potentially lead to an increase in inequalities, as many people would be unable to afford long term OTC statin therapy. In contrast to the situation in the UK, the US FDA advisory committee recently recommended against granting OTC status to statins[158].

2.4 Conclusions

Almost all EU Member States have introduced pharmaceutical cost-containment measures in the last few years and the following general patterns are evident:

- Most countries have introduced some form of price control, such as price cuts or freezes or profit caps.

- There has also been a trend towards setting budgets for pharmaceutical products, often requiring "paybacks" from the pharmaceutical industry if the budget is exceeded.

- There has been a continued emphasis on economic evaluation; the majority of countries now recognise that health economics can make a significant contribution in assisting decision makers identify the inherent value of new products. An increasing number of countries have formal requirements for economic data in their pricing and reimbursement strategy, while in other countries they may be submitted on a voluntary basis.

- A growing number of countries are adopting policies to promote the generics market. Even countries that have not traditionally had a strong generics market, such as Spain and France, have recently implemented strategies to encourage generic competition. Measures adopted by EU Member States to promote the generics market include public educational campaigns, incentives for prescribers, incentives for pharmacists and generic substitution rights for pharmacists.

- Reference pricing for patented drugs has been introduced in a few EU Member States e.g. Germany, the Netherlands and Italy. In Germany, for example, unless a product is truly innovative it will be included in a reference price system and will not achieve a premium price. By rewarding products that are not in a reference price group, reference pricing systems could contribute to a more efficient allocation of R&D resources to truly innovative products. The impact on innovation will depend on how the policy is implemented.

With regard to the future, it can be expected that the cost-containment measures introduced in the last few years, in particular in relation to price regulation, generics and therapeutic

reference pricing, will help control the rising pharmaceutical expenditure. Conversely, the demographic trends in Europe, in particular population ageing, and the change in the product mix of total pharmaceutical expenditure towards newer products would be expected to lead to an increase in overall expenditure[63].

While many countries have demonstrated significant cost savings from implementing cost-containment strategies (e.g. generic substitution in Finland), these evaluations have not examined patient outcomes, spillover costs to other medical services or long-term effects on innovation incentives. One obvious concern is that these adverse consequences may in the longer term offset any immediate cost savings in the prescription drug budgets.

Therefore, before any cost-containment strategy is introduced, a full assessment of the potential impact is essential. All the individual cost-containment strategies are interdependent, and therefore the effect of a single component in a particular setting may not be easily predictable[83]. Consequently, the manner in which these strategies are employed, taking into account local factors (e.g. health policy versus industrial policy objectives), is a key consideration in implementing any changes, as transferring a policy from one country to another may not result in similar outcomes. Finally, any pharmaceutical cost-containment measure must focus on the broader picture i.e. reducing pharmaceutical expenditure may result in increased spending in other areas, such as secondary care.

Chapter 3

Pharmaceutical Pricing: A Comparison of Irish, Danish, Average European and UK Prices

Table of Contents for Chapter 3

3.1 Introduction

3.1.1 The Impact of Pharmaceutical Prices on Pharmaceutical Expenditure

Pharmaceutical expenditure is rising faster than any other area of healthcare in most European countries[74]. This is a source of concern to governments striving to maintain equitable access to medicines at an affordable cost. Pharmaceutical expenditure is determined by price levels and consumption patterns and both factors vary greatly across countries[1].

In order to contain costs, most EU Member States have introduced various policies to control the price of reimbursable medicines. Measures for directly controlling pharmaceutical expenditure include international price comparisons, maximum fixed prices and price freezes or cuts. Indirect approaches to controlling prices include regulating profits (e.g. the UK PPRS system for branded medicines) or setting reference prices (reimbursement limits). These cost-containment policies are described in detail in Chapter 2.

In this chapter, the price of a sample of reimbursed medicines in Ireland is compared with the equivalent Danish price (which is based on an average European price) and UK price (the UK ex-manufacturer price is reported to be the highest in Europe). This research was undertaken for the DoHC when the pricing mechanism for pharmaceuticals was being reconsidered ahead of the new IPHA-DoHC Agreement.

3.1.2 Variation in the Price of Medicines Across the European Union

There are wide variations in the price of medicines across the EU. In general, the Northern European countries have higher prices but lower volumes of use compared to the Southern European countries. In order to control costs most EU Member States, either directly or indirectly, control the prices of reimbursable medicines at the ex-manufacturer level. Pharmacy and wholesale margins are also usually controlled at a national level. In addition, the rates of VAT on medicines vary between countries[86, 159].

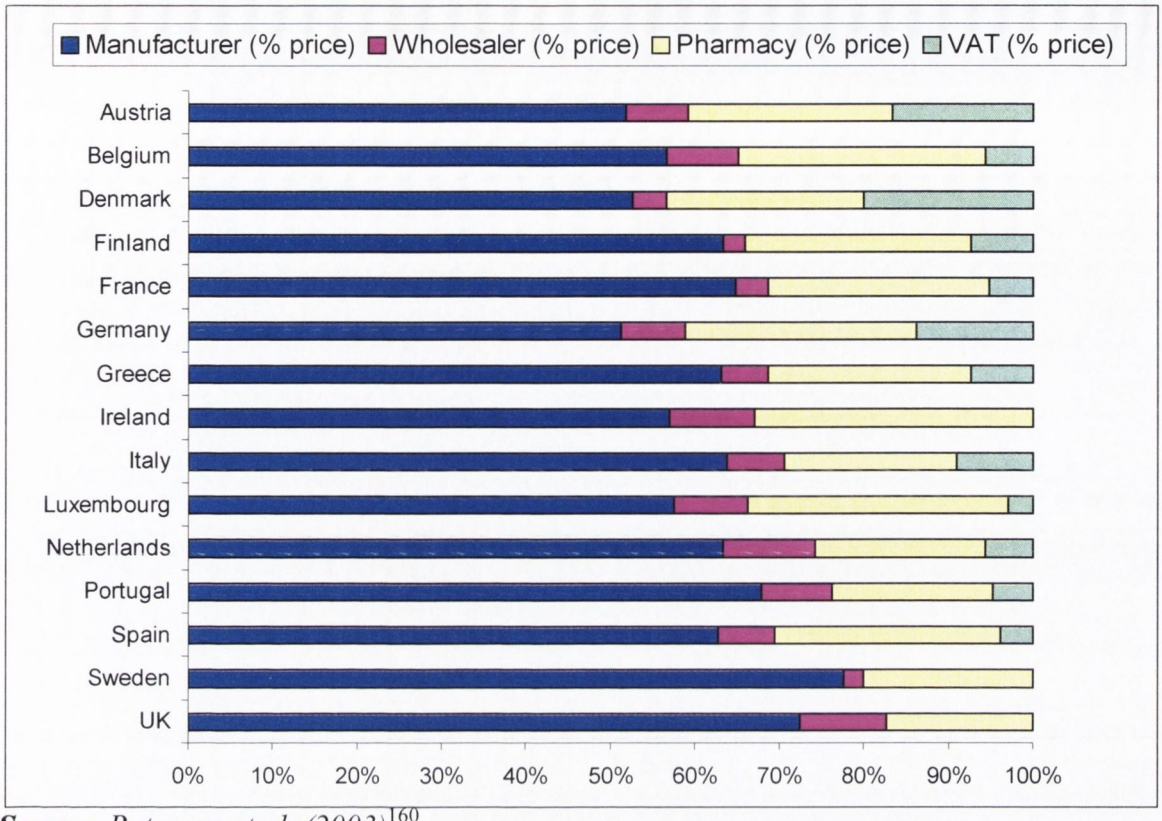
Therefore, it is important to measure the price of pharmaceuticals at the same point in the distribution chain, due to the variation in wholesale and pharmacy margins and rates of VAT between countries (Figure 3.1). Pharmaceutical prices may be obtained at 3 different points in the distribution chain[159]:

1. ***Ex-manufacturer price:*** The ex-manufacturer price is the price at which the manufacturer sells to the wholesaler. Countries that reference their prices to other European countries, often use the ex-manufacturer price to set the reimbursement price of medicines. Ex-manufacturer prices are not usually readily available to national agencies and are often calculated in an arbitrary way from manufacturers' list prices. In addition, ex-manufacturer prices do not reflect what the State actually pays for reimbursed medicines.

2. ***Ex-wholesale price:*** The ex-wholesale price is the price at which the wholesaler sells to the pharmacist. Ex-wholesale prices are more readily available than ex-manufacturer prices and may be a more transparent measure of pharmaceutical prices. However, wholesale margins vary between countries and are fixed in some countries but not in others[86].

3. ***Pharmacy retail / reimbursement price***: The pharmacy retail/reimbursement price is the price at which the pharmacy is reimbursed by the State or sells to the patient (depending on the eligibility of the patient for reimbursement). This price includes a pharmacy mark-up and different rates of VAT. The pharmacy retail/reimbursement price represents the final price paid by the patient or the State and includes all the distribution margins (pharmacy and wholesale) as well as VAT. However, in Ireland the pharmacy retail / reimbursement price varies depending on which Community Drug Scheme the patient is eligible for (see Chapter 1 for a more detailed explanation of the reimbursement price of medicines in Ireland).

Figure 3.1 Composition of the consumer price of medicines in the EU-15 Member States.



Source: *Paterson et al. (2003)*[160].

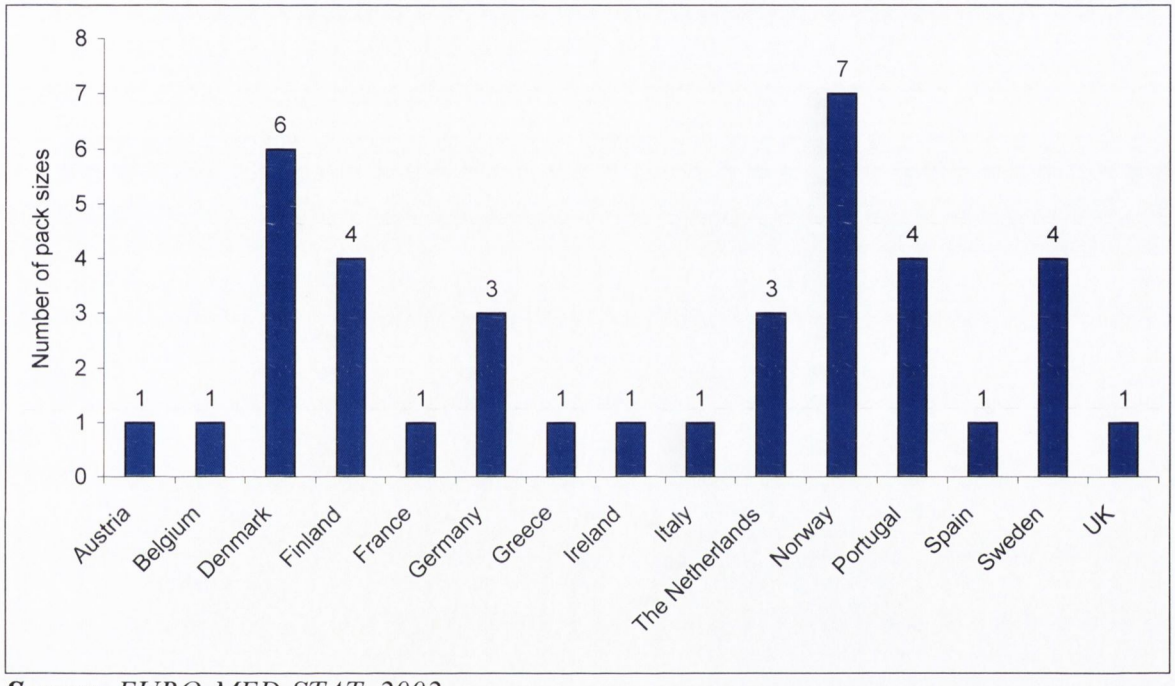
3.1.3 Variation in Availability of Medicines Across the European Union

A number of studies have highlighted the wide variation in availability of medicines across EU Member States[71, 82, 161]. Any international comparison of drug prices is restricted to products which are mutually available across all countries. The Euro-Medicines group found that only 7% of all available active ingredients were marketed in 14 EU countries[71]. Some of the most widely used medicines in some countries have even been withdrawn or were never licensed in others. The range of drugs available in each country represents the differences in regulatory and market policies, as well as cultural and historic differences. There are also wide variations between products in terms of pharmaceutical form, strength, brand and pack size in different countries.

The EURO-MED-STAT project is funded by the European Commission and the aim of this project is to develop a set of indicators for monitoring price, state expenditure and utilisation of medicines in the EU Member States[82]. Preliminary data from this ongoing project illustrates some of the methodological difficulties in making these international comparisons. In the year 2000, for example, there were 13 different pack sizes of simvastatin 20mg available in 15 EU countries (Figure 3.2). Seven countries had a range of

pack sizes available, while in Austria, Belgium, France, Greece, Ireland, Italy, Spain and the UK only one pack size was available, which varied from 10 tablets per pack in Greece and Italy to 30 tablets per pack in Austria[82]. Variations in strengths, pharmaceutical formulations and pack sizes lead to difficulties in obtaining a comprehensive sample of medicines for comparison.

Figure 3.2 Variations in pack sizes of simvastatin 20mg in 2000.



Source: *EURO-MED-STAT, 2002.*

3.1.4 International Pharmaceutical Price Comparisons

International pharmaceutical price comparisons are used for two main purposes[162]. Firstly, cross-national price comparisons are used by some governments as a benchmark for setting domestic pharmaceutical price, at launch and / or throughout a products life cycle e.g. Ireland, the Netherlands and Portugal. Secondly, price comparisons based on a sample of products can be used to draw conclusions about differences in average price levels between countries, to inform policy makers evaluating alternative regulatory systems for setting drug prices.

The variation in price, utilisation of and expenditure on medicines across the EU Member States leads to difficulties in performing international drug price comparisons, which are well recognised [162, 163]. Danzon and Kim have highlighted that international drug price comparisons are extremely sensitive to choices made about certain key methodological

issues, such as sample selection, use of exchange rates or purchasing power parities (PPPs) for currency conversion and the relative weight given to each drug's price difference in the process of calculating an average price differential (i.e. choice of a price index)[162]. There is no ideal way of measuring and comparing pharmaceutical prices in different countries. However, it is generally accepted that a valid comparison should include a representative sample of drugs, which are appropriately weighted by market shares[162-164].

A number of studies have attempted to compare drug prices between countries. Much of this work was undertaken in the 1990s and focused on prices in the US compared with a range of other countries[163, 165-167]. More recently a number of cross-country comparisons were undertaken from the European perspective[168-171]. In 2000 the Australian Productivity Commission examined the differences between manufacturer prices in Australia and seven other countries for 150 medicines[172]. However, it is difficult to compare the results between studies, as few adopted comparable methodologies. Apart from this study, no international pharmaceutical price comparisons have been published from the Irish perspective to date[173].

3.1.5 Weighting Prices

Average price differentials may be based on a price index that weights each product by its relative importance in the market (i.e. volume of sales) or a straight average (i.e. each product is given equal weight in the calculation). Individual drugs have different influences on the general price level of drugs in a country. Drugs with a high volume of use (such as omeprazole) affect the general price level for drugs to a greater extent than a drug with a low volume of use. Therefore, the use of a weighted price index (i.e. weighting the price of a drug with the share of sales in a country) to reflect the relative importance of the price of different products on overall expenditure, is recommended[162, 164, 174].

Several standard price indices have been developed, each of which results in a different measure of cross-country price differences. A price index is used to measure the change in the average price for a basket of products in 2 situations, the base and the comparison, when the prices for most products differ between the 2 situations. The Laspeyres index weights the price using the base country's consumption patterns, whereas the Paasche index weights the price by the comparison country's consumption patterns[162, 164]. Other indices have also been developed, such as the Fisher's index, which represents a combination of base and comparator country weights[162, 164].

As consumption patterns differ considerably across countries, different results are likely to be obtained depending on the country from which the price weights are obtained. As a consequence some studies have recommended that a range of indices are reported[164]. Other studies have argued that it is probably most appropriate for each country to weight prices by its own consumption patterns[163].

3.1.6 Pricing of Medicines in Ireland

Currently, the price of medicines in Ireland reflects a Northern European price which is generally higher than the European average. The pricing system for medicines in Ireland is outlined in the agreement between the DoHC and IPHA and is described in Chapter 1. Although there has been a price freeze on all prescription medicines in Ireland since 1993, the cost per item of medicines has increased from 1993 to 2004, as a result of the introduction of new more expensive medicines to the market. From 1997, there has been a marked year on year increase in the cost per item of medicines reimbursed on the GMS Scheme (Chapter 1; Figure 1.8). One reason for this increase in cost is the introduction of new medicines claiming a therapeutic advantage, over similar medicines in the same therapeutic class, but at a higher price.

3.1.7 Pricing of Medicines in the UK and Denmark

In this study the Irish price was compared to a country reported to have the highest price for medicines in the EU (the UK) and a country whose pricing system is based on an average European price (Denmark).

Denmark: In Denmark, manufacturers and importers of pharmaceutical products are free to set the price of each medicine, unless the product is included on the general reimbursement list. At the time this study was undertaken (2003), the *"reimbursement price"* was calculated from the lower of either the Danish price of the product or the "average European price" (AEP). The AEP was the average of the prices of the drug in 13 other European Economic Area (EEA) countries (i.e. Austria, Belgium, Finland, France, Germany, Iceland, Ireland, Italy, Liechtenstein, the Netherlands, Norway, Sweden and the UK) excluding Greece, Luxemburg, Portugal, and Spain. Countries in which the gross national products (GNP) are more or less than 30% of the Danish per capita GNP were excluded from the pricing formula[60, 175]. This agreement was based on the idea that Danish prices should be comparable to a common European price[86]. Pharmaceutical companies

were obliged to inform the Danish Medicines Agency of this price every 6 months. There was an agreement between the Danish Association of the Pharmaceutical Industry *(LIF)* and Ministry of Health not to set prices higher than the AEP. Medicines not included on the general reimbursement list, may be granted individual reimbursement for a valid indication to a given patient e.g. drugs for managing Alzheimer's disease. The criteria for individual reimbursement are decided by a Reimbursement Committee. The AEP is only assigned to medicines included on the general reimbursement list.

Wholesale margins in Denmark are negotiated between manufacturers/importers and wholesalers. In some cases a fixed amount is agreed for the entire product portfolio, while in others a range modulated according to product price and sales volume (e.g. 4-18%) is utilised.

The UK: The UK has been reported to have the highest ex-manufacturer prices for medicines in Europe[171, 176]. In theory, price setting for drugs in the UK is free. The PPRS is a scheme that indirectly controls the price of branded medicines used within the NHS[86]. The PPRS operates at the level of the individual company and controls the overall profits made. Based on bilateral comparisons and the average annual exchange rate for the period 1999 to 2003, prices in the UK have been reported to be higher than the following European comparator countries: Austria, Belgium, Finland, France, Germany, Italy, the Netherlands and Spain[171].

In the UK, a tariff price is set for generic medicines. This is a market based reimbursement price which is revised monthly[177]. The pharmacist is reimbursed this tariff price regardless of whether a more expensive or cheaper product was dispensed.

The NHS list price for branded medicines is the ex-factory price plus a 12.5% wholesaler margin[98]. The generic market is a free market and wholesalers are allowed to set their own margins[178].

In this chapter the price of medicines in Ireland are compared to the Danish price, an average European price and the UK price.

3.2 Aim

The aims of this chapter were to:

- Undertake a multilateral comparison between the price of medicines in Ireland and the Danish, average European and UK prices for a representative sample of medicines, by calculating both an unweighted and a volume weighted price index.
- Determine potential cost savings on the GMS Scheme, using drug utilisation data from the GMS prescription database, if a Danish, average European or UK price were adopted.

3.3 Method

3.3.1 Sources of Pricing Data

The Irish pricing data was obtained from the GMS (Payments) Board November 2003 monthly drug file of products reimbursed under the GMS Scheme. This file is referred to as the Drugs and Medical Appliances (DMA) file and is received every month without any time lag by the NCPE. The DMA file includes the following information:

- GMS code number
- Brand name
- Pharmaceutical form
- Strength
- Unit of measurement of strength
- Pack size
- Ex-wholesale price
- Effective date of price
- ATC code – World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification 5th level
- Defined Daily Dose (DDD)
- Route of administration
- DMA class (1=Generic, 2=Branded generic, 3=Proprietary with an equivalent generic available, 4=Proprietary with no generic equivalent available).
- Manufacturer

The GMS (Payments) Board codes medications using the WHO ATC classification system. This coding system is used internationally and therefore facilitates the consolidation of different drug related databases containing ATC coded medications. In the

ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified in groups at five different levels[179]. The complete classification of omeprazole illustrates the structure of the code:

A (1st level):	Alimentary tract and metabolism
A02 (2nd level):	Drugs for acid related disorders
A02B (3rd level)	Drugs for peptic ulcer and gastro-oesophageal reflux disease
A02BC (4th level)	Proton Pump Inhibitors
A02BC01 (5th level)	Omeprazole

The Danish and average European prices were obtained from the drug pricing files from the Danish Medicines Agency in November 2003. The Danish Medicines Agency also provided translations from Danish to English for the different pharmaceutical formulations in order to facilitate matching of products on the Irish and Danish market. In addition, definitions of the prices included in the Danish drug pricing files were obtained. The following information was included in the Danish pricing file:

- Brand name
- Pharmaceutical form
- Strength
- Unit of measurement of strength
- Pack size
- Danish ex-wholesale price (AIP)
- Average European ex-wholesale price (AEP)
- ATC classification (5th level)
- Manufacturer

The UK prices were obtained from the British National Formulary (BNF) 46th Edition, September 2003. The following information is available from the BNF:

- International Non-proprietary Name (INN)
- Brand name
- Pharmaceutical form
- Strength
- Unit of measurement of strength
- Pack size
- NHS list price (i.e. the ex-wholesale price)

- Manufacturer

The INN is the unique generic name of a drug which is globally recognised and is used to facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients.

3.3.2 Source of Drug Utilisation Data

Drug utilisation data for the GMS Scheme was obtained from the monthly drug reimbursement files from the GMS (Payments) Board. There is a delay of approximately 5 months in the NCPE receiving the files. The drug utilisation files are stored as monthly data per health region.

Each row of data contains information relating to one prescription item. The columns contain the following information:

- Pharmacy number
- GP number to whom the patient is registered
- GMS patient number
- Sex of patient
- Age group of patient
- Claim number of prescription
- GMS code
- Number of dosage units dispensed
- Pharmacist fee
- VAT on pharmacist fee
- Cost of medicine
- VAT on cost of medicine
- Prescribing doctor
- WHO ATC classification (5th level)

The common link between the GMS file and the DMA file is the GMS code number, which is used to join the 2 files together. This step needs to be carried out in order to identify the pharmaceutical form, strength, brand name and pack size of each drug.

3.3.3 Sample Selection

The top 70 drugs in order of the total ingredient cost to the GMS Scheme for 2002, which account for 70% of the total ingredient cost of medicines on this scheme, were selected for the analysis (Table 3.1). This information was obtained from the annual reports produced by the GMS (Payments) Board[45].

Table 3.1 The top 70 drugs by expenditure on the GMS Scheme in 2002.

	Drug	Ingredient cost (€)	% of scheme total	Included in analysis / Reason for exclusion
1	Omeprazole	20,294,520	4.68	Included
2	Clinical Nutrition Products	19,032,229	4.39	Not a medicinal product
3	Pravastatin	17,007,671	3.92	Included
4	Atorvastatin	10,921,376	2.52	Included
5	Olanzapine	10,792,815	2.49	Included
6	Lansoprazole	8,771,022	2.02	Included
7	Ostomy/Urinary Requisites	8,354,186	1.93	Not a medicinal product
8	Amlodipine	7,647,189	1.76	Included
9	Salmeterol and other drugs for OAD*	7,595,937	1.75	Included
10	Diagnostic products	6,262,975	1.45	Not a medicinal product
11	Beclometasone (inhaled)	6,082,155	1.4	Insufficient proportion of prescriptions with product matches
12	Esomeprazole	5,992,066	1.38	Included
13	Risperidone	5,985,772	1.38	Included
14	Clopidogrel	5,593,183	1.29	Not on General Reimbursement list in Denmark
15	Salbutamol and other drugs for OAD*	5,583,299	1.29	Included
16	Budesonide (inhaled)	5,511,427	1.27	Insufficient proportion of prescriptions with product matches
17	Pantoprazole	5,479,902	1.26	Included
18	Citalopram	5,375,551	1.24	Included
19	Paroxetine	5,350,245	1.23	Included
20	Venlafaxine	4,787,250	1.1	Included
21	Doxazosin	4,570,711	1.05	Included
22	Celecoxib	4,281,593	0.99	Included
23	Tolterodine	4,249,233	0.98	Different strength available in Denmark
24	Nimesulide	4,201,599	0.97	Not available in UK or Denmark
25	Diclofenac (systemic)	3,984,107	0.92	Insufficient proportion of prescriptions with product matches
26	Ramipril	3,951,163	0.91	Included
27	Amoxicillin and enzyme inhibitor	3,946,476	0.91	Combination product
28	Sertraline	3,847,712	0.89	Included
29	Donepezil	3,846,293	0.89	Not on General Reimbursement list in Denmark
30	Fluoxetine	3,821,729	0.88	Included
31	Lisinopril	3,705,988	0.86	Included
32	Isosorbide mononitrate	3,616,311	0.83	Included
33	Rofecoxib	3,481,515	0.8	Included
34	Ranitidine	3,371,983	0.78	Included
35	Fluticasone (inhaled)	3,239,420	0.75	Included
36	Rabeprazole	3,238,041	0.75	Included
37	Captopril	3,221,664	0.74	Included
38	Alendronic acid	3,137,250	0.72	Not on General Reimbursement list in Denmark
39	Salbutamol (inhaled)	3,089,701	0.71	Included

Table 3.1 (continued from page 83).

	Drug	Ingredient cost (€)	% of scheme total	Included / Reason for exclusion
40	Simvastatin	2,997,748	0.69	Included
41	Perindopril	2,957,613	0.68	Included
42	Atenolol	2,802,774	0.65	Insufficient proportion of prescriptions with product matches
43	Aspirin (Antithrombotic)	2,783,291	0.64	Insufficient proportion of prescriptions with product matches
44	Nicotine Replacement Therapy	2,709,954	0.63	Not on General Reimbursement list in Denmark
45	Clarithromycin	2,674,585	0.62	Included
46	Tramadol	2,425,708	0.56	Insufficient proportion of prescriptions with product matches
47	Fentanyl	2,383,013	0.55	Not on General Reimbursement list in Denmark
48	Zopiclone	2,377,727	0.55	Not on General Reimbursement list in Denmark
49	Bisoprolol	2,210,844	0.51	Included
50	Lamotrigine	2,206,043	0.51	Included
51	Latanoprost	2,198,472	0.51	Included
52	Tamsulosin	2,197,691	0.51	Included
53	Gabapentin	2,002,459	0.46	Included
54	Insulin (Human)	1,958,307	0.45	Insufficient proportion of prescriptions with product matches
55	Diltiazem	1,878,984	0.43	Insufficient proportion of prescriptions with product matches
56	Nifedipine	1,865,908	0.43	Insufficient proportion of prescriptions with product matches
57	Orlistat	1,730,924	0.4	Not on General Reimbursement list in Denmark
58	Amoxicillin	1,722,446	0.4	Insufficient proportion of prescriptions with product matches
59	Glyceryl Trinitrate	1,588,421	0.37	Included
60	Losartan	1,551,720	0.36	Included
61	Sildenafil	1,529,390	0.35	Not on General Reimbursement list in Denmark
62	Betahistine	1,488,522	0.34	Not on General Reimbursement list in Denmark
63	Gliclazide	1,481,250	0.34	Included
64	Calcium, combinations	1,475,243	0.34	Insufficient proportion of prescriptions with product matches
65	Furosemide with Potassium-Sparing Agents	1,465,316	0.34	Combination product
66	Ondansetron	1,443,034	0.33	Not on General Reimbursement list in Denmark
67	Salmeterol	1,412,950	0.33	Included
68	Paracetamol combinations excluding Psycholeptics	1,402,712	0.32	Combination product
69	Risedronic acid	1,382,859	0.32	Not available in Denmark
70	Formoterol and other drugs for OAD*	1,352,229	0.31	Insufficient proportion of prescriptions with product matches
	Total	304,881,396	70.31	

*OAD: Obstructive Airways Disease.

Out of 70 drugs, 39 were included in the analysis. The remaining 31 drugs were excluded for a variety of reasons (Table 3.2).

Table 3.2 Criteria for excluding drugs from the analysis.

Reason for exclusion	Number of drugs
Drug not included on General Reimbursement list in Denmark	10
Drug not available in Denmark/UK	2
Non – medicinal products (e.g. ostomy / urinary requisites)	3
Different strength available in Denmark	1
Insufficient proportion of prescriptions with product matches for the analysis	12
Combination products	3

Combination products were excluded because the mix of ingredients is not uniform across countries and the price for the combination cannot be accurately allocated to the separate molecules[180]. A number of drugs were either not available or not included on the General Reimbursement list in Denmark (e.g. donepezil) and for the remainder it was not possible to match the products (e.g. differences in strength of the product). Tolterodine, for example was available as 1.4mg and 2.8mg sustained release capsules in Denmark, whereas 2mg and 4mg sustained release capsules were available in Ireland. Nimesulide was not available in Denmark or the UK and risedronic acid was not available in Denmark. Preparations that could not be matched were excluded from the analysis. Pravastatin 10mg, for example, was not available in Denmark and therefore the comparison was restricted to prescriptions for pravastatin 20mg and 40mg.

The drugs were matched by active ingredient, form, strength, manufacturer (with the exception of glyceryl trinitrate (GTN), which was matched by brand name, as a number of different branded generic products were included in the analysis) and, where possible, pack size. For certain drugs there were a small proportion (<20%) of prescriptions for preparations with matching products on the UK and Danish markets. These drugs were also excluded from the analysis.

Multilateral comparisons, as opposed to bilateral comparisons, were made i.e. only preparations which were mutually available and reimbursed in all 3 countries were compared.

3.3.4 Calculation of the Price Indices

Drug prices were compared at the ex-wholesale price level. Preparations were identified by the ATC classification in the GMS monthly product file and the files from the Danish Medicines Agency. The preparations available in the UK were identified in the BNF by the INN.

The price per dose unit was calculated for each preparation in the sample. The average annual exchange rate for 2003 was used to convert Danish krone (€1=7.43363 krone) and UK pounds (€1=£0.69149) to Euro.

The quantity of each medicine dispensed was derived from the GMS prescription database drug utilisation files by calculating the total number of standard dose units of each preparation dispensed. A standard dose unit is defined as one tablet, one capsule, 5mls of liquid etc. However, the standard dose unit may be an imprecise measure of a dose for inhalers, eye drops and sprays. Therefore, for these formulations, the number of packs dispensed and the price per pack were used as the units of volume and price.

The price indices were calculated using two different methodologies: an unweighted average price index and a volume weighted price index.

a. The unweighted average price index:

The unweighted average price per dose unit over all of the matching forms, strengths, pack sizes and brands of each active ingredient (level 5 of the ATC classification) was calculated. The unweighted average price index was then calculated using the following formula:

$$\text{Unweighted average price index} = \sum p_i^c / \sum p_i^b$$

Where p_i^c = average price of active ingredient 'i' (level 5 of the ATC classification) in comparator country "c", p_i^b = average price of active ingredient 'i'(level 5 of the ATC classification) in baseline country 'b'.

Index values less than 1.00 imply comparator prices lower than Irish prices and index values greater than 1.00 imply comparator prices higher than Irish prices.

b. The volume weighted price index:

The volume weighted price per dose unit over all of the matching forms, strengths, pack sizes and brands of each active ingredient (level 5 of the ATC classification) was calculated. Prices in each country were weighted by the volume of each preparation dispensed on the GMS Scheme i.e. the Laspeyres price index was calculated. The Laspeyres price index P^L is expressed as[164]:

$$P^L = (\sum p_i^c . q_i^b)/(\sum p_i^b . q_i^b)$$

Where p_i^c = price of preparation 'i' in comparator country "c", p_i^b = price of preparation 'i' in baseline country 'b', q_i^b = quantity of drug 'i' in baseline country 'b'.

If the index is less than 1.00, it indicates that comparator prices are, on average, lower than Irish prices. Conversely, index values greater than 1.00 imply comparator prices higher than Irish prices.

3.3.5 Calculation of Potential Savings from Price Substitution

The drug utilisation files from the GMS prescription database were used to calculate the total ingredient cost of these medicines on the GMS Scheme for the year 2002 if a Danish, average European and UK price were adopted. The Irish ex-wholesale price per dose unit was substituted with the equivalent Danish, average European and UK price per dose unit and multiplied by the total number of dose units of all preparations dispensed, to determine potential savings to the net ingredient cost of medicines for the GMS Scheme.

3.3.6 Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2000 and JMP-IN (version 3.2.1, SAS Institute Inc.). The two-sided nonparametric Wilcoxon Signed-rank test was performed to determine whether there was a statistically significant difference in expenditure on drugs when Irish prices were substituted with Danish, average European and UK prices. A non-parametric test was chosen because the distribution of savings for the sample of drugs included in the analysis was non-normal. The level of statistical significance was set at $p<0.05$ throughout.

3.4 Results

Out of the top 70 drugs by expenditure on the GMS Scheme in 2002, 31 drugs were excluded from the analysis (Table 3.2). Therefore, there was a sample of 39 drugs, which represented 44.8% (€ 194.46 million) of the total ingredient cost of medicines and 22.4% (6,631,329) of prescriptions on the GMS Scheme for the year 2002. Of the 39 drugs included in the analysis there were 404 different preparations on the Irish market, and 81.3% of prescriptions for these preparations had matching products on the UK and Danish market. Pack sizes were identical for 72% of the preparations included in the sample of 39 drugs; there was less than 10% difference in pack size for 10% of the preparations and greater than 10% difference for the remainder of the preparations (18%) included in the analysis.

3.4.1 The Unweighted Average Price Index

The unweighted average price index of the 39 drugs included in the study was highest for the UK prices (1.03), followed by Ireland (1.00), the average European (0.90) and Danish prices (0.89) (Table 3.3). Therefore, the unweighted average price index in the UK was 3% higher than the Irish price index. The average European and the Danish price indices were 10% and 11% lower than the Irish price index respectively.

The Irish unweighted average price per dose unit was higher than the other prices for 18 (46%) of the drugs included in the sample. The UK unweighted average price per dose unit was higher than the other prices for 15 (39%) of the drugs and the average European / Danish prices were highest for the remaining 6 (15%) drugs included in the sample. The Irish unweighted average prices per dose unit of the top 5 drugs by expenditure were higher than the Danish, average European and UK prices per dose unit.

Table 3.3 Unweighted average price per dose unit of the 39 drugs included in the analysis (2003).

	Ireland	Denmark	Average European	UK
Omeprazole	**2.01**	1.89	1.95	1.8
Pravastatin	**1.75**	1.4	1.4	1.53
Atorvastatin	**1.86**	1.49	1.49	1.38
Olanzapine	**4.86**	4.25	4.29	4.77
Lansoprazole	**1.51**	0.85	1.08	1.22
Amlodipine	0.75	0.69	0.69	**0.76**
Salmeterol and other drugs for OAD*	59.97	54.86	54.92	**71.24**
Esomeprazole	**1.32**	1.27	1.32	1.23
Risperidone	**69.22**	59.15	59.15	58.15
Salbutamol and other drugs for OAD*	4.38	4.54	4.54	**5.05**
Pantoprazole	**1.08**	0.8	1.03	0.95
Citalopram	**1.31**	1.13	1.14	0.93
Paroxetine	0.82	0.79	0.79	**0.85**
Venlafaxine	1.22	1.12	1.12	**1.24**
Doxazosin	**0.79**	0.67	0.67	0.73
Celecoxib	**0.88**	0.79	0.79	0.87
Ramipril	0.37	0.42	**0.48**	0.4
Sertraline	**1.7**	1.25	1.25	1.11
Fluoxetine	**0.64**	0.54	0.54	0.48
Lisinopril	**0.54**	0.37	0.37	0.45
Isosorbide mononitrate	0.56	0.36	0.36	**0.58**
Rofecoxib	**1.24**	1.15	1.15	1.11
Ranitidine	**0.89**	0.51	0.58	0.69
Fluticasone (inhaled)	29.54	26.82	26.86	**32.57**
Rabeprazole	0.95	**1**	**1**	0.91
Captopril	0.35	0.28	0.28	**0.37**
Salbutamol (inhaled)	3.57	**4.03**	**4.03**	3.33
Simvastatin	1.36	1.19	1.19	**1.38**
Perindopril	0.62	**0.66**	0.61	0.51
Clarithromycin	1.34	1.29	1.34	**1.39**
Bisoprolol	0.37	0.25	0.31	**0.46**
Lamotrigine	1.1	1.01	1.01	**1.24**
Latanoprost	**20.13**	17.33	17.33	17.28
Tamsulosin	1.04	0.88	0.95	**1.06**
Gabapentin	1.05	0.99	0.99	**1.24**
GTN	2.5	3.87	**4.21**	2.61
Losartan	**1.03**	0.97	0.97	1.02
Gliclazide	0.16	**0.2**	0.18	0.19
Salmeterol	32.58	28.8	28.8	**41.36**
Sum	**257.36**	**229.86**	**231.16**	**264.44**
Unweighted Price Index	**1.00**	**0.89**	**0.90**	**1.03**

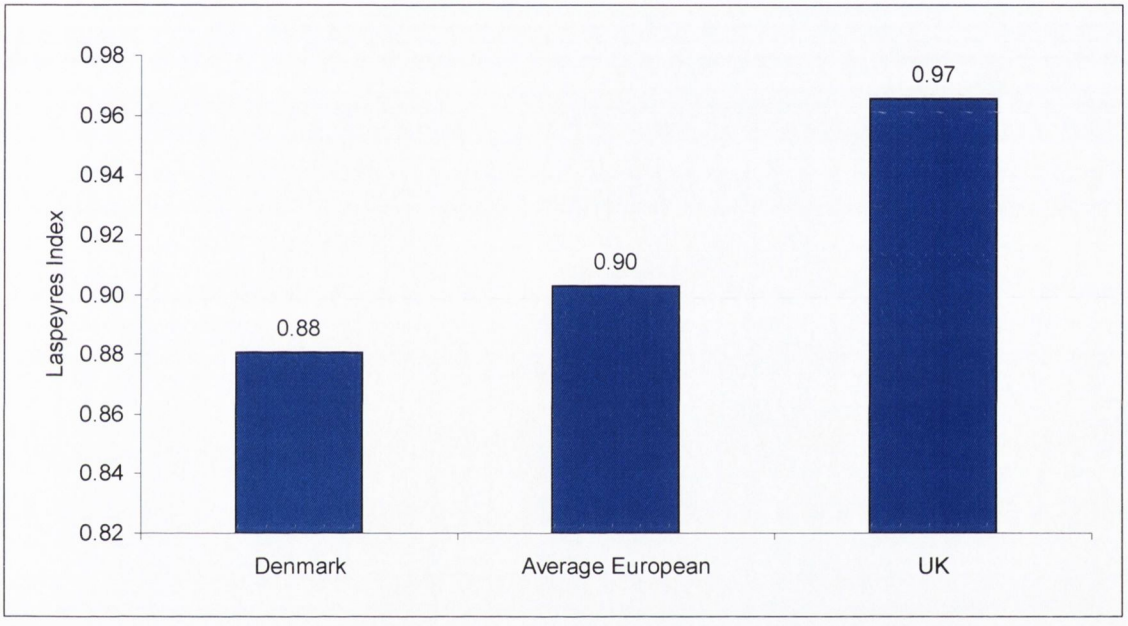
The country with the highest unweighted average price per dose unit is highlighted in red.

* OAD: Obstructive Airways Disease.

3.4.2 The Volume Weighted Price Index

The volume weighted price index (Laspeyres index) was highest for the Irish prices, followed by the UK (0.97), the average European (0.90) and Danish prices (0.88) (Figure 3.3). Therefore, the volume weighted price index in the UK was 3% lower than the Irish price index; the average European and the Danish price indices were 10% and 12% lower than the Irish price index respectively.

Figure 3.3 Volume weighted price indices (Laspeyres indices) for the Danish, average European and UK prices, relative to the Irish price index of 1.00.



3.4.3 Potential Cost Savings from Price Substitution

The estimated potential cost savings to the GMS Scheme of substituting the Irish price with a Danish price for the sample of 39 drugs was €20.7 million; representing 10.7% of the total ingredient cost of the 39 drugs on the GMS Scheme in 2002 (Table 3.4).

The estimated potential cost savings to the GMS Scheme of substituting the Irish price with an average European price for the sample of 39 drugs was €16.2 million; representing 8.4% of the total ingredient cost of the 39 drugs on the GMS Scheme in 2002 (Table 3.4).

The estimated potential cost savings to the GMS Scheme of substituting the Irish price with a UK price for the sample of 39 drugs was €6.8 million; representing 3.5% of the total ingredient cost of the 39 drugs on the GMS Scheme in 2002 (Table 3.4).

Negative values in Table 3.4 (highlighted in red) indicate a more expensive price in the comparator country and would result in an increase in expenditure if the Irish prices were substituted with the comparator country prices. There were 20 drugs with negative values for the UK price estimates ranging from €–0.02 million for clarithromycin to €–1.36 million for salmeterol (Table 3.4). Therefore substitution of the Irish prices of clarithromycin and salmeterol with UK prices would result in an estimated increase in expenditure of €20,000 and €1.36 million respectively. Substitution of the Irish price with the UK price, for the 20 drugs with negative UK values, would result in an increase in drug expenditure of €4.91 million. However, substitution of Irish prices with UK prices for all 39 drugs that were included in the sample would result in overall cost savings (€6.8 million).

Table 3.4 Potential cost savings on the GMS Scheme for 2002 by substituting a Danish, average European and UK ex-wholesale price.

Drug	GMS Total ingredient cost for 2002 (Million €)	% of scheme total	Potential savings from price substitution (Million €)		
			Danish price	Average European Price	UK price
Omeprazole	20.29	4.68	2.16	1.09	2.7
Pravastatin	17.01	3.92	2.85	2.85	0.85
Atorvastatin	10.92	2.52	0.71	0.71	0.1
Olanzapine	10.79	2.49	1.07	1.06	-0.1
Lansoprazole	8.77	2.02	2.74	1.57	1.61
Amlodipine	7.65	1.76	0.56	0.56	-0.13
Salmeterol and other drugs for OAD*	7.60	1.75	0.64	0.63	-1.36
Esomeprazole	5.99	1.38	0.31	0.12	0.79
Risperidone	5.99	1.38	0.9	0.73	-0.07
Salbutamol and other drugs for OAD	5.58	1.29	0.08	0.08	-0.52
Pantoprazole	5.48	1.26	1.38	0.3	0.64
Citalopram	5.38	1.24	0.52	0.52	0.74
Paroxetine	5.35	1.23	0.09	0.09	0.06
Venlafaxine	4.79	1.1	0.46	0.46	-0.09
Doxazosin	4.57	1.05	0.29	0.29	0.15
Celecoxib	4.28	0.99	0.28	0.28	0.03
Ramipril	3.95	0.91	-0.39	-0.85	-0.29
Sertraline	3.85	0.89	1.01	1.01	1.29
Fluoxetine	3.82	0.88	0.18	0.18	0.52
Lisinopril	3.71	0.86	1.02	1.02	0.55
Isosorbide mononitrate	3.62	0.83	0.79	0.79	-0.08
Rofecoxib	3.48	0.8	0.24	0.24	0.33
Ranitidine	3.37	0.78	0.82	0.63	0.46
Fluticasone (inhaled)	3.24	0.75	0.18	0.18	-0.17
Rabeprazole	3.24	0.75	-0.19	-0.19	0.05
Captopril	3.22	0.74	0.18	0.18	-0.04
Salbutamol (inhaled)	3.09	0.71	-0.12	-0.12	0.06
Simvastatin	2.96	0.68	0.71	0.71	-0.07
Perindopril	2.96	0.68	-0.18	0.05	0.5
Clarithromycin	2.67	0.62	0.11	0.03	-0.02
Bisoprolol	2.21	0.51	0.65	0.48	-0.33
Lamotrigine	2.21	0.51	0.18	0.18	-0.27
Latanoprost	2.20	0.51	0.3	0.3	0.3
Tamsulosin	2.20	0.51	0.31	0.18	-0.04
Gabapentin	2.00	0.46	0.14	0.14	-0.22
GTN	1.59	0.37	-0.17	-0.26	-0.4
Losartan	1.55	0.36	0.06	0.06	-0.21
Gliclazide	1.48	0.34	-0.32	-0.23	-0.18
Salmeterol	1.41	0.33	0.18	0.18	-0.32
Total (€ million)	**194.46**	**44.84**	**20.73**	**16.23**	**6.82**
% savings of total ingredient cost			**10.66**	**8.35**	**3.51**

*OAD: Obstructive Airways Disease.

Statistical analysis was undertaken using the two-sided nonparametric Wilcoxon signed-rank test. This demonstrated that there was a statistically significant difference in expenditure on drugs when Irish prices were substituted with Danish ($p<0.0001$) and average European prices ($p<0.0001$) for the sample of 39 drugs. However, no statistically significant difference between Ireland and the UK was demonstrated ($p=0.36$).

3.5 Discussion

3.5.1 The Price of Medicines in Ireland: Comparison with Other Studies

The results of this study demonstrate the high ex-wholesale price for medicines in Ireland and the potential for savings to be made on the GMS Scheme by substituting Danish, average European or UK ex-wholesale prices.

These results are broadly consistent with the findings of other international price comparison studies[168-170]. However, due to the differences in methods, samples and data, the results are not directly comparable with those of other studies. Martikainin *et al.* (2005) compared the prices of 8 newly introduced, innovative medicines in 9 EU Member States. Ireland had, almost without exception, the highest ex-wholesale prices and Belgium and Spain had the lowest. Ireland also had the highest retail prices for these medicines, followed by Denmark[168].

A study commissioned by the Swedish government in 2004 highlighted that Ireland, Switzerland and the UK had the highest ex-wholesale prices for medicines while Greece, Spain, Norway, Belgium, France and Italy had the lowest prices[170]. A study carried out by Intercontinental Marketing Services (IMS) consulting for the Swiss Pharmaceutical Industry (2004) demonstrated that Swiss ex-manufacturer prices were the highest in the European countries analysed (Austria, Denmark, France, Germany, Italy, the Netherlands, Sweden and the UK), followed by Sweden, the UK, Germany and the Netherlands[169]. The study was based on a comparison of the top 100 branded reimbursed medicines in Switzerland (market share of 47% by value and 20% by volume). In Switzerland the ex-manufacturer price of reimbursed medicines in general should not exceed the average of the prices in Germany, the Netherlands, Denmark and the UK. Therefore, although the Irish price was not included in this study, the Swiss price is referenced to the same basket of countries as the Irish price, with the exception of France.

3.5.2 Methodological Aspects of Comparing Drug Prices

In this study, the Irish ex-wholesale price was higher than the Danish, average European and UK prices for the volume weighted price index. However, the UK price was higher than the Irish price when the unweighted average price index was calculated. These findings demonstrate the sensitivity of the results to the method of calculating the price index. The sensitivity of the results of international price comparisons to choices made about key methodological issues has been demonstrated previously by Danzon *et al.*[162, 163]. There is no generally accepted methodology on how to conduct international price comparisons, and many methodological issues remain unresolved.

In this study the impact of substituting Irish prices with the other European prices on actual drug expenditure was also calculated. The results demonstrated that overall savings would be made on the GMS Scheme if the Irish prices were substituted with the UK price. The average unweighted price per dose unit for all paroxetine preparations (Table 3.3), for example, is lower in Ireland than the UK (€0.82 vs. €0.85 per dose unit) but when the Irish price is substituted with the UK price the total expenditure on this drug on the GMS Scheme would fall by €60,000 (Table 3.4). This is because the 20mg tablet is higher in price in Ireland (€0.91 per dose unit) than in the UK (€0.86 per dose unit) but the 30mg tablet is lower in price in Ireland (€1.36 per dose unit) than the UK (€1.50 per dose unit) and a greater proportion of the 20mg tablets (80%) were dispensed than 30mg tablets (20%). From the perspective of the DoHC, the impact of pharmaceutical prices on pharmaceutical expenditure is the most relevant finding as it reflects what the State pays for medicines on the GMS Scheme in Ireland.

Andersson highlighted 6 methodological criteria which need to be met to carry out a high quality international drug price comparison: (1) selection of the appropriate comparator countries, (2) selection of a representative sample of drugs, (3) deciding on drug comparability issues (e.g. dealing with different pack sizes), (4) use of the appropriate price for comparison, (5) method of currency conversion and (6) weighting prices according to volume of use[164].

1. Selection of countries for the international price comparison

Selecting a representative sample of drugs for international price comparisons can be problematic due to the wide variation in product characteristics in the different markets such as manufacturer, dosage form, strength, brand and pack size[162]. In comparing prices

across Europe it is necessary to restrict the analysis to those items which are mutually available across all countries. However, the Euromedicines group found that only 7% of all available active ingredients were available in 14 EU countries[71]. Therefore, it would be impossible to carry out an international price comparison study on a representative sample of drugs across all the EU Member States.

The UK and Denmark were selected as the comparator countries in this study. The UK was selected because, according to the IPHA-DoHC agreement, the Irish ex-manufacturer price should not exceed the UK price. Background research for this study highlighted that the Irish price was higher than the UK price for certain drugs (i.e. omeprazole, lansoprazole and sertraline) and this warranted further investigation. Denmark was selected because it is one of the countries in the basket of countries to which the Irish price is linked. The Danish price is equal to or lower than an average European price and therefore the analysis highlights the potential savings that could be made if the Irish price was changed to an average European rather than the current Northern European price.

2. Selection of the sample of drugs for comparison

Comparisons that are restricted to identical products, in terms of form, strength, pack size and manufacturer, have been criticised because they tend to be unrepresentative of a country's pharmaceutical market[162]. On the other hand, application of less strict matching requirements enables a more representative comparison but with some loss of standardisation[167]. It is therefore generally accepted that it is necessary to strike a balance between comparing truly identical compounds and obtaining a representative sample of drugs[162]. There are many issues which need to be considered when selecting a sample for an international price comparison study, such as the inclusion of generic drugs, inclusion of drugs from different stages of the product life cycles and whether to undertake a multilateral or bilateral comparison.

Generics: In the past many studies have been criticised for focusing on small samples of leading branded products because they may not be representative of drug utilisation patterns in some countries as they exclude generic and OTC drugs. However, this is less of a problem in the Irish setting where the market penetration of generics is less than in many other countries[49]. The majority of the drugs included in the study samples were proprietary medicines (with or without a generic equivalent available). An analysis of all prescriptions dispensed on the GMS Scheme in 2003 highlighted that 80.9% of prescriptions were

dispensed as proprietary drugs (with or without a generic equivalent available)[49]. Therefore, the focus on branded products in this analysis can be considered appropriate as the study was undertaken from an Irish decision makers perspective and the majority of drugs dispensed on the GMS Scheme are proprietary preparations.

The exclusion of generics would be a more significant factor when the base country for the analysis has a large generic share of the market (e.g. the UK). The exclusion of generics biases upward the estimate of the average price level in a country with relatively high generic penetration and low generic prices[174].

***Product life cycle*:** A mix of patented and off patent medicines were included in this study. It is important to include products from different stages of their product life, since prices can vary significantly over the life of a product and this life cycle price profile differs across countries[174].

Multilateral versus bilateral comparisons: A multilateral comparison was undertaken in this study. Multilateral comparisons are more difficult to undertake because, in practice, few medicines are available in the same form and strength in all countries, resulting in the multilateral comparison being based on a much smaller sample of medicines than with a bilateral comparison. A bilateral comparison would have involved 3 separate analyses (Irish versus Danish price, Irish versus AEP and Irish versus UK price) each with different samples. The sample size for the Irish / UK analysis would have been larger as there are more preparations mutually reimbursed in these two settings. However, a multilateral comparison was undertaken because it was considered more useful to obtain results based on the same sample of drugs.

The results of this study apply to the top selling pharmaceuticals on the GMS Scheme and cannot be generalised to all pharmaceuticals that are available in Ireland. Nevertheless, the results are useful to decision makers as the sample represents 44.8% of expenditure on medicines on the GMS Scheme.

3. Drug comparability issues / Variations in pack size

The wide variation in pack sizes of products across Europe is another issue that must be considered when performing price comparison studies[82]. If only drugs with the same pack sizes were included in an analysis the sample size would be reduced dramatically. In this

study the price per dose unit was calculated to allow for this. This method may understate the prices of larger pack sizes, which may have a lower unit price[164, 174]. If prices are related positively to manufacturer and package costs, the price per unit of a small pack will be relatively higher than for a larger pack. However, in this study for the majority of preparations (82%) the pack size was identical or there was less than 10% difference in pack size.

4. Choice of pharmaceutical price for comparison

There are a number of different prices that may be compared in price comparison studies: ex-manufacturers price, ex-wholesale price or pharmacy retail / reimbursement price. Prices must be compared at the same level in the distribution chain because of the differences in distribution costs between countries. However, there is a lack of data sources for pharmaceutical prices at the different levels in the distribution chain in many EU countries[159].

The price available for this analysis was the ex-wholesale price. The main limitation of using the ex-wholesale price is that it fails to highlight at what point in the distribution chain the price difference arises, i.e. at the manufacturer level or the wholesale level. The wholesale margin in Ireland (15%) is higher than in Denmark (4–18%) and the UK (12.5%)[98]. A crude estimate of the ex-manufacturer prices may be derived by adjusting for the maximum wholesale margin in each country. For a number of drugs in the sample (e.g. omeprazole, sertraline and lansoprazole) the estimated Irish ex-manufacturer price remains higher than the price in the comparator countries. Thus, for certain drugs in the sample, the estimated savings cannot be entirely explained on the basis of the difference in wholesale margins between countries alone.

Focusing on the ex-manufacturer price eliminates differentials attributable to wholesaler margins, retailer margins and VAT. The current mechanism for setting the price of medicines in Ireland is based on the ex-manufacturer price. However, there is no official list of ex-manufacturer prices in most EU countries[159]. Therefore, difficulties arise when prices of medicines in Ireland need to be independently revised in accordance with the current IPHA-DoHC agreement. According to the agreement, the calculation of the Irish price should be based on the ex-manufacturer price in the 5 reference countries.

5. *Currency conversion*

Exchange rates play a critical role in international price comparisons. Danzon and Furukawa estimated that the decline in the Canadian dollar during the 1990s contributed to 19% of the overall 33% price difference between Canada and the US. Conversely, the appreciation of the UK pound contributed greatly to the estimated higher UK prices in 1999 compared to 1992, relative to the US[167].

In order to compare prices in this study it was necessary to convert UK pounds and Danish Krone to Euros. The most common approach is to use official exchange rates. A limitation of using official exchange rates is that they reflect short-term capital flows and fluctuate over time. Hence the results may be sensitive to the time period on which the exchange rate is based. This problem can be overcome by calculating average exchange rates over a specified period of time.

The alternative to using official exchange rates is to use purchasing power parities (PPPs), which are designed to reflect the real purchasing power of a national currency. PPPs equalise currencies to allow the purchase of the same basket of goods and services in different countries. Hence, PPPs may be appropriate to assess whether consumers are "better-off" under foreign or Irish prices. It is not certain, however, whether figures for health care PPP or general PPP should be used[159]. PPPs for health are approximate, because although they price a common basket of medical services in all countries, many items, such as a hospital admission or physician visit, represent a very different service in different countries[167]. In addition, figures for PPPs may be outdated[74, 159]. Usual practice is to use official exchange rates and in this study the average annual exchange rate for 2003 was used[164]. In addition, currency conversion is less of a problem in Europe now since the introduction of the Euro.

In addition to the issue of currency conversion, the prices used in this analysis were from 2003 and the GMS drug utilisation data available at the time of this study was from 2002. This is more likely to result in an underestimation of potential savings due to an increase in drug utilisation in 2003.

6. *Weighting prices*

The results of this study illustrate that bias may result from focusing solely on prices as opposed to considering consumption patterns as well. This was apparent because a greater

proportion of preparations had a higher unweighted price per dose unit in the UK but the weighted price index established that the Irish prices were higher. It is important to calculate a weighted average price to ensure that the results are not distorted by the inclusion of preparations that have a large price differential but a small market share.

In this study the Laspeyres price index was used to weight prices (i.e. Irish drug utilisation data was used to weight ex-wholesale prices)[162, 164]. This choice reflects the purpose of the study, which is to compare the prices for a sample of medicines reimbursable on the GMS Scheme with those obtained in comparison countries. Thus the Laspeyres index is most relevant from the Irish perspective, since it uses Irish weights and thus examines the potential cost of medicines to Irish consumers if they faced Danish, average European or UK prices. The Laspeyres index was also chosen as it has the advantage of using the base country's (i.e. Ireland) drug utilisation patterns, for which accurate data are available.

However, estimates of price differences are very sensitive to the index measure used[163]. If weights are sourced from the comparison countries, the resulting index is known as the Paasche index. This provides information on the cost implications to a comparator country if it adopted Irish prices. If pharmaceutical consumption patterns differ across countries, Laspeyres and Paasche indices will give different results when applied to the same price data. Danzon *et al.* have demonstrated that the results vary dramatically depending on the index weight employed[163]. For example, with the Laspeyres index Germany was 24.7% higher than the US, and France and the UK were 32.2% and 16.6% lower than the US, respectively. In contrast, with the Paasche index Germany, France and the UK were 60%, 67% and 44% lower than the US respectively[163]. The Paasche price index was always less than the Laspeyres price index[163]. Therefore there was a tendency for each country to appear cheaper using own weighted indices (Paasche index) rather than comparison-weighted indices (Laspeyres index). Therefore, if the Paasche index was used in this study it could be expected that the difference between the Irish price and the comparator countries would be greater than that estimated using the Laspeyres index. The Laspeyres index can be interpreted as a lower bound estimate of how much Ireland might save by adopting another country's prices. The Paasche indices would provide an upper bound estimate of potential savings[163].

Therefore the results of this study highlight that the difference in price level between countries varies depending on the methodology adopted in comparing prices. The use of

unweighted average prices is inconsistent with basic principles of index numbers and this method is extremely sensitive to the drugs included in the sample[174]. From the literature on international price comparison studies, it is clear that a more appropriate method is to weight prices by sales volumes.

3.5.3 The Influence of Pharmaceutical Rebates and Discounts

Previous international price comparison studies have been criticised because they failed to account for discounts, rebates and other factors that influence the actual price paid[181]. Discounts to pharmacists and wholesalers may vary and they are usually not recorded in any official database on drug prices[164]. Prices in some countries may be overstated by failing to account for rebates paid by manufacturers. In Ireland, according to the IPHA-DoHC agreement, the manufacturer/importer pays a 3% rebate to the GMS Scheme every month (see Chapter 1)[33]. The impact of the rebate on the cost of medicines is outside the scope of this analysis as the aim of this study is to compare the actual price of medicines in Ireland with that in other EU countries: this includes a country with one of the highest European prices and one reflecting an average European price. However, even when the 3% rebate was accounted for in the Irish price, potential savings from adopting the other price models were still observed. The estimated savings for adopting a UK price were not statistically significant.

3.5.4 Price Revisions and the Price Freeze on Medicines in Ireland

A factor that may contribute to the price differences between Ireland and the comparator countries is the price freeze on medications in this country since 1993. Many European countries have negotiated price cuts in recent years[60]. However, there is currently no system for revising drug prices in line with the countries to which the Irish price is linked. This is particularly important for drugs where Ireland is the first country of launch. In addition, a price cut in one of the reference countries may not be reflected in the Irish price. For example, a 7% reduction in the price of branded medicines was negotiated in the UK at the beginning of 2005 and a new pricing and reimbursement system was introduced in Denmark in April 2005[60, 171]. The new Danish system includes phase I reference pricing with generic substitution for off-patent medicines and free pricing for patented medicines. Therefore, Danish prices are no longer linked to the AEP. It is expected that the new system will lead to an overall reduction in the price of medicines in Denmark. Therefore, unless a system for regularly revising Irish prices is introduced, it is expected that the difference between the Irish prices and UK and Danish prices will increase.

Many European countries use cross-national price comparisons to control pharmaceutical prices including Denmark, Greece, the Netherlands and Portugal (until April 2005). However, unlike the situation in Ireland, in many countries the price is revised on a regular basis[2, 86, 87, 95, 169]. In the Netherlands, for example, the maximum price is determined twice a year by calculating the average price in 4 reference countries (Germany, France, Belgium and the UK)[86]. A new regulation was introduced in Switzerland in July 2002 where prices are reviewed 2 years after launch to enable comparison with reference countries (i.e. Germany, the Netherlands, Denmark and the UK) and a further comparison takes place at patent expiry[169].

3.5.5 Price Dynamics and Generic Markets

The greatest savings were estimated with the Danish prices, and one factor that could explain this finding is the system of generic substitution in Denmark, which leads to price competition for products with a generic equivalent on the market[182]. Magazzini *et al.* demonstrated that the dynamics of prices and the diffusion of generic products after patent expiry vary significantly across Europe[183]. In Ireland, there is a small generic market. In 2003, 11% of prescriptions were dispensed as generic drugs on the DP Scheme and 19% on the GMS Scheme[49]. Generic substitution by pharmacists is not permitted in Ireland and there are few incentives to promote the generic market. In 2003 potential cost savings from generic substitution on the GMS and DP Schemes in Ireland were estimated and ranged from €15.4 million (3.7% of total state expenditure of €413 million on the 2 schemes) to €21.8 million (5.3% of total expenditure) depending on whether the most or least expensive drug was substituted respectively (see Chapter 4)[49]. Therefore, focusing on expanding the Irish generic market could potentially lead to greater savings than altering the current pricing system for medicines.

A number of studies have consistently reported that countries with strict price regulation (e.g. France) have lower prices than countries with less stringent regulations for the pricing of new patent protected medicines (e.g. the US, the UK and Germany)[142, 163, 168, 183]. Germany and the UK have indirect control over the pricing of branded medicines. In addition, Germany and the UK are reported to have among the highest prices for medicines and the two of the largest generic markets in Europe. It has been suggested higher prices of original branded medicines can foster generic penetration and create a competitive environment in the off-patent segment of the pharmaceutical market[183]. In contrast, France has a much smaller generic market compared to Germany and the UK. Lower prices

presumably do not attract entry of generic drugs. Generic competition operates as a more effective control on prices in environments with less stringent pricing systems. Reekie (1998) demonstrated that, in markets with greater pricing freedom, competition created by generic drugs lowered the price of medicines[184]. Therefore, it appears that most countries either tend to have high prices for patented medicines and strong generic markets or low prices and a relatively smaller generic market share. In contrast, Ireland has one of the highest ex–wholesale and retail prices for medicines in Europe and also has a low generic market penetration.

3.5.6 Interdependency of Pharmaceutical Prices in Europe

The long-term impact on drug prices throughout Europe needs to be considered when negotiating a change in the current arrangement for pricing of drugs in Ireland. Many other European countries reference their prices to the Irish price, and therefore any change in the current pricing arrangement would potentially have a knock-on effect on the price of drugs in other European countries, such as Denmark. Therefore although the Irish pharmaceutical market is small compared to other EU markets, a change in the current Irish pricing system could have a significant influence on pharmaceutical expenditure in many European countries. This would be a major concern for the pharmaceutical industry and is an important consideration in any negotiations between the DoHC and the pharmaceutical industry, bearing in mind the major contribution that the pharmaceutical industry makes to the Irish economy.

3.5.7 A Single European Price for Medicines

At present pharmaceutical prices are controlled directly or indirectly by individual EU Member States. This leads to considerable heterogeneity in drug prices across Europe and also results in citizens of one Member State having access to new medicines months, or even years, in advance of those in other Member States[29]. There has been considerable debate in the literature regarding a single European price for drugs, and the G10 medicines group has suggested allowing companies to set a single European price but to have rebates based on a companies national revenues[29, 185, 186]. Such a system would benefit manufacturers as it would reduce revenue loss due to parallel import. It would mean a less complex but also more restricted European pharmaceutical market. From national perspectives, it is unlikely that a single European price would be acceptable, since willingness to pay for a drug may vary with national conditions such as relative price levels, epidemiology or patient valuations[135]. One concern, for example, is that a single

European price would be set by reference to expected EU wide demand, and not expected local demand. This could lead to disputes with countries with traditions of low prices. In addition, the issue of negotiating individual country rebates could be a lengthy process. It is therefore unlikely that there will be a single European price for medicines in the near future.

3.6 Conclusion

Conclusions about the relative prices of drugs in different countries are sensitive to the sample and methods used. Nevertheless, the results of this study confirm the high ex-wholesale price of prescription medicines in Ireland and demonstrate the potential for savings to be made on the GMS Scheme by substituting Danish, average European and UK ex-wholesale prices. There is no standard and ideal methodology for comparing pharmaceutical prices internationally and it is important to be aware of the limitations associated with the various methods when interpreting the results of these studies.

Apart from the methodological difficulties associated with international pricing studies, it is difficult to identify specific robust explanations for the observed price differences in cross-country comparisons. The price differences are probably due to a combination of factors influencing drug prices in a given market, including differences in health system structure, generic and OTC markets, patient co-payments, product mix and production costs.

Nevertheless, this international price comparison study, undertaken from the Irish perspective, has identified issues that are worthy of further consideration in future negotiations of the pricing system for medicines in Ireland. The analysis highlights areas where potential savings may be made, such as changing the current pricing mechanism and reducing the wholesale margin. The wholesale margin is higher in Ireland than in Denmark and the UK. In addition, as price cuts for medicines are a feature in other EU Member States, a mechanism for the regular review of drug prices would enable revision of prices in line with the reference countries to which the Irish price is linked. However, any change in the current Irish pricing system would potentially have an impact on the price of drugs across Europe, as many other European countries use Ireland as a reference country.

Since the results of this study were published the DoHC has commissioned the NCPE to undertake a project to estimate the impact of revising Irish prices for a sample of drugs, in line with the 7% price cut for branded medicines in the UK.

Therefore, although a change in the pricing mechanism for medicines in Ireland may not be appropriate, the results of this study may be used to facilitate negotiations between the DoHC and IPHA. In addition, the results highlight the importance of regularly revising prices in line with those of countries to which the Irish price is linked.

Consideration of alternative measures to contain drug expenditure such as expanding the generics market and demonstration of cost-effectiveness (particularly for high cost medicines or those predicted to have a significant budget impact) could potentially lead to greater savings.

Chapter 4

The Potential Impact of Implementing a System of Generic Substitution on the Community Drug Schemes in Ireland

Table of Contents for Chapter 4

4.1 Introduction

4.1.1 Expenditure on Medicines

The growth in expenditure on medicines in Ireland over the last decade is highlighted in Chapter 1. Similar increases in state expenditure on medicines have occurred across other EU Member States and various policies adopted by decision makers in an attempt to contain this rise in pharmaceutical expenditure are outlined in Chapter 2[86]. In many countries, pharmaceutical cost containment policies have included incentives and regulations to encourage prescription and/or substitution of cheaper generic drugs for more expensive original branded products[86].

4.1.2 Definition of a Generic Medicine

A generic medicine is a product with the same active ingredient, pharmaceutical form and bioequivalence as the original branded medicine. The revised EU Pharmaceutical Directive of 2004 provides an EU definition of a "generic medicinal product" and is worded as follows:

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 bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies[70].

Bioavailability is defined as the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action. Bioequivalence is defined as the absence of a significance difference in the rate and extent to which the active ingredient in pharmaceutical equivalents becomes available at the site of drug action when administered at the same dose under similar conditions in an appropriately designed study[187].

Generic medicines are "essentially similar" to, and are therefore intended to be interchangeable with, the original brand. Generic medicines may be licensed using either the INN with or without the manufacturer's name (unbranded generic) or alternative proprietary names (branded generics)[188].

4.1.3 The Economic Role of Generic Medicines

Generic medicines are typically 20% to 80% less expensive than original brands (depending on national pricing policies)[75]. In addition, the price of unbranded generics can

be significantly lower than those of branded generics[142]. The generic manufacturers do not carry out the original R&D for the products they produce and thus they do not incur the R&D costs borne by the original manufacturer. Therefore, generic manufacturers pass on to consumers the benefits of well-tried medicines at lower prices, resulting in savings to final payers.

In general, the more generics there are on the market, the lower their average price[76]. Generic manufacturers compete on price, both with the original branded product and with other generics. Therefore, an increased use of generic medicines stimulates competition. This is the reason why some generic manufacturers invest resources in establishing branded generic medicines[76].

4.1.4 Factors Influencing the Demand for Generic Drugs

There are a number of factors affecting the demand for generic drugs, such as national prescribing and dispensing traditions and specific regulatory and financial incentives offered to prescribers and pharmacists[57, 142]. The factors influencing the demand for generic drugs may be summarised as follows[57, 189-193]:

- Permitting generic substitution in various ways;
- Providing doctors with incentives to prescribe generically;
- Providing pharmacists with incentives to dispense generically;
- Exerting price controls on generic or research based manufacturers;
- Providing official publicity to prescribers and consumers in support of generics;
- Allowing or denying the right of consumers to accept generic substitutes;
- Putting in place co-payment schemes that make consumers price-sensitive and hence likely to favour less expensive medicines.

The manner in which these interventions are applied by different governments varies from country to country and this influences the level of generic penetration in individual markets.

4.1.5 Generic Substitution

Generic substitution is the process whereby pharmacists are either encouraged or obliged to dispense a generic product regardless of whether the prescription is written generically, or for a branded product[76]. This may be undertaken in one of two ways:

1. Positive substitution or a "tick-out" system, whereby a doctor must tick a box on the prescription to prevent generic substitution (otherwise generic substitution will occur automatically by default);
2. Negative substitution or a "tick-in" system, whereby a doctor must tick a box on the prescription to authorise generic substitution.

In Sweden, for example, the cheapest generic equivalent is dispensed unless the prescriber indicates on the prescription that a substitution should not be made. If the patient prefers to receive the branded product, they must pay the difference in price between the generic and the original brand[149]. Over the past five years, systems of generic substitution have been introduced in a number of EU Member States including Denmark, Finland, France, Germany, Spain and Sweden[86].

4.2 Aim

The aims of this chapter were to:

- Investigate the level of generic drug dispensing on the GMS and DP Schemes in 2003.
- Compare the level of generic drug dispensing on the GMS and DP Schemes in 2003 with that in 2001.
- Determine the potential savings if a system of generic substitution were implemented on the GMS and DP Schemes in 2003.
- Determine whether there is a potential for increased savings from generic substitution over time, by comparing the estimated savings for 2003 with estimates from 2001 for the GMS and DP Schemes.
- Establish the difference in price between original branded medicines and generically equivalent products that are reimbursed on the Irish market.
- Estimate the potential savings on the GMS and DP Schemes in 2003 if a fixed percentage reduction in the price of the original branded product was mandated on patent expiry.

4.3 Method

4.3.1 Generic Drug Utilisation on the GMS and DP Schemes

The cost and volume of drugs dispensed in all Health Board areas in Ireland in 2001 and 2003 were analysed using the GMS prescription database for the GMS and DP Schemes. The Community Drug Schemes (including the GMS and DP Schemes) are described in detail in Chapter 1. There were only 3 months data (January to March 2001) available for the DP Scheme in 2001. Therefore the results for the DP Scheme in 2001 were extrapolated from the 3 month period to a full year. The database contains information on the brand name, strength, formulation, pack size, utilisation and cost of prescribed drugs on the GMS and DP Schemes. Drugs are categorised into 4 classes on the database: unbranded generic, branded generic, proprietary drug with a generic equivalent and proprietary drug with no generic equivalent. The GMS prescription database is described in Chapter 3.

4.3.2 Potential Cost Savings from Generic Substitution

a. Sample selection

The potential savings that could be achieved by substituting the minimum, average and maximum priced generically equivalent preparation for the top 30 drugs by expenditure on the GMS and DP Schemes in 2001 and 2003 were determined. This part of the analysis was undertaken with a view to implementing a system of generic substitution in Ireland similar to the Swedish model, whereby the pharmacist is authorised to substitute a generic drug, unless the prescriber or the patient requests that a substitution should not be made.

The October 2002 and 2004 GMS product files (DMA files) were used to select medicines from the top 30 drugs by expenditure on the two schemes which had a generic equivalent available for the 2001 and 2003 data respectively. Medicines were selected from the product files using the WHO ATC classification (see Chapter 3).

Pricing and availability data for October 2002 and 2004 were used as this reflected the most up to date potential impact of generic substitution at the time the analyses were carried out. This was due to the fact that the drug utilisation data is received retrospectively from the GMS (Payments) Board. The NCPE usually receive the data from the GMS (Payments) Board five months after the medications were dispensed. However, as there has been a price freeze in Ireland on prescription medicines since 1993, the October 2004 product file reflects the same prices for all products that were available in 2003 but also includes new generic preparations which have been launched.

The analyses were limited to oral solid dosage forms (therefore no VAT was included in the calculations). If the medication was not considered to be suitable for substitution, according to guidance in the BNF, it was excluded from the analysis (e.g. mesalazine preparations should not be substituted due to varying delivery characteristics of the enteric coated formulation)[194].

b. Generic substitution groups

Products with the same active ingredient, strength and pharmaceutical form were considered generically equivalent and included in a specific generic substitution group. Oral immediate release preparations (i.e. immediate release tablets and capsules) were considered to be of the same pharmaceutical form in accordance with the EU definition of a generic medicine (EU directive 2001/83/EC)[70]. In addition, modified-release preparations were not included in the substitution groups. The composition and pharmacokinetic characteristics of modified-release preparations are more difficult to standardise compared to standard-release formulations. Therefore, modified-release preparations should be written by their brand name and no generic substitution attempted[77, 195].

c. Determination of the minimum, average and maximum prices of generic drugs

The price per dose unit for each generic preparation included in the generic substitution groups was calculated. The minimum, average and maximum generic price for each generic substitution group was then used to determine the potential savings from generic substitution.

d. Estimating potential savings from generic substitution

The total ingredient cost (+ 50% pharmacy mark-up on the DP scheme) and quantity of the drugs included in the analyses that were dispensed on the GMS and DP Schemes in 2001 and 2003 were determined. Drug utilisation data from 2001 and 2003 were analysed, as these were the most recent complete data sets available at the time of the study. The potential savings were calculated as follows:

Potential savings = Total ingredient cost (+ 50% mark-up on the DP Scheme)
- [units dispensed x (generic price per unit + 50% mark-up)].

e. Statistical analysis

The analysis was performed using Excel, SAS (SAS Institute Inc.) and SPSS. Pearsons chi-square test was used to determine whether there was a statistically significant difference in the proportion of prescriptions and the proportion of total expenditure on generic drugs between the GMS and DP Schemes in 2001 and 2003. The level of statistical significance was set at $p<0.05$ throughout.

It must be appreciated that there are some differences in the number of items dispensed and the total ingredient costs obtained from our analysis of the GMS prescription database compared to the figures presented in the GMS (Payments) Board Financial and Statistical Analysis of Claims and Payments. This is due to the different methodological procedures employed in processing the data. Such differences would not significantly alter the estimated savings outlined in this chapter.

4.3.3 Price Difference Between Original Branded Medicines and Generic Equivalents

The difference in price between the original branded medicines and the most and least expensive equivalent generic preparations was determined. The data for this analysis was obtained from the October 2004 GMS product file.

4.3.4 Potential Cost Savings from Reducing the Price of the Original Branded Medicine

This part of the analysis was undertaken with a view to implementing a system similar to the Austrian model, whereby the manufacturer must agree to a fixed percentage reduction in the price of original branded products when a generic becomes available on the market. A 20%, 25% and 30% reduction in the price of the original branded products included in this analysis was calculated. The same sample of drugs that were used to estimate the potential savings from generic substitution was used in this part of the analysis (i.e. 7 drugs on the GMS Scheme and 8 drugs on the DP Scheme). The actual price of the preparations included in the sample was substituted with the reduced prices (i.e. 20%, 25% and 30% below the price of the original brand) and the potential savings that could have been achieved on the GMS and DP Schemes in 2003 were calculated.

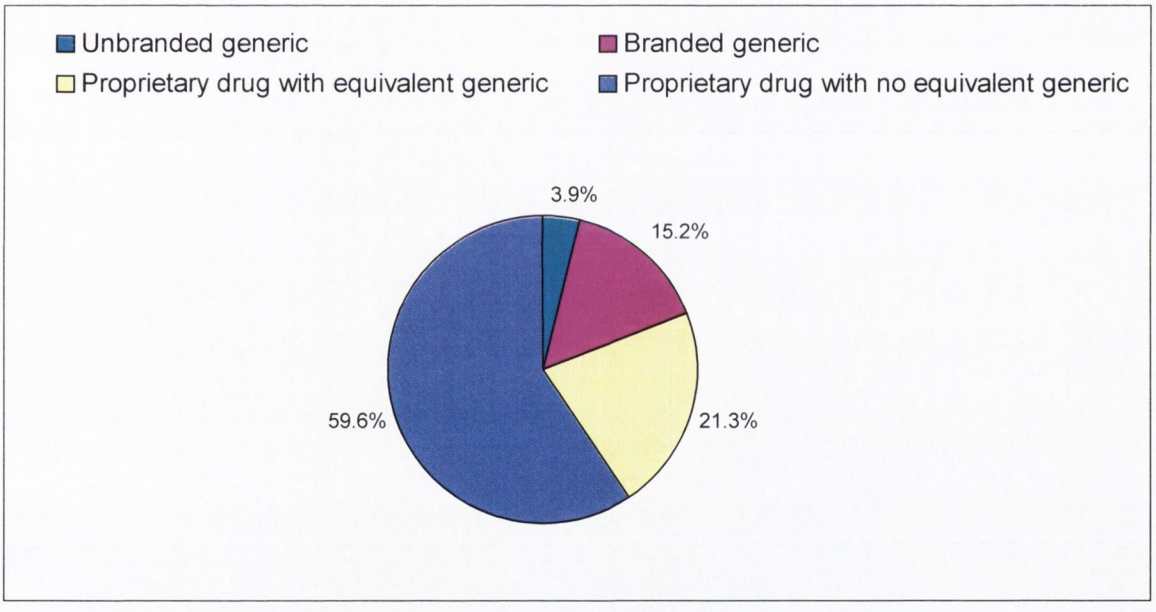
4.4 Results

4.4.1 Generic Drug Utilisation on the GMS and DP Schemes

a. GMS Scheme:

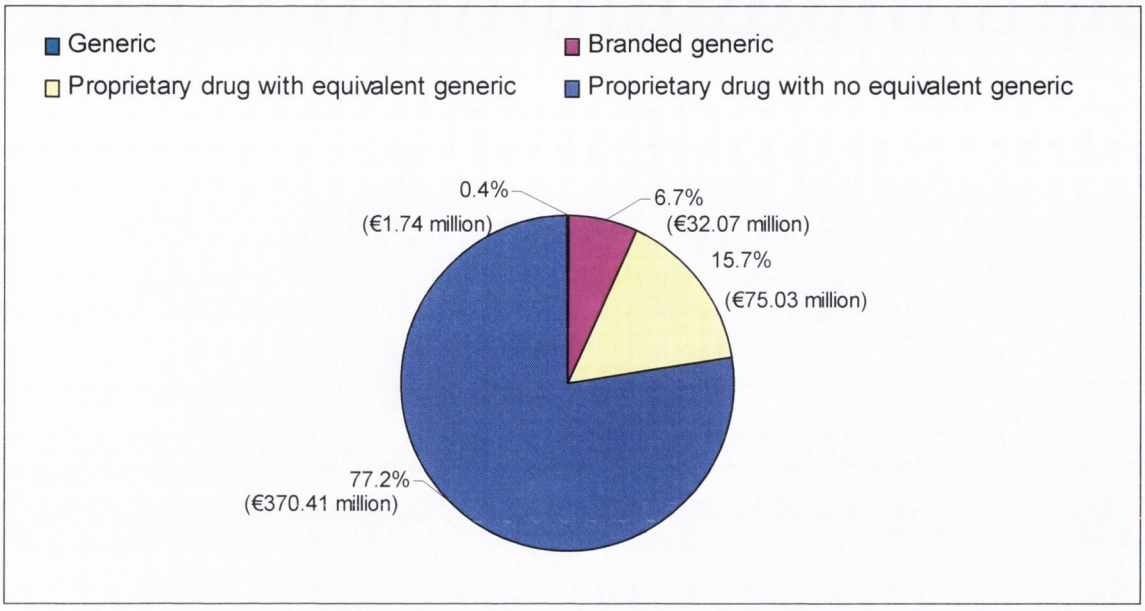
Payment to pharmacies for the GMS Scheme in 2003 was €650.66 million (this includes the total ingredient cost of medicines and a standard dispensing fee per item of €2.98 +/- 21% VAT), representing 62% of state expenditure on the Community Drug Schemes. Nineteen per cent of prescription items were dispensed generically in 2003 (branded generics, 15%; unbranded generics, 4%). Twenty one per cent of prescription items were dispensed as proprietary preparations when a generic equivalent was available (Figure 4.1).

Figure 4.1 Percentage of prescription items dispensed generically on the GMS Scheme in 2003.



Seventy seven per cent (€370.41 million) of the total ingredient cost of medications for the GMS Scheme was spent on proprietary drugs with no equivalent generic. Sixteen per cent (€75.03 million) of the total ingredient cost of medications was spent on proprietary drugs where there was an equivalent generic product available. Only 7% (€33.81 million) of the total ingredient cost of drugs on the GMS Scheme was spent on generic drugs (Figure 4.2).

Figure 4.2 Percentage of the ingredient cost spent on generic items on the GMS Scheme in 2003.

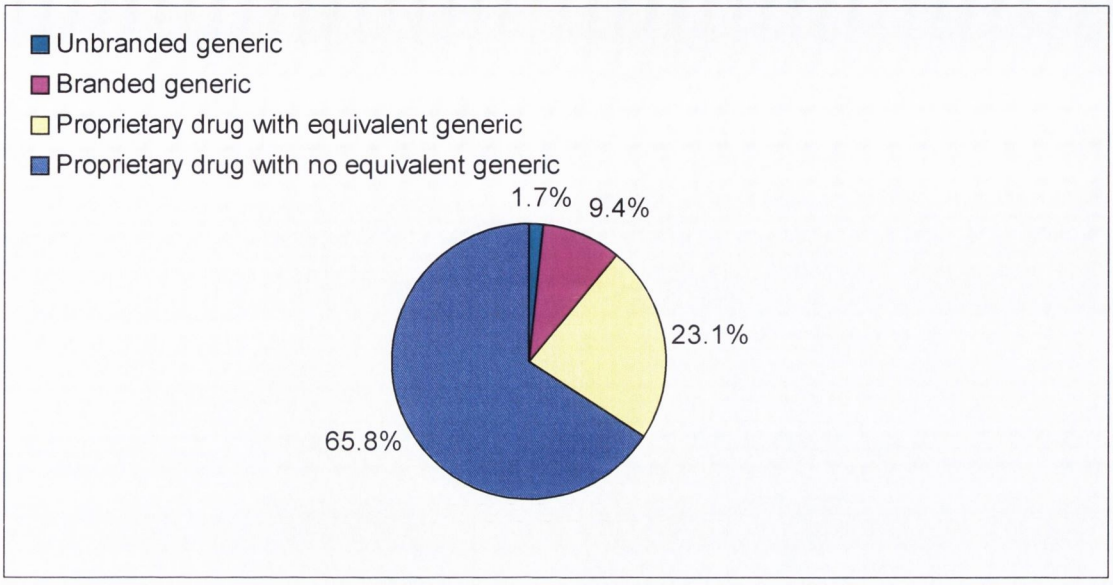


b. DP Scheme:

Payment to pharmacies under the DP Scheme in 2003 was €204.42 million (this includes the ingredient cost of the medicines, a 50% pharmacy mark-up on the ingredient cost and a standard dispensing fee per item of €2.59 +/- 21% VAT), representing 20% of state expenditure on the Community Drug Schemes for that year.

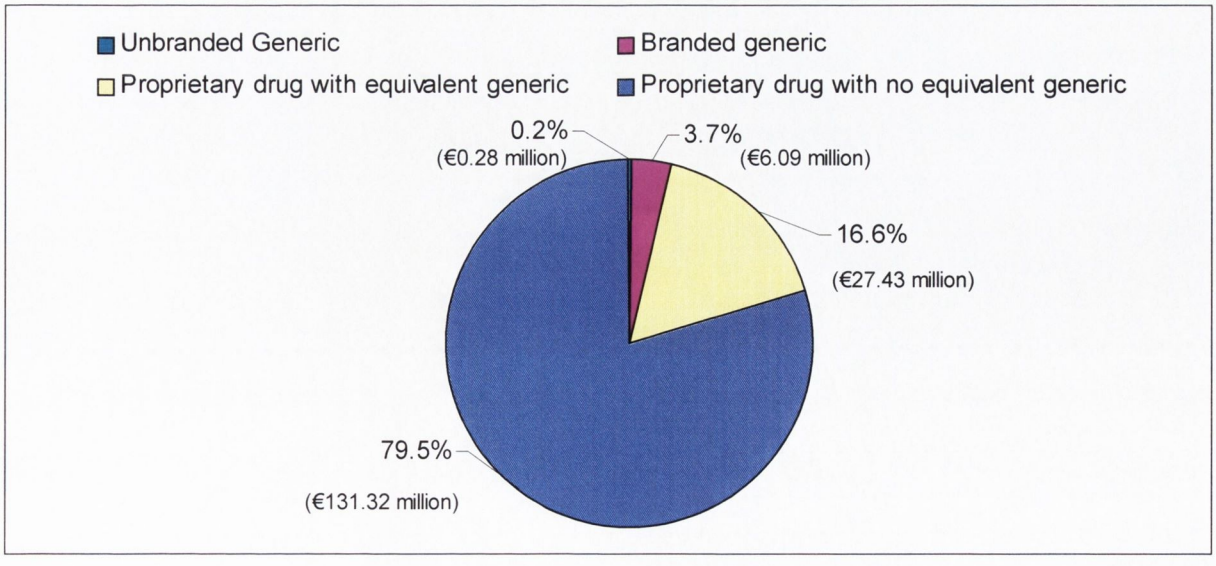
Eleven per cent of prescription items were dispensed generically in 2003 (branded generics, 9.4%; unbranded generics, 1.7%). Twenty three per cent of prescription items were dispensed as proprietary preparations when a generic equivalent was available (Figure 4.3).

Figure 4.3 Percentage of prescription items dispensed generically on the DP Scheme in 2003.



Eighty per cent (€131.32 million) of the total ingredient cost of medications for the DP Scheme was spent on proprietary drugs with no equivalent generic. Almost 17% (€27.43 million) of the total ingredient cost of medications dispensed in this period was spent on proprietary drugs where there was an equivalent generic product available. Only 4% (€6.37 million) of the total ingredient cost was spent on generic drugs (Figure 4.4).

Figure 4.4 Percentage of the ingredient cost spent on generic items on the DP Scheme in 2003.

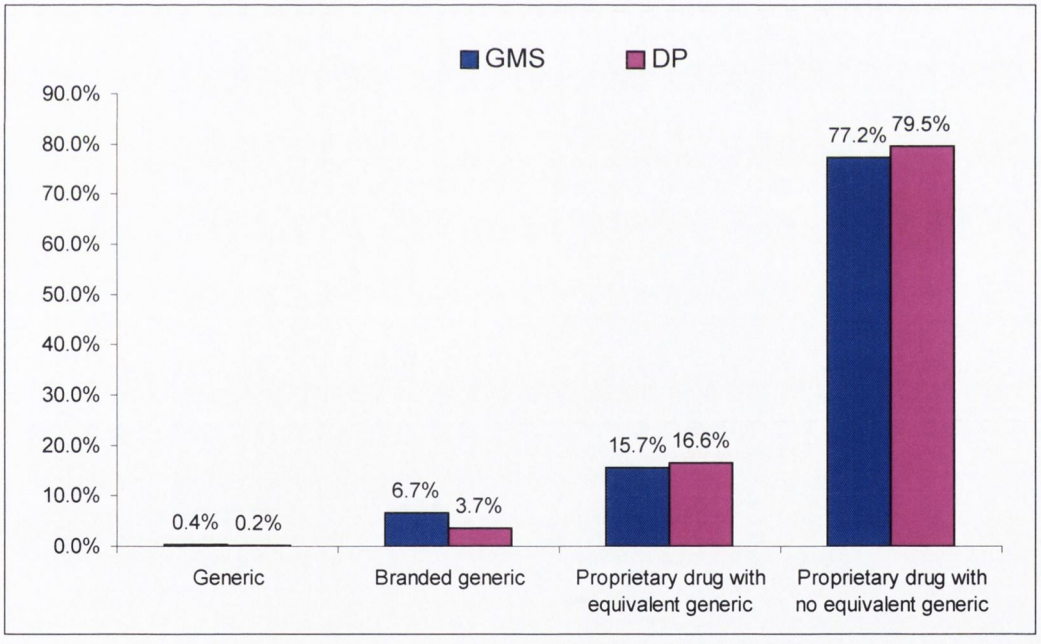


c. Comparison of generic drug utilisation on the GMS and DP Schemes in 2003

A greater proportion of generic drugs were dispensed on the GMS compared to the DP Scheme in 2003 (19.1% versus. 11.1%). A smaller proportion of proprietary drugs with and without a generic equivalent were dispensed on the GMS Scheme compared to the DP Scheme (80.8% versus 88.9%). Similar trends were observed when the proportion of the ingredient cost spent on these drugs on the 2 schemes were analysed (Figure 4.5).

Pearsons chi square test demonstrated a statistically significant difference in the proportion of generic prescriptions dispensed (p=<0.001) and the proportion of expenditure on generic drugs between the 2 schemes (p=<0.001).

Figure 4.5 Percentage of the ingredient cost spent on generic items on the GMS and DP Schemes in 2003.



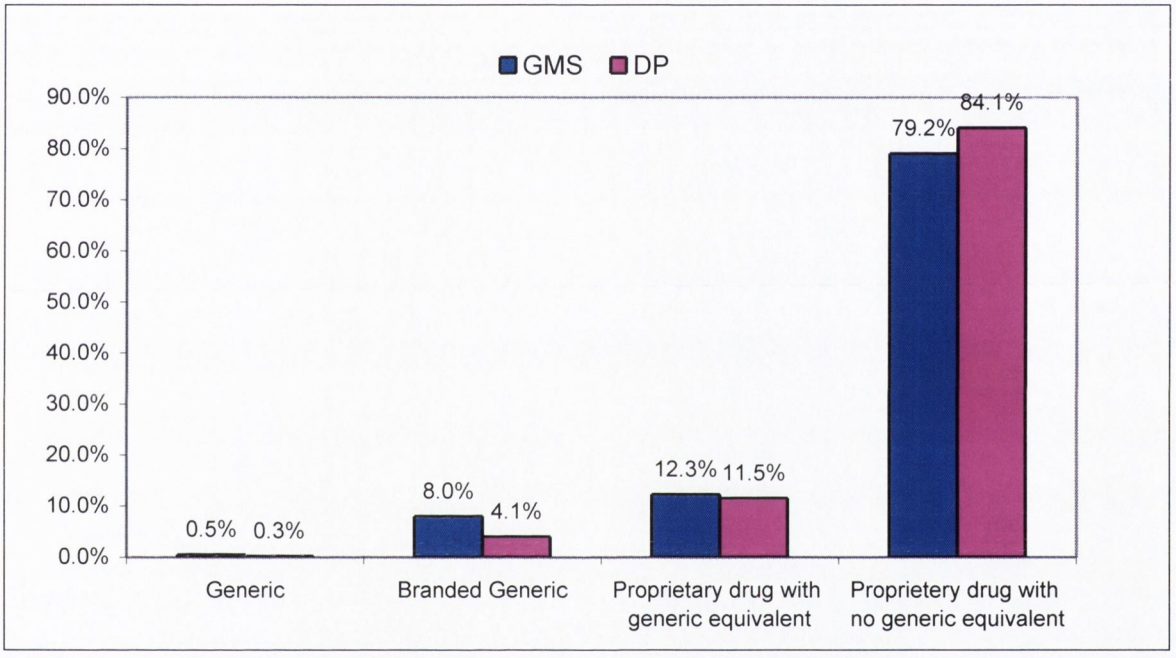
d. Comparison of generic drug utilisation on the GMS and DP Schemes in 2001

A greater proportion of generic drugs were dispensed on the GMS compared to the DP Scheme in 2001 (21.2% versus 12.1%). A greater proportion of proprietary drugs with a generic equivalent were dispensed on the GMS Scheme compared to the DP Scheme (19.5% versus. 18.7%). A smaller proportion of proprietary drugs without a generic equivalent were dispensed on the GMS Scheme compared to the DP Scheme (59.3%

versus 69.2%%). Similar trends were observed when the ingredient cost of these drugs on the 2 schemes were analysed (Figure 4.6).

Pearsons chi square test demonstrated a statistically significant difference in the proportion of generic prescriptions dispensed (p=<0.001) and proportion of expenditure on generic drugs between the 2 schemes (p=<0.001).

Figure 4.6 Percentage of the ingredient cost spent on generic items on the GMS and DP Schemes in 2001.

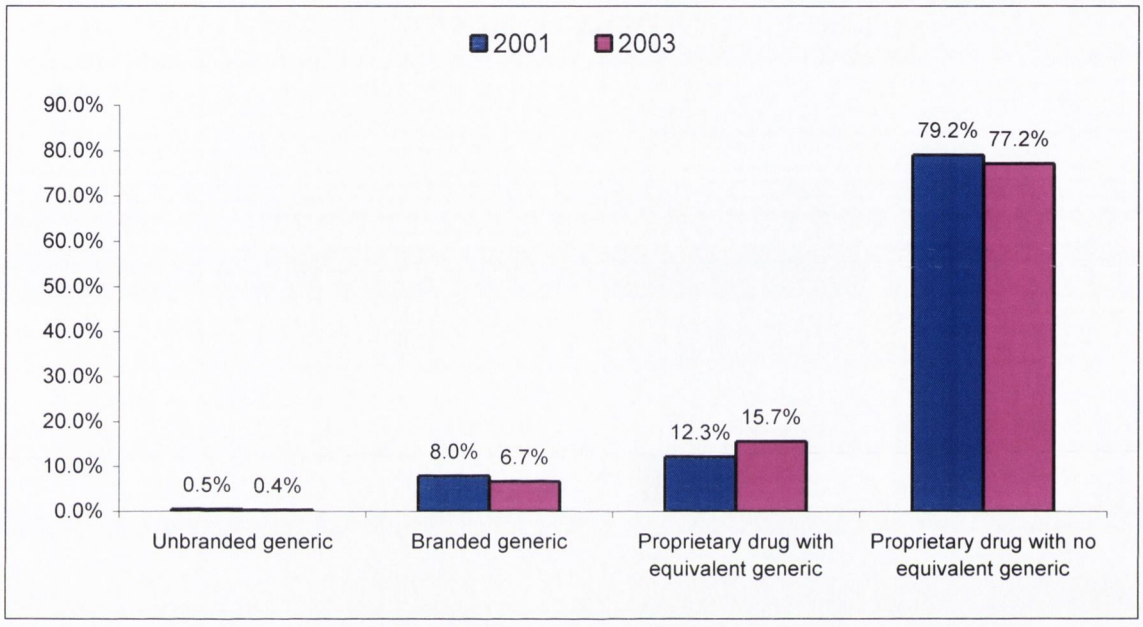


e. Comparison of generic drug utilisation on the GMS Scheme in 2001 and 2003

The total number of items dispensed on the GMS Scheme increased from 25,658,179 in 2001 to 32,240,507 in 2003 (a 26% increase)[56, 196]. Comparison of generic drug utilisation on the GMS Scheme in 2001 and 2003 illustrated that, although the total number of prescriptions for generic drugs increased during this period, a greater proportion of the total number of prescriptions was dispensed as generic drugs in 2001 compared to 2003 (21.2% versus. 19.1%). Conversely, a smaller proportion of proprietary drugs with a generic equivalent was dispensed on the GMS Scheme in 2001 compared to 2003 (19.5% versus 21.3%). Similar trends were observed when the total ingredient cost of these drugs in 2001 and 2003 were compared (Figure 4.7).

Pearsons chi square test demonstrated a statistically significant difference in the proportion of prescriptions dispensed generically ($p<0.001$) and the proportion of total expenditure on these drugs between 2001 and 2003 ($p<0.001$).

Figure 4.7 Percentage of the ingredient cost spent on generic items on the GMS Scheme in 2001 and 2003.

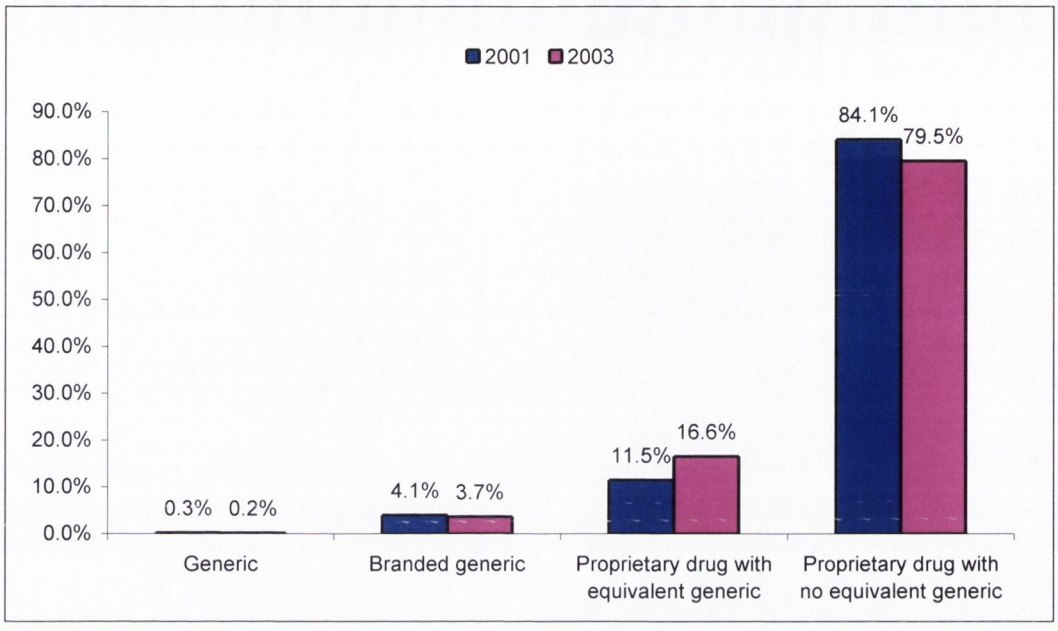


f. Comparison of generic drug utilisation on the DP Scheme in 2001 and 2003

The total number of reimbursed items dispensed on the DP Scheme increased from 8,985,460 in 2001 to 9,311,284 in 2003 (a 3.6% increase)[56, 196]. Comparison of generic drug utilisation on the DP Scheme in 2001 and 2003 illustrated that, although the total number of prescriptions for generic drugs increased during this period, a greater proportion of the total number of prescriptions was dispensed as generic drugs in 2001 compared to 2003 (12.1% versus. 11.1%). Conversely, a smaller proportion of proprietary drugs with a generic equivalent was dispensed on the DP Scheme in 2001 compared to 2003 (18.7% versus 23.1%). Similar trends were observed when the total ingredient cost of these drugs in 2001 and 2003 were compared (Figure 4.8).

Pearsons chi square test demonstrated a statistically significant difference in the proportion of prescriptions dispensed generically ($p<0.001$) and the proportion of total expenditure on these drugs between 2001 and 2003 ($p<0.001$).

Figure 4.8 Percentage of the ingredient cost spent on generic items on the DP Scheme in 2001 and 2003.



4.4.2 Potential Cost Savings from Generic Substitution

a. GMS Scheme in 2003:

The top 30 drugs by expenditure on the GMS Scheme represented 51% (€261 million) of the total ingredient cost of drugs for 2003 (Table 4.1)[196]. Seven of the top thirty drugs by expenditure on the GMS Scheme had a generic equivalent available and were included in this analysis of 2003 data (based on pricing and availability data from October 2004) (Table 4.1).

Table 4.1 **Top 30 products of highest ingredient cost to the GMS Scheme in 2003.** *(The boxes highlighted in blue represent the drugs with a generic equivalent available).*

ATC code	Drug Name	Total ingredient cost	% of total ingredient cost
	Clinical Nutrition Products	€ 22,651,788	4.4
C10AA03	Pravastatin	€ 21,437,488	4.17
A02BC01	Omeprazole	€ 21,017,146	4.09
C10AA05	Atorvastatin	€ 17,683,588	3.44
N05AH03	Olanzapine	€ 13,471,438	2.62
R03AK06	Salmeterol and other drugs for OAD*	€ 11,188,767	2.17
A02BC03	Lansoprazole	€ 10,826,542	2.1
	Ostomy/urinary devices	€ 9,637,182	1.87
B01AC04	Clopidogrel	€ 9,172,561	1.78
A02BC05	Esomeprazole	€ 8,762,179	1.7
C08CA01	Amlodipine	€ 8,722,863	1.7
	Diagnostic products	€ 7,897,928	1.54
N05AX08	Risperidone	€ 7,093,953	1.38
A02BC02	Pantoprazole	€ 6,936,108	1.35
N06AX16	Venlafaxine	€ 6,411,602	1.25
R03AK04	Salbutamol and other drugs for OAD*	€ 6,222,794	1.21
N06AB04	Citalopram	€ 6,063,547	1.18
M01AH01	Celecoxib	€ 5,843,608	1.14
R03BA01	Beclometasone (inhaled)	€ 5,730,257	1.11
C02CA04	Doxazosin	€ 5,727,768	1.11
M05BA04	Alendronic acid	€ 5,598,558	1.09
R03BA02	Budesonide (inhaled)	€ 5,520,865	1.07
C09AA05	Ramipril	€ 5,294,538	1.03
N06DA02	Donepezil	€ 5,271,613	1.02
G04BD07	Tolterodine	€ 5,253,772	1.02
N06AB05	Paroxetine	€ 4,737,505	0.92
J01CR02	Amoxicillin and enzyme inhibitor	€ 4,521,915	0.88
M01AX17	Nimesulide	€ 4,265,166	0.83
N06AB06	Sertraline	€ 4,247,962	0.83
M01AH02	Rofecoxib	€ 4,140,018	0.8
	Total	**€ 261,351,019**	**50.8**

*OAD: Obstructive Airways Disease

Annual savings from substituting the cheapest, average and most expensive equivalent generic drugs (based on preparations available on the market in October 2004) were estimated at €12.7 million, €10.9 million and €9.0 million respectively (Table 4.3). These savings represent 4.9%, 4.2% and 3.4% of the total ingredient cost of the top 30 drugs by expenditure (€261 million), according to whether the cheapest, average or most expensive generic is dispensed, respectively.

b. DP Scheme in 2003:

The top 30 drugs by expenditure on the DP Scheme represented 53% (€102 million) of the total ingredient cost of drugs under the DP Scheme for 2003 (Table 4.2)[196]. Eight of the top thirty drugs by expenditure on the DP Scheme had a generic equivalent available and were included in this analysis of 2003 data (based on pricing and availability data from October 2004) (Table 4.2).

Table 4.2 **Top 30 products of highest ingredient cost to the DP Scheme in 2003.** *(The boxes highlighted in blue represent the drugs with a generic equivalent available).*

ATC code	Drug Name	Total ingredient cost	% of total ingredient cost
C10AA05	Atorvastatin	€ 9,677,290	5.09
C10AA03	Pravastatin	€ 9,652,887	5.08
A02BC01	Omeprazole	€ 9,237,058	4.86
R03AK06	Salmeterol and other drugs for OAD*	€ 7,964,408	4.19
A02BC05	Esomeprazole	€ 4,804,565	2.53
A02BC03	Lansoprazole	€ 4,036,828	2.12
N06AX16	Venlafaxine	€ 3,939,436	2.07
G03GA06	Follitropin Beta	€ 3,676,569	1.93
	Ostomy/urinary appliances	€ 3,341,972	1.76
	Clinical Nutrition Products	€ 3,261,101	1.72
N05AH03	Olanzapine	€ 2,805,198	1.48
C08CA01	Amlodipine	€ 2,625,052	1.38
B01AC04	Clopidogrel	€ 2,570,000	1.35
N06AB04	Citalopram	€ 2,547,080	1.34
N06AB06	Sertraline	€ 2,443,118	1.29
N06AB05	Paroxetine	€ 2,206,632	1.16
A02BC02	Pantoprazole	€ 2,203,364	1.16
M01AH01	Celecoxib	€ 2,091,309	1.1
C10AA01	Simvastatin	€ 2,053,773	1.08
R03AC13	Formoterol and other drugs for OAD*	€ 2,014,446	1.06
C02CA04	Doxazosin	€ 2,010,235	1.06
M05BA04	Alendronic acid	€ 1,984,588	1.04
R03BA01	Beclometasone (inhaled)	€ 1,899,559	1
R03BA05	Fluticasone (inhaled)	€ 1,876,853	0.99
N06AB03	Fluoxetine	€ 1,863,014	0.98
A07EC02	Mesalazine	€ 1,831,850	0.96
A08AB01	Orlistat	€ 1,823,414	0.96
J01FA09	Clarithromycin	€ 1,800,492	0.95
M01AH02	Rofecoxib	€ 1,684,357	0.89
J01CR02	Amoxicillin and enzyme inhibitor	€ 1,563,425	0.82
	Total	**€ 101,489,873**	**53.4**

* OAD: Obstructive Airways Disease

Annual savings (including savings due to the 50% pharmacy mark-up) from substituting the cheapest, average and most expensive equivalent generic drugs were estimated at €9.1 million, €7.7 million and €6.4 million respectively (Table 4.4). These estimated savings represent 6.0%, 5.1% and 4.2% of the total ingredient cost (and 50% pharmacy mark-up)

for the top 30 drugs by expenditure (€152 million), according to whether the cheapest, average or most expensive generic drug is dispensed.

The results presented in Table 4.4 refer to the total ingredient cost of medicines, as well as the 50% mark-up. A similar analysis was repeated for the total ingredient cost of these drugs excluding the 50% pharmacy mark-up. Annual savings from substituting the cheapest, average and most expensive equivalent generic drugs were estimated at €6.1 million, €5.1 million and €4.3 million respectively. Therefore, approximately an additional €3 million in savings are estimated for the DP Scheme as a result of the 50% mark-up if the cheapest generic equivalent is substituted.

Table 4.3 Potential savings on the GMS Scheme for all health board areas for 2003 by substituting the cheapest, average and most expensively priced generic drug.

Drug	Total Ingredient Cost to the GMS Scheme for 2003	Cheapest generic available	Potential savings from substitution of the cheapest generic	% savings	Potential savings from substitution of the average generic price	% savings	Potential savings from substitution of the most expensive generic price	% savings
Pravastatin	€ 19,988,233	Pravitin tablets	€ 2,961,670	14.8	€ 2,961,670	14.8	€ 2,961,670	14.8
Omeprazole	€ 19,795,681	Losepine gastro-resistant tablets 10mg Lopraz capsules 20mg No generic 40mg preparation	€ 6,837,652	34.5	€ 5,138,956	26.0	€ 3,534,632	17.9
Citalopram	€ 5,621,658	Ciprapine (10mg and 20mg) and Citrol (20mg only) tablets No generic liquid preparation	€ 1,363,603	24.3	€ 1,257,661	22.4	€ 1,051,788	18.7
Doxazosin	€5,145,225	Doxatan 1mg, 2mg and 4mg tablets No generic XL 4mg and 8mg preparations	€ 214,651	4.2	€ 214,651	4.2	€ 214,651	4.2
Paroxetine	€ 4,394,011	No generic 10mg tablet Meloxat, Paroser and Parox tablets and Paxt (film coated) 20mg tablets. Paxt 30mg film coated tablets	€ 519,556	11.8	€ 519,556	11.8	€ 519,556	11.8
Amoxicillin and enzyme inhibitor	€ 4,097,453	Germentin 375mg tablets (21) Pinaclav 625mg tablets (15)	€ 419,777	10.2	€ 372,700	9.1	€ 334,479	8.2
Nimesulide	€ 3,941,811	Mesulid 100mg tabs Mesulid 100mg granules	€ 428,814	10.9%	€ 428,814	10.9%	€ 428,814	10.9%
Total	**€ 62,984,072**		**€ 12,745,723**	**20.2%**	**€ 10,894,008**	**17.3%**	**€ 9,045,590**	**14.4%**

Table 4.4 Potential savings on the DP Scheme for all health board areas for 2003 by substituting the cheapest, average and most ` expensively priced generic drug.

Drug	Total ingredient cost + 50% mark-up to the DP Scheme for 2003	Cheapest generic available	Potential savings from substitution of the cheapest generic	% savings	Potential savings from substitution of the average generic price	% savings	Potential savings from substitution of the most expensive generic price	% savings
Pravastatin	€ 12,918,073	Pravitin tablets	€ 1,916,788	14.8%	€ 1,916,788	14.8%	€ 1,916,788	14.8%
Omeprazole	€ 12,085,915	Losepine gastro-resistant tablets 10mg Lopraz capsules 20mg No generic 40mg preparation	€ 4,404,464	36.4%	€ 3,351,141	27.7%	€ 2,356,336	19.5%
Citalopram	€ 3,332,876	Ciprapine (10mg and 20mg) and Citrol (20mg only) tablets No generic liquid preparation	€ 815,446	24.5%	€ 751,877	22.6%	€ 627,833	18.8%
Paroxetine	€ 2,926,660	No generic 10mg tablet Meloxat, Paroser and Parox tablets and Paxt (film coated) 20mg tablets. Paxt 30mg film coated tablets	€ 292,665	10.0%	€ 292,665	10.0%	€ 292,665	10.0%
Simvastatin	€ 2,775,152	Simator tablets	€ 846,375	30.5%	€ 669,748	24.1%	€ 558,924	20.1%
Doxazosin	€2,683,105	Doxatan 1mg, 2mg and 4mg tablets No generic XL 4mg and 8mg preparations	€ 106,938	4.0%	€ 106,938	4.0%	€ 106,938	4.0%
Fluoxetine	€2,457,164	Biozac 20mg capsules No generic liquid preparation No generic 60mg and 90 mg capsules	€ 464,148	18.9%	€ 382,993	15.6%	€ 335,038	13.6%
Amoxicillin and enzyme inhibitor	€ 2,039,788	Germentin 375mg tablets (21) Pinaclav 625mg tablets (15)	€ 264,976	13.0%	€ 243,365	11.9%	€ 226,645	11.1%
Total	**€ 41,218,733**		**€ 9,111,800**	**22.1%**	**€ 7,715,515**	**18.7%**	**€ 6,421,167**	**15.6%**

c. Comparison of estimated savings from generic substitution in 2003 with estimates from 2001.

The same analysis was undertaken on the top 30 drugs by expenditure on the GMS Scheme in 2001. The top 30 drugs by expenditure on the GMS Scheme in 2001 represented 48% (€162 million) of the total ingredient cost of drugs that year. Ten of the top thirty drugs by expenditure on the GMS Scheme had a generic equivalent available and were included in this analysis (based on pricing and availability data from October 2002) (Table 4.5).

Table 4.5 **Top 30 products of highest ingredient cost to the GMS Scheme in 2001.** *(The boxes highlighted in blue represent the drugs with a generic equivalent available).*

ATC code	Drug Name	Total ingredient cost	% of total ingredient cost
A02BC01	Omeprazole	€ 17,315,990	5.12
	Clinical Nutrition Products	€ 14,547,510	4.3
C10AA03	Pravastatin	€ 11,227,459	3.32
N05AH03	Olanzapine	€ 7,699,129	2.27
	Ostomy/urinary appliances	€ 6,928,020	2.05
A02BC03	Lansoprazole	€ 6,596,529	1.95
C10AA05	Atorvastatin	€ 6,351,261	1.88
C08CA01	Amlodipine	€ 6,077,030	1.8
R03BA01	Beclometasone (inhaled)	€ 6,018,262	1.78
R03BA02	Budesonide (inhaled)	€ 5,004,569	1.48
N06AB05	Paroxetine	€ 4,848,196	1.43
	Diagnostic products	€ 4,828,599	1.43
N05AX08	Risperidone	€ 4,510,442	1.33
R03AK04	Salbutamol and other drugs for OAD*	€ 4,364,403	1.29
A02BC02	Pantoprazole	€ 4,244,405	1.25
R03AK06	Salmeterol and other drugs for OAD*	€ 4,125,223	1.22
M01AB05	Diclofenac	€ 3,787,938	1.12
N06AB04	Citalopram	€ 3,706,802	1.1
N06AB03	Fluoxetine	€ 3,691,297	1.09
C02CA04	Doxazosin	€ 3,532,125	1.04
J01CR02	Amoxicillin and enzyme inhibitor	€ 3,512,350	1.04
M01AX17	Nimesulide	€ 3,359,683	0.99
A02BA02	Ranitidine	€ 3,355,120	0.99
C01DA14	Isosorbide Mononitrate	€ 3,352,436	0.99
C09AA01	Captopril	€ 3,285,967	0.97
N06AB06	Sertraline	€ 3,227,473	0.95
C09AA03	Lisinopril	€ 3,176,652	0.94
R03AC02	Salbutamol (inhaled)	€ 2,983,805	0.88
N06AX16	Venlafaxine	€ 2,951,782	0.87
R03BA05	Fluticasone (inhaled)	€ 2,914,239	0.86
	Total	**€ 161,524,696**	**47.73**

* OAD: Obstructive Airways Disease

Annual savings from substituting the cheapest, average and most expensive equivalent generic drugs were estimated at €5.9 million, €4.6 million and €2.9 million, respectively (Table 4.6). These savings represent 3.7%, 2.8% and 1.8% of the total ingredient cost of the top 30 drugs by expenditure (€162 million), according to whether the cheapest, average or most expensive generic is dispensed, respectively. This demonstrates the potential for increased savings (an average of an additional €6.4 million between 2001 and 2003) to be

made over time if a system of generic substitution was implemented for the top 30 drugs by expenditure on the GMS Scheme.

Table 4.6 Potential savings from generic substitution on the GMS Scheme in 2001 and 2003.

	Minimum price of generic	**Average price of generic**	**Maximum price of generic**
2001	€5.9m	€4.6m	€2.9m
2003	€12.7m	€10.9m	€9.0m
Potential increase in savings over time (percentage increase)	€6.8m (115%)	€6.3m (137%)	€6.1m (210%)

A similar analysis was undertaken on the top 30 drugs by expenditure on the DP Scheme in 2001. The top 30 drugs by expenditure on the DP Scheme in 2001 represented 52% (€82 million) of the total ingredient cost of drugs that year. Six of the top thirty drugs by expenditure on the DP Scheme had a generic equivalent available and were included in this analysis (based on pricing and availability data from October 2002) (Table 4.7).

Table 4.7 **Top 30 products of highest ingredient cost to the DP Scheme in 2001.** *(The boxes highlighted in blue represent the drugs with a generic equivalent available).*

ATC code	Drug Name	Total ingredient cost	% of total ingredient cost
A02BC01	Omeprazole	€ 10,633,565	6.74
C10AA03	Pravastatin	€ 7,582,268	4.81
C10AA05	Atorvastatin	€ 5,185,312	3.29
R03AK06	Salmeterol and other drugs for OAD*	€ 4,603,794	2.92
A02BC03	Lansoprazole	€ 3,270,164	2.07
	Ostomy/urinary appliances	€ 3,241,875	2.06
	Clinical Nutrition Products	€ 3,064,096	1.94
N06AB05	Paroxetine	€ 2,967,143	1.88
R03BA05	Fluticasone	€ 2,580,110	1.64
N06AX16	Venlafaxine	€ 2,515,433	1.6
C08CA01	Amlodipine	€ 2,461,608	1.56
R03BA01	Beclometasone (inhaled)	€ 2,400,437	1.52
N06AB06	Sertraline	€ 2,317,907	1.47
R03BA02	Budesonide (inhaled)	€ 2,215,073	1.4
N06AB04	Citalopram	€ 2,180,331	1.38
A02BC05	Esomperazole	€ 2,001,638	1.27
A08AB01	Orlistat	€ 1,990,812	1.26
N06AB03	Fluoxetine	€ 1,981,980	1.26
A02BC02	Pantoprazole	€ 1,915,682	1.22
G03GA06	Follitropin beta	€ 1,871,414	1.19
N05AH03	Olanzapine	€ 1,792,679	1.14
C10AA01	Simvastatin	€ 1,659,751	1.05
C02CA04	Doxazosin	€ 1,640,662	1.04
J01FA09	Clarithromycin	€ 1,598,737	1.01
M01AB05	Diclofenac	€ 1,528,703	0.97
J01CR02	Amoxicillin and enzyme inhibitor	€ 1,389,945	0.88
M01AH02	Rofecoxib	€ 1,385,375	0.88
M01AX17	Nimesulide	€ 1,339,149	0.85
A07EC02	Mesalazine	€ 1,304,969	0.83
R03AK04	Salbutamol and other drugs for OAD*	€ 1,262,001	0.8
	Total	**€ 81,882,613**	**51.93**

* OAD: Obstructive Airways Disease

Annual savings (including savings due to the 50% mark-up) from substituting the cheapest, average and most expensive equivalent generic drug were estimated at €2.6 million, €2.3 million and €2.0 million, respectively (Table 4.8). These savings represent 3.2%, 2.8% and 2.4% of the total ingredient cost of the top 30 drugs by expenditure (€82 million), according to whether the cheapest, average or most expensive generic is dispensed, respectively. This demonstrates that an increase in savings of approximately €6.5 million,

€5.4 million or €4.4 million would have been achieved between 2001 and 2003, according to whether the cheapest, average or most expensive equivalent generic drug was dispensed (Table 4.8). This growth in savings over time for the DP Scheme is relatively larger than the growth rate for the GMS Scheme.

Table 4.8 Potential savings from generic substitution on the DP Scheme in 2001 and 2003.

	Minimum price of generic	**Average price of generic**	**Maximum price of generic**
2001	€2.6m	€2.3m	€2.0m
2003	€9.1m	€7.7m	€6.4m
Potential increase in savings over time (percentage increase)	€6.5m (250%)	€5.4m (235%)	€4.4m (220%)

4.4.3 Comparison of Generic Prices with Original Product Prices in October 2004.

There was an average 21.6% difference in price (median 21.1%; interquartile range (IQR) 15.0%, 29.6%) between the cheapest generic and the original branded products included in the analysis carried out on the drug utilisation data from 2003. Similarly there was an average 18.3% difference in price (median 19.4%; IQR 14.9%, 20.3%) between the most expensive generic and the original branded products included in this analysis (Table 4.9). There were a number of products with only one generic preparation available on the market including pravastatin, omeprazole 10mg, doxazosin, paroxetine 30mg and nimesulide. The generic nimesulide granules were the same price as the original brand.

Table 4.9 The percentage difference in price between the least and most expensive generic preparations and the original branded products in October 2004.

Drug	% Difference between minimum priced generic and original brand	% Difference between maximum priced generic and original brand
Pravastatin 10mg	14.5	14.5
Pravastatin 20mg	14.9	14.9
Pravastatin 40mg	14.9	14.9
Omeprazole 10mg	27.7	27.7
Omeprazole 20mg	41.9	22.1
Citalopram 10mg	21.1	19.5
Citalopram 20mg	25.0	18.9
Doxazosin 1mg	19.0	19.0
Doxazosin 2mg	19.4	19.4
Doxazosin 4mg	28.8	28.8
Paroxetine 20mg	15.0	15.0
Paroxetine 30mg	10.3	10.3
Amoxicillin and enzyme inhibitor 375mg	18.6	14.8
Amoxicillin and enzyme inhibitor 625mg	21.5	20.3
Nimesulide 100mg tabs	15.2	15.2
Nimesulide 100mg granules	0.0	0.0
Simvastatin 10mg	30.3	20.2
Simvastatin 20mg	30.5	19.9
Simvastatin 40mg	30.5	19.9
Simvastatin 80mg	30.5	30.5
Fluoxetine 20mg	25.0	19.5

4.4.4 Potential Cost Savings from Reducing the Price of the Original Branded Medicine

a. GMS Scheme in 2003:

The potential savings on the GMS Scheme by setting prices 20%, 25% and 30% below the price of the original brand were estimated at €11.6 million, €14.8 million and €17.9 million, respectively (Table 4.10).

Table 4.10 Potential savings on the GMS Scheme in 2003 by pricing 20%, 25% and 30% below the original brand.

Drug	Total Ingredient Cost to the GMS for 2003	Potential savings by pricing 20% below the original brand	Potential savings by pricing 25% below the original brand	Potential savings by pricing 30% below the original brand
Pravastatin	€ 19,988,233	€3,994,572	€ 4,994,176	€ 5,993,780
Omeprazole	€ 19,795,681	€ 3,577,288	€ 4,590,938	€ 5,604,587
Citalopram	€ 5,621,658	€ 1,115,199	€ 1,396,853	€ 1,678,506
Doxazosin	€5,145,225	€1,018,828	€ 1,274,361	€ 1,529,895
Paroxetine	€ 4,394,011	€ 801,844	€ 1,026,355	€ 1,250,865
Amoxicillin and enzyme inhibitor	€ 4,097,453	€ 409,510	€ 591,421	€ 773,969
Nimesulide	€ 3,941,811	€ 685,612	€ 889,124	€ 1,092,636
Total	**€ 62,984,072**	**€ 11,602,853**	**€ 14,763,228**	**€ 17,924,238**

b. DP Scheme

The potential savings on the DP Scheme by setting prices 20%, 25% and 30% below the price of the original brand were estimated at €7.7 million, €9.7 million and €11.8 million, respectively (Table 4.11).

Table 4.11 Potential savings on the DP Scheme in 2003 by pricing 20%, 25% and 30% below the original brand.

	Total Ingredient Cost + 50% mark-up for 2003	Potential savings by pricing 20% below the original brand	Potential savings by pricing 25% below the original brand	Potential savings by pricing 30% below the original brand
Pravastatin	€ 12,918,073	€ 2,581,596	€ 3,227,626	€ 3,873,656
Omeprazole	€ 12,085,915	€ 2,362,301	€ 2,970,027	€ 3,577,753
Citalopram	€ 3,332,876	€ 664,679	€ 831,441	€ 998,204
Paroxetine	€ 2,926,660	€ 571,525	€ 718,721	€ 865,917
Simvastatin	€ 2,775,152	€ 367,343	€ 460,014	€ 552,686
Doxazosin	€ 2,683,105	€ 534,466	€ 668,168	€ 801,869
Fluoxetine	€ 2,457,164	€ 395,201	€ 524,074	€ 652,946
Amoxicillin and enzyme inhibitor	€ 2,039,788	€ 256,076	€ 345,038	€ 434,257
Total	**€ 41,218,733**	**€ 7,733,187**	**€ 9,745,109**	**€ 11,757,288**

c. Summary of potential savings from generic substitution and from applying a fixed percentage reduction in the price of the original brand on patent expiry

A 20% reduction in the price of the original brand on patent expiry would be estimated to save €19.3 million on the GMS and DP Schemes (Table 4.12). Implementation of generic substitution using the minimum or average generic price would result in savings of €21.8 million and €18.6 million respectively, assuming 100% substitution occurs. It is seen therefore that a 20% reduction on the price of the original brand would provide savings equivalent to 100% generic substitution if a substitution price between the minimum and average generic price were adopted.

Table 4.12 Summary of potential savings from generic substitution versus application of a fixed percentage reduction to the price of the original brand on patent expiry.

Scheme	Minimum generic price	Average generic price	Maximum generic price	20% below the price of the original brand	25% below the price of the original brand	30% below the price of the original brand
GMS	€12.7m	€10.9m	€9.0m	€11.6m	€14.8m	€17.9m
DP (including 50% mark-up)	€9.1m	€7.7m	€6.4m	€7.7m	€9.7m	€11.8m
Total	€21.8m	€18.6m	€15.4m	€19.3m	€24.5m	€29.7m

4.5 Discussion

4.5.1 Generic Drug Utilisation on the GMS and DP Schemes

a. Generic drug utilisation on the GMS Scheme

The results of this study highlight that a smaller proportion of prescriptions were dispensed generically in 2003 compared to 2001 (19.1% versus 21.2%). In 1993 a study investigating the rate of generic prescribing in the GMS Scheme in Ireland reported that 17.4% of drug items were dispensed generically (branded and unbranded together)[197]. Therefore the rate of generic dispensing increased between 1993 and 2001 and subsequently fell between 2001 and 2003.

The rate of generic dispensing on the GMS Scheme in 1993 was significantly lower than Northern Ireland and England where unbranded generics alone comprised 25% and 38% respectively of total dispensing in the National Health Services in the same year[197]. The rate of generic dispensing has increased in England to 55.4% by volume and 23.7% by value in 2003[198]. In the UK, the use of generics is dependent on doctors prescribing by the generic name. A tariff price is set for generic medicines and pharmacists are reimbursed a fixed price for a generic prescription. The pharmacist is reimbursed this tariff price regardless of whether a more expensive or cheaper product was dispensed[60]. This system promotes the generic market in the UK.

However, in contrast to the situation in the UK, there are few incentives to promote the generics market in Ireland. When a GP prescribes generically, the pharmacist decides

which brand, or generic version of the drug to dispense. If a prescription bears the brand name, only the branded product should be dispensed. There is little incentive for physicians to prescribe generically because the pharmacist then has the choice of products to dispense and there are no financial incentives for pharmacists to dispense less expensive generics. Therefore, the current system tends to encourage prescribing by brand name. A trend towards generic prescribing was reported after the prescribing incentive savings scheme, the IDTS (see Chapter 1) was introduced in 1993[52]. However, as highlighted in Chapter 1, the savings achieved on the IDTS in recent years have not matched expectations and it is felt that the IDTS as currently structured has reached its limit[40].

b. Comparison of generic drug utilisation trends on the GMS and DP Schemes

A greater proportion of generic drugs were dispensed on the GMS Scheme compared to the DP Scheme during both of the periods that the analysis was carried out. In contrast a smaller proportion of proprietary drugs were dispensed on the GMS Scheme compared to the DP Scheme in 2001 and 2003. One possible explanation for the difference between the two schemes is that there is a prescribing incentive savings scheme (i.e. the IDTS) on the GMS Scheme but there is no such incentive in place for drugs prescribed on the DP Scheme. However, as described previously, the savings achieved on the IDTS in recent years have not matched expectations.

Another possible explanation for the difference in prescribing between the two schemes is that pharmacists' revenues on the DP Scheme depend on the sales price of the drugs dispensed. Therefore, there is no incentive for pharmacists to dispense a less expensive generic medicine, as this would lead to a conscious reduction of their income. In contrast, on the GMS Scheme pharmacists are paid a flat rate dispensing fee, regardless of the product dispensed.

c. Comparison of drug utilisation trends on the GMS and DP Schemes in 2001 and 2003

There was a statistically significant decrease in the proportion of expenditure on generic drugs between 2001 and 2003 on both the GMS and DP Schemes, despite the fact that more generics were available in 2003. There was a smaller proportion of expenditure on proprietary drugs with a generic equivalent available in 2001 compared to 2003 for both schemes. These results highlight the potential for increased savings to be made from generic substitution over time as a number of high cost and widely prescribed preparations

are losing patent protection and cheaper generic equivalents are becoming available on the market. However, unless an incentive is created to promote increased generic drug utilisation it is anticipated that these trends will continue in the future.

4.5.2 Potential Savings from Generic Substitution

a. Potential savings from generic substitution on the GMS and DP Schemes in 2003

The results of this analysis demonstrate the potential for savings to be made on the GMS and DP Schemes by promoting increased generic drug utilisation. The estimates of potential savings from generic substitution may be considered conservative in several important ways. Firstly, the analysis was restricted to the top 30 drugs by expenditure, which represents approximately 50% of total drug expenditure for the GMS and DP Schemes. The remaining 50% of drug expenditure covers less expensive drugs and the potential for savings in this group of drugs, although substantial, would probably be lower than the estimated savings for the sample included in this analysis. Furthermore, the analysis was restricted to solid oral dosage forms, due to a number of difficulties in substituting other formulations, such as different concentrations of syrups and the reluctance of some prescribers to prescribe inhaled drugs generically[199]. Potential savings from other formulations included in the top 30 drugs by expenditure, such as beclometasone inhalers, were not included in the estimates of potential savings.

However, the results of this study are based on the assumption that generic substitution would occur for all prescriptions where an equivalent generic drug is available. In practice, it is likely that generic substitutions will only be made for a proportion of these prescriptions. For example, during the first year of the generic substitution scheme in Sweden, only 60% of the total possible savings from generic substitution were realised[149]. If it is assumed that only 60% of savings would be realised then the potential savings from generic substitution in Ireland in 2003 would have been in the range of €5.4 to €7.6 million (2.1%-2.9% of the total ingredient cost of the top 30 drugs) on the GMS Scheme and €3.8 to €5.5 million (2.5% - 3.6% of the total ingredient cost plus 50% mark-up of the top 30 drugs) on the DP Scheme.

b. Comparison of estimated savings from generic substitution on the GMS and DP Schemes in 2001 and 2003.

There was an increase in estimated savings for the top 30 drugs by expenditure on the GMS and DP Schemes from generic substitution between 2001 and 2003. An analysis of

GMS data, undertaken by the Comptroller and Auditor General in 1996, highlighted the potential benefits of generic prescribing. It was estimated that by substituting generic drugs (at the average price) for more expensive proprietary drugs, while maintaining the same level of prescribing, annual savings of €1.65 million could be made[51]. The estimates of potential savings in 2003 are much greater than the estimates from 2001 and 1996. One explanation for this is that there are now more high cost and widely prescribed drugs on the market which are no longer protected by a patent or period of data exclusivity (e.g. omeprazole and simvastatin).

The growth in savings over time for the DP Scheme is relatively larger than the growth rate for the GMS Scheme. One explanation for this is the inflationary effect of the 50% pharmacy mark-up on the ingredient cost of drugs dispensed under the DP Scheme. Another factor could be the influence of the threshold co-payment system for the DP Scheme. The willingness of patients to accept a generic medicine may be related to the individuals co-payment towards the cost of that medicine[76, 192]. Threshold co-payment systems, such as the DP Scheme in Ireland, do not overtly favour generic medicines, but they may have that effect. Those who will exceed the threshold (€85 per month in Ireland since January 2005) are likely to ask for the more expensive branded product. Below the threshold, patients may opt for generics to save money rather than pay for a branded original[76]. The more any co-payment system sensitises consumers to the cost of prescribed medicines, the more likely it is to engage both prescribers and consumers in discussion about what is an optimal choice of product in each individual's circumstances. In some countries, for example, the patient can refuse to accept generic substitution but may be required to pay the difference in price between the prescribed medicine and the substitute medicine[60].

c. Setting a reimbursement price for generic drugs

The potential savings estimated from generic substitution of the top 30 drugs on the GMS and DP Schemes ranged from €15.4 million (€9.0 million on the GMS and €6.4 million on the DP Scheme) to €21.8 million (€12.7 million on the GMS and €9.1 million on the DP Scheme) depending on whether the most or least expensive generic preparation was substituted. Therefore, the decision of whether to reimburse a medicine at the price of the cheapest, average or most expensive generic preparation could have a substantial impact on any potential savings. For example, omeprazole was the drug of highest cost to the GMS Scheme from 1994 to 2002. The results of this study demonstrate that if the cheapest

generic preparation of omeprazole was dispensed on the GMS and DP Schemes in 2003, annual savings of €11.2 million could be made. If the most expensive generic preparation was dispensed on both schemes approximately half those savings would be achieved (€5.9 million).

4.5.3 The G10 High Level Group on Medicines

The promotion of the European generics market was strongly emphasised by the G10 High Level Group on Medicines, in its report of May 2002, which called upon Member States to introduce measures "*to secure a competitive generic market in Europe*"[200]. The G10 group emphasised the importance of achieving the balance between encouraging and rewarding the development of innovative medicines, by providing sufficient intellectual property protection, and creating a genuine market in generic medicines. At the G10 workshop on generic medicines, in January 2003, a number of key measures for promoting generic markets were recommended for implementation at national level including[75]:

- Educating doctors to prescribe using INN names;
- Assisting doctors in understanding the economic implications of prescribing decisions;
- Increasing the use of electronic prescribing;
- Creating substitution lists;
- Increasing incentives for generic dispensing and substitution;
- Improving consumer awareness of generic quality and availability;
- Adopting reference pricing and free pricing systems instead of controlled price systems;
- Reducing the time delay between receiving market authorisation for a generic product and making pricing and reimbursement decisions.

There have subsequently been a number of important changes in the revised EU pharmaceutical legislation (2004) in relation to promoting the use of generic drugs including: a new Decentralised Procedure for granting marketing authorisations, a harmonised data exclusivity period and a scientific and legal definition of generic medicines[70]. Furthermore, the new legislation will introduce a "European reference product" i.e. the legislation allows for the reference product for a generic application to come from any EU Member State, whereas previously the reference product had to be authorised in the Member State in which the generic was to be marketed[70, 201]. Therefore,

in light of the encouragement to promote generic markets at a European level, it is appropriate to explore potential ways of developing the Irish generics market.

4.5.4 International Generic Substitution Policies

A growing number of European countries have implemented generic substitution policies as a cost-saving measure with varying levels of success (e.g. Denmark, Finland, France, Germany, the Netherlands, Norway, Spain and Sweden). Finland introduced a generic substitution policy in April 2003 and is therefore the most recent EU Member State to implement such a system. The Social Insurance Institution of Finland reported that the amount saved approximated to 5.8% of the total cost of reimbursed medicines during the first year (April 2003 to March 2004) of introducing the scheme[145]. The results of this Irish study demonstrated the potential for savings of a similar magnitude (4.9% and 6.0% of the total ingredient cost of the top 30 drugs by expenditure on the GMS and DP schemes, respectively). However, the savings estimated for Ireland assume 100% substitution whereas in Finland substitution was refused in approximately 11% of cases. Furthermore, the amount saved in Finland fell to 1.7% of the total cost of reimbursed medicines during the second year of the scheme (see Chapter 2).

There have also been examples of substitution schemes which have had a low impact for a variety of reasons including a lack of incentives for doctors / pharmacists to substitute a generic drug e.g. Germany[147]. Under the *"aut idem"* (generic substitution) regulation, which was introduced in Germany in 2002, pharmacists were obliged to dispense drugs from the cheapest third of the price range of generic equivalent drugs, unless the prescriber prohibited this by marking the *aut idem* box on the prescription[147, 202]. The actual savings from the *aut-idem* regulation were less than expected and were estimated to be in the range of €45 million in 2003 (approximately 0.25% of pharmaceutical expenditure)[203]. Doctors resisted the *aut idem* regulation, maintaining that it was introduced too hastily, that it eroded doctors' authority and that certain groups of patients may be clinically vulnerable to sudden changes in their medicines[204]. In addition, various strategies were adopted by the pharmaceutical industry to circumvent the regulation e.g. price cuts and increases were made to optimally position products[203, 204]. Furthermore, at this time the pharmacy margin was only slightly regressive and still penalised generics[142].

An assessment of the generic substitution scheme in Sweden, during the first year of its implementation (2002), demonstrated that the actual savings achieved in practice were on

average 60% of the total possible savings and were largely dependent on the extent to which the pharmacies kept the cheapest brand in stock[149]. However, this study demonstrated that the majority of prescribers and patients accepted generic substitution in Sweden, indicating that it has been well implemented in practice[149].

In France, initial efforts to promote the generics market depended essentially on physicians choosing to prescribe generically and on patients' willingness to accept generic medicines. This has been one of the rare attempts to develop the generics market without initiating various regulatory incentive plans. In comparison with other countries, it has been reported that this method may have slowed the development of the generic market in France[205]. More recently, several tools aimed at prescribers, pharmacists and patients have been introduced in France to promote the use of equivalent cheaper generics. In 1999, for example, pharmacists obtained the right to substitute original brands with a corresponding generic [206]. Furthermore, the pharmacy mark-up and discounts to pharmacies were modified so that pharmacists generated, on average, higher profits by dispensing generic drugs as opposed to original brands[206]. Since 2002, GPs have been required to prescribe a certain proportion of their prescriptions by the INN, in return for a fee increase. In 2003, a reference price system was introduced whereby patients make a co-payment when they request the brand name drug instead of the generic[205]. Consumption of generics has been reported to have almost doubled over the past 3 years (2002-2005), with generics now accounting for 6% of total French community pharmacy sales[206, 207]. However, the objective of the French government to reach at least 50% generic penetration is far from being achieved[206].

Generic substitution policies have also been adopted in other countries outside Europe, including Australia and the US. In Australia, McManus *et al.* demonstrated the success of the introduction of the Minimum Pricing Policy which involved generic substitution by pharmacists[208]. Under this system, the government reimburses a drug at the price of the cheapest generic equivalent and patients may still receive a preferred brand name drug on payment of the cost differential[208, 209]. Introduction of the generic substitution policy at the pharmacist level, resulted in a marked increase in the percentage of items dispensed at the lowest price level[208].

Since the 1980s, almost every state in the US has enacted laws to allow and in some cases mandate generic substitution[210]. A study undertaken by Mott and Cline using prescription

data from a Midwestern state in the US (2002), reported that more than 60% of prescriptions were written for drugs that allowed the opportunity for generic drug use and 83.8% of these prescriptions were generically substituted[211]. They found that generic substitution was significantly more likely for prescriptions for acute conditions relative to chronic conditions and significantly less likely for patients who had previously taken the original brand. Two recent studies carried out in the US have estimated the potential savings from increased use of generic drugs[212, 213]. In 2004, Fischer and Avorn reported that there were unrealised annual savings, that could be achieved from more widespread use of generic drugs, of $3.4 million (3.6% of total drug expenditure) in the Medicaid program (this is a program that pays for medical assistance for certain individuals and families with low incomes and resources in the US) studied and $13.7 million (9.5% of total drug expenditure) in the non-Medicaid drug insurance program for the elderly[212]. In 2005, Haas *et al.* estimated that a policy of switching from branded to generic drugs whenever possible could save approximately $8.8 billion, or approximately 11% of drug expenditure for the adults included in this nationally representative sample in the US each year[213]. These estimates are higher than the estimates for the Irish setting and one explanation for this may be the greater difference in price between generic drugs and the original brand, in the US compared to Europe[214].

4.5.5 Potential Barriers to Promoting the Irish Generic Market

There are a number of potential barriers to promoting generic drug utilisation in Ireland, such as the acceptability to patients of switching from a branded to a generic preparation, concerns with the quality of generic medicines, a potential negative impact on the pharmaceutical industry and a lack of incentives for prescribers and pharmacists to use generic drugs. The potential barriers to promoting the Irish generic market may be summarised as follows:

a. Patient Acceptability

Generic drugs usually differ in appearance from the original branded equivalent, and if there is more than one generic equivalent available they may differ from one another. The colourants, excipients (i.e. inactive ingredients which are added to a drug formulation, usually to provide stability or bulk), size, and shape may differ considerably from the branded product. These differences can result in anxiety and uncertainty for patients and may occasionally result in a patient taking two formulations simultaneously[215]. It has also been demonstrated that patients believe generic prescription drugs are less safe and

effective than brand name prescription drugs[216]. However, acceptability of a generic product may be increased if the reasons behind the substitution are explained and reassurances about the quality assurance and therapeutic equivalence are given[188].

A multicentre study undertaken in Spain assessed patients' acceptability of the substitution of brand name drugs for generic drugs and reported that individual educational intervention resulted in a high rate of generic acceptability. Although the study was carried out in Spain, the authors state that it is valid for many other primary healthcare systems[217]. However, in certain cases, no amount of reassurance will convince some patients that a generic medicine, or an alternative brand, is equivalent to their previous medication. Prescribing a branded product may be the only way to ensure that such patients continue to take their medication as directed[199].

b. Implications for the Pharmaceutical Industry

While an increase in generic prescribing can generate savings for healthcare systems, the effect this may have on innovation in the pharmaceutical industry has been highlighted repeatedly[215]. The pharmaceutical industry in Ireland makes a major contribution to the economy in terms of investment and employment. Ireland is the world's largest pharmaceutical exporter, with net exports exceeding €13.3 billion annually[30]. Employment in the sector has grown from 5,200 in 1988 to 21,000 in 2004[30, 218]. Therefore, any considerations to promote the Irish generic market will be affected by the relative importance of the proprietary pharmaceutical industry in Ireland.

Nevertheless, recent thinking demonstrates that the concept that any form of competition from generic medicines has a negative impact on originator pharmaceutical companies, is far from the truth. Competition can be a major stimulation to innovation. This is seen in the US which is the country with the highest rate of global pharmaceutical innovation and also the world's largest generics market[75].

c. Concerns with the Quality of Generic Medicines

Manufacturers of generic medicines are required to show "essential similarity" to the original branded drug i.e. that the product is of the same pharmaceutical form and has the same quality and quantity of active ingredient. They are required to show that the preparation is bioequivalent to the original brand[219]. Typically, tests of bioequivalence are carried out in groups of 18 to 24 healthy adult male and female volunteers aged 18 to 55

and of normal body weight[77, 220]. Products are tested in a crossover design and usually in single-dose studies[77]. In general, therapeutic equivalence is assumed once the drugs have been shown to be bioequivalent[195, 221]. Therapeutic equivalence indicates that comparable clinical efficacy and safety has been demonstrated[222]. There is no requirement for therapeutic equivalence to be demonstrated in order to obtain generic drug approval[222].

A number of controversial issues associated with bioequivalency testing have been raised, which include[222]:

- Applicability of young, healthy volunteers to a target population who are likely to deviate markedly from this ideal (concomitant diseases, old age, children, polypharmacy);
- Extrapolation of single dose studies to a steady state, particularly with long half-life drugs;
- Testing under fasting conditions;
- Effects (pharmacological or adverse) of excipients.

These issues and concerns continue to undermine patients' and healthcare providers' confidence in generic products[77]. In Ireland, in order to obtain a product authorisation (PA) the generic manufacturer must satisfy the Irish Medicines Board (IMB) that the bioavailability of its product matches that of the original brand.

d. Potential resistance at the prescriber and pharmacy level

As mentioned at the beginning of this discussion there are a lack of incentives for pharmacists to dispense generic drugs and for doctors to prescribe generically. The results of a GP survey published in 1997 found that GPs in Ireland were concerned about the reliability and quality of generic products on the market, possible legal liabilities associated with their use and the fact that pharmacists could legally dispense more expensive proprietary preparations in the case of private prescriptions written generically[197]. In addition, there are also regulatory hurdles precluding generic substitution at the pharmacist level and a lack of financial incentives to encourage pharmacists to dispense less expensive generics.

Therefore, there are many potential barriers to promoting the generic drug market in Ireland.

4.5.6 Pricing of Generic Drugs

If cost savings are to be made by increasing the use of generic medicines, then it is important to address not only how to increase volume, but also how to decrease the price of these drugs.

The average difference in price between the most expensive generic and the original brand, for the sample of drugs included in this analysis, was 18.3% (range 0% to 30.5%). In some countries, the generic manufacturer is free to increase or decrease the price at will and thus the prices are determined by market forces[76]. In other countries, the reimbursement price of an original brand is reduced when a generic is launched. In Austria, for example, when a generic becomes available the manufacturer must agree to a 30% discount on the original brand and generic drugs are priced below the price of the originator product[60]. In countries with reference price systems the manufacturer may reduce the price of the original brand in line with the reference price[76]. In some countries there is a requirement for the generic price to be a fixed percentage below the price of the original brand. In Portugal, for example, generics are required to be priced 35% below the original brand[151, 223]. Similar measures in the Irish setting would lead to greater savings from increasing generic drug utilisation.

4.5.7 Potential Cost Savings from Reducing the Price of the Original Branded Medicine

The estimate of savings from reducing the price of the original brand are conservative as this price was applied to all products dispensed. In reality some generic dispensing would occur and the generics would most likely be priced below the discounted original brand price.

The results of this analysis demonstrated that a 20% reduction in the price of the original branded product would lead to similar savings that would be achieved with 100% substitution at the minimum / average generic price. Experience from other countries, such as Finland and Sweden, highlights that a 100% generic substitution rate would most likely not be achieved in practice[145, 149]. Many European countries have implemented generic substitution policies with varying degrees of success. It is clear from the experience of these countries that such policies need to be supported with other regulatory measures to promote the use of generic drugs. Appropriate incentives for pharmacists to dispense

generic drugs, for prescribers to allow generic substitution by pharmacists and for patients to accept generic drugs would need to be introduced.

In contrast, a fixed percentage reduction in the price of the original brand would provide guaranteed savings without the need to introduce such incentives and regulatory changes. In addition, reducing the price of the original brand could enhance further savings from generic drugs, as it would be necessary to reduce their price below the originator product. This is of importance because the price of some generic medicines are set just below (<15%) the price of the original brand (Table 4.9).

4.5.8 Implications for Decision Makers

Although this study demonstrates the potential for savings to be made from promoting generic drug utilisation, it does not account for the costs associated with implementing such a system e.g. administration costs and public educational campaigns. There are also wider implications which need to be considered including the controversies associated with the issue of generic substitution.

Substitution of generic drugs for brand name products is controversial for a number of reasons. Concerns arise from the fact that the development of generic products does not require large or extensive trials in patients for claimed indications. This has lead to the belief that generic products are potentially inferior to their branded counterparts. Public confidence was further undermined following the generic drug scandal in the US in 1987, in which the US FDA approval of a number of generic drugs was shown to be fraudulent[77]. In 1992, attempts were made to re-establish the credibility of the generic drug market with the introduction of legislation that enforces stricter monitoring of product quality and bioequivalence[81]. However, there is still debate over the appropriate circumstances in which to substitute a brand name product with a generic alternative[77].

The issue of the acceptability of generic substitution to patients must also be considered. A study was carried out in 1994 to investigate what would happen to prescribing patterns over a 6 month period when patients had their repeat prescription changed from branded products to generic drugs. Patients did not receive prior notification but a note was attached to the first repeat prescription explaining that although the drug might look different it had not actually been changed. Six months later, 90.5% of patients were still taking the generic drug but 9.8% of patients stopped taking the drug completely[224].

Furthermore, this study does not account for the effect generic substitution would have on patient compliance. In addition, a recent study in Sweden showed a positive relationship between generic market shares and reported side-effects[225]. Therefore, further research should be aimed at investigating the cost-effectiveness of implementing a system of generic substitution by accounting for the effect on patient outcomes, as well as the potential cost savings.

An alternative option for decision makers would be to mandate a reduction in the price of original branded medicines post patent expiry. Such a system would ensure value for money as the DoHC would not continue to pay a premium price for medicines whose patent has expired.

Furthermore, there is a limit to the potential savings that may be generated from generic substitution because the majority of expenditure on the GMS and DP Schemes is on proprietary drugs, which are still protected by patent. Greater savings could potentially be realised by focusing on promoting the cost-effective prescribing of high cost patent protected medicines.

4.6 Conclusion

The results of this study demonstrate the potential for savings to be made from introducing a system of generic substitution. However, the current system in Ireland offers few incentives to promote the generic market.

Many EU countries have implemented policies to promote generic substitution with varying degrees of success. It is clear that generic substitution policies are rarely implemented without other regulatory measures to promote the use of generic drugs. If policy makers wish to promote the generics market in Ireland, it appears from the experience of other countries that, implementation of a generic substitution policy alone may not be sufficient. Decision makers would also need to consider introducing appropriate incentives for pharmacists to dispense generically, for prescribers to allow generic substitution by pharmacists and for patients to accept generic drugs. Therefore, although promotion of the Irish generics market to ensure the State is only paying high prices for patent protected medicines is recommended, any reforms should be considered with a careful analysis of the consequences for patients, healthcare professionals, the pharmaceutical industry and the public purse.

Chapter 5

The Value of the GMS Prescription Database in Determining Utilisation of and Expenditure on Pharmaceuticals: an Example Using Nicotine Replacement Therapy

Table of Contents for Chapter 5

5.1 Introduction

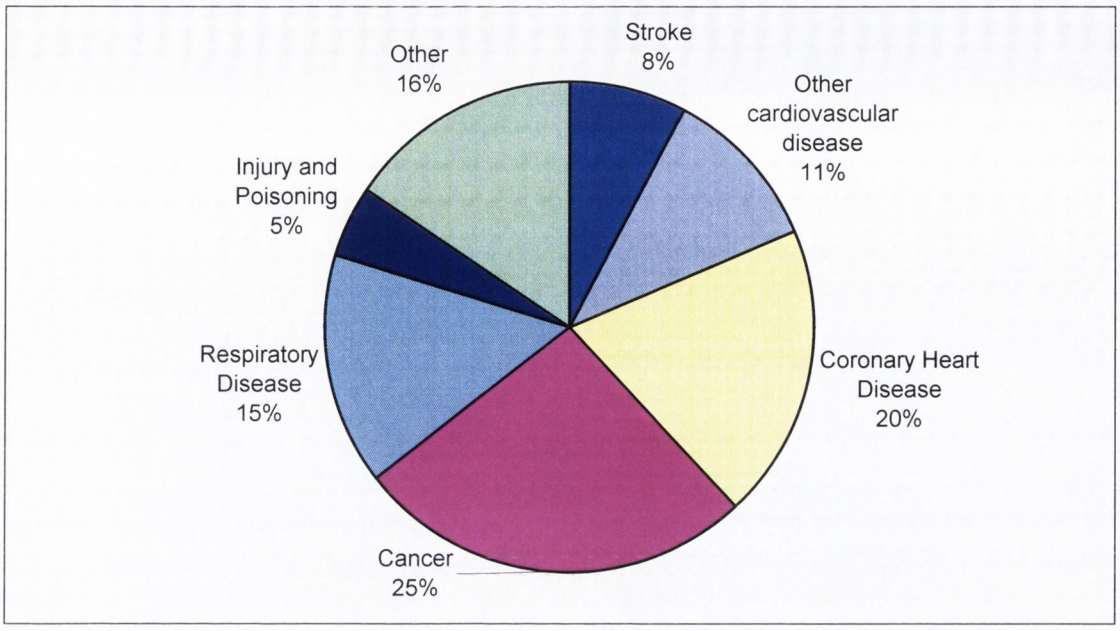
5.1.1 Background

In this chapter the value of the GMS prescription database in determining prescribing rates, monitoring quality of prescribing and assessing utilisation of and expenditure on reimbursed medicines is explored. Nicotine Replacement Therapy (NRT) is used as an example.

Smoking is the largest single preventable and treatable public health problem, leading to disease and premature death in many individuals. NRT is considered to be among the most cost-effective of all healthcare interventions[226]. However, although NRT preparations have been available for over 20 years, they have been excluded until recently (i.e. April 2001) from State reimbursement in Ireland and many other countries. There has been little research as yet into the prescribing patterns of these drugs in Ireland, since the time of their inclusion on the GMS reimbursement list. This research was conducted in response to a request from DoHC, who were considering whether the reimbursement of NRT on the GMS Scheme should continue. This was undertaken at the time when the ban on smoking in all workplaces in Ireland was being implemented. Ireland was the first country in the EU to implement a ban on smoking in all workplaces.

Smoking is a global epidemic and poses a significant challenge to healthcare systems. In the EU, more than 500,000 citizens die prematurely each year as a result of smoking, some 7,000 of them in Ireland[227, 228]. The report from the Cardiovascular Health Strategy Group (1999) "*Building Healthier Hearts*" highlights the fact that smoking is the largest single cause of preventable mortality and morbidity in Ireland[25]. Cardiovascular disease is the single largest cause of death in Ireland, followed by cancer and respiratory disease (Figure 5.1).

Figure 5.1 Principal causes of death at all ages, Ireland 2003.



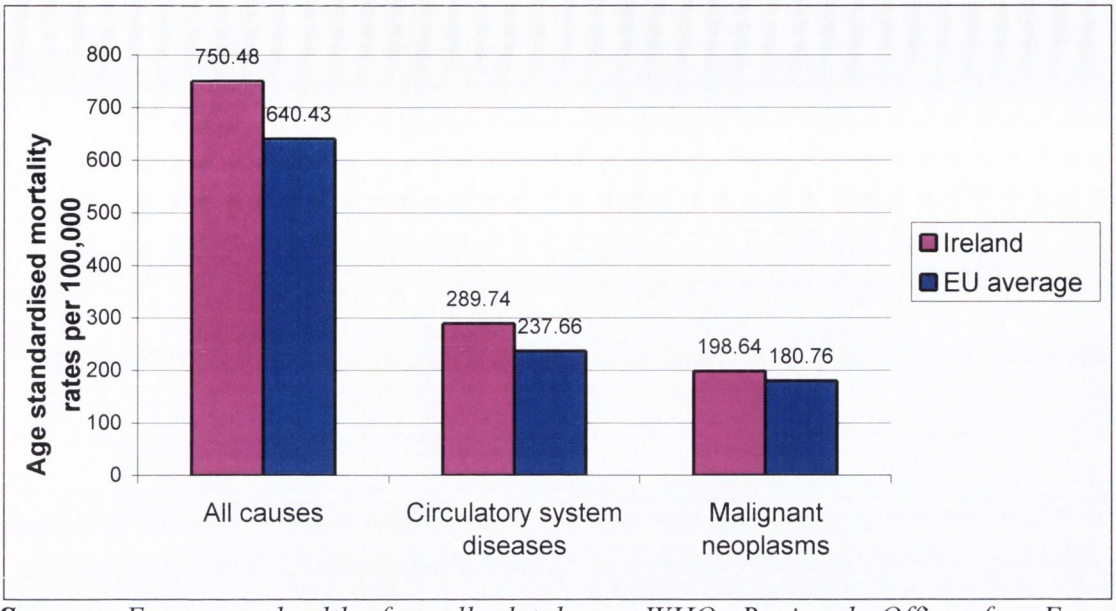
Source: *Central Statistics Office, http://www.cso.ie.*

The causative relationship between smoking and cardiovascular disease, cancer and respiratory disease is well established[229]. In addition, there is evidence that passive smoking causes illness and premature loss of life, at all ages from the prenatal period to late adult life. A recently published (2005) large prospective study highlighted that exposure to environmental tobacco smoke is associated with increased risks of lung cancer and other respiratory diseases, in former smokers and those who have never smoked[230].

5.1.2 Life Expectancy in Ireland

Life expectancy in Ireland is lower than the EU average[231, 232]. Data from 2001 illustrate the higher mortality rates in Ireland compared to the EU average (Figure 5.2). The rate of mortality from circulatory system diseases, for example, is 290 per 100,000 population in Ireland compared to the EU average mortality rate of 238 per 100,000. Malignancy and circulatory system diseases can occur as a direct consequence of smoking. Therefore, strategies aimed at reducing the prevalence of smoking in Ireland would be expected to result in increased life expectancy for both smokers as well as non-smokers.

Figure 5.2 Mortality rates in Ireland compared with the EU average in 2001.



Source: *European health for all database, WHO Regional Office for Europe, Copenhagen, Denmark.*

5.1.3 Smoking Prevalence in Ireland

There is a high prevalence of smoking in Ireland. Two baseline surveys of health related behaviours among adults and school-going young people were undertaken by the Department of Health Promotion, University of Galway, in 1998 and in 2002. The Survey of Lifestyles, Attitudes and Nutrition (SLÁN) focused on adults over 18 years of age and the Health Behaviour in School-aged Children (HBSC) focused on school-going children aged 10-17 years[233, 234]. These studies provide information on the prevalence of smoking in Ireland.

A representative cross-section of the Irish adult population was surveyed for the SLÁN study in 1998, with a follow-up in 2002. The sample was generated randomly from the electoral register. The results of the surveys highlighted a fall in the overall prevalence of smoking between 1998 and 2002. In 2002, 27% of the adult population reported being regular or occasional cigarette smokers compared with 31% in 1998. Marked age related patterns exist among both men and women, with highest smoking rates among younger people (Table 5.1). The first SLÁN Survey (1998) identified the high prevalence of smoking in women and particularly, in teenage girls. The second SLÁN Survey (2002) has shown that across all demographic categories smoking rates have fallen but this trend has been most marked among young women. There is also an inverse relationship with level of education and socio-economic status[233, 234]. Smoking prevalence differed significantly

between GMS and non-GMS respondents. In 2002, 37% (42% in 1998) of those with a medical card reported smoking regularly/occasionally compared to 24% (30% in 1998) of those without a medical card[233].

Table 5.1 Percentage prevalence of smokers in the general population by age and gender[233, 234].

Age	Male		Female		Total	
	1998 (n=3027)	**2002** (n=2330)	**1998** (n=3414)	**2002** (n=3354)	**1998** (n=6441)	**2002** (n=5684)
18 – 34 years	38%	35%	40%	33%	39%	34%
35 – 54 years	32%	26%	29%	25%	30%	25%
55 + years	22%	19%	18%	16%	20%	17%

The HBSC, was a World Health Organisation (European) collaborative study. Sampling was conducted in order to be representative of the proportion of children in each Health Board. Among school-going children, 19% reported that they were current smokers in 2002 compared with 21% in 1998. The most notable finding of this study was the drop in reported smoking prevalence rates in the 12 to 14 year age group[233].

More recently, the Office of Tobacco Control has reported that the overall prevalence of cigarette smoking has declined to 24.1% of the overall population in November 2004[235]. Therefore, there is a high prevalence of smoking in Ireland, although recent figures show that it is falling.

5.1.4 Benefits of Smoking Cessation

Half of all smokers die prematurely of a smoking-related illness. Stopping smoking, even after many years, has major health benefits[236-238]. Smokers who quit before the age of 30 years have a life expectancy only slightly less than those who have never smoked[229]. Even cessation in middle age improves health and substantially reduces the excess risk of death[229, 239]. Quitting at any age provides both intermediate and long term health benefits. However, in general, less than 3% of attempts to quit result in sustained (12 months) cessation, though the chances of success are slightly higher in women of childbearing age, parents of young children, and spouses of non-smokers[240].

In addition to the most obvious health benefits of smoking cessation, there are also wider economic benefits. Smoking imposes a significant economic burden on society, accounting for up to 15% of total healthcare costs in developed countries[241].

5.1.5 Smoking Cessation Strategies in Ireland

A key focus of health promotion activity in Ireland in recent years has been in the area of smoking cessation[242]. A number of measures have been introduced to reduce the prevalence of smoking in Ireland including government health promotion strategies, increases in the price of cigarettes, media campaigns and a ban on smoking in all work places. The introduction of these measures have been facilitated by the Public Health (Tobacco) Acts, 2002 and 2004[243]. The Acts provide a strengthened legislative basis for regulating and controlling the sale, marketing and smoking of tobacco products[244]. Ireland is now regarded as a world leader in tobacco control.

a. The Cardiovascular Health Strategy:

Government targets for health improvement in Ireland include a reduction in deaths related to cancer and heart disease, both of which can be achieved by reducing the number of people who smoke. The Cardiovascular Health Strategy Group was established in March 1998 with a remit *"to develop a strategic approach to reduce avoidable death and illness caused by cardiovascular disease"*[25]. In 1980, 51% of all deaths in Ireland were attributed to cardiovascular disease and this decreased to 41% of deaths in 2000[244]. However, Ireland continues to have high death rates from cardiovascular disease compared to other EU countries[244].

b. The National Cancer Strategy:

There is a general consensus that smoking is the single most important factor that is linked to high incidences of cancer in Ireland. The National Cancer Strategy Group was established in 1996 with the key goal of reducing the death rate from cancer in the under-65 year age group by 15% in the 10 year period from 1994. This was achieved in 2001, which was 3 years ahead of target[242]. However, new cancer cases are increasing by about 2% every year in Ireland. The Report from the National Cancer Registry (1994-2000) highlighted that the most common cause of death was lung cancer, accounting for 20% of cancer deaths[245]. Cancer survival in Ireland was close to the European average for the common cancers, with the exception of breast and lung cancer, for which survival was reported to be well below average[245]. Approximately 95% of lung cancer is caused by

cigarette smoking[246]. Thus, a key focus of health promotion has been in the area of smoking cessation.

c. Pricing of cigarettes:

For every 1% increase in the price of cigarettes it is estimated that there is a decrease of approximately 0.5% in consumption[227]. Cigarette prices in Ireland are among the highest in the EU and taxes account for 80% of the price of the packet[242].

d. Advertising bans:

Tobacco advertising on television and radio was banned in the 1970s. More recently, advertising of cigarettes in newspapers and magazines and sponsorship of events by the tobacco industry has been banned[227].

e. Media campaigns:

The Health Promotion Unit of the DoHC conducts, on an ongoing basis, multimedia campaigns. These campaigns have particularly targeted teenage girls, given that almost half of Irish children have tried a cigarette and by the age of 15 more girls smoke than boys[244]. Furthermore, each year the DoHC co-ordinates a National Anti-Smoking Campaign which commences on National No Smoking Day (Ash Wednesday)[227].

f. The Office of Tobacco Control:

The Office of Tobacco Control was established in 2002 to support the government policy of promoting a tobacco free society. A variety of functions come under the remit of the Office of Tobacco Control including conducting research into tobacco and communicating the findings, organising a national inspection programme and enforcing the tobacco control laws generally[247].

g. Non-pharmacological smoking cessation interventions:

Non-pharmacological smoking cessation interventions include counselling, hypnotherapy and acupuncture. Additional funding has been provided, via the Cardiovascular Health Strategy, to establish smoking action groups and smoking cessation clinics at a regional level to co-ordinate tobacco health promotion[244].

h. Pharmacological smoking cessation interventions:

Bupropion sustained release (SR) has been reimbursed on the GMS and DP Schemes since its launch in September 2000. NRT has been reimbursed on the GMS Scheme since April 2001[244].

i. A ban on smoking in all workplaces:

Enclosed workplaces became smoke-free by law in Ireland on 29th March 2004 under provisions in the Public Health (Tobacco) Acts, 2002 and 2004[243]. The ban was introduced in an effort to protect employees and the public from the harmful effects of exposure to and inhalation of second-hand smoke. A review, undertaken one year after implementation of the smoke-free workplace legislation, highlights that compliance with and support for the legislation is high[248].

Therefore a wide range of strategies have been implemented in Ireland to reduce the prevalence of smoking, including the reimbursement of NRT preparations for all medical card holders.

5.1.6 Pharmacological Smoking Cessation Interventions

For many smokers, it is difficult to quit smoking using will-power alone. When nicotine is stopped abruptly, withdrawal symptoms occur and include: aggressiveness, anxiety, confusion, impatience, inability to concentrate, irritability, nicotine craving, restlessness, constipation, dizziness, headache, sweating and difficulty sleeping[249, 250]. The symptoms usually develop within a few hours of abstinence, peak after 2 to 3 days, and may last for weeks or months[251]. NRT and bupropion SR are two pharmacological agents available to aid smokers in their attempt to achieve smoking cessation.

a. Nicotine Replacement Therapy

The aim of taking NRT is to replace the nicotine from cigarettes, thus reducing withdrawal symptoms when stopping smoking[252]. The most recent Cochrane review of NRT for smoking cessation (2004) reported that NRT leads to a near doubling of the cessation rates achieved by non-pharmacological intervention[253].

Five NRT formulations (i.e. patch, gum, sublingual tablet, lozenge and inhaler) are currently available on the GMS Scheme. Nicotine patches deliver a steady level of nicotine throughout the day and provide reliable nicotine concentrations from the first day of use.

The patches have the advantages of ease of use and can be worn unobtrusively[254]. The dose of the nicotine gum, lozenge, sublingual tablets and inhaler may be adjusted as needed and, like smoking, their use involves some behavioural activity[254]. The Nicorette® nasal spray was available and reimbursed on the GMS Scheme in 2002 but has subsequently been withdrawn from the Irish market. The nasal spray is still available in the UK and, according to the manufacturers, was discontinued in Ireland as a result of a low demand for the product. The NRT preparations reimbursed on the GMS Scheme include:

1) **Nicotine transdermal patches:**

There are three brands of nicotine patch: Nicorette® (5mg, 10mg, 15mg), Nicotinell® (7mg, 14mg, 21 mg) and NiQuitin CQ® (7mg, 14mg, 21 mg). The Nicorette® patches are designed to be applied for 16 hours per day, while the Nicotinell® and NiQuitin CQ® patches are designed to be applied for 24 hours.

2) **Nicotine gum:**

There are two brands of nicotine gum: Nicorette® (2mg and 4mg) and Nicotinell® (2mg and 4mg). Nicotine is released from the gum over about 30 minutes of intermittent chewing and is mainly absorbed into the blood through the buccal mucosa[255]. The maximum dose is 15 pieces of 4mg gum daily[256].

3) **Nicotine sublingual tablet:**

There is only one brand of nicotine sublingual tablet available: Nicorette® 2mg microtab. The manufacturer advises using 1-2 tablets hourly, depending on usual cigarette consumption, up to a maximum of 40 tablets daily[257].

4) **Nicotine lozenge:**

There are two brands of nicotine lozenge available: Nicotinell® (1mg) and NiQuitin CQ® (2mg and 4mg). Nicotinell® 1 mg lozenge is recommended in smokers with a medium nicotine dependency. The usual dosage is 8-12 lozenges per day. The maximum daily dose is 30 lozenges[258]. NiQuitin CQ® 2 mg lozenges are suitable for medium dependency smokers and NiQuitin CQ® 4 mg lozenges are suitable for high dependency smokers. The maximum daily dose is 15 lozenges per day[259]. The NiQuitin CQ lozenges have only been available in Ireland since 2003.

5) Nicotine inhaler:

There is only one brand of nicotine inhaler available: Nicorette® 10mg refill inhaler (Pfizer). The device consists of a mouthpiece into which cartridges are inserted. By sucking on the inhaler, nicotine vapour is drawn into the mouth, where it is absorbed through the buccal mucosa. Little or no nicotine reaches the lungs[255]. The device is aimed at smokers who miss the hand-to-mouth movements associated with smoking and who smoke less than 20 cigarettes per day (i.e. medium dependency smokers)[260].

The dosage instructions and duration of therapy vary according to the preparation of NRT dispensed. There is currently insufficient evidence to conclude that one form of NRT is more effective than another; thus the choice of product should generally be guided by the smoker's preference, tolerance for side effects and cost considerations[253, 261, 262].

b. Bupropion

Bupropion SR (Zyban®) is a prescription only medicine licensed for use in smoking cessation. Bupropion SR was developed and initially introduced in the US as an antidepressant but was subsequently noted to reduce the desire to smoke cigarettes and was shown in clinical trials to be effective in smoking cessation[263]. It has been reimbursed on the GMS and DP Schemes since its launch in September 2000. Bupropion SR is a relatively weak but selective inhibitor of the neuronal re-uptake of dopamine and noradrenline. Although the exact mechanism of action is unclear, it is presumed to work directly on brain pathways involved in addiction and withdrawal[264, 265].

The recommended dose of bupropion SR is 150mg daily for six days, increasing on day seven to 150mg twice daily. Patients should be treated for 7 to 9 weeks[266]. The most clinically important adverse events associated with bupropion SR are seizures, which occur in about 1 in 1000 patients[266]. Smokers with a low seizure threshold must not be prescribed bupropion SR unless the potential benefits of smoking cessation outweigh the increased risks. Factors that may increase the risk of bupropion SR associated seizures include concomitant administration of any drug known to lower the seizure threshold, alcohol abuse, head trauma, the use of glucose lowering drugs or insulin in people with diabetes, and the use of stimulants and drugs to induce anorexia. Additionally, drug interactions between bupropion SR and several other medicines have been reported[266].

c. The price of therapies for nicotine dependence

Although it appears from Table 5.2 that bupropion SR is more expensive than NRT (e.g. €116.97 for a month supply of bupropion SR versus €50.68 for a month supply of Nicorette® patches) it is important to be aware that 21% VAT is added to non-oral preparations (i.e. NRT patches) and that the recommended duration of therapy for the patches (12 weeks) is longer than for bupropion SR tablets (7-9 weeks). Furthermore, the other NRT preparations are taken on an as required basis therefore the costs will vary depending on individual usage. Therefore, there is little overall difference in price between the various therapies for nicotine dependence.

Table 5.2 Therapies for nicotine dependence reimbursed on the GMS Scheme.

Product and manufacturer	Pack size	Ingredient Cost per Pack
Nicorette® *(Pfizer)*		
Gum 2mg*	210	€29.31
Gum 4mg*	210	€36.16
Patch (high strength)	14 patches (15mg/16hrs)	€25.34
Microtab 2mg*	105	€17.56
Inhaler 10mg*	42 cartridges	€19.22
Nicotinell® *(Novartis)*		
Gum 2mg*	96	€12.64
Gum 4mg*	96	€15.67
Patch (high strength)	7 patches (21mg/24hrs)	€13.50
Lozenge 1mg*	96	€13.87
NiQuitin CQ® *(GSK)*		
Patch (High strength)	7 patches (21mg/24hrs)	€13.95
Lozenge 2mg*	72	€17.33
Lozenge 4mg*	72	€17.33
Bupropion SR (Zyban®) *(GSK)*		
Prolonged release 150mg tablet	100 (~1 month supply)	€116.97
Prices quoted are for the pack sizes which would result in a two week supply of NRT where possible. * Exact daily usage varies depending on the patient.		

Source: *GMS product file, May 2005.*

5.1.7 Reimbursement of NRT in Ireland

NRT has been reimbursed on the GMS Scheme since April 2001. Some of the key factors leading to this decision were that lower socio-economic groups have a higher incidence of smoking, spend a higher proportion of disposable income on tobacco, have worse general health and therefore would benefit more from assistance to quit smoking[267]. NRT is not reimbursed on the DP Scheme.

The following guidance was issued for the prescribing and dispensing of NRT on the GMS Scheme[268]:

- The quantity to be prescribed on an initial prescription should be limited to two weeks of therapy;
- NRT should not be prescribed on Repeat GMS Prescription forms. [There are two types of GMS prescription form: Single GMS prescriptions (allows up to 1 months supply) and Repeat GMS prescriptions (3 month supply)].

The GMS (Payments) Board report for the year ended 31/12/2002 indicates that NRT was 90th of the top 100 most commonly prescribed products under the GMS Scheme. NRT was 44th of the top 100 products in order of their total ingredient cost, with a total ingredient cost amounting to €2,709,954 which accounted for 0.63% of the total ingredient cost of medicines for the GMS scheme in 2002[45]. In light of the significant expenditure on NRT in 2002, the GMS Division of the DoHC commissioned the NCPE to carry out an evaluation of the use of these drugs on the GMS Scheme in July 2003.

5.2 Aim

The aims of this study were to:

- Analyse prescribing trends for therapies for nicotine dependence on the GMS Scheme using the GMS prescription database.
- Investigate prescribing of NRT on the GMS Scheme by determining:
  - The demographic characteristics of patients prescribed NRT;
  - The pharmaceutical form of NRT;
  - The strength of NRT;
  - The duration of therapy;
  - The use of combination therapies for nicotine dependence.

5.3 Method

5.3.1 Prescribing Trends for Therapies for Nicotine Dependence

The GMS (Payments) Board maintains a large primary care prescription database (known as the GMS prescription database) and this has been described in detail in Chapter 3. All GMS prescriptions for therapies for nicotine dependence for all Health Board areas in 2002 were analysed using this database. The analysis was carried out using a statistical package called JMP-IN (version 3.2.1, SAS Institute Inc). Data for 2002 was analysed, as this was the only complete annual data set available at the time of the request from the DoHC.

Medications were identified using the WHO ATC classification system (see Chapter 3)[179]. The ATC classification of therapies for nicotine dependence is as follows:

- N07BA01 - NRT
- N07BA02 – Bupropion SR

There is only one preparation of bupropion SR on the Irish market and thus the ATC code was used to identify all of the prescriptions for bupropion SR. There is also only one ATC code for all of the different NRT preparations. However, each individual preparation reimbursed on the GMS Scheme is assigned a GMS code number and this was used to identify the brand name, strength, formulation and pack size of the different NRT preparations.

a. Rate of prescribing of NRT and bupropion SR on the GMS Scheme

The rate of prescribing of bupropion SR before April 2001, and prescribing rates of bupropion SR and NRT after April 2001 were determined. The prescribing rate was calculated as the number of patients prescribed therapies for nicotine dependence per 1000 GMS eligible population in 2002. The number of eligible persons on the GMS Scheme was obtained from the GMS (Payments) Board annual report (2002)[45].

b. Utilisation and expenditure on therapies for nicotine dependence

The total number of patients dispensed the different NRT formulations and bupropion SR in the year 2002 was determined. The total expenditure (including ingredient cost, dispensing fees and VAT) on the different NRT formulations and bupropion SR for the year 2002 was also recorded. There is no VAT on oral medications and 21% VAT is added to all non-oral preparations. Thus, there was no VAT on bupropion SR tablets as well as nicotine gum, sublingual tablets, inhaler and lozenges but 21% VAT was added to nicotine

patches and nasal spray. The seasonal variation in prescribing was determined by analysing monthly utilisation data from December 2001 to January 2003.

c. Prescribing of therapies for nicotine dependence before and after the introduction of the ban on smoking in all work places

The potential impact of the smoking ban, which was introduced in March 2004, on prescribing of therapies for nicotine dependence was determined by analysing monthly prescription data from January 2002 to December 2004.

d. Comparison of prescribing trends for therapies for nicotine dependence in 2002 and 2004

Utilisation of and expenditure on NRT and bupropion SR in 2002 was compared with 2004 data. The rate of prescribing in 2002 was compared with 2004, using the rate ratio. Stata (Version 7) was used to undertake the statistical analysis and significance at $p<0.05$ was assumed.

5.3.2. Analysis of Prescribing of NRT on the GMS Scheme

a. Demographic characteristics of the sample

The age and gender of patients prescribed therapies for nicotine dependence in the year 2002 was standardised by the age and gender distribution of the GMS eligible population for the same year. The number of patients prescribed therapies for nicotine dependence per 1000 eligible GMS population, by age and gender, was calculated i.e. (number of patients/GMS eligible population) x 1000. The number of eligible persons by age and gender on the GMS Scheme was obtained from the GMS (Payments) Board annual report (2002)[45].

b. Pharmaceutical form of NRT

The pharmaceutical form of each of the NRT preparations dispensed was determined. Expenditure and utilisation of the various preparations was established.

c. Strength of nicotine patch and gum

The strength of nicotine patches and gum that were dispensed was determined. The other formulations were excluded from this part of the analysis because there is only one strength of the nasal spray, microtab and inhaler on the market. Moreover, less than 0.1% of patients were prescribed the lozenges.

d. Duration of therapy of nicotine patches

The duration of therapy of nicotine patches during the year 2002 was analysed. Patients receiving a prescription in December 2001 and January 2003 were excluded from this part of the analysis in order to determine the exact duration of therapy for prescriptions dispensed in the year 2002 (i.e. the aim was to include those patients whose NRT therapy started and finished in the 12 month period of the analysis). The GMS prescription database only contains information on strength and quantity of preparations dispensed and there is no information on dosage. Therefore, it was not possible to determine duration of therapy for the other nicotine formulations because they are taken on an as required basis. However, nicotine patch therapy is administered once daily. Thus, by analysing the total quantity of patches dispensed during the 12 month period, the duration of therapy was estimated. It was assumed that all patients were dispensed the patches as a single course rather than repeat courses throughout the 1 year period. In reality patients may have received repeat courses but this was not investigated in this analysis due to the low number of patients receiving more than 6 weeks of therapy.

e. Combination therapy

The GMS prescription database was analysed to determine whether any patient received a combination of NRT preparations or NRT and bupropion SR simultaneously. Individual patient data was grouped by month and the number of different preparations for nicotine dependence dispensed per patient each month in 2002 was determined.

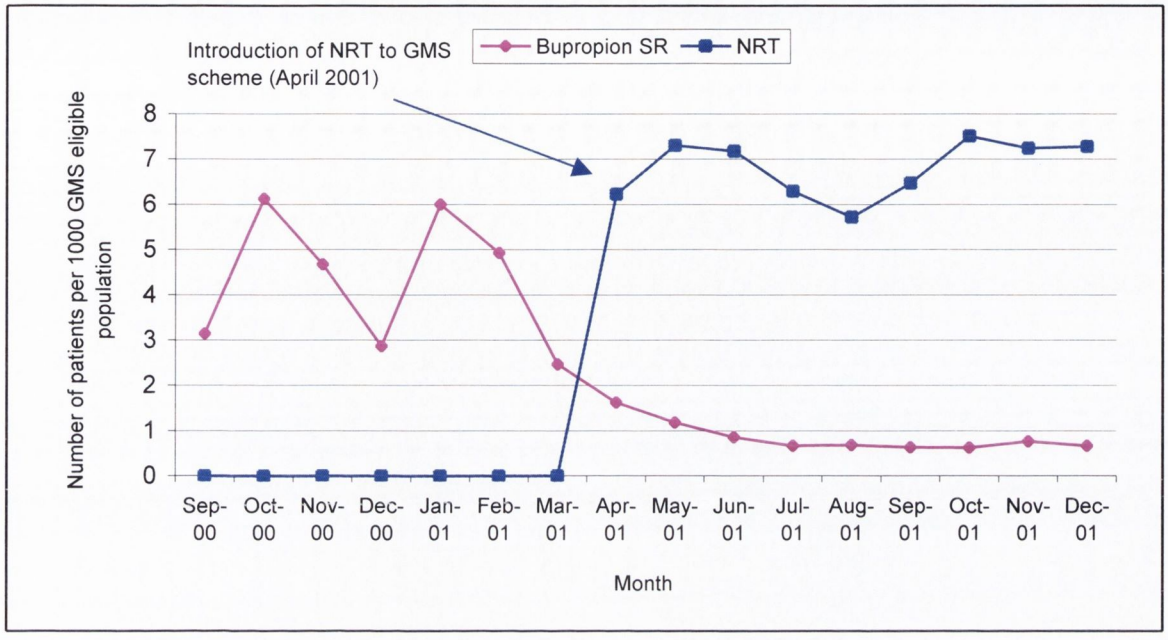
5.4. Results

5.4.1. Prescribing Trends for Therapies for Nicotine Dependence

a. Rate of prescribing of NRT and bupropion SR on the GMS Scheme

Following the introduction of NRT to the GMS Scheme in April 2001, a prescribing rate of approximately 6 per 1000 GMS eligible patients was recorded within the first month. (Figure 5.3). A marked reduction in the prescribing of bupropion SR occurred at this time with prescribing rates declining from 6 per 1000 patients in January 2001 to approximately 1 per 1000 patients in June 2001.

Figure 5.3 Rate of prescribing of NRT and bupropion SR on the GMS Scheme from September 2000 to December 2001.



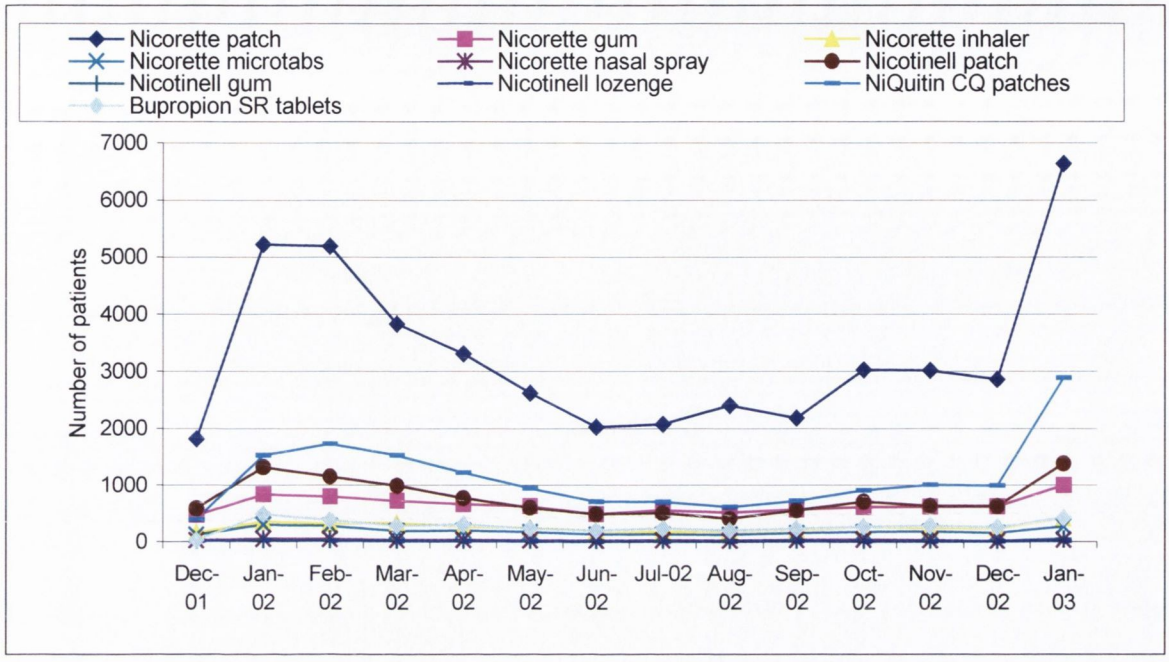
b. Utilisation and expenditure on all therapies for nicotine dependence in 2002

Some 49,826 patients (Male: Female 23,169: 26,657) (4.3% of the GMS eligible population) received smoking cessation products on the GMS Scheme in 2002. Of these 94.6% (47,147 patients) were prescribed NRT and the remaining 5.4% (2,679 patients) received bupropion SR.

Total expenditure (including dispensing fees and VAT) on therapies for nicotine dependence on the GMS Scheme in 2002 was €3,260,726 (representing 0.63% (€2.71 million) of the total ingredient cost (excluding dispensing fees and VAT) for the GMS Scheme that year). Of this, 7.5% (€243,225) of expenditure was on bupropion SR and the remaining 92.5% (€3,017,501) of expenditure was on NRT.

The monthly prescribing trends illustrate that the number of patients receiving smoking cessation therapies is greatest for the months January and February (Figure 5.4). Consequently, expenditure on smoking cessation therapies is highest in the first quarter of each year.

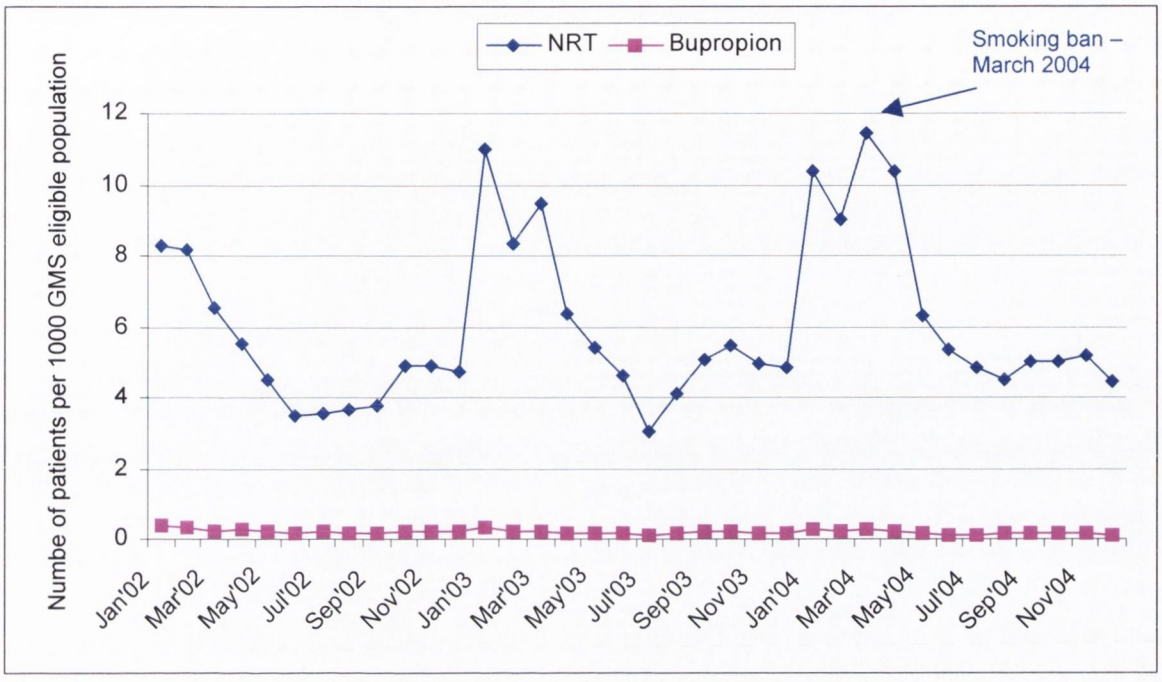
Figure 5.4 Total number of patients prescribed therapies for nicotine dependence under the GMS Scheme from December 2001 to January 2003.



c. Prescribing of therapies for nicotine dependence before and after the introduction of the smoking ban

The rate of prescribing of NRT in 2003 and 2004 peaked in the months of January and March (Figure 5.5). The rate of prescribing of NRT was highest in March 2004 at 11.4 per 1000 GMS eligible population. However, the rate of prescribing subsequently declined in line with the expected seasonal variation in utilisation of NRT preparations. The rate of prescribing of bupropion SR remained low (<1 patient per 1000 GMS population) compared to NRT.

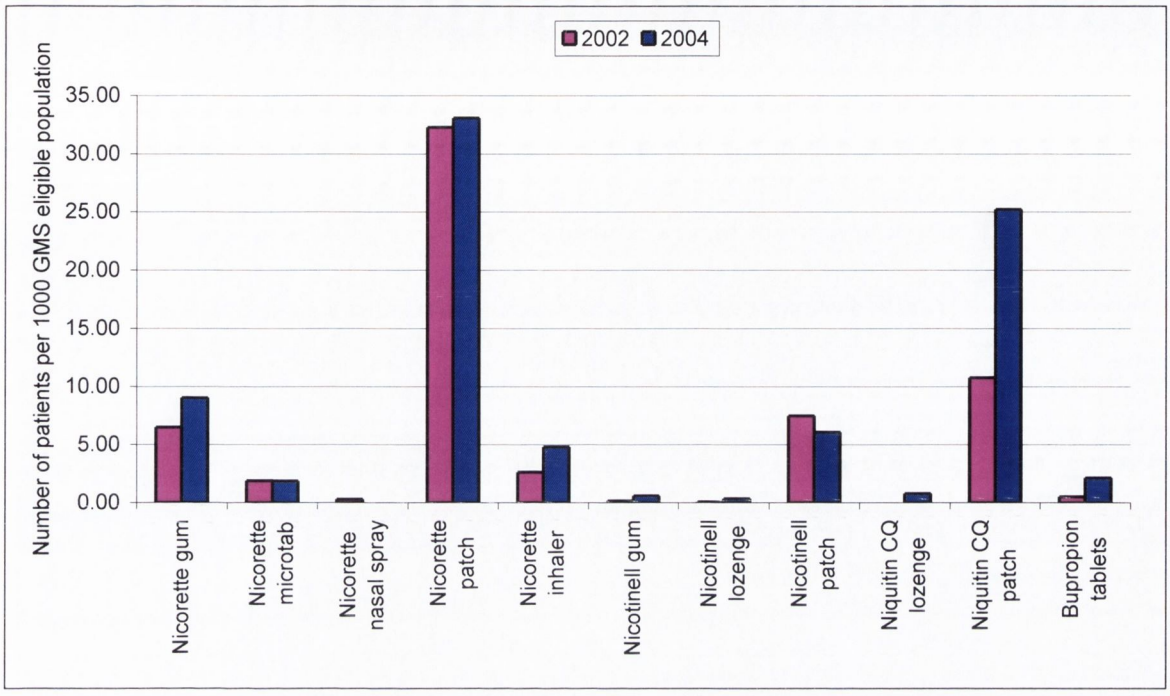
Figure 5.5 **Rate of prescribing per 1000 GMS eligible population of NRT and bupropion SR on the GMS Scheme between January 2002 and December 2004.**



d. Comparison of prescribing trends for therapies for nicotine dependence in 2002 and 2004

Although the GMS eligible population fell from 1,168,745 to 1,148,914 between 2002 and 2004, the prescribing frequency of NRT increased from 91,139 prescriptions in 2002 to 115,480 in 2004[15, 269]. Comparison of the rate of prescribing of therapies for nicotine dependence from 2002 to 2004 shows a significant increase in the rate of prescribing of Nicorette® gum, Nicorette® patch, Nicorette® inhaler, Nicotinell® gum, Nicotinell® lozenge, NiQuitin CQ® patches and bupropion SR tablets ($p<0.0001$) and a significant decrease in the rate of prescribing of Nicotinell® patches ($p<0.0001$) (Figure 5.6). The nasal spray was withdrawn and the NiQuitin CQ® lozenges were launched after the 2002 analysis was undertaken.

Figure 5.6 Rate of prescribing per 1000 GMS eligible population of therapies for nicotine dependence in 2002 and 2004 on the GMS Scheme.



As a percentage of total prescribing, the rate of prescribing per 1000 GMS eligible population of nicotine patches fell from 80.7% in 2002 to 76.6% in 2004 and the rate of prescribing of nicotine gum increased from 10.6% in 2002 to 11.5% in 2004. There was also an increase in prescribing rate of the lozenge, the inhaler and bupropion SR tablets. There was a decrease in the rate of prescribing of the nicotine microtabs (Table 5.3).

Table 5.3 The rate of prescribing for the different therapies for nicotine dependence on the GMS Scheme in 2002 and 2004.

	Rate of prescribing per 1000 GMS eligible population		Rate of prescribing per 1000 GMS eligible population as a percentage of total prescribing of therapies for nicotine dependence	
Formulation	**2002**	**2004**	**2002**	**2004**
Patch	50.51	64.38	80.7%	76.6%
Gum	6.64	9.62	10.6%	11.5%
Inhaler	2.65	4.81	4.2%	5.7%
Microtab	1.90	1.88	3.0%	2.2%
Lozenge	0.07	1.17	0.1%	1.4%
Bupropion SR tablet	0.54	2.15	0.9%	2.6%
Nasal spray	0.30	0.00	0.5%	0.0%

There was an increase in the total ingredient cost of NRT of 29% between 2002 and 2004, from €2.7 million in 2002 to €3.5 million in 2004[39, 45]. The greatest overall rise in expenditure was with the NiQuitin CQ® patch (Table 5.4).

Table 5.4 Total GMS expenditure on therapies for nicotine dependence in 2002 and 2004.

Drug	Expenditure (€) in 2002	Expenditure (€) in 2004	Increase in expenditure (€)	Percentage increase in expenditure
Nicorette® gum	230,892	434,441	203,549	88.2%
Nicorette® microtab	51,881	69,915	18,034	34.8%
Nicorette® nasal spray	10,752	Discontinued	-	-
Nicorette® patch	1,708,689	2,074,136	365,447	21.4%
Nicorette® inhaler	93,710	216,806	123,096	131.4%
Nicotinell® gum	2,765	16,356	13,591	491.5%
Nicotinell® lozenge	1,425	10,180	8,755	614.4%
Nicotinell® patch	339,333	365,639	26,306	6.9%
NiQuitin CQ® lozenge	Not available	31,066	-	-
NiQuitin CQ® patch	594,874	1,602,923	1,008,049	169.5%
Bupropion SR tablets	45,550	193,567	148,017	325.0%

NiQuitin CQ® patches are the most expensive of the nicotine patches available on the Irish market (Table 5.5). The Nicotinell® patches are the least widely prescribed and the least expensive of the patches available on the Irish market (with the exception of the Nicotinell® 21mg pack size 7 which is more expensive than Nicorette®) (Table 5.5). There was a fall in the prescribing rate for Nicotinell® patches between 2002 and 2004.

Table 5.5 The price per patch of the nicotine patches available on the GMS Scheme.

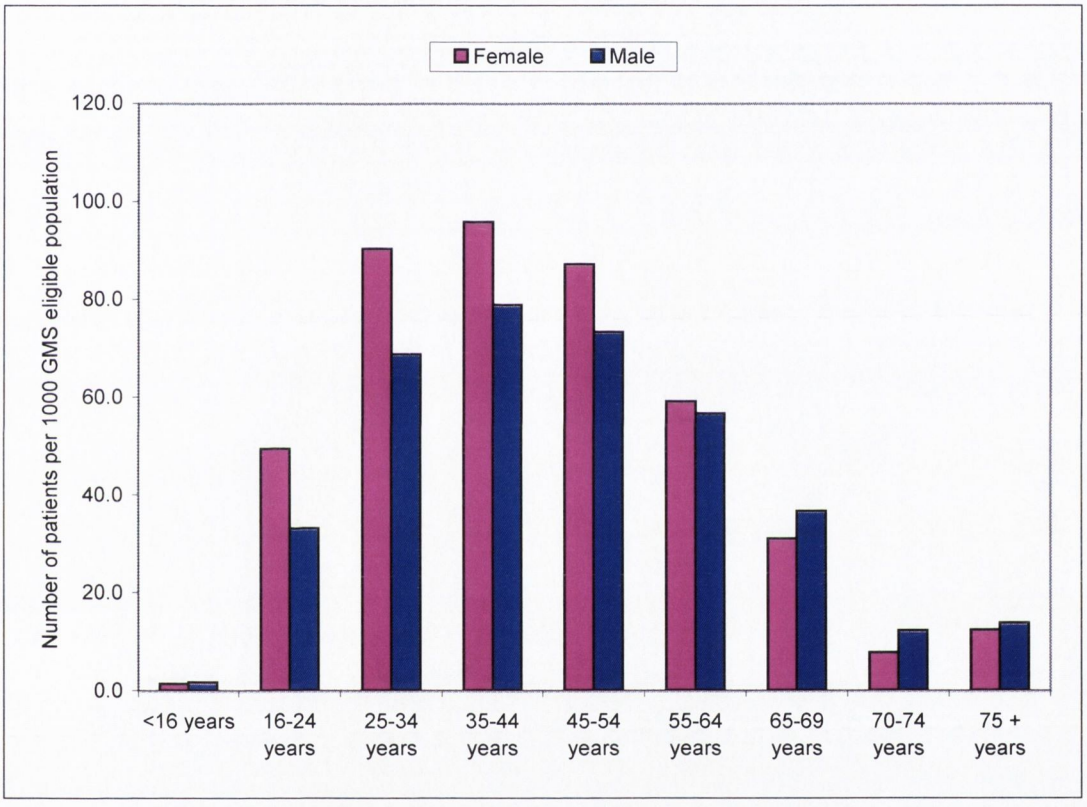
Strength	Nicotinell®	Nicorette®	NiQuitin CQ®
5/7mg	€1.77	€1.81	€1.99
10/14mg	€1.85	€1.81	€1.99
15/21mg	€1.93 (pack size 7) €1.55 (pack size 21)	€1.81	€1.99

5.4.2. Analysis of Prescribing of NRT on the GMS Scheme

a. Demographic characteristics of the sample

Prescribing of therapies for nicotine dependence was greatest amongst the 25 to 54 year age group with peak prescribing for females between the ages of 35 to 44 years (Figure 5.7). The ratio of males to females prescribed NRT was 1.00:1.16.

Figure 5.7 Number of patients per 1000 GMS eligible population prescribed therapies for nicotine dependence on the GMS Scheme in 2002 (standardised by age and gender of the GMS eligible population).



b. Pharmaceutical form of NRT

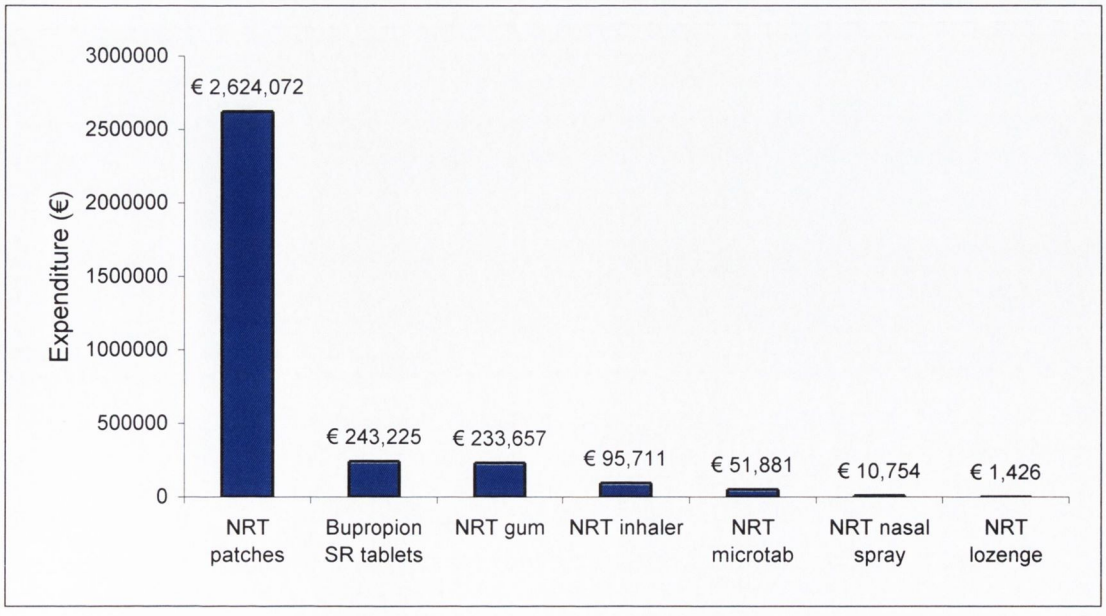
The main form of NRT utilised under the GMS Scheme was the patch preparation, which was prescribed for almost 83% of all patients and accounted for approximately 87% of total expenditure on NRT. In contrast, nicotine gum was prescribed for over 8% of patients, accounting for 7.8% of total expenditure on NRT under the GMS Scheme in 2002 (Table 5.6).

Table 5.6 **The number of patients prescribed each of the available smoking cessation therapies together with total expenditure on the GMS Scheme in 2002.**

	Number of patients	% of patients	Expenditure (€)	% of expenditure
Nicorette® patch	25,005	53.0%	1,688,642	56.0%
NiQuitin CQ® patch	8,324	17.7%	594,874	19.7%
Nicotinell® patch	5,717	12.1%	340,556	11.3%
Nicorette® gum	3,947	8.4%	230,893	7.7%
Nicorette® inhaler	2,091	4.4%	95,711	3.2%
Nicorette® microtab	1,577	3.3%	51,881	1.7%
Nicorette® nasal spray	287	0.6%	10,754	0.4%
Nicotinell® gum	129	0.3%	2,764	0.1%
Nicotinell® lozenge	70	0.1%	1,426	0.0%
Total	47,147	100.0%	3,017,501	100.0%

Nicotine patches accounted for the majority of expenditure on therapies for nicotine dependence, followed by bupropion SR tablets and nicotine gum respectively (Figure 5.8).

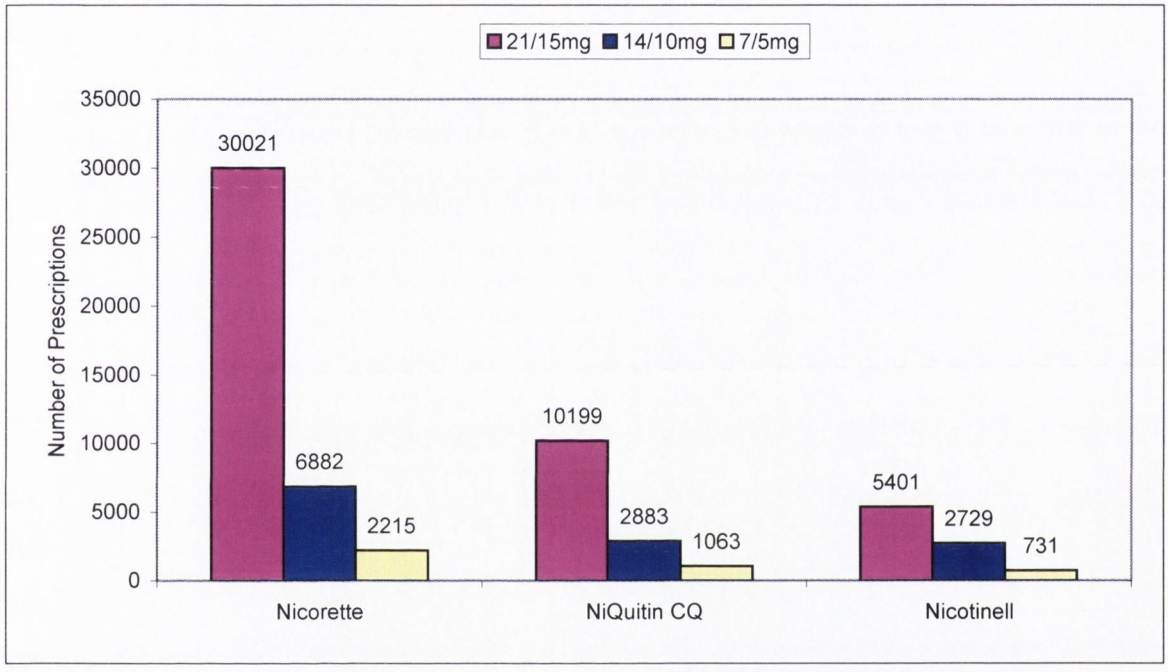
Figure 5.8 **Expenditure on therapies for nicotine dependence on the GMS Scheme in 2002.**



c. Strength of nicotine patches and gum

The highest strength of nicotine patch therapy (15/21mg per day) was dispensed for the majority (73%) of prescriptions (Figure 5.9). Only 7% of prescriptions were for the lowest strength.

Figure 5.9 Strength of nicotine patches dispensed on the GMS Scheme in 2002 (Nicorette® 15, 10, 5mg, NiQuitin CQ® 21, 14, 7mg and Nicotinell® 21, 14, 7mg).

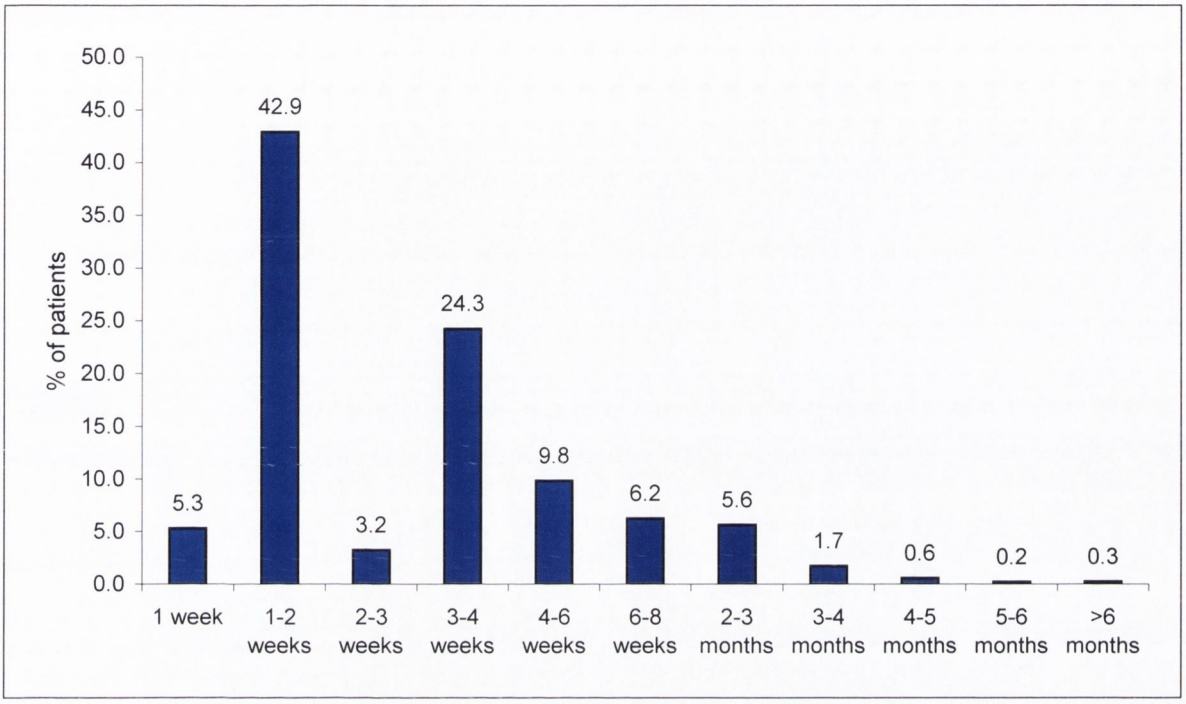


A greater proportion of prescriptions for the 4mg strength of the gum (63%) were dispensed compared to the 2mg strength (37%). Some 57% of patients were dispensed the 4mg strength, approximately one third of patients (34%) received the 2mg strength of the gum and 9% of patients were dispensed a combination of both strengths of the gum during the period of the analysis.

d. Duration of therapy of nicotine patches

Over three quarters (75.7%) of all patients were prescribed nicotine patch therapy for a period of less than or equal to 4 weeks during the 12 month period from January to December 2002 (Figure 5.10). Approximately half of all patients (48.2%) received less than or equal to 2 weeks of nicotine patch therapy.

Figure 5.10 Duration of therapy for nicotine patches for the year 2002 (excluding any patients prescribed therapies for nicotine dependence in December 2001 and January 2003).



e. Combination therapy

All patients were prescribed smoking cessation products as monotherapy. There were no combinations of NRT preparations (e.g. combined use of nicotine patch and gum) or combinations of bupropion SR and NRT dispensed for individual patients in any month in the year 2002.

5.5 Discussion

5.5.1 Prescribing Trends for Therapies for Nicotine Dependence

The impact of reimbursing NRT under the GMS Scheme in April 2001 is highlighted in Figure 5.3. This corresponds with a marked reduction in the prescribing of bupropion SR. However, the decline in bupropion SR prescribing commenced prior to the introduction of NRT. This may be partly explained by the seasonal variation in prescribing of smoking cessation therapies and the fact that more people attempt to quit smoking in January than in December. Moreover, the decline in prescribing of bupropion SR from February 2001 onwards coincided with the safety warning in relation to adverse effects (e.g. seizures) and potential drug interactions (i.e. antipsychotics, antidepressants, theophylline) issued in December 2000 by the IMB[270]. Further safety warnings issued by the IMB in April 2001

and significant media attention highlighting fatalities occurring in patients receiving this treatment in the UK may have contributed to the decline in bupropion SR prescribing[271].

Efficacy of bupropion SR

Several studies have reported the efficacy of bupropion SR as a smoking cessation intervention[265, 272-274]. A recent Cochrane review of antidepressants for smoking cessation identified 24 trials of bupropion SR. When used as monotherapy and compared to placebo, bupropion SR doubled the odds of cessation (19 trials including over 4,000 participants, odds ratio (OR)=2.06, 95% confidence intervals (CI) 1.77 to 2.40)[275].

Efficacy of NRT

The efficacy of bupropion SR is similar to that reported for NRT[253]. The recent Cochrane review of NRT for smoking cessation (2004) identified 123 trials involving over 35,600 participants[253]. The main outcome measure was abstinence from smoking after at least 6 months follow-up. All forms of NRT were found to be effective and increased quit rates from 1.5 to 2 fold regardless of the level of additional support and encouragement. The pooled OR of abstinence for any form of NRT relative to control was 1.77 (95% CI 1.66-1.88). Current evidence suggests that bupropion SR may be more effective than NRT but, given the limited availability of data directly comparing NRT and bupropion SR, no firm conclusion can be drawn regarding their relative efficacy in smoking cessation[276].

Cost of therapies for nicotine dependence

There is also little difference in the cost of the various smoking cessation interventions. A 7 to 9 week course of bupropion SR costs about €110-€140 (excluding dispensing fees), whereas a 12 week course of Nicorette® patches costs about €180 (including 21% VAT and excluding dispensing fees). However, in practice, the duration of therapy varies between patients and over three quarters of patients in this study were prescribed nicotine patches for a period of less than or equal to 4 weeks.

Safety and tolerability of therapies for nicotine dependence

There is a difference between NRT and bupropion SR in terms of adverse events and safety profiles[276]. Overall, the safety profile of NRT is more favourable, particularly given the small but real risk of seizure with bupropion SR[276].

Therefore, despite the efficacy of bupropion SR as a smoking cessation intervention, it appears that prescribers exercised caution in its prescription and were likely to have been influenced by safety concerns and the introduction of freely available NRT to the GMS eligible population.

a. Rate of prescribing of smoking cessation therapies in 2002 on the GMS Scheme

Some 49,826 patients (4.3% of the GMS eligible population) received smoking cessation products in 2002. However, the results of the SLÁN study in 2002 illustrated that 37% of those with a medical card reported smoking regularly/occasionally[233]. Therefore, although NRT accounts for a significant proportion of the expenditure on reimbursed medicines, there are still many smokers who have not been prescribed therapies for nicotine dependence on the GMS Scheme in Ireland. However, recent recommendations from NICE and the Cochrane Collaboration both state that smoking cessation therapies should be preferentially directed to those who are motivated to quit (as demonstrated by their initiative to request assistance or expression of a desire to quit)[253, 277]. It was not possible to determine the motivation of the sample included in this study but prescribing may have been restricted to those who were motivated to quit. In addition, some smokers may initiate use of OTC NRT independently; although it is unlikely that medical card holders would purchase OTC NRT when it is available to them free of charge on the GMS Scheme.

A survey carried out by the manufacturers of Nicorette® (Pfizer) in Ireland in 2002 found that 61% of smokers wanted to quit but that the availability of NRT on the GMS Scheme was unknown to 79% of smokers[278]. Therefore, healthcare professionals could encourage more smokers to quit by making them aware of the availability of NRT on the GMS Scheme.

The attitudes of GPs and smokers to prescribing of NRT has not been investigated in the Irish setting. A UK study reported that GPs accepted that NRT and bupropion SR should be reimbursable on prescription[279]. However, a number of those who received requests from patients for prescriptions did not issue any (8% of GPs for NRT and 26% for bupropion SR). A number of reasons were cited as to why prescriptions were not issued which were related to beliefs about whether smokers should have to pay for treatment themselves, the cost-effectiveness of therapies for nicotine dependence and the low priority they would give these medicines in the drug budget[279]. Moreover, the higher rate of non-prescribing of bupropion SR may have been a result of safety concerns. Another study

undertaken in the UK found that GPs appeared to be divided in their attitudes to medications to aid smoking cessation and 50% thought that NRT should not be available on NHS prescription[280].

b. Seasonal variation in prescribing of therapies for nicotine dependence

Prescribing trends for therapies for nicotine dependence show that the number of patients receiving such therapy is greatest between January and March (Figure 5.4 and Figure 5.5). Consequently, expenditure on these medicines is greatest during the first quarter. The largest monthly increase in prescriptions is noted for the month of January for the years 2002 and 2003. Prescriptions for Nicorette® patch and NiQuitin CQ® patches increased over two-fold between December 2001 and January 2002 and between December 2002 and January 2003 (Figure 5.4). These trends correspond with seasonal trends in cigarette smoking habits. The Office of Tobacco Control reported that smokers tend to attempt to quit at particular times in the year, mainly at the start of the New Year and on Ash Wednesday, which is usually in February or March. In Ireland National No Smoking Day is held on an annual basis on Ash Wednesday[247].

c. Precribing of therapies for nicotine dependence before and after the introduction of the ban on smoking in all workplaces

The rate of prescribing of NRT reached a peak in March 2004, the month the ban on smoking in all workplaces was introduced. However, the rate of prescribing subsequently fell, and followed a similar seasonal variation to the trend observed between 2001 and 2003. Therefore, from the data available at the time of the analysis, it appears that the smoking ban was associated with an increase in prescribing of NRT in the first month, but the rate of prescribing subsequently declined after that. Further analysis of 2005 data would be required to determine whether the smoking ban had an effect on prescribing of NRT on the GMS Scheme.

d. Comparison of prescribing trends for therapies for nicotine dependence in 2002 and 2004

The overall prescribing frequency for NRT increased between 2002 and 2004, although the GMS eligible population fell[15, 269]. There was a decrease in the proportion of patients prescribed nicotine patches and microtabs and an increase in the proportion of patients prescribed gum, lozenges and inhaler. However, nicotine patches still accounted for the majority of prescriptions. There was also an increase in the prescribing rate of NiQuitin

CQ® patches, the most expensive brand of nicotine patches reimbursed on the GMS Scheme, which corresponds with a strong marketing campaign by the manufacturers of this preparation. NiQuitin CQ® lozenges were not available in 2002 but were included in the analysis of 2004 data. This explains the increase in prescribing rate of nicotine lozenges.

5.5.2 Analysis of Prescribing of NRT on the GMS Scheme

a. Demographic characteristics of the sample

Prescribing of NRT is greatest in the 25 to 54 year age group with peak prescribing between the ages of 35 to 44 years. The prevalence of cigarette smoking is greatest in the 18 to 34 year age group and the first SLÁN study (1998) highlighted that the number of female smokers exceed the number of male smokers (40% versus 38%). However, the second SLÁN Survey (2002) has shown that across all demographic categories smoking rates have fallen, but this trend has been most marked among young women. A higher proportion of patients receiving therapies for nicotine dependence were female. This could be a direct result of health promotion campaigns specifically targeting young Irish women[281]. The lowest prevalence of cigarette smoking is in those aged 55 years of age or over. In 1999, Stapleton *et al.* demonstrated that NRT is most cost-effective when prescribed for smokers between the ages of 35 to 44 years[282]. Therefore, the age and gender of patients dispensed therapies for nicotine dependence on the GMS Scheme suggests appropriate prescribing in the general practice setting.

b. Choice of pharmaceutical form of NRT

This study has shown that the most widely prescribed NRT formulation, in Ireland in the GMS eligible population, is the patch, followed by the gum. The majority of clinical efficacy data for NRT come from studies of the patch and gum. A number of large double blind, placebo controlled randomised clinical trials have been conducted in general practice to determine the efficacy of the nicotine patch[283-286]. The Imperial Cancer Research Fund General Practice Research Group randomised 1686 heavy smokers (mean cigarette consumption 24 per day) to 12 weeks treatment with a 24-hour transdermal nicotine patch versus placebo[285]. Smoking cessation was confirmed in 163 patients (19.4%) using the nicotine patch and in 99 patients (11.7%) using the placebo patch (difference 7.6%; 95% CI 4.2% to 11.1% $p<0.0001$). The authors concluded that nicotine patches are effective in the general practice setting. A one-year follow up of this trial confirmed that 9% of patients who received the nicotine patch continued to refrain from cigarettes as compared with 6.3% of patients who received placebo[287]. Eight year follow up of people who had

participated in this trial illustrated that just under half of the 9% who had stopped smoking for a year had relapsed, leaving 5% of all trial participants continuously abstinent for 8 years[288].

Another large randomised double blind placebo controlled trial of cigarette smokers (n=1,200) recruited from 30 general practices in 15 English counties investigated the efficacy of transdermal nicotine patches. Participants in this study were aged between 20 and 60 years and smoked at least 15 cigarettes per day. After one year the smoking cessation rate was 9.3% for the nicotine patch versus 5% for placebo[286].

Although there are no data to indicate that other forms of NRT are less efficacious, prescribers have selected the preparations with the largest evidence base. Few studies have directly compared the different formulations of NRT so it is difficult to recommend one over another. The Cochrane review of NRT for smoking cessation (2004) reported that the odds ratios (ORs) of abstinence from smoking for the different forms of NRT ranged from 1.66 for the gum to 2.35 for the nasal spray[253]. For the transdermal patch, inhaler and sublingual tablet, the ORs were 1.81, 2.14 and 2.05 respectively. Although the ORs were higher for the nasal spray, inhaler and sublingual tablet, this is based on a small number of trials with small sample sizes[253]. The authors of this review concluded that there is no evidence that one form of NRT is more effective than any other.

The Cochrane review of NRT recommended that the choice of formulation should reflect patient preference, tolerability and cost considerations and stated that patches are likely to be easier to use than nicotine gum or nasal spray[253]. The transdermal patch is considered to have an advantage over the chewing gum preparation in that it is discreet, convenient to use, requires minimal instruction and is well-tolerated[289]. However, unlike nicotine gum, the patch cannot deliver a bolus of nicotine to satisfy cravings.

The results of this analysis of NRT on the GMS Scheme illustrate that the most commonly prescribed brand of nicotine patch was Nicorette®. The Nicorette® patch delivers a controlled amount of nicotine over 16 hours, whereas the other patches are used for a 24 hour period. The most recent Cochrane review of NRT for smoking cessation (2004) reported that there is no evidence of a difference in clinical efficacy between the 16 hour and 24 hour patches[253]. Therefore the choice of NRT patch should be based on patient preference and cost.

In relation to cost, Nicorette® and Nicotinell® patches are less expensive than NiQuitin CQ®. Furthermore, 15 pieces of the 4mg nicorette gum (i.e. the maximum daily dose) results in an ingredient cost of €2.61 per day as compared with the 15mg nicorette patch at €1.81 per day. It is appreciated that the daily cost will vary, as the amount of gum required will differ between patients.

The majority of patients receiving NRT in the general practice setting in Ireland received the patch formulation and, in view of the advantages mentioned above (i.e. ease of use and good tolerability) together with the available clinical trial data and the fact the cost difference may not be significant, this would appear appropriate.

c. Strength of NRT dispensed

Evidence exists that higher strength patches are more effective then lower strength patches in those smoking more than 10 cigarettes a day[262]. The manufacturers of Nicorette® patches recommend a dose of 15mg daily for 8 weeks followed by 10mg daily for 2 weeks and 5mg daily for 2 weeks[290]. The results of this study show that 77% of Nicorette® patches were dispensed as the 15mg strength, and 17% and 6% of prescriptions were for the 10mg and 5 mg patches respectively. Similar recommendations apply to the other two brands of nicotine patches and similar trends in prescribing were observed. It is expected that a greater proportion of high strength patches would be dispensed as it appears, from the results of this analysis, that many patients do not complete a full course of NRT (Figure 5.10). Moreover, the recent Cochrane review of NRT for smoking cessation reports that use of nicotine patches for up to 8 weeks was as effective as longer courses of treatment and that there was no difference in effect in trials where the dose was tapered, compared to those where withdrawal was abrupt[253].

In addition, in highly dependent smokers there is evidence of a significant benefit of 4mg gum compared with 2mg gum[253]. The results of this study show that approximately two thirds of the prescriptions for nicotine gum were for the higher strength of 4mg.

Therefore, although it was not possible to establish whether the patients included in this analysis were heavy or light smokers, these results, which highlight a greater level of utilisation of the higher strength gum and patches, could be considered a marker of appropriate prescribing.

d. Duration of therapy of nicotine patches

The manufacturers of nicotine patches recommend a course of 10 to 12 weeks therapy for smoking cessation. However, in 2004, a review of NRT for smoking cessation recommended that NRT is prescribed in blocks, usually of two weeks, and continued in those maintaining abstinence for a total of 6 to 8 weeks, and then discontinued[262]. It stated that the risk of dependence on NRT is small, and only a minority of patients (about 5%) who quit successfully continue to use medicinal nicotine regularly in the longer term[262]. In addition, the recent Cochrane review of NRT for smoking cessation reports that use of nicotine patches for up to 8 weeks was as effective as longer courses of treatment[253]. Furthermore, when NRT was introduced on the GMS Scheme it was recommended that the quantity on an initial prescription should be limited to 2 weeks of therapy[268]. The results of this analysis of GMS data illustrate that over three quarters (75.6%) of all patients were prescribed nicotine patch therapy for a period of less than or equal to 4 weeks with only 2.8% of patients receiving in excess of 3 months therapy.

Previous studies suggest 50% of smokers who initiate treatment continue for a second month, and only 30% of those who start continue for a third month[291, 292].

In a trial conducted by Abelin *et al.* (n=199) about 80% of patients completed the twelve-week treatment programme, and cessation rates of 36% were obtained for the nicotine patch therapy at the end of the 12 week period[284]. The investigators of The Imperial Cancer Research Fund General Practice Research Group Study found that more than half the patients (57.3%) had stopped using patch therapy before the 12 weeks study period had been completed[285]. The smoking cessation rates were less impressive than the study by Abelin *et al.*, with cessation rates of 19.4% for nicotine patch therapy versus 11.7% for placebo at 12 weeks[284]. However, this was a larger study (n=1,686), which possibly obtained a more representative sample of the heavy smoking general practice population. In addition, Abelin *et al.* deemed subjects as abstinent even if they smoked occasionally (up to 3 cigarettes a week).

In the placebo controlled trial by Russell *et al.* 1,200 subjects were randomised to nicotine patch therapy or placebo in 30 general practices in the UK[286]. Patients were prescribed 15mg of nicotine patch therapy for 12 weeks. At the end of the 12 week period only 59% of patients were still on active therapy and smoking cessation rates were 17.5% for nicotine patches as compared with 7.5% for placebo. The main impact of the nicotine patch

therapy was to increase the initial smoking cessation rate during the first 3 weeks. The authors suggest that there was no evidence that active treatment reduced relapse during the treatment period between 3 weeks and 3 months, and about half the subjects in each group relapsed during the period.

Other studies have identified that any smoking during the first week or two of treatment is a powerful predictor of failure to stop smoking by the end of treatment and at 6 months follow-up[293, 294].

In March 2002, NICE issued recommendations in relation to the duration of smoking cessation therapy[277]. NICE recommended that the initial supply of prescribed smoking cessation therapy should be sufficient for only 2 weeks after the target stop date. A second prescription should be issued only if the smoker demonstrates a continued attempt to stop smoking. If an attempt to stop smoking is unsuccessful the NHS is advised not to fund a further attempt within 6 months.

Therefore, although the duration of therapy for the majority of patients prescribed NRT patches on the GMS Scheme would be considered too short according to manufacturers recommendations, it appears to be consistent with current NICE guidelines and clinical evidence.

e. Combination therapy

The results of this study highlighted that all patients were prescribed therapies for nicotine dependence as single agents and there were no combinations of NRT preparations or NRT and bupropion SR prescribed.

There is limited evidence that combining NRT products is more effective than using single agents alone[253, 262]. It has been suggested that the combined use of patch and gum is a convenient therapeutic option as it gives the user a steady intake of nicotine (with the patch) that can be supplemented with nicotine gum to respond to momentary nicotine cravings. In one trial, the combination of bupropion SR and nicotine patch therapy produced slightly higher, but not statistically significant, quit rates than the patch alone[272]. However, in this study the rate of abstinence with nicotine patches was no different to placebo, a result that is not consistent with other studies. Moreover, these findings were not replicated in a second unpublished study combining bupropion SR and nicotine patch[275].

NRT products are not licensed for use in combination therapy. In addition, there is not enough evidence to guide healthcare professionals in advising on the most safe and effective use of combination products. The results of this study demonstrate that NRT was prescribed for GMS patients in accordance with the manufacturers' recommendations of not combining therapies.

5.5.3 Cost-Effectiveness of Smoking Cessation Therapies

It is widely acknowledged that smoking cessation interventions are one of the most cost-effective of all healthcare interventions. Published economic evaluations of smoking cessation interventions have adopted different methods and assumptions. For example, studies differ in terms of the comparator intervention, the study perspective, the discount rate and the measure of outcomes [e.g. life years saved versus quality adjusted life years (QALYs)][226, 276, 282, 295-302]. However, all the evaluations consistently indicate that smoking cessation interventions are cost-effective, even when rigorous sensitivity analysis has been applied. In fact, in April 2002 NICE stated that both "*bupropion and NRT are considered to be among the most cost-effective of all healthcare interventions*"[277].

In 1998, Parrott *et al.* evaluated the cost-effectiveness of 4 smoking cessation interventions: (1) a basic intervention of 3 minutes of opportunistic brief advice, (2) brief advice plus self help material, (3) brief advice plus self help material and NRT and (4) brief advice plus self help material, NRT, and a recommendation to attend a smoking cessation clinic[226]. The most cost-effective intervention, from the societal perspective, was brief advice alone (£136 per life year saved, £212 per discounted life year saved), although the most intensive intervention still represents good value for money at £873 per discounted life year saved. As the intensity of smoking cessation interventions increases, both cost and effectiveness increases but costs increase more rapidly. However, this observation should not be used to reject the use of more resource intensive interventions. Some smokers may only respond to more resource intensive interventions although it may be difficult to predict who may respond. Cost-effectiveness evaluations have not attempted to separate smokers into different subgroups (e.g. levels of motivation of smokers or levels of dependency of smokers). In addition, the incremental cost-effectiveness ratio (ICER) of more resource intensive interventions still compare favourably with many accepted healthcare interventions.

In 1999, Stapleton *et al.* used data from a randomised placebo controlled trial of nicotine patches and a survey of resource use to evaluate the incremental cost per life year saved by GP counselling with nicotine patch therapy, compared to GP counselling alone[282]. The analysis demonstrated that if GPs were to prescribe nicotine patches on the NHS for up to 12 weeks the incremental cost per life year saved would be £398 per person for patients younger than 35 years, £345 for those aged 35 to 44 years, £432 for those aged 45 to 54 years and £785 for those aged between 55 and 65 years. The study indicates that NRT is most cost-effective when used to treat smokers between the ages of 35 to 44 years[282]. Precribing rates of smoking cessation therapies on the GMS Scheme are highest for the 35 to 44 year age band. However it should be emphasised that interventions resulting in a cost per life year saved of less than £20,000 would be considered highly cost-effective, therefore treatment of all age groups in this study by Stapleton *et al.* was highly cost-effective[303]. However, it should also be highlighted that health should not be valued more highly in some age groups than others[304]. These findings, from the UK setting, are consistent with results from other studies undertaken in the US[295-298].

A study carried out in Switzerland evaluated the cost-effectiveness of counselling plus either nicotine gum, patch, nasal spray, inhaler or bupropion SR compared to counselling alone[299]. The ICERs ranged from €1,768 to €6,897 per life year saved for men and from €2,146 to €8,799 per life year saved for women. The most cost-effective treatments were bupropion SR and nicotine patch, and then, in descending order, the spray, the inhaler and, lastly, gum. The authors reported that the differences in ICERs were primarily due to differences in retail prices[299].

A systematic review of the clinical and cost-effectiveness of bupropion SR and NRT for smoking cessation, conducted on behalf of NICE, included 17 economic studies. However, no studies of the cost-effectiveness of bupropion SR were identified. A decision analysis model was therefore produced to compare the cost-effectiveness of four smoking cessation interventions: (1) advice or counselling only, (2) advice plus NRT, (3) advice plus bupropion SR and (4) advice plus NRT plus bupropion SR. The model was conducted from the perspective of the NHS and the primary outcome measure was the number of people achieving abstinence from smoking at 12 months. In this model life years saved were projected over a shorter period than the model adopted by Parrott *et al.* and hence produced higher cost-effectiveness estimates. The incremental cost per life year saved is approximately £1,000 to £2,399 for NRT, £639 to £1,492 for bupropion SR and £890 to

£1,969 for NRT plus bupropion SR. The incremental cost per QALYs are about £741 to £1,777 for NRT, £473 to £1,106 for bupropion SR and £660 to £1,459 for NRT plus bupropion SR. The authors concluded that smoking cessation interventions using either bupropion SR or NRT may be considered very cost-effective compared with other healthcare interventions[276].

Similar findings have been reported in other economic evaluations comparing NRT and bupropion SR[300-302]. Although bupropion SR seems more cost-effective than NRT, it has been highlighted that the evidence base for the efficacy of bupropion SR is much less extensive than for NRT and the cost of adverse events of bupropion SR were not included in any of the economic evaluations.

In summary, all the available evidence suggests that therapies for nicotine dependence can be provided at a very low cost per QALY or cost per life year saved[305]. All of the cost-effectiveness models, however, assume that people who quit smoking using NRT or bupropion SR would otherwise have never quit, or would only have a small chance of quitting each year during their lifetime. The assumption may overstate the reality. However, while this might effectively make NRT and bupropion SR more expensive per unit of benefit gained, they would almost certainly still be cost-effective. On the other hand, the cost-effectiveness of smoking cessation interventions may be underestimated by failing to account for the benefits to passive smokers. In addition, some studies have quantified outcomes in life years saved, not allowing for changes in quality of life, thereby potentially underestimating the cost-effectiveness of smoking cessation interventions.

While both NRT and bupropion SR are effective compared with no cessation aids, the majority of smokers who are prescribed them will still fail to quit at any single attempt. While this is often disappointing for prescribers and smokers themselves, the relatively low success rates are still a highly cost-effective use of resources. Smoking cessation in the general practice setting, with an incremental cost per QALY of about £741 to £1,777 for NRT, is more cost-effective than many other interventions e.g. the incremental cost per life year gained for prescribing pravastatin for primary prevention of coronary heart disease was estimated to be between £5,601 (undiscounted) and £13,995 (discounted) and the cost per discounted life year saved of simvastatin for secondary prevention was £5,502[306, 307]. Furthermore, statins are prescribed throughout a patient's lifetime, whereas NRT is only prescribed for a few weeks.

Care should be taken when extrapolating the results of these evaluations, as cost-effectiveness estimates are likely to be time and country specific and highly dependent on the healthcare system in question. However, ICERs for smoking cessation interventions are well below the threshold considered to be cost-effective and therefore it has been assumed that appropriate prescribing of NRT would also be cost-effective in the Irish setting.

5.5.4 Implications for Decision Makers

NRT may be classed as a lifestyle drug. A lifestyle drug may be defined as one used to alleviate: (i) a lifestyle problem or condition (as opposed to a health problem), regardless of the cause, or for lifestyle enhancement (e.g. medications for alopecia); or (ii) a health problem for which the underlying cause is assumed to be within the realm of personal responsibility, and behaviour modification is an alternative treatment (e.g. medications for smoking cessation)[308].

Lifestyle drugs have attracted much attention over the last few years, with concerns for the future funding of health services around the world if such therapies are publicly reimbursed. As overstretched healthcare budgets are almost universal, funding these drugs inevitably means limiting other forms of treatment for other patients. The issue therefore is essentially one of rationing and how services are prioritised. Nevertheless, those lifestyle drugs, such as NRT, with public health benefits are likely to be funded, as in the long run they are likely to be cost-effective[309].

The Dunning Report in the Netherlands described four filters to be passed before a treatment should be considered for public funding: (1) it should constitute necessary care; (2) it should be effective; (3) it should be efficient and (4) it should be more an issue of public and collective responsibility rather than individual responsibility[310]. How does this apply to NRT in Ireland? With regard to the second and third criteria the efficacy and cost-effectiveness of NRT for smoking cessation are well established. The remaining criteria are more difficult as they are not technical issues but depend on making value judgements. The first issue relates to "necessary care" and it may be argued that NRT constitutes necessary care given that smoking is the largest preventable cause of morbidity and mortality in Ireland. The final issue is difficult; how can the limits of collective versus individual responsibility be defined? Debates on these issues have undermined the use of the Dunning principles in the Netherlands[310]. Thus the technical issues are often the easiest to address but do not aid in the difficult political, ethical and social considerations.

Given that the analysis of NRT prescribing on the GMS Scheme suggests quality prescribing, and that clinical and cost-effectiveness evidence favours the use of NRT, consideration should be given to implementing policies to further promote the use of NRT in the Irish primary care setting.

5.6. Conclusion

This evaluation of prescribing of therapies for nicotine dependence, utilising the GMS prescription database, suggests high quality prescribing of NRT in the general practice setting. NRT appears to have been prescribed for the appropriate patient group at the recommended strength. The duration of therapy is in keeping with NICE guidance to optimise cost-effectiveness. The results of economic evaluations in other settings indicate that NRT is one of the most cost-effective healthcare interventions. Thus, this study demonstrates that prescribing of NRT on the GMS Scheme is in accordance with current clinical and cost-effectiveness evidence and should achieve value for money.

However, this study also highlighted that, although expenditure on NRT on the GMS Scheme is significant, only a small proportions of smokers in the GMS eligible population are prescribed NRT. Health care professionals could encourage more smokers to quit by increasing public awareness of the availability of NRT on the GMS Scheme.

Since the report on NRT from the NCPE (which includes the results reported in this chapter) was presented to the DoHC, a decision was made to continue to reimburse NRT on the GMS Scheme. In addition, some consideration was given to reimburse NRT on the DP Scheme but this did not come to fruition.

This study demonstrates that the GMS prescription database is a valuable tool for evaluating the quantity and quality of prescribing of reimbursable medicines on the GMS Scheme in Ireland. This information could be more widely used in planning, monitoring and assessing the effectiveness of government pharmaceutical policy in the future.

Chapter 6

Conclusions

Table of Contents for Chapter 6

6.1 Pharmaceutical Cost-Containment Strategies

Almost all EU Member States have introduced pharmaceutical cost-containment measures in the last few years which include price cuts, pharmaceutical rebates, policies to promote generic markets, reference pricing systems and requirements for the economic evaluation of new drugs. It can be expected that these cost-containment measures will help to control rising pharmaceutical expenditures. However, demographic trends in Europe, in particular population ageing, and the change in the product mix of total pharmaceutical expenditure towards newer products will be expected to lead to an increase in overall expenditure.

It is difficult to establish which of the different cost-containment strategies adopted by the different EU Member States has been most effective as they are rarely applied in isolation and it is often difficult to determine the influence of each in an overall effect[74]. All the individual cost-containment strategies are interdependent, and therefore the effect of a single component in a particular setting may not be easily predictable[83]. Consequently, the manner in which these strategies are employed, taking into account local factors (e.g. health policy versus industrial policy objectives), is a key consideration in implementing any changes, as transferring a policy from one country to another may not result in similar outcomes. Therefore, before any policy is introduced, a full assessment of the potential impact is essential.

In this thesis the potential impact of introducing policies to control the rising drug expenditures in the Irish healthcare setting were evaluated. In addition, the use of the GMS prescription database to monitor drug utilisation and expenditure on reimbursed pharmaceuticals was examined. As a result of the research described in this thesis, the DoHC has, for the first time, a detailed analysis of the issues which are up for discussion in the negotiation of the new IPHA-DoHC Agreement.

6.2 The Irish Pharmaceutical Pricing and Reimbursement System

In Ireland the Agreement between the DoHC and IPHA (1993-2005) on the supply terms, conditions and prices of medicines is currently being renegotiated. The agreement has remained relatively unchanged for a 12-year period. This has provided a stable environment for the pharmaceutical industry in Ireland. It is in the interest of policy makers to promote a favourable environment for the pharmaceutical industry, given the major contribution it makes to the Irish economy in terms of exports and employment.

However, over the last decade there has been a major increase in expenditure on pharmaceuticals and healthcare in general in Ireland. It is clear that pharmaceutical expenditure in Ireland will continue to grow should current trends continue. As a result of this the issue of obtaining value for money from pharmaceutical expenditure arises.

These conflicting objectives of pharmaceutical policy making, where issues related to quality of healthcare, public expenditure and industrial growth must all be considered, is not unique to the Irish setting. In general, policy makers tend to be torn between the conflicting demands to contain rising costs, improve health, support industrial growth and remain within the EU legislative framework[1]. These areas are highly interconnected and decisions concerning one area usually affect the other two areas.

6.3 European Pharmaceutical Pricing and Reimbursement Systems

The review of the existing pharmaceutical cost-containment policies in Europe (Chapter 2) illustrates the complexities of drug policy decision making. Part of the work for this thesis involved compiling an up-to-date comprehensive review of the European pharmaceutical pricing and reimbursement strategies[60]. However, it is well known that there are difficulties in obtaining comprehensive and accurate information on the European pharmaceutical pricing and reimbursement systems because pharmaceutical policies in the EU Member States are constantly changing and therefore this information very rapidly becomes out of date.

In order to overcome this problem the Pharmaceutical Pricing and Reimbursement Information (PPRI) project was commissioned and funded by European Commission, Health and Consumer Protection Directorate-General and will run from April 2005 to spring 2007. The project is co-funded by the Federal Ministry for Health and Women's Issues, Austria. The objective of the project is to develop a network of institutions in order to improve information and knowledge about the pharmaceutical systems in an enlarged Europe on an ongoing basis. This group will provide an important network for the NCPE and decision makers in Ireland in the future.

6.4 Pharmaceutical Pricing in Ireland

The price of medicines in Ireland reflects a Northern European price, which is higher than the European average. In this thesis, Irish pharmaceutical prices were compared to prices in Denmark (which were linked to an average European price at the time of the study) and the UK (which is reported to have one of the highest prices for medicines in the EU). This is the first international price comparison study undertaken from the Irish perspective.

Comparison of the Irish ex-wholesale price with a Danish, average European and UK price highlighted that potential savings ranging from €6.8 million to €20.7 million (which represents between 3.5% and 10.7% of the total ingredient cost of the sample of drugs) could be achieved if the Irish price of a sample of medicines were substituted with a UK or a Danish price respectively. Therefore the results of this study demonstrate the high ex-wholesale price of prescription medicines in Ireland and the potential for savings to be made by substituting a Danish, average European and UK ex-wholesale price.

However, another important finding from this study is that conclusions about the relative prices of drugs in different countries are sensitive to the sample and methodology used. There is no standard methodology for comparing pharmaceutical prices and as a result it is important to be aware of the limitations of the various methods when interpreting the results of these studies.

The results of this international price comparison study have identified issues that are worthy of consideration in future negotiations of the pricing system for medicines in Ireland. The analysis highlights that potential savings could be made by, for example, changing the current pricing mechanism and reducing the wholesale margin. The Irish wholesale margin is higher than in Denmark and the UK. In addition, as price cuts are a feature in other EU Member States, a system for the regular review of prices would facilitate revision of prices in line with the reference countries to which the Irish price is linked. This is particularly important for drugs which are launched in Ireland prior to the other countries to which the Irish price is linked. The results of the price comparison study in this thesis illustrate that savings could be achieved if Ireland revised its prices in line with those of the UK and Denmark on a regular basis.

However, any change in the current Irish pricing system would potentially have an impact on the price of drugs across Europe, as many other European countries link their price to

the Irish price. Therefore, such a measure may conflict with Irish industrial policy objectives. Consideration of alternative measures to contain pharmaceutical expenditure in Ireland, such as promoting the generic market and demonstration of cost-effectiveness of high cost drugs, could potentially lead to greater savings.

6.5 The Irish Generic Market

It is generally accepted that the prescribing of less expensive generic drugs is cost-effective. An analysis of the potential impact of increasing generic drug utilisation on the GMS and DP schemes (for the top 30 drugs by expenditure) demonstrated that savings in the region of €15.4 million to €21.8 million could be achieved, depending on whether most or least expensive generic was dispensed respectively. These estimated savings represent between 3.7% and 5.3% of the total ingredient cost for the top 30 drugs by expenditure on the two schemes (€413 million), according to whether the most or least expensive generic drug was dispensed. In addition, there is the potential for increased savings to be made from generic substitution over time, as more high cost and widely prescribed medicines lose patent protection and less expensive generic equivalents become available on the market.

Nevertheless, the current system in Ireland offers few incentives to promote the use of generic drugs. Furthermore, there are a number of barriers to implementing policies to promote the generic market. Experience from other countries, illustrates that the savings achieved in practice may be considerably less than total possible savings. Successful implementation of a generic substitution policy would require legislative changes, as well as the introduction of appropriate incentives for pharmacists to dispense generically, for prescribers to allow generic substitution and for patients to accept generic drugs. Furthermore, while generic substitution may reduce spending on drugs, it can only tackle part of the problem of containing costs, as new drugs are patent protected and their increased use will not be affected. In 2003, patent protected drugs accounted for 77% of expenditure on the GMS Scheme and 80% of expenditure on the DP Scheme. Therefore, consideration should also be given to evaluating the cost-effectiveness of new drugs and to monitoring the actual use of high cost drugs on the GMS and DP Schemes to ensure value for money is achieved.

Ultimately, the decision to introduce pro-generic policies will depend on specific national health versus industry policy objectives. An alternative strategy, to implementing a generic substitution policy, was proposed in Chapter 4. This would involve introducing a fixed percentage reduction (e.g. 20%) in the price of medicines on patent expiry. Similar savings could be achieved without the potential barriers to implementing generic substitution if such a policy was adopted.

6.6 Monitoring Drug Utilisation and Expenditure on the GMS Prescription Database

Finally, the use of the GMS prescription database to monitor utilisation of and expenditure on pharmaceuticals was investigated.

6.6.1 Prescribing of NRT on the GMS Scheme

The analysis of prescribing of NRT highlighted the level of detail that may be obtained from this primary care database, which covers all medicines reimbursed under the GMS, DP and LTI Schemes in Ireland. The evaluation suggests high quality prescribing of NRT in the primary care setting. NRT appears to have been prescribed for the appropriate patient group, at the recommended strength. The duration of therapy was in keeping with NICE guidance to optimise cost-effectiveness. The results of economic evaluations in other settings indicate that NRT is one of the most cost-effective healthcare interventions. Therefore, this study demonstrated that prescribing of NRT on the GMS Scheme is in accordance with current clinical and cost-effectiveness evidence.

This study also identified that only a small proportion of smokers in the GMS eligible population were prescribed NRT. Therefore, given that NRT is one of the most cost-effective healthcare interventions, health promotion efforts should focus on increasing prescribing of NRT to the GMS eligible population.

6.6.2 The Value of the GMS Prescription Database

The three studies described in this thesis demonstrate that the GMS prescription database is a valuable source of information. The database could be used in the future to plan, monitor and assess the effects of pharmaceutical policy. In 1995 in Quebec, Tamblyn *et al.* assessed the accuracy of drug information within a prescription claims database. They reported that this may be "*one of the most accurate means of determining drugs dispensed*

to individuals"[311]. Prescription databases provide drug related information for "real-world" patients. However, as Sculpher and Drummond have stated, "*gathering, synthesising and scrutinising data is a valuable exercise but it is costly*"[312]. Part of the challenge for the NCPE and Irish decision makers is that this information is used in an appropriate way to maximise health gain and achieve value for money.

The GMS prescription database is currently being used to provide information on prices, utilisation of and expenditure on medicines to the EURO-MED-STAT project. The aim of the EURO-MED-STAT project is to collate this data from all the EU Member States. In the future, using the same methodology adopted in Chapter 3 (International Price Comparison Study) an attempt will be made to undertake an international price comparison study using the price and utilisation data from the EURO-MED-STAT project. This will be the first time that such data will be able from one source from all of the EU Member States.

6.7 Recommendations

The review of the European pharmaceutical pricing and reimbursement strategies illustrated that most countries either tend to have high prices for patented medicines and strong generic markets (e.g. the UK and Germany) or low prices and a relatively smaller generic market share (e.g. Spain and France). In contrast, Ireland has one of the highest ex-wholesale prices for medicines in Europe and also has a low generic market penetration. There are a number of issues which may be addressed in the renegotiation of the current IPHA-DoHC Agreement:

- Regular price revisions to take account of changes in the price of drugs in the other countries to which the Irish price is linked.

- Implementation of policies to ensure that the State is only paying high prices for medicines that are protected by patent. This could be achieved by promoting the generic market in Ireland by authorising generic substitution by pharmacists. Alternatively, or in addition to this, a reduction in the price of original branded medicines on patent expiry could be negotiated.

- Consideration should be given to including other criteria for directly setting prices in Ireland, for example, demonstration of the therapeutic value and cost-effectiveness of the drug compared to similar products already on the market. This option would be particularly important when Ireland is the first country of launch of a product. At present, if Ireland is the first country in which a product is launched in the EU, there is essentially a system of free pricing.

- One of the main drivers of the growth in pharmaceutical expenditure is the introduction of new drugs. Therefore, perhaps the most important development in pricing and reimbursement policy in Ireland would be to link drug reimbursement with a demonstration of cost-effectiveness of potentially high cost medicines. The first step towards evaluating new technologies was the creation of HIQA, as part of the recent reform of the health service. However, it is not clear yet how the economic evaluation of medicines will be incorporated into the decision making process.

- Revision of the current system for directly controlling the price of medicines. Prices are set by comparing the price of a drug to the price in 5 other Northern European countries. Consideration should be given to changing the basket of countries to which the Irish price is linked. However, this will not only affect prices on the Irish market but also the price in other EU Member States, which link their price to an Irish price. Therefore, this option may not favour the pharmaceutical industry.

Finally, when considering implementing any pharmaceutical pricing and reimbursement policy it is also important to focus on the broader healthcare perspective, that is, reducing pharmaceutical expenditure may result in increased spending in other areas, such as secondary care.

6.8 Conclusion

As the current system operates there is no requirement and little incentive to prescribe less expensive but equally effective medicines. Furthermore, pharmacists may benefit financially from the prescription of higher cost drugs on the DP and LTI Schemes. Pharmaceutical companies will, naturally, influence prescribers and pharmacists to use

drugs which will maximise their profits. Therefore, the current system of prescribing and dispensing of medicines is not conducive to achieving value for money. The results of this thesis highlight the potential impact of introducing policies to control the rising drug expenditures in the Irish healthcare setting and the use of the GMS prescription database to monitor drug utilisation and expenditure on reimbursed pharmaceuticals.

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List of Publications

Publications Resulting from This Thesis

1. **The potential impact of implementing a system of generic substitution on the community drug schemes in Ireland.**
   Tilson L, Bennett K, Barry M.
   Eur J Health Econ 2005 Sept; 6 (3): 267-273.

2. **The high cost of medicines in Ireland: Is it time to change the pricing mechanism?**
   Tilson L, McGowan B, Bennett K, Barry M.
   Eur J Health Econ 2004 Dec; 5 (4): 341-4.

3. **Prescribing trends for nicotine replacement therapy in primary care.**
   Tilson L, Bennett K, Barry M.
   Ir Med J. 2004 Oct; 97 (9): 270-3.

4. **Generic drug utilisation on the General Medical Services (GMS) Scheme in 2001.**
   Tilson L, McGowan B, Ryan M, Barry M.
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Other Publications Relevant to the Thesis

1. **European Pharmaceutical Pricing and Reimbursement Strategies (2005).**
   Tilson L and Barry M. Available from: http://www.ncpe.ie.

2. **Cost effective prescribing of Proton Pump Inhibitors (PPIs) in the GMS Scheme.**
   McGowan B, Bennett K, Tilson L, Barry M.
   Ir Med J. 2005 Mar; 98 (3) :78-80.

3. **Pricing and reimbursement of drugs in Ireland.**
   Barry M, Tilson L, Ryan M.
   Eur J Health Econ. 2004 Jun; 5 (2): 190-4.

4. **Patient co-payment for prescription medicines across Europe--how do we compare?**
   Barry M, Tilson L, Ryan M.
   Ir Med J. 2004 Mar; 97 (3): 69-70.

Appendices

Appendix 1: IPHA-DoHC Agreement

Agreement between the Association of Pharmaceutical Manufacturers of Ireland (APMI) and the Department of Health and Children on Supply Terms, Conditions and Prices of Medicines Supplied to the Health Services i.e. the General Medical Services (GMS) and Other Community Drugs Schemes, Health Boards and Hospitals.

1. **INTRODUCTION**

The Association and the Department of Health and Children have agreed on the terms set out below to replace the arrangements contained in the Agreement dated June 1993. This Agreement will come into effect on 1 August 1997 and will govern all supplies of medicines.

2. **DURATION**

The duration of the Agreement is the period 1 August 1997 to 31 July 2004, after which twelve months notice to renegotiate may be given by either party.

3. **SCOPE & COVERAGE**

3.1 The Agreement covers all medicines prescribable and reimbursable in the GMS Scheme and the Community Drugs Schemes and all medicines supplied to hospitals and health boards.

3.2 Medicines reimbursable in the GMS Scheme at the date of the commencement of this Agreement will, subject to routine deletions and provided they conform with this Agreement and with the reimbursement criteria published by the Minister, pursuant to EC Directive 89/105EC, remain reimbursable in GMS Scheme for the duration of the Agreement.

The list of medicinal items reimbursable under the Drugs Payment Scheme will not be less than that reimbursable under the GMS Scheme.

New items of medicines granted a Product Authorisation by the Irish Medicines Board, provided they conform with this Agreement and with the published reimbursement criteria, will be reimbursable in the GMS and Community Drugs Schemes for the duration of the Agreement.

3.3 Doctors will be free to prescribe the medicines of their choice from the list of medicines available under the GMS or Community Drug Schemes as appropriate. Pharmacists will be required, in accordance with their contracts with the health boards, to dispense to patients the medicines prescribed by doctors.

3.4 The Department of Health and Children reserves the right to influence the prescribing habits of doctors.

3.5 All health boards and hospitals are bound by the terms of this Agreement.

4. PRICES

4.1 Price Freeze

The price to wholesaler on 1 August 1997 of each item of medicine covered by this Agreement will not be increased for the term of the Agreement (save as might be required under Clauses 4.2 and 4.4).

4.2 International Price Movements

From 1 August 1997, if the cumulative, currency adjusted, average increase or decrease in the indices of wholesale prices of prescription medicines, in the following EU. States, Denmark, France, Germany, the Netherlands and the UK exceeds 10%, the application of Clause 4.1 will be reviewed by both sides.

4.3 New Medicines Introduced to Ireland after 1 August, 1997

The price to wholesaler (Irish Wholesale Price) of any new item of medicine, introduced to Ireland on or after 1 August 1997 and covered by this Agreement shall not, on the date of initial price notification to the GMS (Payments) Board, exceed the lesser of the currency adjusted UK wholesale price and the average of the currency adjusted wholesale prices in the following EU States, Denmark, France, Germany, the Netherlands and the UK.

If any new item of medicine is not available in all nominated EU States on the date of initial price notification to the GMS (Payments) Board, the Irish wholesale price shall not exceed the lesser of the currency adjusted UK wholesale price and the average of the currency adjusted wholesale prices in the nominated EU States in which the new item of medicine is available.

If any new item of medicine is not available in the UK on the date of initial price notification to the GMS (Payments) Board, the Irish wholesale price shall not exceed the average of the currency adjusted wholesale prices in the nominated EU States in which the new item of medicine is available.

If any new item of medicine is not available in any of the nominated EU States, the Irish wholesale price will be agreed between representatives of the manufacturer/importer concerned and the Department of Health and Children.

4.4 Price Modulation

Product price modulation will be permitted under this Agreement, on an exceptional basis and on condition that any such product price modulation will be demonstrably cost neutral in each year of this Agreement.

The Department of Health and Children may require audited documentation of any price modulation and shall have the sole discretion to accept, reject or seek variation in any modulation application and to seek an appropriate refund if the terms of this clause are not adhered to.

4.5 New Chemical Entities

The Department of Health and Children reserves the right to seek cost benefit studies for any new chemical entity introduced to Ireland on or after August 1st 1997 and to raise these in discussions with the Association.

4.6 Applicable Exchange Rates

The applicable exchange rates for initial price notification of medicines will be the exchange rates published by The Central Bank of Ireland, on the date of price notification to the GMS (Payments) Board.

4.7 Prices referred to in this Agreement are VAT exclusive prices.

5. GENERAL MEDICAL SERVICES SCHEME (GMS SCHEME)

5.1 In regard to medicines for the General Medical Services Scheme, it is agreed that:

(i) manufacturers and principal importers shall supply wholesalers at the appropriate wholesale discount;

(ii) wholesalers shall supply retail pharmacists at the Irish trade price:

(iii) manufacturers and importers shall themselves be free, if they so wish, to supply to retail pharmacists at the Irish trade price.

5.2 The General Medical Services (Payments) Board, on behalf of the health boards, will reimburse retail pharmacists at cost for the medicines properly dispensed by them under the Scheme.

5.3 The Board will advise each manufacturer or importer of each quantity and value of his/her medicines dispensed under the GMS Scheme each month. The manufacturer/importer will rebate to the Board an amount equal to 4% of the value (at trade price level) within 30 days of the date of invoice. On 1 August 1998, and for each subsequent year of the Agreement, the rebate will be an amount equal to 3% of the value (at trade price level) of medicines dispensed in the GMS Scheme.

6. HOSPITAL SUPPLIES

6.1 Supplies to hospitals or to health boards will be invoiced at the Irish trade price less wholesale discount (currently trade price less 15%) on orders over €634.87 where orders are placed:

(a) with the manufacturer or importer of the products concerned
or
(b) with a wholesaler who is the agent for the products concerned.

6.2 No discount will be given in the case of orders under €634.87 or orders placed with a wholesaler for products for which he/she is not the agent or importer. In all cases, the

€634.87 refers to products of a single manufacturer. These discounts are offered on the basis of normal monthly settlement of accounts.

6.3 Health boards may be authorised to appoint one hospital within each region to combine single orders (normally placed monthly) from satellite hospitals, so as to qualify them for any discounts.

6.4 These terms are binding on all hospitals and health boards, however hospitals and health boards will have the right to negotiate revised arrangements with individual manufacturers, importers or agents, designed to secure more favourable terms than those referred to in paragraph 6.1 (save by way of documentary tenders other than those required to comply with European Community Procurement Directives).

Additional terms secured by hospitals and health boards under this clause may be withdrawn by manufacturers, importers or agents if agreed credit terms are exceeded.

7. EXCEPTIONAL CIRCUMSTANCES

7.1 Manufacturers or other importers oppressed by the terms of this Agreement may make direct representations to the Department of Health and Children for variation of any term of this Agreement, including its price terms.

7.2 The Department of Health and Children shall have the final decision on whether to vary the terms of this Agreement in any case, but will consult with IPHA before reaching its decision.

8. VACCINES

This Agreement will not prevent arrangements being made for the supply of vaccines or similar products for the healthcare services.

9. CONTINUITY OF SUPPLY

In the interest of an uninterrupted supply to patients of medicines for which there is no therapeutic alternative available in the market, manufacturers, importers or their agents must provide at least 12 months notice to the Department of Health and Children of their intention to withdraw such medicines from the market. Reasons for withdrawal must be given in writing to the Department at the time of the notice of the intention to withdraw.

Where a manufacturer, importer or his or her agent intends to provide notification of intention to withdraw such medicines from the market, he or she shall first write to the Department of Health and Children with a view to initiating discussions regarding the circumstances surrounding the intended withdrawal in accordance with agreed guidelines, these discussions to be concluded within a reasonable period of time.

10. **MISCELLANEOUS**

The operation of this Agreement will be reviewed by the Department of Health and Children and the Association at regular intervals and any matter relating to the interpretation of these terms, including prices terms, or the operation of this agreement will be resolved in discussions between the Association and the Department.

DATED JUNE 2002

Appendix 2. Reimbursement Criteria for Inclusion of Medicines on the Positive List.

An Roinn Sláinte agus Leanaí

Council Directive of 12 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (89/105/EEC).

Pursuant to Article **11.2** of the above Directive, the Minister for Health and Children hereby advises that the following criteria apply in respect of the consideration of applications from pharmaceutical companies concerning the inclusion of medicinal products in the General Medical Services Scheme **(GMS)** and the Drug Payment Scheme **(DPS)**:

1. The product must be an 'allopathic' medicinal product which is the subject of a current product authorisation granted by the Irish Medicines Board under the Medicinal Products (Licensing and Sale) Regulations, 1998 (S.I. No. 142 of 1998) or an authorisation granted or renewed by the European Commission in accordance with EU Council Regulation (EEC) No. 2309/93 laying down Community procedures for the authorisation and supervision of medicinal products;

2. The product must be such that it is ordinarily supplied to the public only on foot of a medical prescription;

3. The product should be one which may be used under the supervision of a general medical practitioner and which is not restricted to hospital or medical specialist use;

4. The product should not be advertised or promoted to the public excluding special arrangements made with regard to nicotine replacement therapy;

5. The product should not be one for the purpose of obtaining a cosmetic effect (e.g. hair restorers);

6. The price of the product should be in accordance with the agreements in place between the Department of Health and Children and the pharmaceutical industry;

7. Notwithstanding paragraph 2, products in the following categories which otherwise comply with these criteria are eligible for inclusion in the GMS Scheme-
    i. anthelmintics;
    ii. anti-diarrhoeals;
    iii. non - sedating oral liquid antihistamines and other antihistamines in solid unit dosage forms;
    iv. products authorised and recommended for the treatment of scabies;
    v. products authorised and recommended for the treatment of psoriasis;
    vi. vitamin drops intended for infants;

vii. iron drops intended for infants;

viii. iron and folic acid in solid unit dosage forms;

ix. products containing iron salts as their single active component;

x. products (not being antacids) authorised and recommended for the treatment of ulcers in the gastrointestinal tract;

xi. medicinal products authorised and recommended as phosphate-binding agents in the treatment of renal failure in patients on renal dialysis;

xii. bulk forming products authorised and recommended for colostomy or ileostomy control;

xiii. products, being antacids, acting in the gastro-intestinal tract (in all forms);

xiv. products, (in solid unit dosage forms) being analgesics, acting on the central nervous system;

xv. medicinal products which are specifically authorised and recommended for use in the treatment of chronic constipation;

xvi. folic acid tablets, 400 mcg specifically authorised and intended only for the prevention of Neural Tube Defects in children;

xvii. products containing calcium and vitamin D, specifically authorised and intended for the prophylaxis and treatment of osteoporosis and osteomalacia;

xviii. products for nicotine replacement therapy.

8. Where under the forgoing criteria products in a particular therapeutic category have been deleted from the GMS and DPS Schemes except for product(s) in that category which are present by virtue only of their prescription classification, and the said product(s) have a recognised abuse potential by virtue of their being controlled drugs under the Misuse of Drugs Acts, 1977 and 1984, then those product(s) shall, in those circumstances, not be eligible for inclusion in the GMS and DPS Schemes.

30 April 2003