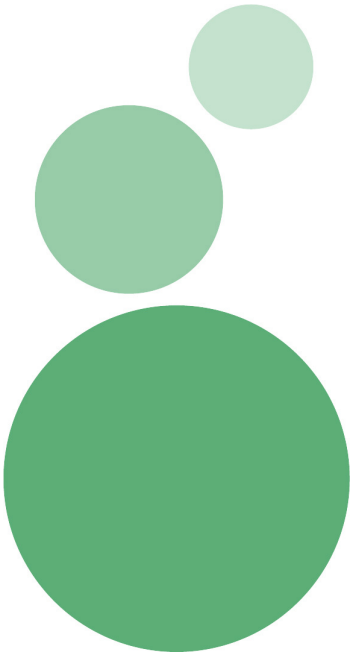
matrix insight

Executive Agency for Health and Consumers

Health Reports for Mutual Recognition of Medical Prescriptions: State of Play

24 January 2012

Final Report



Acknowledgements

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For questions about the report, please contact Dr Gabriele Birnberg (gabriele.birnberg@matrixknowledge.com).

Executive Summary

This study has been carried out in the context of Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare (CBHC). The CBHC Directive stipulates that the European Commission shall adopt measures to facilitate the recognition of prescriptions issued in another Member State (Article 11). At the time of submission of this report, the European Commission was preparing an impact assessment with regards to these measures, designed to help implement Article 11. The results of this study were to inform specifically the baseline analysis underlying the status quo policy option (cf. 'Option 1 – "no policy change"' in associated Roadmap). More specifically, this study provides a scientifically valid baseline measurement of existing problems associated with the mutual recognition of medical prescriptions, including an estimation of the impact in terms of financial cost and patient harm.

Study Design

In addition to targeted evidence reviews and stakeholder interviews, the analysis was informed to a large extent by a **survey completed by nearly 1,000 dispensers across seven Member States** (Denmark, Germany, Greece, France, Netherlands, Poland, UK) sharing their views on dealing with foreign prescriptions across eight pathologies (Asthma, COPD, Depression, Diabetes, Epilepsy, Hypertension, Ischaemic Heart Disease, Osteoarthritis/Rheumatoid Arthritis).

The seven sampled Member States represent 56% of the EU population[1] and 53% of all prescriptions[2]. The sampled pathologies account for 25% of the disease burden in men and 29% of the diseases burden in women[3] across the WHO Europe A region and between 19% and 64% of all prescriptions in Denmark, the Netherlands, France, Germany and England.[4]

The research team made a conscious decision not to engage in any form of 'mystery shopping'. The concern was that pharmacists would be reluctant to engage with the research in such a way that could raise questions of professional liability. The research team thus opted to engage with pharmacists in their capacity as experts, asking them for their opinion on possible problems associated with the dispensing of prescriptions originating in another EU Member State.

Main Findings

An **estimated 2.33 million foreign prescriptions** are presented for dispensing across the EU annually. Our analysis suggests that **55% of these prescriptions are not dispensed immediately.**

[1] Eurostat (2011). Population on 1 January by age and sex. Available at: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjan&lang=en. Retrieved on 24th January 2011.
[2] If prescriptions are assumed to be proportional to the amount of pharmacists, according to PGEU data outlined above.
[3] Diseases burden measured here in DALYs, according to WHO data.
[4] Various national sources, outlined in the annex.

Key challenges are verification of prescriber and prescription; possibly exacerbated by handwritten prescription, those presented in an unfamiliar language, or missing information. The availability of (substitute) drugs has been mentioned as a problem less often.

In case of a problem prescription, patients may incur a short delay or medication gap as they obtain a new prescription from a local physician. Existing evidence suggests that although a short-term health effect following a medication gap cannot be ruled out for the majority of pathologies, the relative frequency of it is not clear and **the anticipated level of harm tends to be low.**

The major cost associated with a medication gap due to a delay in dispensing is thus the **cost of going to a local physician**. Assuming that for each of the 1.28 million delayed prescriptions a visit to a local physician is required (estimated at €34 per visit), **the associated costs amount to approximately € 43.6 million per year.**

Contents

1.0 Introduction

This document contains the final report produced by Matrix Insight Ltd for (**EAHC/2010/Health/01/Lot1): Health Reports for the Mutual Recognition of Medical Prescriptions: State of Play**.

1.1 Context and Study Objective

This study has been carried out in the context of **Directive 2011/24/EU** of the European Parliament and of the Council of 9 March 2011 **on the application of patients' rights in cross-border healthcare (CBHC).** The CBHC Directive stipulates that the European Commission shall adopt measures to facilitate the recognition of prescriptions issued in another Member State (Article 11).[5] At the time of submission of this report, the European Commission was preparing an impact assessment with regards to these measures, designed to help implement Article 11. The results of this study were to inform specifically the baseline analysis underlying the status quo policy option (cf. 'Option 1 – "no policy change"' in associated Roadmap[6]). More specifically, this study provides a scientifically valid baseline measurement of existing problems associated with the mutual recognition of medical prescriptions, including an estimation of the impact in terms of financial cost and patient harm.

According to research carried out by Mäkinen (2007), **problems exist in the area of mutual recognition of medical prescriptions among EU Member States.** Mäkinen studied the delivery of non-national (cross-border) prescriptions from the 15 EU Member States in 1999-2003. Her study evaluated the dispensing outcomes for 29 typed prescriptions for phenoxymethyl penicillin, 15 from Finland and 14 from Luxembourg, for imaginary patients with a sore throat. The prescriptions bore the relevant brand name plus the generic drug name, and were taken to pharmacies across the EU by healthy adults. Of the 29 prescriptions, 10 (34%) were either not dispensed or a substitute drug given, illustrating problems related to the unavailability of the prescribed drug. Fourteen pharmacies dispensed penicillin, four gave amoxicillin and two, both in Italy, gave cephalexin. The UK did not dispense either prescription as the prescriber was not licensed to practice in the UK, showing that mutual recognition of qualifications was not considered sufficient by these UK pharmacists. Reflecting adherence to the Nordic countries' agreement[7], Sweden would only dispense prescriptions from Finland, not Luxembourg (Mäkinen, 2007).

With the exception of Mäkinen (2007), publications in this area are limited. At the time of writing this report, several research institutes were undertaking relevant research. The Netherlands

[5] European Union (2011). Directive on the Application of Patients' Rights in Cross-Border Healthcare (L88/45). Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF

[6] European Commission (2011). Roadmap for Implementing measures for improving the recognition of prescriptions issued in another Member State under Article 11 para. 2 of the Directive on the Application of Patients' Rights in Cross-Border Healthcare (CBHC). Available at: http://ec.europa.eu/governance/impact/planned_ia/docs/2013_sanco_004_mutual_recognition_of_prescriptions_en.pdf

[7] The Nordic countries (Sweden, Denmark, Finland) mutually recognise (most) prescriptions since 1977.

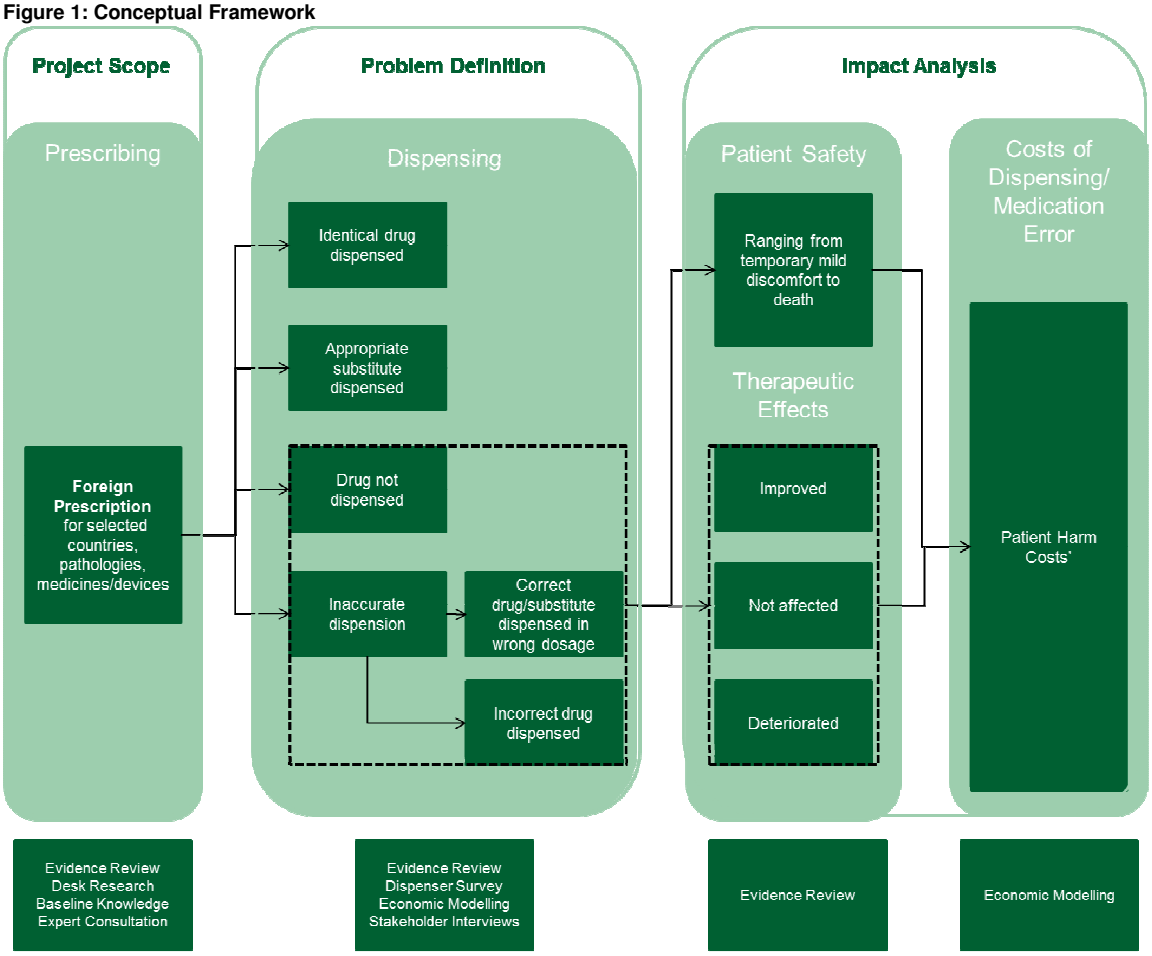
Institute for Health Service Research (NIVEL) was carrying out a pan European research project on a core set of data items needed on cross border prescriptions between Member states. Using a complementary methodological approach to that of Matrix, the Observatoire Social Européen (OSE) was also looking into problems that may occur when attempting to have medication dispensed in one Member State which was prescribed by a professional registered in another Member State.

1.2 Study Design and Report Structure

By examining the state-of-play across a selection of Member States and pathologies, this study contributes to the provision of a research base in this area. Figure 1 provides an overview of the conceptual framework underpinning this study. The study can be divided into three key steps – outlining the study scope, describing the problem, and finally analysing its impact for patient safety, therapeutic effects and associated costs. The structure of the report reflects these key steps.

- **Study Scope (Section 2.0):** The starting point is the 'foreign prescription' issued in one Member State for a specific medicine/device and in relation to a particular pathology. In this section and relevant appendices, the rationale and process for selecting Member States, pathologies and medicines/devices included in this study is described in more detail.
- **Problem Definition (Section 3.0):** In attempting to have a 'foreign prescription' dispensed, a number of problems may occur. By means of a survey amongst dispensers across a selection of EU Member States, we explore the nature of the problem as well as the underlying problem drivers.
- **Impact Analysis (Section 4.0):** Drawing on the information collected as part of the dispenser survey and the evidence review, in this section we present the economic model estimating the likelihood of patient harm occurring as a result of a medication error and furthermore estimate the associated costs.

Figure 1: Conceptual Framework



2.0 Project Scope

As illustrated in Figure 1, the starting point for this study has been the **'foreign prescription' issued in one Member State, and sought to be dispensed in another Member State, for a specific medicine/device and in relation to a particular pathology**. In the following paragraphs we present the Member States, pathologies and medicines/devices that have been included in the study and describe our selection rationale. A more detailed discussion of our methodological approach is provided in Appendix 6.2.

2.1 Selection of Member States

The table below sets out **the seven Member States that have been included in this study**.[8] These have been chosen according to specific selection criteria. A detailed description of our methodological approach for selecting the participating Member States may be found in Appendix 6.2.1.

Table 1: Final Member State Selection

Rationale	France	Germany	Denmark	UK	Poland	Greece[9]	Netherlands
Popular tourist destination	x	x		x			
High levels of health tourism actually undertaken and willingness to travel abroad for treatment in the future (2006/2007 figures)			x				
High flows of intra-EU migration	x	x		x	x		
Conditional recognition of EU prescriptions	x						
Availability of licensed drugs		High[10]	Low[11]	High	Low		
Other				x[12]			
Hand-written & paper based prescriptions						x	
Cyrillic/Greek alphabet likely to cause interpretation errors by pharmacists in countries with Latin-based						x	

[8] The original study design had foreseen the inclusion of six Member States. Following discussions with the Pharmaceutical Group of the European Union (PGEU) in April 2011, we proposed to the Commission/EAHC to include seven Member States instead.
[9] We received only one survey response from Greece (completed by the national association of pharmacists). While this means we were unable to analyse Greece as a 'dispenser country', we were still able to test it as a 'prescriber country'.
[10] has the greatest number of licensed drugs for the 8 conditions so prescribers most likely to prescribe drugs not available in dispensing country
[11] has relatively few drugs licensed for the 8 conditions so dispensers least likely to be able to dispense prescribed drug
[12] Makinen (2007) found that UK pharmacists refused to dispense if prescriber was not registered to practice in the UK

Rationale	France	Germany	Denmark	UK	Poland	Greece[9]	Netherlands
alphabets, and *vice versa*							
Recommended to be included in the study by PGEU						x	x
Generic drug names							x

2.2 Selection of Pathologies

With help of the in-house health experts, **we have identified the following eight chronic conditions to study for this project,** which require on-going use of medication but are not sufficiently severe that they would prevent cross-border travel or employment:

- Asthma;
- Chronic obstructive pulmonary disease (COPD);
- Depression and bipolar disease;
- Diabetes (type 1 and 2);
- Epilepsy;
- Hypertension;
- Ischaemic heart disease; and
- Osteoarthritis and rheumatoid arthritis.

These conditions are common[13], and are likely to affect people working or travelling abroad. They are typically treated with medication that has been associated with harm when it is not available, given in a different formulation or dose, administered via a different device, or mistaken for an alternative drug. They are therefore good examples to study to identify the likely impact of failure to dispense or dispensing errors from cross-border prescribing.

To substantiate our choice of pathologies, we have carried out a rapid evidence review of published studies on the prevalence of these eight pathologies in (working-age) adults resident in European countries, in particular focusing on those countries included in our survey. We have also summarised the impact of these pathologies on adults of working age across Europe, from World Health Organization data on standard disability-adjusted life years (DALY) in the European region in 2004.[14] The results are summarised in the sections below.

[13] Accounting for 24.8% (men) and 29.4% (women) of all DALYs in WHO Europe A region (see Table 2).
[14] http://apps.who.int/ghodata; DALY6.

Table 2: Prevalence Selected Pathologies in Adults Resident in Europe (WHO Europe A Region): Summary

Condition	Population	Prevalence in Target Countries	Disability-adjusted Life Years (DALYs) (15-69 years (% of all DALYs for that gender))
Asthma	working age adults	2% to 7%	Men: 478,238 (1.4%) Women:308,786 (1.3%)
Chronic Obstructive Pulmonary Disease	working age adults (moderate to severe)	3% to 5%	Men:1,117,644 (3.0%) Women: 1,066,985 (3.0%)
Bipolar disorder	adults	1%	Men:750,759 (1.2%) Women: 746,195 (1.2%)
Depression	adults	3% to 12%	Men: 2,485,939 (5.0%) Women: 5,265,198 (10.4%)
Diabetes	adults	4% to 12%	Men: 942,207 (2.3%) Women:1,076,922 (2.9%)
Epilepsy	adults	0.5% to 1%	Men:280,977 (0.5%) Women: 205,264 (0.5%)
Hypertension	adults (clinically diagnosed)	6% to 11%	Hypertensive heart disease: Men: 349,876 (0.5%) Women:276,562 (0.7%)
Hypertension	working age adults (BP measurement surveys)	25% to 50%	/
Ischaemic heart disease	working age adults	3% to 5%	Men:7,797,462 (8.7%) Women:3,217,580 (5.2%)
Osteoarthritis	adults	8% to 18%	Men:1,098,385 (1.8%) Women: 1,541,518 (2.9%)
Rheumatoid arthritis	adult men	0.3%	Men:224,025 (0.4%)
Rheumatoid arthritis	adult women	1.2%	Women: 681,024 (1.3%)

Asthma

The prevalence of asthma has increased over the past 30 years, and is 10-times more common in Western than Eastern Europe (European Observatory, 2009). The **self-reported prevalence of asthma in adults** ranges from 1.8% in Germany to 7% in France, with approximately 3-6% of adults in most of the target countries reporting that they currently have asthma. One UK study found that approximately one-quarter of adults had a diagnosis of asthma recorded at some time in their primary care medical record (Simpson & Sheikh 2010). **Rates in children** vary from less than 5% in Greece and Romania to more than 30% in the UK (European Observatory, 2009).

COPD

Although the prevalence of and mortality from COPD is falling in men, (European Observatory 2009; Soriano et al. 2010), COPD prevalence is increasing in women and it remains a substantial health burden in older adults across Europe (European Observatory 2009). Studies using spirometry to diagnose COPD consistently report **a prevalence of 3 to 5% for stage II to**

IV (moderate to severe) COPD in working-age adults. However, the prevalence can be as high as 40% if older adults are included, and diagnosis includes the milder, and possibly asymptomatic, stage I disease.

Depression and Bipolar Disease

Mental health problems are the cause of approximately 20% of the total disease burden across Europe, and depression accounts for one-third of all mental health problems. Approximately 7% of adults in Europe will experience depression in any year (European Observatory 2010), with **between 3% and 12% of adults in our target countries reporting depression sufficiently severe to require treatment.** Depression is also a substantial cause of disability, accounting for 8.1% of all disability-adjusted life-years (DALYs) in Belgium, 10.3% of DALYs in France and 7.8% in the Netherlands (European Observatory 2009).

Bipolar disease is less prevalent than major depression, with almost 1% of people affected at any one time (European Observatory 2009).

Diabetes

Diabetes has been estimated to be the fourth leading cause of death in Europe, directly and as a risk factor for other diseases such as cardiovascular disease. The overall prevalence in the European population aged 20 to 79 is estimated to increase from 7.8% in 2003 to 9.1% by 2025 (International Diabetes Federation 2010). More than four out of five people with diabetes have type 2 diabetes, and more than 50% of people with diabetes are likely to be unaware of their condition (European Observatory, 2009). **Prevalence of diabetes (usually type 1 plus type 2) in our target countries ranges from 4% in the UK to 12% in Germany**, with the other five countries reporting prevalence close to the EU average of 7-9%.

Epilepsy

Most studies from across Europe or in our target countries identified patients with epilepsy by combining data from multiple sources such as primary and secondary care and prescribing data, and found **a prevalence of around 0.5% to 1%.** The prevalence of epilepsy in other European countries was slightly higher, ranging from 0.5% to 1.8%.

Hypertension

Hypertension is extremely common across adults in Europe, and frequently under-diagnosed. The IMMIDIET study of 1,604 citizens from south-west London in the UK, Limburg in Belgium and Abruzzo in Italy found that 24% of participants had high blood pressure and 56% of these people were not aware of their condition. Of those who were aware, less than half had their high blood pressure under control (Costanzo et al. 2008).

Studies reporting hypertension prevalence across Europe or in our target countries based on measurement of blood pressure, found **between one-quarter and one-half of working-age adults had hypertension,** with higher rates in older adults. The **lower prevalence of 6% to 11%** found in studies relying on primary care diagnoses recorded in the patients' notes (for example, van der Meer et al. 2010; Saxena et al. 2007) compared with studies that screened all adults by measuring their blood pressure (such as Wagner et al. 2011; Falaschetti et al. 2009) suggests that under-diagnosis remains a problem.

Ischaemic Heart Disease

Standardised death rates for heart disease have fallen in Western Europe over the last 25 years as a result of lower rates of smoking, and improved detection and management of hypertension and high cholesterol. Despite this, the prevalence of ischaemic heart disease remains substantial, especially in Germany, the UK and other Northern European countries, which traditionally have reported higher rates than southern European countries such as Italy and France (European Observatory, 2009). Recent studies have found that **the prevalence of ischaemic heart disease in European countries is around 3% to 5% of working-age adults**, with annual event rates of approximately 1%.

Osteoarthritis/Rheumatoid Arthritis

Typically around 50% of the population report musculoskeletal pain at one or more sites for at least one week in the last month. Population surveys show that back pain is the most common site of regional pain in younger and middle aged adults, and knee pain in older people. The prevalence of radiological osteoarthritis rises with age (EC 2011). In our target countries, the prevalence of osteoarthritis is very high, with self-reported pain and x-ray diagnosed osteoarthritis affecting between one-third and half of adults. However, clinically-diagnosed osteoarthritis is less common, with **between 8% and 18% of adults having this diagnosis.** Rheumatoid arthritis is more common in women than men, **with 0.3% to 0.4% of men and approximately 1.2% of women diagnosed with the condition.**

2.3 Selection of Drugs & Devices

The table below illustrates the complete list of drugs/devices and regimes included in the dispenser survey. The identification of drugs/devices used in the dispenser survey has undergone a rigorous two-step selection process:

1. **Desk Research:** We relied on desk research and evidence review to answer questions on drug availability and drug use and constructed the selection of drug examples for each of the pathologies.
2. **Expert Consultation:** In order to confirm the individual regimens/dosages for our drugs/devices, we contacted representatives of the relevant national pharmacists associations (national members of the PGEU). Each of the seven members contacted, provided feedback on the list of proposed drugs/devices. Their recommendations were fully incorporated in the survey questionnaires.

To test whether **drug availability** is a likely cause for non-dispensing, two sets of drugs/devices have been developed using national and international guidelines on the management of the eight selected pathologies across the seven target countries:

- Drug A (unlikely to cause dispensing problems): commonly used and available in all 7 Member States;

- Drug B (more likely to cause dispensing problems): available in 3 or fewer Member States and/or less frequently used.

A detailed description of the methodology underlying the selection of drugs and devices is provided in Appendix 6.2.2.

Table 3: Drugs and Devices included in Dispenser Survey: Drug A (commonly available in all MS)

		Prescriber						
		DE	DK	EL	FR	NL	PL	UK
Dispenser	DE		Fluticason 250 mikrogram/ dosis	Tiotropium bromide monohydrate Inhpd	Seropram® 20 mg cp pellic séc	Metformine HCl 500 PCH	Lamotriginum tabletki 25 mg	Ramipril 2.5 mg
	DK	Tiotropium 18 Mikrogramm Kapsel mit Inhalationspulver		Citalopram hydrobromide F.C. tab 20 mg	Glucophage® 500mg cp pellic	Lamotrigine CF 200 mg	Ramiprilum tabletki 1,25 mg	Simvastatin 20 mg
	EL	Citalopram 20 mg Filmtabletten	Tablet Metformin "Bluefish" ® 500 mg		Lamictal ® 100mg cp dispers	Ramipril 2.5 mg	Simvastatinum tabletki powlekane 20 mg	Naproxen 250 mg tablets
	FR	Metformin 1000 mg Filmtabletten	Lamotrigen "Arrow" ®100 mg	Ramipril tab 5 mg		Simvastatine 20 mg	Naproxenum natricum tabletki powlekane 275 mg	Fluticasone proprionate Evohaler® 250 micrograms/metered inhalation
	NL	Valproinsäure 300 mg magensaftresistente Filmtabletten	Tablet Enalapril "Actavis" ® 5 mg	Simvastatin F.C. tab 20 mg	Apranax ® 500 mg;		Fluticasoni propionas aerozol wziewny 50 mcg/dawkę inh	Tiotropium 18 mcg inhalation powder
	PL	Ramipril 2.5 mg	Tablet Simvastatin "Aurobino" ® 20 mg	Naproxen sodium C. Tab 220 mg	Flixotide 250µg/ dose pdre p inhal	Tiotropium 18 microgram, inhalatiepoeder in harde capsules		Citalopram 20 mg
	UK	Simvastatin 20mg Filmtabletten	Tablet Ibumetin ® 600 mg	Fluticasone proprionate Inh. Sus. P 250 mcg	Tiotropium 18µg pdre p inhal en gél	Citalopram 20 mg, filmomhulde tabletten 20 mg	Metformini hydrochloridum tabletki powlekane 1000 mg	

Table 4: Drugs and devices included in Dispenser Survey: Drug B (not commonly available in all MS)

		Prescriber						
		DE	DK	EL	FR	NL	PL	UK
Dispenser	DE		Bambuterol 10 mg	Hexoprenaline sulphate tab 0.5 mg	Marsilid® 50mg cp séc	Insuline glargine 100 Eenheden/ml	Phenobarbitalum tabletki100 mg	Nisoldipine 10 mg
	DK	Tulobuterol hydrochlo		moxapine tab 50 mg	Umuline profil 30 100 UI/ml	Felbamaat tabs 400 mg	Chlortalidonum tabletki 50 mg	Nadolol 80 mg

		Prescriber						
		DE	DK	EL	FR	NL	PL	UK
		ride 2 mg			susp inj en cart			
	EL	DisTranylcypromin 20 mg Filmtabletten	Injektionsvæske Humulin® NPH 100 IE/ml Pen		Aparoxal® 100 mg 2 comprimés par jour	Chloorthiazide 250 mg tablet	Torasemidum tabletki 5 mg	Penicillamine 250 mg
	FR	Actraphane 30 FlexPen® 100 IE/ml	Tablet Topimax® 200 mg	Barnidipine hydrochloride Mod. R. CA. H. 20 mg/cap		Barnidipine hydrochloride 10 mg	Nimesulidum tabletki 100 mg	Bambuterol 20 mg
	NL	Mesuximid 150 mg Kapseln	Tablet CentylÂ® med KCL	Spirapril hydrochloride tab 6 mg	Minalfene 300mg cp pellic		Zafirlukastum tabletki powlekane 20 mg	Ciclesonide 80 micrograms / metered inhalation
	PL	Penbutolol 40 mg Filmtabletten	Tablet Trandate® 100 mg	Nimesulide 100 mg	Theostat® L.A. 200mg gél LP	Ciclesonide 80 Inhalator, aërosol, oplossing 80 microgram/ dosis		Nortriptyline hydrochloride 25 mg
	UK	Molsidomin 8 mg Tabletten	Tablet Methetrexat “Sandoz” ® 2,5 mg	Reproterol hydrochloride aer. Md. Inh. 0,5mg	Bamifyllin e 300mg cp enr	Fenelzine 15 mg tablet	Polhumin Mix-3 Insulinum humanum zawiesina do wstrzykiwań 100 j.m/ ml	

3.0 Problem Definition

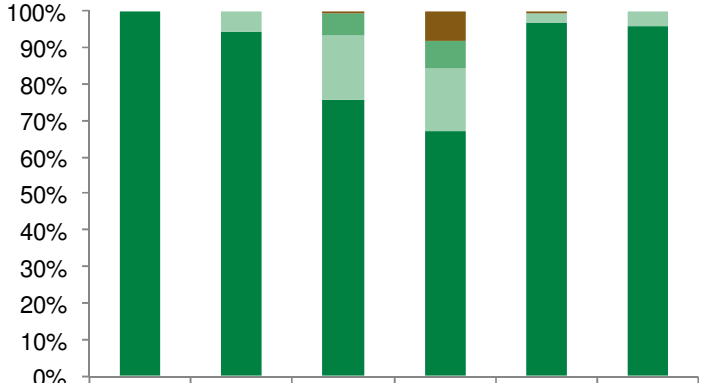
As illustrated in Figure 1, **looking to have a 'foreign prescription' dispensed may lead to several different outcomes and ultimately problems**. A mix of evidence review, survey work, and economic modelling has been used to better understand the nature and size of the problem as well as its underlying drivers. Much of the discussion in this section is based on the results of the dispenser survey. A summary of the methodological approach may be found in Appendices 6.3 to 6.7.

3.1 Frequency of Foreign Prescriptions Presented

There was generally a **low level of experience in dealing with foreign prescriptions amongst the survey participants**, nearly all of whom (96%) described themselves as pharmacists.[15] Of the 99% of all respondents who detailed how much experience they had with being given foreign prescriptions, **82% were given fewer than five of these a month**. An average 10% dealt with 5 to 10 of these a month, 4% with between 11 and 20 and only 3% with over twenty foreign prescriptions a month.[16]

Experience varied between Member States, however. **8% of all Dutch pharmacists received more than 20 foreign prescriptions per month[17], compared to 1% or less across all other countries**. These country-specific experiences are summarised in the figure below.

Figure 2: Experience with Prescriptions from other EU Member States (per month)



	DE	DK	FR	NL	PL	UK
Above 20	0%	0%	1%	8%	1%	0%
Between 11 and 20	0%	0%	6%	8%	0%	0%
Between 5 and 10	0%	6%	18%	17%	3%	4%
Below 5	100%	94%	76%	67%	97%	96%

Note: *No experience responses from Greece; experience does not always sum to 100% due to rounding.*

[15] A further 2% described themselves as assistant pharmacists, 1% as technicians and the rest as pharmacy managers, students and internal pharmacists.
[16] 1% discrepancy due to rounding.
[17] Many Dutch pharmacists, in the comments section of the survey, attributed this to being located near to the German border and German patients coming to the Netherlands for the lower prices.

3.1.1 Number of Foreign Prescriptions

Using the survey results as basis, it is possible to estimate the range of foreign prescriptions presented for dispensing across the six Member States per month.[18] As is illustrated in the table below, an estimated 50,206 to 351,763 foreign prescriptions are sought to be dispensed each month across the six countries included in this study.

Table 5: Range Estimates of Absolute Number of Prescriptions (per month)

Dispensing Country	Lower Bound	Upper Bound	Number of Pharmacies[19]	Absolute Lower Bound	Absolute Upper Bound
Germany	0.00	4.00	21,580	0	86,320
UK	0.22	4.26	12,898	2,804	54,957
Poland	0.26	4.42	10,628	2,713	46,931
Denmark	0.28	4.33	260	72	1,127
France	1.69	6.37	22,462	37,998	143,008
Netherlands	3.39	9.96	1,950	6,619	19,420
TOTAL			69,778	50,206	351,763

Note: shaded squares indicate approximations based on 'more than 20' meaning 'between 21 and 50'

Lower/upper bounds are calculated for each country by taking the weighted average of the minimum/maximum value across the individual response categories (i.e. less than five, 5-10, 11-20, above 20).

Equation 1: Number of Foreign Prescription (across 6 MS, per month)

$$Lower\ Bound_{MS} = W_{0-4}(min1) + W_{5-10}(min2) + W_{11-20}(min3) + W_{21-50}(min4)$$

$$Upper\ Bound_{MS} = W_{0-4}(max1) + W_{5-10}(max2) + W_{11-20}(max3) + W_{21-50}(max4)$$

Note: *W = percentage of overall responses per category; min/max = respective minimum and maximum value per category.*

An initial problem in calculating this absolute number of foreign prescriptions is the fact that the 'more than 20' foreign prescriptions option offers a theoretically unlimited scope for the number of prescriptions received a month. For France, the Netherlands and Poland (all of which detailed experience with more than 20 foreign prescriptions per month), it was thus only possible to specify an approximate upper bound with the explicit assumption that 'more than 20' means between 21 and 50.

[18] Greece has been excluded from this part of the analysis, as only one survey response was received.
[19] Pharmaceutical Group of the European Union (PGEU) (2010). Providing Quality Pharmacy Services to Communities in Times of Change: Annual Report 2010. Available at: http://www.pgeu.eu/Portals/6/documents/2011/PGEUFINAL_AR2010_singlepage.pdf, Retrieved on 21 November 2011.

A range estimate of such a large scale makes any concrete conclusions on harm costs of non-dispensing problems difficult – **a point estimate would be preferred**. Because the data is positively skewed (i.e. the vast majority of respondents have very little experience with foreign prescriptions and only a few respondents have a lot of experience), the arithmetic mean would overstate the experience pharmacists have with foreign prescriptions. Therefore, the following process was conducted:

a) **Standardising Responses:** Taking into account the varying response rates across the six dispenser countries, the country-specific averages were weighted according to the total number of pharmacies in that country.

Table 6: Weighted Distribution of Foreign Prescriptions (per month)

	Percentage Distribution
Below 5	90%
Between 5 and 10	7.3%
Between 11 and 20	2.1%
Above 20	0.6%

b) **Positively Skewed Distribution:** It was assumed that the overall positively skewed distribution was also reflected within the individual intervals. Consequently, each interval was divided into four equally-sized sections to which the overall distribution weights were assigned.[20]

c) **Interval Average:** The arithmetic averages of the four sections for each of the four intervals were multiplied by the respective weights to obtain a point estimate of the 'average experience' within each interval.

d) **Overall Distribution Average:** The resulting range-specific point estimates were subsequently multiplied by the weights again to obtain an overall point estimate of the average prescription per pharmacist.

Accordingly, the average pharmacy across the six targeted member states deals with 1.4632 foreign prescriptions a month. Multiplied by the number of pharmacies in the six targeted countries (69,778), this implies that an estimated 102,096 foreign prescriptions are dealt with a month in the six targeted Member States (1.23 million foreign prescriptions per annum). Extrapolated to the EU by assuming that this represents around 53% of all prescriptions[21], this means that **194,192 foreign prescriptions are dealt with EU-wide per month (2.33 million foreign prescriptions per annum).**

3.1.2 Number of Total Prescriptions

The range of foreign prescriptions should be seen in the context of the overall number of prescriptions that are dispensed in the EU in any one year. According to England's National

[20] For example, this divides the 0-4 interval into a 0-1, 1-2, 2-3 and 3-4 sections, which are assumed to be distributed with the following weights respectively: 90%, 7.4%, 2.1% and 0.7%.
[21] According to Table 7, 5,238,567,000 prescriptions are dispensed in the six target countries annually. This is 52.5749% of the total 9,963,999,000 dispensed across the EU.

Health Service, 926,657,600 prescriptions were dispensed in England in 2010[22], resulting in an estimated 1.1 billion prescriptions in the UK as a whole (England represents 84% of the UK's population[23]). For indicative purposes, and with the caveats of UK-specific characteristics possibly influencing the numbers in mind, these figures are extrapolated to the rest of the European Union. Under the assumption that each pharmacist dispenses 27,000 prescriptions every year[24], **an estimated 10 billion EU prescriptions were dealt with in 2010.[25]**

Table 7: Estimated Number of Dispensed Prescriptions (Annually)

	Number of Pharmacists	Estimated Number of Prescriptions per Year	Data Year
AT	5,579	150,633,000	2010
BE	12,450	336,150,000	2009
BG	n/a	n/a	n/a
CY	168	4,536,000	2008
CZ	5,915	159,705,000	2009
DE	49,892	1,347,084,000	2009
DK	2,489	67,203,000	2008
EE	857	23,139,000	2009
EL	9,837	265,599,000	2006
ES	37,000	999,000,000	2010
FI	5,844	157,788,000	2008
FR	73,298	1,979,046,000	2010
HU	5,731	154,737,000	2009
IE	4,567	123,309,000	2010
IT	53,110	1,433,970,000	2009
LT	2,270	61,290,000	2003
LV	1,340	36,180,000	2008
LU	352	9,504,000	2009
MT	301	8,127,000	2010
NL	3,463	93,501,000	2009
PL	24,238	654,426,000	2009
PT	7,467	201,609,000	2009
RO	11,894	321,138,000	2009
SE	6,751	182,277,000	2008

[22] http://www.ic.nhs.uk/webfiles/publications/007_Primary_Care/Prescribing/Prescription_Cost_Analysis_England_2010/Prescription_Cost_Analysis_2010.pdf

[23] http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/mid-2010-population-estimates/annual-mid-year-population-estimates--2010.pdf

[24] Given that the World Health Organisation specifies that there were 40,641.2 pharmacists working in the UK in 2010, the average pharmacist dispenses around 27,000 prescriptions per year. Under the assumption of each pharmacist working on around 270 days a year and 8 hours a day, this implies each pharmacist dispenses around 100 prescriptions a day and 12 an hour, which seem reasonable estimates. Note that the number of pharmacists in 2010 was not available in each country. For those countries in which 2010 data was not obtainable, the most recent figure was used. The WHO database did not contain any information on the number of pharmacists in Bulgaria

	Number of Pharmacists	Estimated Number of Prescriptions per Year	Data Year
SI	1,066	28,782,000	2009
SK	2,517	67,959,000	2007
UK	40,641	1,097,307,000	2010
Total	**369,037**	**9,963,999,000**	**N/A**

By comparison, using a different methodology focusing on the number of prescriptions per inhabitant, a 2008 study conducted by Gesundheit Österreich GmbH (GÖG) came to the conclusion that around 11.8 prescriptions per inhabitant were dispensed across the Pharmaceutical Pricing and Reimbursement Information (PPRI) countries.[26] This implies that with an EU population of around 500 million[27], the annual number of prescriptions is around 6 billion. This illustrates a difference of 4 billion (40% lower) in comparison to our estimate, which may be partially explained by the fact that the PPRI study refers to outpatient prescriptions only.[28]

3.2 Non-Dispensing Probabilities for Foreign Prescriptions

Following consultations with the PGEU and its national associations of countries included in this study, the research team made a conscious decision not to engage in any form of 'mystery shopping'. The concern was that pharmacists would be reluctant to engage with the research in such a way that could raise questions of professional liability. The research team thus opted to engage with pharmacists in their capacity as experts. Consequently, pharmacists were asked whether, in their opinion as experts, any of a list of seven factors[29] would 'definitely not' (0), 'unlikely' (1), 'likely' (2) or 'definitely' (3) cause a problem in dispensing a particular drug.

The probability that a particular prescription would not be dispensed was calculated as follows:

1. **Coding Responses:** Each response was coded as follows[30]:

$$(Definitely\ Not = 0; Unlikely = 1; Likely = 2; Definitely = 3)$$

2. **Calculating the Weighted Average:** For each prescription the weighted average code was calculated using the formula below. A response in which only one factor was scored has an equal weight as one where all seven factors are scored.

$$Weighted\ Average\ (Prescription) = \frac{W_{F1}(y) + W_{F2}(y) + \cdots + W_x(y)}{\sum y}$$

[26] http://www.tlv.se/Upload/Ovrigt/PPRI_Report.pdf
[27] e.g. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-QA-09-031/EN/KS-QA-09-031-EN.PDF
[28] Conversely, the NHS estimate also concerns prescriptions written in a hospital, provided they were dispensed by a community pharmacist. Unfortunately, there is no indication as to which proportion of prescriptions consists of 'outpatient' and 'inpatient' prescriptions.
[29] These factors are: (1) verifying prescriber authenticity; (2) verifying prescription authenticity; (3) language; (4) handwritten prescription; (5) drug availability; (6) availability of substitute; (7) insufficient information on prescription
[30] 'Don't know responses were coded as blanks.

3. **Calculating the Probability :** For each prescription the probability of this prescription to not be dispensed was calculated as follows – proportion of overall range:

$$P(Not\ Dispensed) = \frac{Weighted\ Average\ (Prescription)}{3}$$

Table 8: Example Calculation

Question: Would the following issues definitely not / unlikely / likely definitely cause dispensing problems?

1. Response:

Verifying authenticity	Verifying prescribing physician	Prescription language	Handwritten prescription	Insufficient information	Access to correct drug/device	Access to alternative drug
likely	*definitely*	*likely*	*definitely not*	*unlikely*	*likely*	*likely*

2. Responses coded:

likely	definitely	likely	definitely not	unlikely	likely	likely
2	*3*	*2*	*0*	*1*	*2*	*2*

3. Codes averaged out per prescription observation:

$$\frac{(2+3+2+0+1+2+2)}{7} = 1.71$$

4. Average codes divided by code range (3) to obtain non-dispensing probability:

$$\frac{1.71}{3} = 0.57$$

5. Multiplied by 100 to obtain non-dispensing probability in percentage terms:

$$0.57(100) = 57\%$$

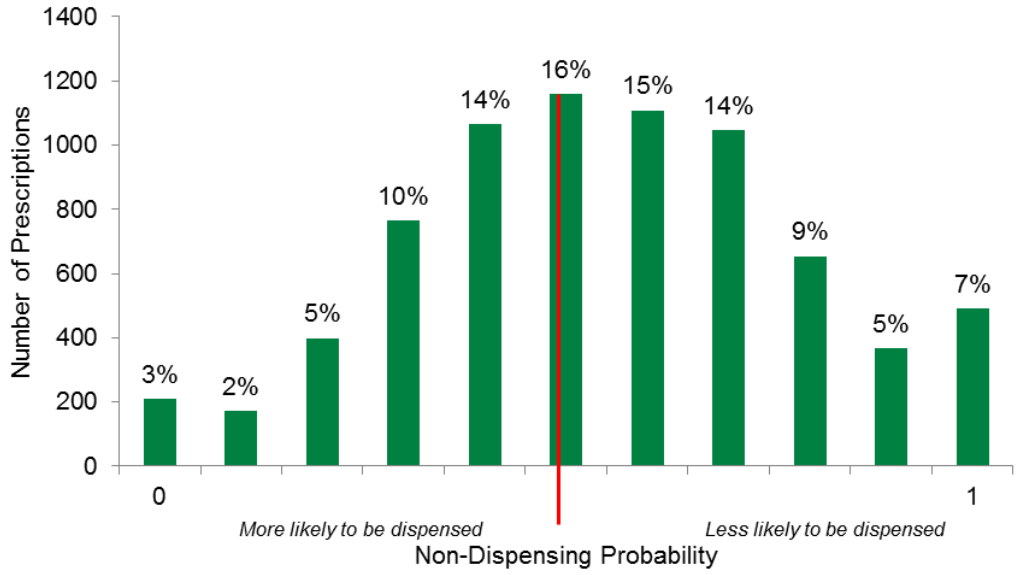
57% probability of that prescription not being dispensed

As the below histogram of the distribution of probabilities shows, across all suitable prescription responses (7,440[31] out of 11,952 responses)[32], it is **more likely that a drug is not dispensed rather than dispensed**, based on survey responses. The overall percentage probability,

[31] Note that whilst the survey technically yielded 7452 responses, 12 of these observations were by a Dutch pharmacist working in Belgium. These responses were omitted, because Belgium was not one of the targeted countries.
[32] See annex for an in-depth discussion of unsuitable (i.e. blank) responses by pathology and country.

according to the methodology outlined above[33], of not obtaining a drug when using a foreign prescription is 55%, i.e. the probability of being able to obtain a drug is 45%[34].

Figure 3: Distributional Histogram of Non-Dispensing Probabilities



The histogram graphs discrete probability categories between 0 and 1 (all 7,440 individual probabilities are rounded to the nearest decimal point so that they can be grouped together in these discrete categories) against their relative frequency in the whole sample. This means that, for example, whilst 3% of all observations have a non-dispensing probability nearest to 0, 7% of all observations have a non-dispensing probability nearest to 1. Accordingly, 223 prescriptions out of 7440 would be expected to definitely be dispensed, whereas 521 prescriptions out of 7440 would be expected to definitely not be dispensed.

Regardless of which methodology is implemented to indirectly calculate the probability, the fact that **there are more likely to be problems in dispensing than no problems remains apparent**. In the following paragraphs, we disaggregate the information by pathology, drug type, prescribing countries and dispensing countries.

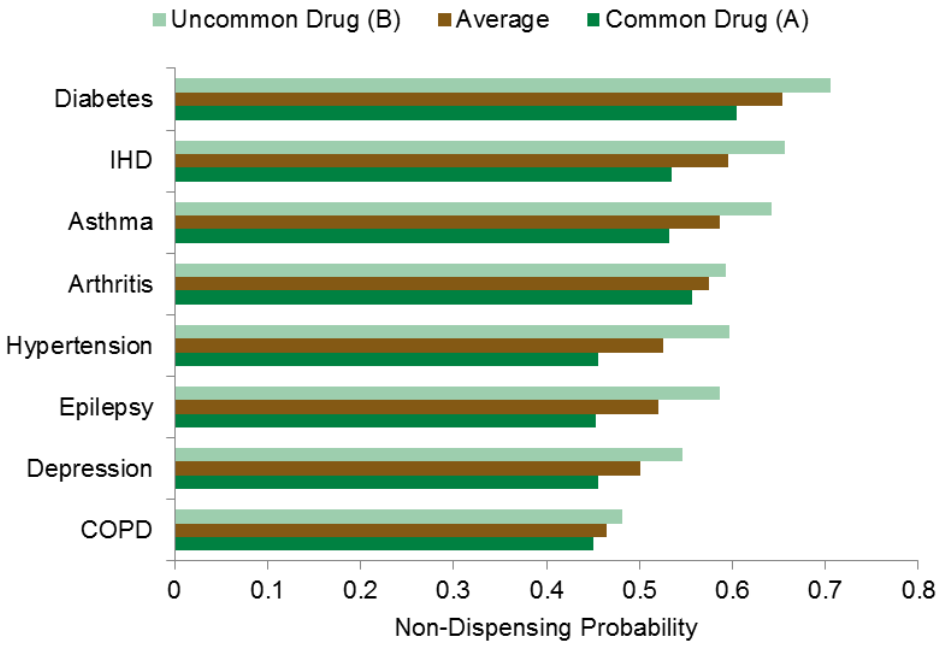
3.2.1 Pathologies and Drug Type

Variations exist across pathologies and by drug type. Medicinal products for diabetes, if requested via a foreign prescription, are the most likely not to be dispensed (65% of the time) according to the survey responses, whilst COPD drugs are the least likely not to be dispensed

[33] Calculating the mean average of all 7,440 prescription average probabilities.
[34] Note that this means that observations containing only one problem driver response are thus weighted equally to those with seven problem driver responses. However, using an alternative methodology of taking the average of all codes yields an average code of 1.63. Divided by the code range of 3, this results in a non-dispensing percentage probability estimate of 54%, i.e. nearly identical to the 55% estimate found using the methodology outlined above.

(47% of the time). As expected, dispensing problems are less often associated with Drug A medication (dispensed without any problems 50% of the time), compared to Drug B (dispensed without any problems 41% of the time).

Figure 4: Non-Dispensing Probabilities by Pathology



More detailed non-dispensing probabilities by drug type and by pathology are outlined in the table below.[35]

Table 9: Mean Non-Dispensing Probabilities, Standard Deviations and Standard Errors of the Mean Estimates

Pathology	Drug Type	Non-Dispensing Probability	Difference B – A	Sample Standard Deviation	Standard Error of the Mean
Arthritis	Overall	**0.58**		0.22	0.01
Arthritis	A	**0.56**	0.03	0.23	0.01
Arthritis	B	**0.59**		0.21	0.01
Asthma	Overall	**0.59**		0.22	0.01
Asthma	A	**0.53**	0.11	0.21	0.01
Asthma	B	**0.64**		0.21	0.01
COPD	Overall	**0.47**		0.24	0.01
COPD	A	**0.45**	0.03	0.24	0.01
COPD	B	**0.48**		0.24	0.01
Depression	Overall	**0.50**		0.27	0.01

[35] Note that average pathology results are simply the arithmetic mean of the drug A and drug B probabilities. Because there was no significant difference in the number of responses to 'A' and 'B' prescriptions, this is a legitimate way in which to estimate the pathology-specific probabilities.

Depression	A	**0.46**	0.09	0.27	0.02
Depression	B	**0.55**		0.28	0.02
Diabetes	Overall	**0.65**		0.21	0.01
Diabetes	A	**0.60**	0.09	0.20	0.02
Diabetes	B	**0.71**		0.21	0.02
Epilepsy	Overall	**0.52**		0.21	0.01
Epilepsy	A	**0.45**	0.14	0.20	0.01
Epilepsy	B	**0.59**		0.20	0.01
Hypertension	Overall	**0.53**		0.24	0.01
Hypertension	A	**0.46**	0.14	0.23	0.01
Hypertension	B	**0.60**		0.22	0.01
IHD	Overall	**0.60**		0.22	0.01
IHD	A	**0.53**	0.13	0.21	0.01
IHD	B	**0.66**		0.21	0.01

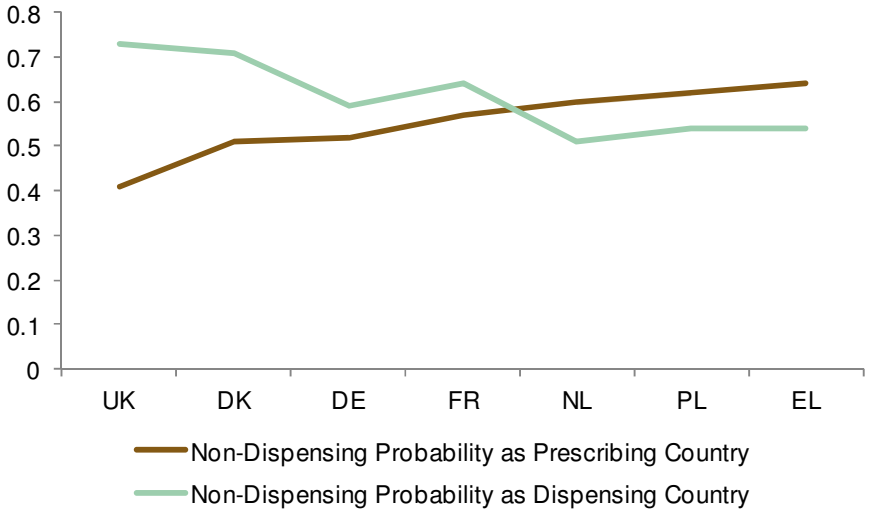
The non-dispensing probabilities by pathology type range from 0.45 (COPD/A, Epilepsy/A) to 0.71 (Diabetes/B). As noted above, for every single pathology, drug A was always more likely to be dispensed than drug B. For hypertension and epilepsy, it seems to make a large difference whether the drug prescribed is of type A or B, whilst for arthritis or COPD, the difference in dispensing probabilities between A and B drugs is around five times lower. Finally, while the sample standard deviations of each point estimate of the probability are relatively large, because the sample sizes of each estimation base are also rather large, the standard error of each point estimate is quite small[36].

3.2.2 Prescribing and Dispensing Countries

Differences in the probability of a drug not being dispensed exist in terms of the country in which it was prescribed as well as the country in which dispensing of the prescription is sought; as is illustrated by the figure below. Interestingly, prescriptions originating in the UK, Denmark, Germany and France are more likely to be dispensed abroad than foreign prescriptions that are presented to pharmacists in those countries. The opposite is the case for Netherlands, Poland and Greece.

[36] Whilst the sample standard deviation denotes the square root of the sample variance, the mean standard error denotes an estimate of how far the actual probability is likely to vary from our estimate of the probability. The mean standard error equals the standard deviation divided by the square root of the sample size, which is why our large data set reduces standard errors and gives our probability estimates more reliability. This also explains why the standard errors of the depression and diabetes estimates are larger than those of other pathologies – as highlighted in the annex, we received fewer responses to questions about diabetes and depression than to questions about other pathologies.

Figure 5: Probabilities by Prescribing and Dispensing Country



Somewhat unsurprisingly, prescriptions from the UK are the least likely not to be dispensed (41% of the time), for which the tentative explanation of English being the most widely-understood language across the EU can be offered (see below for a more in-depth analysis). Prescriptions originating from Greece or Poland are the least likely to be dispensed (64% and 62% of the time, respectively), which is particularly interesting given the fact that when acting as dispensing countries, these are the most likely to dispense[37].

[37] Probabilities here refer to an average of 'A' and 'B' drug probabilities.

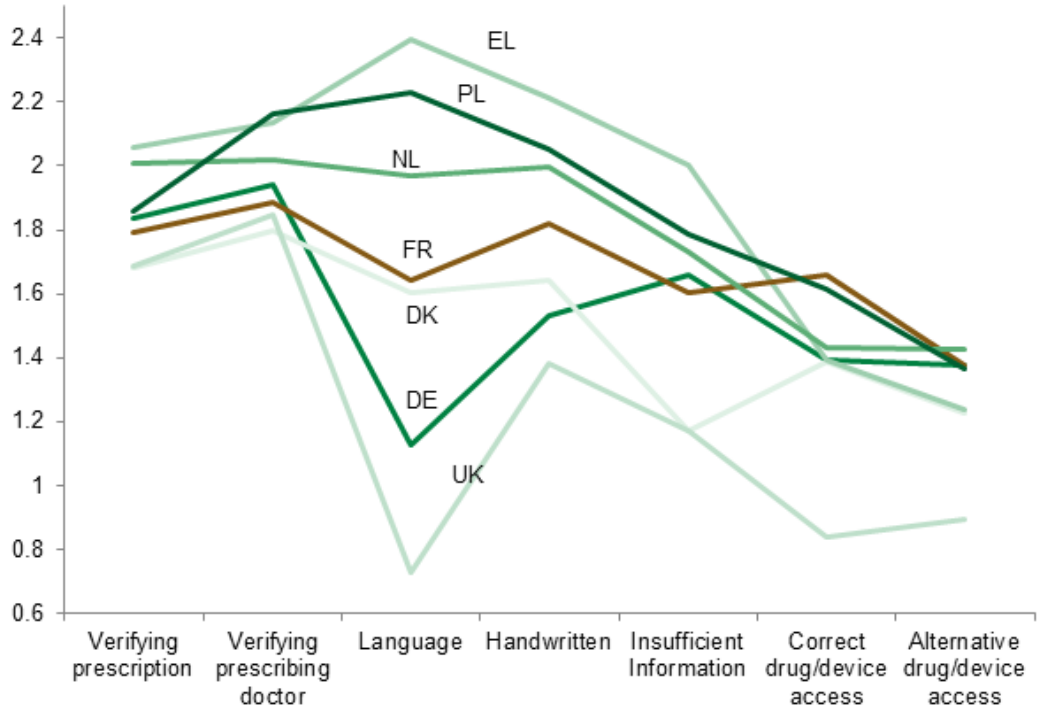
3.3 Underlying Problem Drivers for Non-Dispensing

In this section we analyse the underlying problem drivers for non-dispensing. To this end, we consider each of the five key factors from the perspective of the prescribing country, the dispensing country, as well as by drug type.

3.3.1 Prescribing Countries

The figure below illustrates the key problem drivers which contribute to problems in dispensing foreign prescriptions. It graphs the seven problem drivers against their average code score, by country. The measure used here, again, is the 0-3 scale that was used to code pharmacists' responses to questions – a higher code score denotes more problems.

Figure 6: Key Problem Drivers (prescribing country)



The most significant barriers to obtaining medicine are associated with verification and authenticity problems. The average codes for the questions on 'verifying the authenticity of the prescription' and 'verifying the prescribing physician' are 1.83 and 1.96, respectively. There is little country-by-country variation in average codes, indicating that verification and authenticity problems are inherent and widespread across the EU, no matter which country a prescription

originates from. Whilst prescriptions from Denmark and the UK display the lowest average codes on verifying prescription authenticity (1.68 and 1.69, respectively), these are not far off from Greece's score of 2.06. Similarly, the average codes for prescribing physician verification are lowest in Denmark and the UK (1.8 and 1.85, respectively); these values are close to the highest code, found in Poland (2.16).

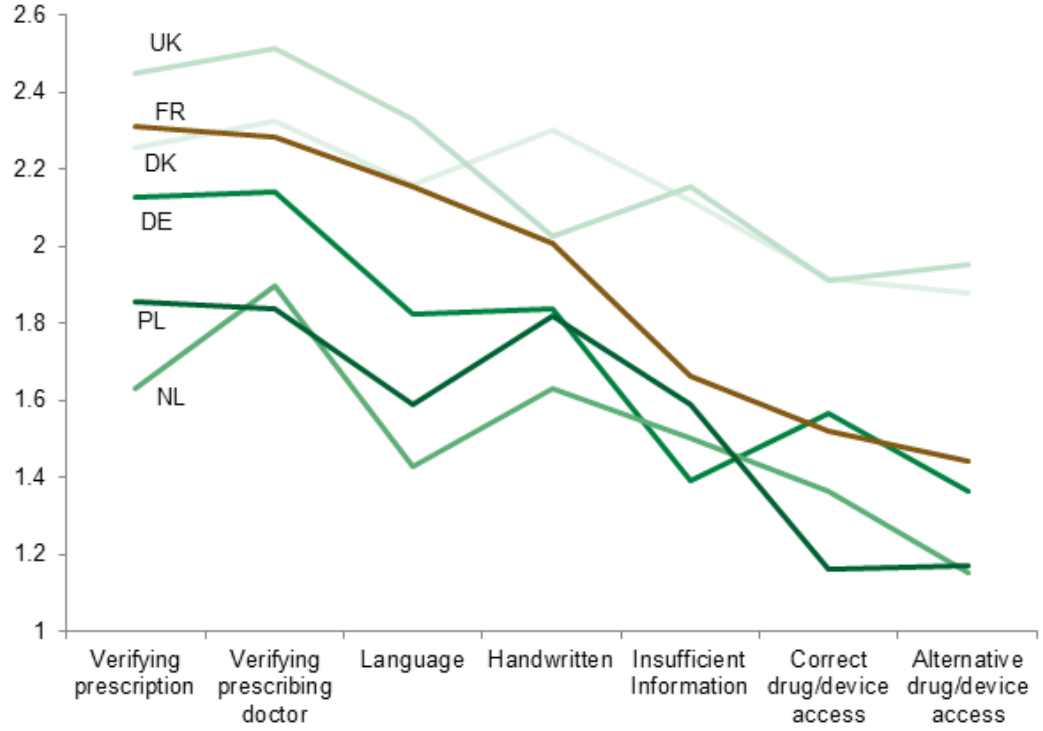
Unsurprisingly, the fewest problems arising from the prescription **language** or the prescription being **written by hand** are also associated with prescriptions from the United Kingdom. Whilst the average code for the language question is 0.73 for prescriptions originating from the UK, it is 2.4 for Greece. It is extremely likely that this is due to the Greek alphabet causing problems for pharmacists in other countries. The high average **'handwritten'** code score for Greece (2.21) in comparison to the low average 'handwritten' code score for the UK (1.38) may actually serve as a further proxy for this effect (or a combination effect, i.e. that it is harder to decipher handwriting in unfamiliar languages). The correlation between 'handwritten' and 'language' codes is 0.64 across all observations, which means these two problem drivers are more highly correlated each other than almost all other problem drivers.[38]

3.3.2 Dispensing Country

The figure below illustrates the key problem drivers which contribute to problems in dispensing foreign prescriptions. It graphs the seven problem drivers against their average code score, by country. The measure used here, again, is the 0-3 scale that was used to code pharmacists' responses to questions – a higher code score denotes more problems.

[38] The correlation between 'verifying physician' and 'verifying prescription' is 0.85, between 'access to correct drug' and 'access to alternative drug' is 0.79, whilst all other correlations between two problem drivers are lower.

Figure 7: Key Problem Drivers (dispensing country)



Studying the average codes by **dispensing country** allows us to gain an insight into whether **particular dispensing countries have large availability problems in comparison to others**, or whether their verification processes are stricter than those in other countries. It was already shown above that the Netherlands and Greece are the most likely to dispense foreign prescriptions (though the Greek result is not robust, because it is based on just one pharmacist's response), whilst the UK is the country least likely to dispense foreign prescriptions.

Again, **access and availability problems are less severe than those associated with other categories**. The Netherlands and Poland have the lowest average codes for **'access to the correct drug/device'** and **'access to alternative drug or device if the one on the prescription is unavailable'**, indicating that these two countries have the most experience with cross-border prescriptions (according to the qualitative comment responses from pharmacists, the bulk of these come from Germany, for both countries) and thus stock a wider range of drugs and devices to accommodate this. The highest average codes for these two questions are displayed by Denmark and the UK, indicating that these countries do not prepare particularly stringently or stock extensively for the eventuality of having to process foreign prescriptions.

Whilst prescriptions **from** the UK presented the least language difficulties in other countries, as a dispensing country, **pharmacists from the UK have the most language difficulty with foreign prescriptions**. Denmark and the UK have the most problems with prescriptions written by hand. Conversely, the Netherlands and Poland have the fewest problems with both categories, indicating a **general familiarity amongst pharmacists from both of these countries with foreign prescriptions and the language/format in which they come**.

Pharmacists from the UK and Denmark also have the most problems with '**not all the information you need [being] written on the prescription'**, by quite a large margin (UK: 2.15, Denmark: 2.12). Disregarding the one Greek score due to its non-robust nature, Germany displays the fewest problems with missing information (1.39).

Finally, **verification and authenticity issues again display the largest barrier to the dispensing of drugs and devices, also amongst dispensing countries**, with the highest average codes of all seven questions. The most verification problems were found in the UK. Conversely, the lowest verification problems, presumably due to the abovementioned familiarity with foreign prescriptions (primarily from Germany), the Netherlands and Poland displayed the lowest average codes.

Interestingly, the differences between the lowest and highest average codes for these two questions are much larger than the differences found in the context of dispensing countries. This suggests that whilst the country of origin does not significantly the verification process, **some countries are more adept and efficient at verifying foreign prescriptions than others**. This implies that some dispensing problems associated with dealing with foreign prescriptions in the UK, Denmark or France, for example, may be eliminated by an improvement of the verification process on the national level. However, given that the overall average code for all countries is highest for these categories, there are clearly still **EU-wide verification and authenticity problems associated with foreign prescriptions**.

The correlation matrix below highlights that relatively strong correlations exist between verifying prescription/prescriber; language/handwritten prescription and availability of the correct/substitute drug.

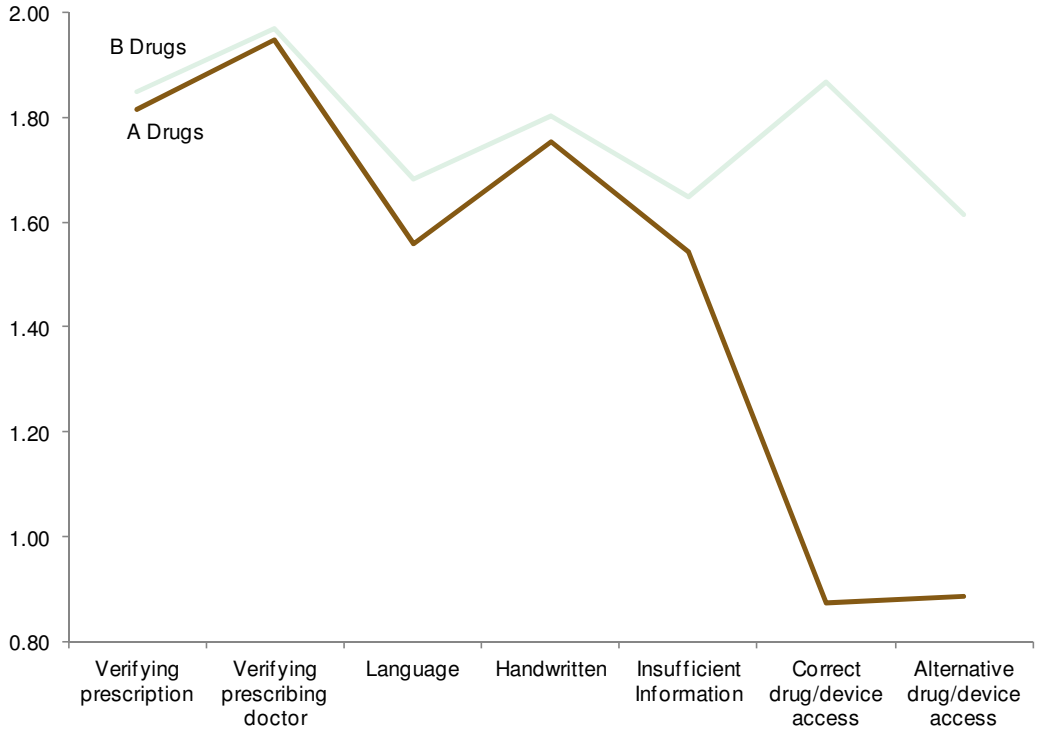
Table 10: Correlation Matrix

	Verifying prescription	Verifying prescriber	Language	Handwritten	Information	Access to correct drug	Access to alternative drug
Verifying prescription		0.85	0.43	0.42	0.47	0.17	0.19
Verifying prescriber	0.85		0.40	0.40	0.44	0.17	0.17
Language	0.43	0.40		0.64	0.49	0.31	0.29
Handwritten	0.42	0.40	0.64		0.49	0.26	0.28
Information	0.47	0.44	0.49	0.49		0.31	0.34
Access to correct drug	0.17	0.17	0.31	0.26	0.31		0.79
Access to alternative drug	0.19	0.17	0.29	0.28	0.34	0.79	

3.3.3 Drug Type

As is illustrated in the figure below, although type A drugs generally cause fewer dispensing problems, the differences between the two drug types are not large; with the exception of questions around drug availability. This supports our hypothesis that those drugs that are less commonly available will present greater challenges in being dispensed abroad.

Figure 8: Key Problem Drivers (by drug type A / B, whole sample)



4.0 Impact Analysis

'Therapeutic effect' and 'patient safety' are two fundamental principles of health care. A therapeutic effect is a consequence of a medical treatment of any kind, the results of which are judged to be desirable and beneficial. This is true whether the result was expected, unexpected, or even an unintended consequence of the treatment. Patient safety may be adversely affected as a result of problems in practice, products, procedures or systems.[39,40] For the purpose of this study, we summarise these terms as **patient harm.**

As illustrated in Figure 1 (Section 2), dispensing errors and ultimately medication errors may have implications in terms of patient harm. While in theory the effect of dispensing the wrong medicinal product could be positive, it is more likely to have no effect at all, or an adversary effect resulting in patient harm. We are using a mix of evidence review and economic modelling to better **understand possible effects of dispensing errors and subsequent medication errors on patient harm.**

4.1 Medication Errors and Associated Patient Harm

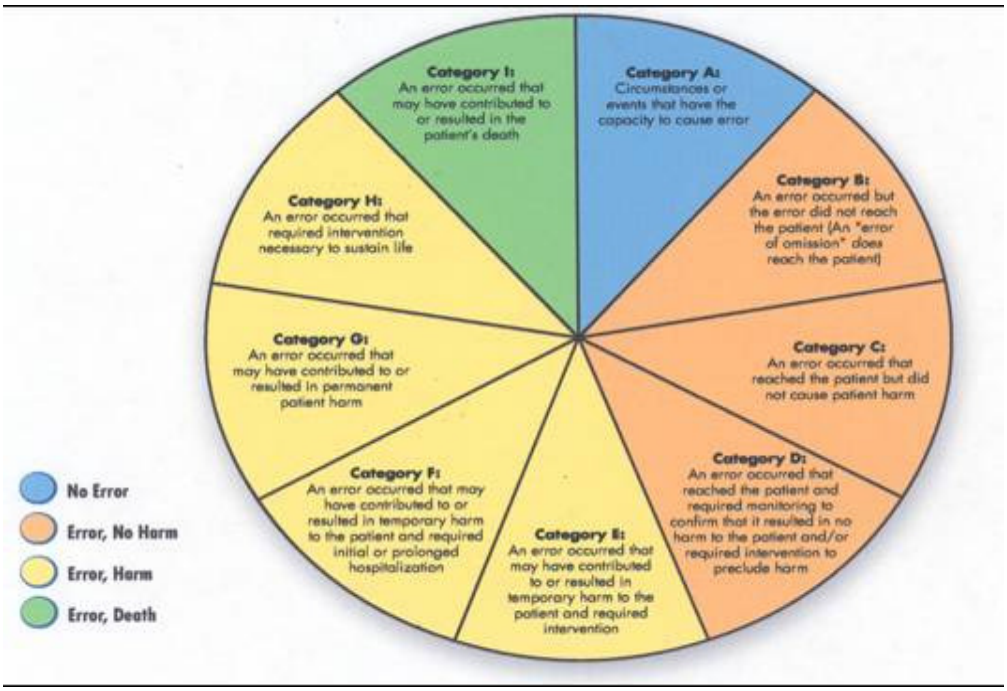
According to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) of the USA, **a medication error is "any preventable event that may cause or lead to inappropriate medication use or patient harm** while the medication is in the control of the healthcare professional, patient or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use". The figure below illustrates the types of errors and associated harms[41] which may occur.

[39] World Health Organisation (2010) Patient Safety. Available at: http://www.who.int/topics/patient_safety/en/. Retrieved on: 4 November 2010

[40] The Community, through the Seventh Framework Programme for Research and Development (Decision No 1982/2006/EC) supports research in health systems, in particular in the quality of healthcare provision under the Health Theme, including a focus on patient safety.

[41] Harm is defined as impairment of the physical, emotialn or psychological function or structure of the body and/or pain resulting the therefrom.

Figure 9: NCC MERP Index for Categorizing Medication Errors



Source: National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) of the USA,

Broadly speaking, the index distinguishes between four categories. Category A refers to circumstance/events which have the capacity to cause a medication error, but none has actually occurred. Categories B to D refer to events where a medication error has occurred, but ultimately the patient has not been harmed as a result of it. Categories E to H refer to events where a medication error has occurred. As a result the patient has been harmed at least temporarily and required some form or intervention. Finally, category I refers to events where an error has occurred which resulted in patient death.

Medication errors may arise from inaccurate or erroneous prescribing, dispensing or administration of drugs. For example, patients may:

- **Receive the wrong drug**: This could be the case because of inaccurate prescribing (e.g. Clarke and Narendran 2005; Courtenay et al. 2007; Cox 2009; McIver et al. 2009); dispensing (e.g. Carrière et al. 2003; Pestaner 2004; Sinicini et al. 2005); administration (e.g. Adlersberg et al. 2002; Berkowitz 2002; DeToledo et al. 2001; Sinicini et al. 2005). The patient is therefore exposed to adverse effects of the drug they have taken as well as being deprived of the beneficial effects of the drug they should have received.
- **Receive the correct drug but at an incorrect dose:** This could be the case because of an error in prescribing or dispensing, or failure to adjust the standard dose to account for individual patient differences (e.g. Amitai and Degani 1990; Yoshikawa et al. 2000;

Sinicini et al. 2005; Gregory et al. 2010; Sims et al. 2010). The patient receives duplicate dosing with the same drug, such as when it is prescribed as two different brands or generic plus branded preparations (e.g. Cox 2009; Karch and Karch, 2002). The patient may suffer toxic effects from an overdose, or have a lack of benefit from a dose that is clinically ineffective.

- **Receive the correct drug and dose but in an incorrect formulation**: The patient receives the same chemically active drug but in a different formulation or brand that is metabolised differently by the body, leading to higher or lower blood levels (e.g. Kuhlmann and Marre, 2010; LeLorier et al. 2008; Lloyd-Mostyn 1990; Makus and McCormick 2007). This could also lead to toxic local effects or lack of effect where it was needed (e.g. McIver et al. 2009).

- **Receive the correct drug, dose and formulation but the drugs interact with other drugs taken:** This could lead to adverse effects relating to exposure to a higher or lower effective level of either or both drugs. For example, one study in the UK found an estimated 33 potentially serious drug interactions involving prescribed medication for asthma per 1000 young people aged 12 to 17 years per year (Novak et al. 2005).

- **Incur a medication gap:** The patient stops taking or is unable to obtain a new supply of medication and suffers harm from sudden discontinuation of therapy (e.g. Davis 1995; Ho et al. 2007).

According to the generic error-modelling system (GEMS), these errors can arise through mistakes (e.g. errors in planning an intentional act, often because of a lack of knowledge about how best to manage a complex situation, or applying a poor or inappropriate rule to guide such management), slips (e.g. acting incorrectly, such as picking the wrong drug dose from a computer list), lapses (e.g. failure to carry out a required action) and violations (e.g. wilfully not following safe practice, such as by-passing safety checks) (Cox 2009).

4.2 Modelling the Effect of Medication Gaps on Patient Harm

In the following paragraphs, we model the effect of medication errors on patient harm. In the first instance, we rely on the information collected for the selected pathologies across the Member States included in this study. Where possible, we extrapolate the information across the EU27. The modelling exercise is underpinned by the following assumptions:

1. **Focus on Medication Gaps:** Consultations with pharmacists/pharmacist representatives[42] have highlighted that pharmacists operate in a professional environment where they exercise a duty of care. As our survey results illustrate, if the dispensing pharmacist is unable to verify the authenticity of prescription and/or prescriber, they are unlikely to fulfil the request. Moreover, they would also not substitute drugs in instances in which they are not fully aware of the patient history. This

[42] 21 June 2011, PGEU General Assembly in Berlin ; 30 September 2011, Breakfast Meeting with PGEU Members in Brussels

is to avoid possible allergic reactions. As a result, the focus of the analysis is exclusively on medication gaps.

2. **Consultation with Local Physician:** If in doubt, the pharmacist is likely to refer the patient to a local doctor to obtain a new prescription. We assume that every case of non-dispensing will result in a visit to a local physician. While some individuals may choose not to consult with a local physician and wait to have their prescription refilled in their home country, there is no evidence to this effect. For this reason we err on the side of caution in assuming one visit to the local doctor in every case of non-dispensing.

3. **Minimal Delays and Short Term Harm:** As described in the previous point, if in doubt, the pharmacist is likely to refer the patient to a local doctor to obtain a new prescription. We assume that at the most this will result in a maximum delay of three days. For this reason, the focus of the analysis is furthermore on short-term harm associated with such a medication gap.

Modelling Patient Harm as a Result of Medication Gaps

A rigorous review of existing evidence has been carried out to better understand time scales and levels of harm associated with a medication gap across the selected pathologies. As is illustrated in the table below, a total of 62 relevant publications, including controlled observational studies, survey studies, retrospective data analysis studies and case studies, were identified. A detailed overview of the studies may be found in Appendix 6.3.3.

Table 11: Overview of Relevant Publications: Patient Harm as a Result of Medication Gaps

Pathology	Publications
Asthma	7
COPD	5
Depression	6
Diabetes	8
Epilepsy	12
Hypertension	11
IHD	9
Rheumatoid Arthritis	4
Other	2
Total	**62**[43]

We focused our analysis on time-scales and levels of harm associated with a medication gap.

- **Time Scales:** In terms of time-scales we differentiated between short-term (less than 1 month), short to medium term (between 1 month and 6 months), medium term (6 to 12 months) and long-term (above 12 months).

[43] One publication, Pladevall et al (2004) covers three pathologies.

- **Level of Harm**: We distinguished between the following five levels of harm: Level 1 (mild increase in symptoms requiring a consult with a physician); Level 2 (increase in symptoms requiring hospitalisation); Level 3 (acute and severe symptoms requiring emergency surgery), Level 4 ((likely) death).

Of the 62 studies identified, a total of eight studies reported a short-term effect of a medication gap for one of the selected pathologies, of up to a month. The table below summarises the results.

Table 12: Overview of Studies Reporting on Some Level of Harm in the Short-Term Due to Medication Gap (average scores across the studies)

Number of Studies Reporting:	Short Term Effect (STE) *(0=less than 1 month; 1=1 to 6 months; 2= 6 to 12 months; 3= more than 12 months)*	Average Level of Harm associated with STE *(Level 1 = consult physician; Level 2 = hospitalisation; Level 3 emergency surgery; Level 4 = likely death)*
Asthma	0	n/a
COPD	1	1
Depression	3	1
Diabetes	0	n/a
Epilepsy	3	2.3
Hypertension	1	1
IHD	1	3
Rheumatoid Arthritis	0	n/a

The relevant study results are briefly described below (no relevant information found for Asthma, Diabetes, and rheumatoid arthritis), with a detailed summary of each study provided in Appendix 6.3 :

- **Chronic obstructive pulmonary disease (COPD):** A sudden withdrawal of Tiotropium after a clinical trial led to an increase in shortness of breath, lung function and worse health status over the following 3 weeks (Adams et al. 2009).
- **Depression and Bipolar Disease:** Discontinuation syndromes start within a few days of stopping the medication (Tricyclics, MAOIs, and SSRIs). Most require no treatment but some can be serious (Haddad 2001). A 10-day gap between finishing one prescription of SSRIs and getting the next prescription filled meant that antidepressant therapy was needed for twice as long (Gardarsdottir et al. 2010). The symptoms that are reported following the withdrawal of these drugs can be classified into the following groups: influenza-like symptoms, psychic symptoms, gastrointestinal symptoms, sleep disorders, equilibrium disorders, sensory disturbances, and extrapyramidal symptoms. It is characteristic of these symptoms that they appear 1-4 days after reduction of the dose or the last administration of the drug (Schatzberg et al. 1997; Vlaminck et al. 2005).

- **Epilepsy:** Handoko et al (2007) found that, discontinuation of an anti-epileptic drug showed a trend towards an increased risk of hospitalisation among patients admitted to hospital, comparing medication use in the 28 days before the admission with medication use in four earlier 28-day periods. In one case study, a 76 year old woman was unable to get her prescription (Gabapentin) filled. 4 days later she was admitted to hospital with agitation and restlessness. The symptoms resolved when Gabapentin was restarted (See et al 2011). In another instance, immediately following the abrupt discontinuation of lamotrigine in a 68 year old man, disordered sleep symptomatology was severely aggravated, with dreams becoming more vivid and frightening and occurring almost every night (Economou et al. 2011).
- **Hypertension:** Rose et al (2011) found that blood pressure following 7 days of excellent adherence was between 12/7 mm Hg and 15/8 mm Hg lower than after 7 days of poor adherence.
- **Ischaemic heart disease (IHD):** In one instance, a 68 year old lady who had a drug-eluting coronary stent had an acute MI 2 days after stopping her antithrombotic therapy (aspirin plus clopidogrel) (Cardona et al 2011).

The results suggest that **although a short-term health effect following a medication gap cannot be ruled-out for the majority of pathologies, the relative frequency of it is not clear and the anticipated level of harm tends to be low.** An exception appears to be epilepsy, where discontinuation of medication may lead to hospitalisation and IHD, where a two-day medication gap in one case resulted in an acute MI (see example above).

Modelling Economic Impact of Non-Dispensing Diabetes Foreign Prescriptions

The results of the desk-based modelling exercise are presented in the tables below. We present the information first for the Member States included in the study, before extrapolating the information to the EU27. The economic model is underpinned by the following assumptions:

- **Total of Foreign Prescriptions:** We estimate a total of 1.23 million foreign prescriptions are presented for dispensing each year across the six Member States selected for this study. The extrapolated EU27 figure is 2.33 million. The underlying calculations are discussed in detail in Section 3.0.

- **Likelihood of Non-Dispensing**: Based on the dispenser survey results, we assume that 55% of foreign prescription will not be dispensed.[44]

- **Likelihood and Level of Harm Due to Medication Gap:** As discussed above, existing evidence suggests that although a short-term health effect following a medication gap cannot be ruled-out for the majority of pathologies, the relative frequency of it is not clear and the anticipated level of harm tends to be low. It has thus been decided not to model likelihood and level of harm due to a medication gap.

[44] We consider this to be a liberal estimate, because pharmacists where asked within a hypothetical framework. It would be interesting to run the model with the results from the OSE study once completed.

- **Cost of Visiting a Local Physician**: The major cost associated with a medication gap due to a delay in dispensing expected to be the **cost of going to a local physician**. There is no systematic EU-wide evidence on the cost of an average GP visit. Whilst a widely-used figure within the UK is £36 for a 12 minute consultation[45] this is likely to be above the EU average, i.e. not implementable as a reliable EU estimate. Because the main component of GP visit costs is GP's salaries, a way in which to proxy a more reliable EU-wide estimate for GP visit costs is to weight the £36 according to how far above the EU average UK GP salaries are. Combining OECD data on GP salaries in 10 Member States[46] and WHO 'Health for All' Database[47] data on the number of GPs across the EU shows that UK GP salaries are around 125% of the EU average GP salary. This weights the EU GP visit estimate down to £28.80, or around €34.

[45] estimated by PSSRU, http://www.pssru.ac.uk/pdf/uc/uc2011/uc2011.pdf)
[46] (http://www.oecd.org/dataoecd/51/48/41925333.pdf)
[47] (http://data.euro.who.int/hfadb/)

Table 13: Economic Model

		Likelihood Non-Dispensing	Number of Cases	Per Unit Cost of Visiting a Local Physician	Total Cost
Total Foreign Prescriptions (6 MS per annum)	**1,225,154**	0.55	673,834	€ 34.00	€ 22,910,356
Total Foreign Prescriptions (EU27 per annum)	**2,330,301**		1,281,666		€43,576,644

The results of the economic model suggest that approximately 1.28 million foreign prescriptions across the EU are not immediately dispensed annually. While in most cases there will be no effect/very little effect on patient harm (and thus did not warrant inclusion in our model), we estimate that in each of these cases a visit to a local physician is required. The associated costs amount to approximately € 43.6 million per year.

5.0 Conclusion

This study has been carried out in the context of Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare (CBHC). The CBHC Directive stipulates that the European Commission shall adopt measures to facilitate the recognition of prescriptions issued in another Member State (Article 11). At the time of submission of this report, the European Commission was preparing an impact assessment with regards to these measures, designed to help implement Article 11. The results of this study were to inform specifically the baseline analysis underlying the status quo policy option (cf. 'Option 1 – "no policy change"' in associated Roadmap). More specifically, this study will provide a scientifically valid baseline measurement of existing problems associated with the mutual recognition of medical prescriptions, including an estimation of the impact in terms of financial cost and patient harm.

In addition to targeted evidence reviews and stakeholder interviews, the analysis was informed to a large extent by a **survey completed by nearly 1,000 dispensers across seven Member States** (Denmark, Germany, Greece, France, Netherlands, Poland, UK) sharing their views on dealing with foreign prescriptions across eight pathologies (Asthma, COPD, Depression, Diabetes, Epilepsy, Hypertension, Ischaemic Heart Disease, Osteoarthritis/Rheumatoid Arthritis).

The seven sampled Member States represent 56% of the EU population[48] and 53% of all prescriptions[49]. The sampled pathologies account for 25% of the disease burden in men and 29% of the diseases burden in women[50] across the WHO Europe A region and between 19% and 64% of all prescriptions in Denmark, the Netherlands, France, Germany and England.[51]

The research team made a conscious decision not to engage in any form of 'mystery shopping'. The concern was that pharmacists would be reluctant to engage with the research in such a way that could raise questions of professional liability. The research team thus opted to engage with pharmacists in their capacity as experts, asking them for their opinion on possible problems associated with the dispensing of prescriptions originating in another EU Member State.

Main Results and Limitations of the Study

- **Overall Low Number of Foreign Prescriptions:** An estimated 2.33 million EU prescription are sought to be dispensed in another EU Member State each year (estimated min = 1.1 million; estimated max = 8 million)[52]. This makes up a very small

[48] Eurostat (2011). Population on 1 January by age and sex. Available at: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjan&lang=en. Retrieved on 24th January 2011.
[49] If prescriptions are assumed to be proportional to the amount of pharmacists, according to PGEU data outlined above.
[50] Diseases burden measured here in DALYs, according to WHO data.
[51] Various national sources, outlined in the annex.
[52] Note that this estimate is based on the assumption that the experience distribution within the ranges specified by pharmacists (i.e. 0-4 a month, 5-10 a month, etc.) mirrors the total positively skewed experience distribution of range

portion of the overall number of prescriptions dealt with by pharmacists across the EU annually (between 6.5 and 10 billion).

- **Relatively High Rate of Non-Dispensing:** Nevertheless, over half of foreign prescriptions (55%) are likely to incur a delay in being dispensed (approximately 1.25 million prescriptions). The survey results furthermore illustrated that 7% (521) of prescriptions would definitely not be dispensed while 3% (223) of all prescriptions would definitely be dispensed. Key challenges are verification of prescriber and prescription; possibly exacerbated by handwritten prescription, those presented in an unfamiliar language, or missing information. The availability of (substitute) drugs has been mentioned as problem less often.

- **Reasonably Small Effect on Patient Harm**: Existing evidence suggests that although a short-term health effect following a medication gap cannot be ruled-out for the majority of pathologies, the relative frequency of it is not clear and the anticipated level of harm tends to be low.

- **Low Patient Harm Costs:** The major cost associated with a medication gap due to a delay in dispensing is the cost of going to a local physician, which is estimated at €34 for each twelve minute consultation. The results of the economic model suggest that approximately 1.28 million foreign prescriptions across the EU are not immediately dispensed annually. We estimate that in each of these cases a visit to a local physician is required. The associated costs amount to approximately € 43.6 million per year.

answers (i.e. that very few pharmacists specify having substantial experience with foreign prescriptions). Most pharmacists are confronted with fewer than 5 foreign prescriptions each month.

6.0 Annexes

6.1 Bibliography

Adlersberg, M.A., Fernando, S., Spollett, G.R., Inzucchi, S.E. (2002).Glargine and lispro: two cases of mistaken identity. *Diabetes Care*, 25(2): pp.404-405.

Adams SG, Anzueto A, Briggs DD Jr, et al. Evaluation of withdrawal of maintenance tiotropium in COPD. Respir Med. 2009 Oct;103(10):1415-20. Epub 2009 Jun 11.

Akbaraly TN, Brunner EJ, Ferrie JE et al. (2009). Dietary pattern and depressive symptoms in middle age. Br J Psychiatry. 2009 Nov;195(5):408-13.

Alkerwi A, Sauvageot N, Donneau AF, et al. (2010). First nationwide survey on cardiovascular risk factors in Grand-Duchy of Luxembourg (ORISCAV-LUX). *BMC Public Health* 10:468.

Altshuler L, Suppes T, Black D et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry. 2003 Jul;160(7):1252-62.

Amitai, Y., Degani, Y. (1990). Treatment of phenobarbital poisoning with multiple dose activated charcoal in an infant. *Journal of Emergency Medicine*, 8 (4); pp.449-450.

Anagnostopoulos I, Zinzaras E, Alexiou I, et al. (2010). The prevalence of rheumatic diseases in central Greece: a population survey. *BMC Musculoskelet Disord* 11:98.

Bailey JE, Wan JY, Tang J et al. Antihypertensive medication adherence, ambulatory visits, and risk of stroke and death. J Gen Intern Med 2010;25(6):495-503.

Balkau B, Lange C, Vol S, et al. (2010). Nine-year incident diabetes is predicted by fatty liver indices: the French D.E.S.I.R. study. *BMC Gastroenterol* 10:56.

Berkowitz, K. (2002). Practice errors. Lantus? Or lente? Both insulin, not the same drug. *American Journal of Nursing* , 102 (8): pp. 55.

Bielen I, Cvitanovic-Sojat L, Bergman-Markovic B et al. (2007). Prevalence of epilepsy in Croatia: a population-based survey. *Acta Neurol Scand* 116(6):361-7.

Bischoff EW, Schermer TR, Bor H, et al. (2009). Trends in COPD prevalence and exacerbation rates in Dutch primary care. *Br J Gen Pract* 59(569):927-33.

Biver E, Beague V, Verloop D, et al. (2009). Low and stable prevalence of rheumatoid arthritis in northern France. *Joint Bone Spine* 76(5):497-500. Epub 2009 Sep 19.

Bonnett LJ, Shukralla A, Tudur-Smith C et al. Seizure recurrence after antiepileptic drug withdrawal and the implications for driving: further results from the MRC Antiepileptic Drug Withdrawal Study and a systematic review. J Neurol Neurosurg Psychiatry. 2011 Jan 13. [Epub ahead of print]

Bosmans JE, de Bruijne MC, de Boer MR, et al. (2010). Health care costs of depression in primary care patients in The Netherlands. Fam Pract. 2010 Oct;27(5):542-8. Epub 2010 Jun 8.

Bramley TJ, Gerbino PP, Nightengale BS et al. Relationship of blood pressure control rto adherence with antihypertensive monotherapy in 13 managed care organiszations. J Manag Care Pharm. 2006;12(3):239-45.

Brocklebank, D., Ram, F., Wright, J. et al. (2001). Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technology Assessment*, 5(26).

Brocq O, Millasseau E, Albert C et al. Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis. Joint Bone Spine. 2009 Jul;76(4):350-5. Epub 2009 Apr 11.

Brodie MJ et al. (1997). Commission on European Affairs: Appropriate standards of epilepsy care across Europe. Epilepsia 38: 1245-1250. http://www.eucare.org/download/appropriate_standards_of_care.pdf

Brodtkorb E, Sjaastad O. (2008). Epilepsy prevalence by individual interview in a Norwegian community. *Seizure* 17(7):646-50. Epub 2008 Apr 22.

Browatzki A, Ulrik CS, Lange P. (2009). Prevalence and severity of self-reported asthma in young adults, 1976-2004. *Eur Respir J* 34(5):1046-51. Epub 2009 Jul 2

Cantrell CR, Eaddy MT, Shah MB et al. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. Med Care. 2006 Apr;44(4):300-3.

Cardona L, Simas A, Lousinha A et al. Very late coronary stent thrombosis after discontinuation of antiplatelet therapy. Rev Port Cardiol 2011; 30 (03): 333-339

Carey, N., Courtenay, M., James, J., Hills, M., Roland, J. (2008). An evaluation of a Diabetes Specialist Nurse prescriber on the system of delivering medicines to patients with diabetes. *Journal of Clinical Nursing*, 17 (12): pp.1635-1644.

Carrière, B., Bailey, B., Chabot, G., Lebel, D. (2003). Dispensing error leading to alendronate ingestion. *Ann Pharmacother*, 37(1):pp. 87-89.

Carroll K, Majeed A, Firth C et al. (2003). Prevalence and management of coronary heart disease in primary care: population-based cross-sectional study using a disease register. J Public Health Med 25(1):29-35.

Cazzola M, Puxeddu E, Bettoncelli G et al. (2011). The prevalence of asthma and COPD in Italy: a practice-based study. *Respir Med* 105(3):386-91. Epub 2010 Oct 15.

Center for Financing, Access and Cost Trends, Agency for Healthcare Research and Quality: Medical Expenditure Panel Survey, 2008. Available at: http://www.ifhp.com/documents/IFHPPricereportfinal.pdf

Cífková R, Skodová Z, Bruthans J, et al. (2010). Longitudinal trends in cardiovascular mortality and blood pressure levels, prevalence, awareness, treatment, and control of hypertension in the Czech population from 1985 to 2007/2008. *J Hypertens* 28(11):2196-203.

Clarke, N.R., Narendran, P. (2005). Insulin prescribing is unsafe: education results in a significant but insufficient improvement. *Diabetic Medicine*, 22 (12) . pp. 1779-1780.

COM (2008/414 final) Proposal for a Directive on the Application of Patients' Rights in Cross-Border Healthcare.

Conradi, P. (1995). Health ministers look at cross-border prescriptions. *BMJ*, 311: 1524.

Contreras-Yáñez I, Cabiedes J, Villa AR et al. Persistence on therapy is a major determinant of patient-, physician- and laboratory- reported outcomes in recent-onset rheumatoid arthritis patients. Clin Exp Rheumatol. 2010 Sep-Oct;28(5):748-51. Epub 2010 Oct 22.

Corrao G, Conti V, Merlino L, et al. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. Clin Ther. 2010 Feb;32(2):300-10.

Corrao G, Parodi A, Nicotra F et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011 Mar;29(3):610-8.

Costanzo S et al. (2008). Prevalence, awareness, treatment and control of hypertension in healthy unrelated male-female pairs of European regions: the dietary habit profile in European communities with different risk of myocardial infarction--the impact of migration as a model of gene-environment interaction project. J Hypertens 26: 2303-11.

Courtenay M, N., Carey, J., James, M., Hills, J. (2007). Roland An evaluation of a specialist nurse prescriber on diabetes in-patient service delivery. *Practical Diabetes International*, 24 (2): pp. 69-74.

Cox, A.R. (2009). Prescribing errors in diabetes. *British Journal of Diabetes & Vascular Disease*, 9 (2): pp. 84-88.

Crowe, D. (2009). Analysis of studies that compare the dose accuracy of prefilled insulin pens. Journal of Diabetes Science and Technology, 3(1):pp.154-155.

Dahl, R., Backer, V., Ollgaard, B., Gerken, F., Kesten, S. (2003). Assessment of patient performance of the HandiHaler compared with the metered dose inhaler four weeks after instruction. *Respir Med,* 97(10): pp.1126-33.

Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia. 2008 Mar;49(3):446-54. Epub 2007 Nov 21.

Davis, N.M. (1995). Preventing omission errors. *Am J Nurs,* 95(4): pp.17.

de Moraes Souza, M.L., Meneghini, A.C., Ferraz, E. et al. (2009). Knowledge of and technique for using inhalation devices among asthma patients and COPD patients. *J Bras Pneumol,* 35(9):pp. 824-831.

De Vera MA, Choi H, Abrahamowicz M, et al. Statin discontinuation and risk of acute myocardial infarction in patients with rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis. 2011 Jun;70(6):1020-4. Epub 2011 Mar 6.

Delea TE, Stanford RH, Hagiwara M et al. Association between adherence with fixed dose combination fluticasone propionate/salmeterol on asthma outcomes and costs*. Curr Med Res Opin. 2008 Dec;24(12):3435-42.

Delmas MC, Fuhrman C; pour le groupe épidémiologie et recherche clinique de la SPLF. (2010). Asthma in France: a review of descriptive epidemiological data. Rev Mal Respir. 2010 Feb;27(2):151-9. Epub 2010 Feb 8.

Demoly P, Gueron B, Annunziata K, et al. (2010). Update on asthma control in five European countries: results of a 2008 survey. Eur Respir Rev. 2010 Jun 1;19(116):150-7.

Demoly P, Paggiaro P, Plaza V et al. (2009). Prevalence of asthma control among adults in France, Germany, Italy, Spain and the UK. Eur Respir Rev. 2009 Jun 1;18(112):105-12.

DeToledo, J.C., Lowe,M.R., Rabinstein, A., Villaviza, N. (2001). Cardiac arrest after fast intravenous infusion of phenytoin mistaken for fosphenytoin. *Epilepsia*, 42(2): pp. 288–291.

Donihi, A.C., DiNardo, M.M., DeVita, M.A., Korytkowski, M.T. (2006). Use of a standardized protocol to decrease medication errors and adverse events related to sliding scale insulin. *Quality & Safety in Health Care*, 15 (2): pp. 89-91.

Doyle, S., Lloyd, A., Williams, A. et al. (2010). What happens to patients who have their asthma device switched without their consent? *Primary care Respiratory Journal*, 19(2): pp.131-139.

Dragomir A, Côté R, Roy L, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Med Care. 2010 May;48(5):418-25.

EC Health & Consumer Protection Directorate-General. (2004). Actions against depression. http://ec.europa.eu/health/ph_determinants/life_style/mental/docs/depression_en.pdf)

Economou NT, Bonakis A, Ghika A, et al. Lamotrigine withdrawal may worsen RBD symptoms. Neurologist. 2011 Sep;17(5):279-81.

Ekerljung L, Andersson A, Sundblad BM et al. (2010). Has the increase in the prevalence of asthma and respiratory symptoms reached a plateau in Stockholm, Sweden? *Int J Tuberc Lung Dis* 14(6):764-71.

Encinosa WE, Bernard D, Dor A. Does prescription drug adherence reduce hospitalizations and costs? The case of diabetes. Adv Health Econ Health Serv Res. 2010;22:151-73.

Englund M, Jöud A, Geborek P, et al. (2010). Prevalence and incidence of rheumatoid arthritis in southern Sweden 2008 and their relation to prescribed biologics. *Rheumatology (Oxford)* 49(8):1563-9. Epub 2010 May 5.

Eurobarometer (2007).*Cross-Border Health Services in the EU.* Flash Europe Barometer 210 – The Gallup Organisation

European Commission. (2011). Indicators for Monitoring Musculoskeletal Conditions Project, http://ec.europa.eu/health/archive/ph_information/dissemination/diseases/musculo_3.pdf

European Observatory on health systems and policies. (2009). Health in the European Union. http://www.euro.who.int/__data/assets/pdf_file/0003/98391/E93348.pdf

European Union (2011). Directive on the Application of Patients' Rights in Cross-Border Healthcare (L88/45). Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF

European Commission (2011). Roadmap for Implementing measures for improving the recognition of prescriptions issued in another Member State under Article 11 para. 2 of the Directive on the Application of Patients' Rights in Cross-Border Healthcare (CBHC). Available at:
http://ec.europa.eu/governance/impact/planned_ia/docs/2013_sanco_004_mutual_recognition_of_prescriptions_en.pdf

Eurostat (2010). Population and Tourism Statistics Available at: http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/

Falaschetti E, Chaudhury M, Mindell J, et al. (2009). Continued improvement in hypertension management in England: results from the Health Survey for England 2006. *Hypertension* 53(3):480-6. Epub 2009 Feb 9.

Faught E, Duh MS, Weiner JR et al (b). Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. Neurology. 2008 Nov 11;71(20):1572-8. Epub 2008 Jun 18.

Faught RE, Weiner JR, Guérin A et al. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia. 2009 Mar;50(3):501-9. Epub 2008 Oct 3.

Fung V, Huang J, Brand R et al. Hypertension treatment in a medicare population: adherence and systolic blood pressure control. Clin Ther. 2007 May;29(5):972-84.

Gabriel R, Alonso M, Segura A, et al. (2008). Prevalence, geographic distribution and geographic variability of major cardiovascular risk factors in Spain. Pooled analysis of data from population-based epidemiological studies: the ERICE Study. *Rev Esp Cardiol* 61(10):1030-40.

Gardarsdottir H, Souverein PC, Egberts TC, et al. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol. 2010 Apr;63(4):422-7. Epub 2009 Oct 31.

Gardete-Correia L, Boavida JM, Raposo JF, et al. (2010). First diabetes prevalence study in Portugal: PREVADIAB study. *Diabet Med* 27(8):879-81.

Gasquet I, Nègre-Pagès L, Fourrier A et al. (2005). Psychotropic drug use and mental psychiatric disorders in France; results of the general population ESEMeD/MHEDEA 2000 epidemiological study. Encephale. 2005 Mar-Apr;31(2):195-206.

Geldmacher H, Biller H, Herbst A, et al. (2008). The prevalence of chronic obstructive pulmonary disease (COPD) in Germany. Results of the BOLD study. *Dtsch Med Wochenschr* 133(50):2609-14. Epub 2008 Dec 3.

Ghaemi SN, Ostacher MM, El-Mallakh RS et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry. 2010 Apr;71(4):372-80.

Gibson TB, Song X, Alemayehu B et al. Cost sharing, adherence, and health outcomes in patients with diabetes. Am J Manag Care. 2010 Aug;16(8):589-600.

Gray LJ, Tringham JR, Davies MJ et al. (2010). Screening for type 2 diabetes in a multiethnic setting using known risk factors to identify those at high risk: a cross-sectional study. *Vasc Health Risk Manag* 6:837-42.

Gregoire, L. (2003). Alberta MDs warned not to co-sign American prescriptions. *CMAJ*, 168: 886.

Gregory, M.D., Mersfelder, T.L., Jamieson, T. (2010). Accidental overdose of tiotropium in a patient with atrial fibrillation. *Annals of Pharmacotherapy*, 44; pp. 391-393.

Haddad PM. Antidepressant discontinuation syndromes. Drug Saf. 2001;24(3):183-97.

Handoko KB, Zwart-van Rijkom JE, Hermens WA et al. Changes in medication associated with epilepsy-related hospitalisation: a case-crossover study. Pharmacoepidemiol Drug Saf. 2007 Feb;16(2):189-96.

Hansen JG, Pedersen L, Overvad K, et al. (2008). The Prevalence of chronic obstructive pulmonary disease among Danes aged 45-84 years: population-based study. *COPD* 5(6):347-52.

Hansen RN, Campbell JD, Sullivan SD. Association between antiepileptic drug switching and epilepsy-related events. Epilepsy Behav. 2009 Aug;15(4):481-5. Epub 2009 Jul 16.

Heisler M, Choi H, Rosen AB et al. Hospitalizations and deaths among adults with cardiovascular disease who underuse medications because of cost: a longitudinal analysis. Med Care. 2010 Feb;48(2):87-94.

Heisler M, Langa KM, Eby EL et al. The health effects of restricting prescription medication use because of cost. Med Care. 2004 Jul;42(7):626-34.

Hepke KL, Martus MT, Share DA. Costs and utilization associated with pharmaceutical adherence in a diabetic population. Am J Manag Care. 2004 Feb;10(2 Pt 2):144-51.

Ho PM, Magid DJ, Shetterly SM et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J. 2008 Apr;155(4):772-9.

Ho PM, Rumsfeld JS, Masoudi FA et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med. 2006 Sep 25;166(17):1836-41.

Ho, P.M., Fihn, S.D., Wang, L., Bryson, C.L., Lowy, E., Maynard, C., et al. (2007). Clopidogrel and long-term outcomes after stent implantation for acute coronary syndrome. *American Heart Journal*, 154(5): pp.846-851.

Holtermann A, Mortensen OS, Burr H, et al. (2010). Physical work demands, hypertension status, and risk of ischemic heart disease and all-cause mortality in the Copenhagen Male Study. *Scand J Work Environ Health* 36(6):466-72. Epub 2010 Sep 20.

Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Med Care. 2011 Apr;49(4):378-84.

Horswell RL, Wascom CK, Cerise FP et al. Diabetes mellitus medication assistance program: relationship of effectiveness to adherence. J Health Care Poor Underserved. 2008 Aug;19(3):677-86.

Hvidsten SC, Storesund L, Wentzel-Larsen T, et al. (2010). Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. *Clin Respir J* 4(1):13-21.

International Diabetes Federation (2010). Prevalence estimates of diabetes mellitus (DM) 2010. http://www.idf.org/content/eur-data

Joseph J, Svartberg J, Njølstad I, et al. (2010). Incidence of and risk factors for type-2 diabetes in a general population: the Tromsø Study. *Scand J Public Health* 38(7):768-75. Epub 2010 Aug 9.

Karch, A.M., Karch, F.E. (2002). Practice errors. Double dosing: one drug can have two brand names and two indications. *American Journal of Nursing* 102 (10): pp.23.

Kettani FZ, Dragomir A, Côté R et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. Stroke 2009;40:213-220.

Kleinberg A, Aluoja A, Vasar V. (2010). Point prevalence of major depression in Estonia. Results from the 2006 Estonian Health Survey. Eur Psychiatry. 2010 Dec;25(8):485-90. Epub 2010 Sep 1.

Kroon, L. (2009). An analysis of patient acceptance and safety of a pre-filled insulin injection device. *Journal of Diabetes Science and Technology*, 3(6):pp. 1439-1441.

Krosnar, K. (2005). Cross-border trade in medicines causes concern in the EU. *Lancet*, 365 pp 1297 – 1298.

Kuhlmann, M., Marre, M. (2010). Lessons learned from biosimilar epoetins and insulins. *British Journal of Diabetes & Vascular Disease*, 10 (2): pp. 90-97.

Laxafoss E, Jacobsen S, Gosvig KK, et al. (2010). Case definitions of knee osteoarthritis in 4,151 unselected subjects: relevance for epidemiological studies: the Copenhagen Osteoarthritis Study. *Skeletal Radiol* 39(9):859-66. Epub 2010 Jan 30.

Lehto SM, Ruusunen A, Niskanen L, et al. (2010). Elevated depressive symptoms and compositional changes in LDL particles in middle-aged men. Eur J Epidemiol. 2010 Jun;25(6):403-9. Epub 2010 Apr 23.

LeLorier, J. (2008). Clinical consequences of generic substitution of lamotrigine for patients with epilepsy. *Neurology*, 70 (22 Part 2): pp. 2179-2186.

Linehan C, Kerr MP, Walsh PN, et al. (2010). Examining the prevalence of epilepsy and delivery of epilepsy care in Ireland. *Epilepsia* 51(5):845-52. Epub 2009 Dec 1.

Lloyd-Mostyn, R.H. (1990). Alteration in diabetic control after a change in insulin manufacture. *BMJ*, 300(6720): pp. 328–329.

Löfgren E, Pouta A, von Wendt L, et al. (2009). Epilepsy in the northern Finland birth cohort 1966 with special reference to fertility. *Epilepsy Behav* 14(1):102-7. Epub 2008 Oct 10.

Lteif AN., Schwenk, WF. (1999). Accuracy of pen injectors versus insulin syringes in children with Type 1 diabetes. *Diabetes care*, 22: pp.137-140.

Mäkinen, M. (2007). *Delivery of European cross-border healthcare and the relevance and effects of EU regulations and judicial processes*. Turku University, Finland.

Mäkinen, M., Forsstrom, J., Aarimaa, M., Rautava, P. (2006). A European survey on the possibilities and obstacles of electronic prescriptions in cross-border healthcare. *Telemedicine and e-Health*, 12, pp 484-489.

Mäkinen, M., Rautava, P., Forsstrom, J. (2005). Do online pharmacies fit European internal markets? *Health Policy* 72: 245-252.

Makus, K.G., McCormick, J. (2007). Identification of adverse reactions that can occur on substitution of generic for branded lamotrigine in patients with epilepsy. *Clinical Therapeutics*, 29 (2): pp. 334-341.

Manjunath R, Davis KL, Candrilli SD et al. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. Epilepsy Behav. 2009 Feb;14(2):372-8. Epub 2009 Jan 4.

Marceau C, Lemière C, Berbiche D, et al. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol. 2006 Sep;118(3):574-81.

Mattke S, Martorell F, Hong SY et al. Anti-inflammatory medication adherence and cost and utilization of asthma care in a commercially insured population. J Asthma. 2010 Apr;47(3):323-9.

Mazzaglia, G, Ambrosioni E, Alacqua M et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation 2009;120:1598-1605.

McCombs JS, Nichol MB, Newman CM et al. The Costs of Interrupting Antihypertensive Drug Therapy in a Medicaid Population. Medical Care, Vol. 32, No. 3 (Mar., 1994), pp. 214-226.

McIver, F.B., Mitchell, C.A., Finn, C.P., Kamp, M.C. (2009). Standardising practices through form design and education improves insulin management. *Australian Health Review*, 33 (3): pp. 434-441.

Meisinger C, Strassburger K, Heier M et al. (2010). Prevalence of undiagnosed diabetes and impaired glucose regulation in 35-59-year-old individuals in Southern Germany: the KORA F4 Study. *Diabet Med* 27(3):360-2.

Merikangas KR, Jin R, He JP, et al. (2011). Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011 Mar;68(3):241-51.

Milgrom H, Bender B, Ackerson L, et al. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol. 1996 Dec;98(6 Pt 1):1051-7.

Miravitlles M, Soriano JB, García-Río F, et al. (2009). Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 64(10):863-8. Epub 2009 Jun 23.

Morgan CL, Peters JR, Currie CJ. (2010). The changing prevalence of diagnosed diabetes and its associated vascular complications in a large region of the UK. *Diabet Med* 27(6):673-8.

National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP)

Navaratnam P, Friedman HS, Urdaneta E. The impact of adherence and disease control on resource use and charges in patients with mild asthma managed on inhaled corticosteroid agents. Patient Prefer Adherence. 2010 Jun 24;4:197-205.

Neovius M, Simard JF, Askling J; ARTIS study group. (2011). Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. *Ann Rheum Dis* 70(4):624-9. Epub 2010 Dec 13.

Novak, P.H., Ekins-Daukes, S., Simpson, C.R., Milne, R.M., Helms, P., McLay, J.S. (2005). Acute drug prescribing to children on chronic antiepilepsy therapy and the potential for adverse drug interactions in primary care. *British Journal of Clinical Pharmacology*, 59(6): pp. 712-717.

OECD (2009). Health at a Glance 2009. Available at: http://www.oecd.org/document/14/0,3343,en_2649_33929_16502667_1_1_1_37407,00.html

Oliveira-Martins S, Oliveira T, Gomes JJ, et al. (2011). Factors associated with arterial hypertension in pharmacy users in Portugal. *Rev Saude Publica* 45(1):136-44. Epub 2010 Dec 10.

Olofson J, Bake B, Tengelin MN, et al. (2008). COPD 'diagnosis' based on spirometric reference equations. *Clin Respir J* 2(4):214-9.

Oude Griep LM, Geleijnse JM, Kromhout D, et al. (2010). Raw and processed fruit and vegetable consumption and 10-year coronary heart disease incidence in a population-based cohort study in the Netherlands. *PLoS One* 5(10):e13609.

Palm, Willy (21 October 2010). *Access to Cross-Border Healthcare in the EU: Background and Principles,* European Observatory on Health Systems and Policies and Helsedirektoratet.

Pascual-Ramos V, Contreras-Yáñez I, Villa AR et al. Medication persistence over 2 years of follow-up in a cohort of early rheumatoid arthritis patients: associated factors and relationship with disease activity and with disability. Arthritis Res Ther. 2009;11(1):R26. Epub 2009 Feb 19.

Perreault S, Dragomir A, Blais L et al. Impact of adherence to statins on chronic heart failure in primary prevention. Br J Clin Pharmacol 2008;66(5):706-716.

Pestaner, J.P. (2004). Fatal mix-up between prednisone and primidone. *Am J Health Syst Pharm,* 61:pp. 1552.

PGEU. Report; Prescriptions in EU

Picot MC, Baldy-Moulinier M, Daurès JP et al. (2008). The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. *Epilepsia* 49(7):1230-8.

Piette JD, Wagner TH, Potter MB, et al. Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. Med Care. 2004 Feb;42(2):102-9.

Pittman DG, Tao Z, Chen W, et al. Antihypertensive medication adherence and subsequent healthcare utilization and costs. Am J Manag Care 2010;16(8):568-576.

Pladevall M, Williams LK, Potts LA, et al. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. Diabetes Care. 2004 Dec;27(12):2800-5.

Pugliatti M, Beghi E, Forsgren L, et al. (2007). Estimating the cost of epilepsy in Europe: a review with economic modeling. *Epilepsia* 48(12):2224-33.

Rifel J, Svab I, Pavlič DR, et al. (2010). Longstanding disease, disability or infirmity and depression in primary care. Wien Klin Wochenschr. 2010 Oct;122(19-20):567-71. Epub 2010 Oct 1.

Rogers, R. (2004). International standards: harmony or confusion? *Br J Healthcare Comput Info Manage*, 21: 15-17.

Rokosky, J.M. (2005). Teaching correct use of inhaled medications. *Home Healthcare Nurse*, 23 (12): pp. 766-776.

Rose AJ, Glickman ME, D'Amore MM, et al. Effects of daily adherence to antihypertensive medication on blood pressure control. J Clin Hypertens (Greenwich). 2011 Jun;13(6):416-21. doi: 10.1111/j.1751-7176.2011.00427.x. Epub 2011 Feb 16.

Ruidavets JB, Ducimetière P, Evans A, et al. (2010). Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *BMJ* 341:c6077. doi: 10.1136/bmj.c6077.

Ruokoniemi P, Korhonen MJ, Helin-Salmivaara A, et al. Statin adherence and the risk of major coronary events in patients with diabetes: a nested case-control study. Br J Clin Pharmacol. 2011 May;71(5):766-76. doi: 10.1111/j.1365-2125.2010.03895.x.

Ryvlin P, Tomson T, Montavont A. Excess mortality and sudden unexpected death in epilepsy. Presse Med. 2009 Jun;38(6):905-10. Epub 2009 Jan 25.

Saxena S, Car J, Eldred D et al. (2007). Practice size, caseload, deprivation and quality of care of patients with coronary heart disease, hypertension and stroke in primary care: national cross-sectional study. *BMC Health Serv Res* 7:96.

Schäper C, Gläser S, Obst A et al. (2010). Symptoms and diagnosis of asthma in a general population – longitudinal results from the SHIP database. *J Asthma* 47(8):860-4.

Schatzberg AF, Haddad P, Kaplan EM, et al. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. Discontinuation Consensus panel. J Clin Psychiatry. 1997;58 Suppl 7:5-10.

Schmidt D. AED discontinuation may be dangerous for seizure-free patients. J Neural Transm. 2011 Feb;118(2):183-6. Epub 2010 Dec 17.

Schnabel E, Karrasch S, Schulz H, et al. (2011). High blood pressure, antihypertensive medication and lung function in a general adult population. *Respir Res* 12(1):50.

See S, Hendriks E, Hsiung L. Akathisia induced by gabapentin withdrawal. Ann Pharmacother. 2011 Jun;45(6):e31. Epub 2011 Jun 7.

Sihvo S, Wahlbeck K, McCallum A, et al. (2010). Increase in the duration of antidepressant treatment from 1994 to 2003: a nationwide population-based study from Finland. Pharmacoepidemiol Drug Saf. 2010 Nov;19(11):1186-93.

Simpson CR, Sheikh A. (2010). Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med* 103(3):98-106.

Sims, J., Richardson, T., Kerr, D. (2010). Insulin errors in hospital: time for a radical re-think on risk? *Clinical Risk* , 16 (3): pp. 89-92.

Sinicina, I., Mayr. B., Mall, G., Keil, W. (2005). Deaths following methotrexate overdoses by medical staff. *Journal of Rheumatology*, 32 (10): pp. 2009-2011.

Sirven JI, Sperling M, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev. 2001;(3):CD001902.

Soriano JB, Ancochea J, Miravitlles M, et al. (2010). Recent trends in COPD prevalence in Spain: a repeated cross-sectional survey 1997-2007. *Eur Respir J* 36(4):758-65. Epub 2009 Dec 8.

Spollett, G. (2008). Pharmacy update. Insulin devices: addressing barriers to insulin therapy with the ideal pen. *Diabetes Educator*, 34 (6): pp. 9579-60, 963, 967.

Stranjalis G, Tsamandouraki K, Gazonis S, et al. (2009). Low occurrence of epileptic seizures and epilepsy in a defined area of Northwest Greece. *Seizure* 18(3):206-10. Epub 2008 Nov 14.

Sundell KA, Gissler M, Petzold M, et al. (2011). Antidepressant utilization patterns and mortality in Swedish men and women aged 20-34 years. Eur J Clin Pharmacol. 2011 Feb;67(2):169-78. Epub 2010 Nov 10.

Svendsen T, Lossius M, Nakken KO. (2007). Age-specific prevalence of epilepsy in Oppland County, Norway. *Acta Neurol Scand* 116(5):307-11.

Takemura M, Mitsui K, Itotani R et al. Relationships between repeated instruction on inhalation therapy, medication adherence, and health status in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2011;6:97-104. Epub 2011 Jan 20.

Tamblyn R, Laprise R, Hanley JA, et al. Adverse events associated with prescription drug cost-sharing among poor and elderly persons. JAMA. 2001 Jan 24-31;285(4):421-9.

The ISAAC Steering Committee. (1998). Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 12:315-335.

Tomio J, Sato H, Mizumura H. Interruption of medication among outpatients with chronic conditions after a flood. Prehosp Disaster Med. 2010 Jan-Feb;25(1):42-50.

Toy EL, Beaulieu NU, McHale JM et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. Respir Med. 2011 Mar;105(3):435-41. Epub 2010 Sep 29.

Urwin M, Symmons D, Allison T et al. (1998). Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis* 57(11):649-55.

Vallejo, P, et.al (2009). *Volume and Diagnosis: An Approach to Cross-Border Care in Eight European Countries*. BMJ Quality and Safety in Healthcare, Volume 18, i8-i14.

van der Meer V, Wielders HP, Grootendorst DC et al. (2010). Chronic kidney disease in patients with diabetes mellitus type 2 or hypertension in general practice. *Br J Gen Pract* 60(581):884-90.

Vasankari TM, Impivaara O, Heliövaara M, et al. (2010). No increase in the prevalence of COPD in two decades. *Eur Respir J* 36(4):766-73. Epub 2010 Aug 6.

Vestbo J, Anderson JA, Calverley PM et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax. 2009 Nov;64(11):939-43. Epub 2009 Aug 23.

Vlaminck JJ, van Vliet IM, Zitman FG. Withdrawal symptoms of antidepressants. Ned Tijdschr Geneeskd. 2005 Mar 26;149(13):698-701.

Wagner A, Sadoun A, Dallongeville J, et al. (2011). High blood pressure prevalence and control in a middle-aged French population and their associated factors: the MONA LISA study. *J Hypertens* 29(1):43-50.

Wei L, Wang J, Thompson P et al. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. Heart 2002;88:229-233.

Wennerholm C, Grip B, Johansson A, et al. (2011). Cardiovascular disease occurrence in two close but different social environments. *Int J Health Geogr* 10:5.

WHO Global Health Observatory. Non-communicable diseases; risk factors data 2008. Available at: http://apps.who.int/ghodata. Retrieved on 7 October 2011.

Williams LK, Peterson EL, Wells K et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol. 2011 Oct 20.

Williams LK, Pladevall M, Xi H, Peterson EL et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol. 2004 Dec;114(6):1288-93.

Woldu H, Porta G, Goldstein T et al. Pharmacokinetically and clinician-determined adherence to an antidepressant regimen and clinical outcome in the TORDIA trial. J Am Acad Child Adolesc Psychiatry. 2011 May;50(5):490-8. Epub 2011 Mar 9.

World Health Organisation (2010) Patient Safety. Available at: http://www.who.int/topics/patient_safety/en/. Retrieved on: 4 November 2010

Wouters EF, Postma DS, Fokkens B et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax. 2005 Jun;60(6):480-7.

Yoshikawa, H., Abe, T., Oda, Y.(2000). Purple glove syndrome caused by oral administration of phenytoin. *J Child Neurol*, 15(11): pp.762.

6.2 Rationale Project Design

6.2.1 Selecting Member States

The process of selecting Member States involved two steps:

1. **Initial Ranking**: We ranked all Member States according to key selection criteria and selected the top six Member States.
2. **Secondary Qualitative Analysis**: We then subjected our results to a secondary qualitative analysis, testing and triangulating the initial ranking.

Initial Ranking

We created an index on the basis of the below selection criteria:

Relevant Population Flows: A country must display sufficient levels of cross- border activity to justify its inclusion in the study. We used data on tourism/health tourism and figures on intra-EU migration as a basis for our selection.

- **Tourism**[53,54]**:** The two columns on tourism report the number of hotel nights by EU residents and the number of EU tourists who stay more than 4 days as reported by Eurostat (2009). The reported figures are percentages calculated by using the maximum value as baseline, providing the basis for a ranking.

- **Intra-EU Migration:**[55] The figures on intra-EU migration – immigration and emigration – are taken from Eurostat (2009). The reported figures are percentages calculated by using the maximum value as baseline, providing the basis for a ranking

- **Health Tourism:** Using a Eurobarometer (2007) survey, we provide figures on the percentage of respondents who have travelled abroad for medical treatment in 2006/2007 and those who would be willing to go abroad for medical treatment in the future. The reported figures are percentages of survey participants responding in the affirmative, disaggregated by Member State.

Prescribing/Dispensing Problems: Since the objective of the study is to examine problems that may occur in dispensing 'foreign prescriptions', we consider it important to include Member States which, based on some structural factors, could reasonably be expected to be particularly

[53] http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&plugin=1&language=en&pcode=tin00043
[54] http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tin00045&plugin=1

[55] Eurostat (2009), Emigration by Sex, Age Group and Citizenship, Available at: http://appsso.eurostat.ec.europa.eu/nui/show.do

prone to prescribing/dispensing problems (e.g. national guidance available on dispensing cross-border prescriptions, prescriptions hand-written or issued electronically, average duration of a prescription, drug availability). The three relevant columns provide information on whether or not a policy is in place regulating dispensing of cross-border prescription, whether a prescription is paper-based or electronically issued and the average duration of a prescription. The information has been compiled using the *PGEU Report: Prescriptions in Europe.*

- **Duration:** We assume that long-term prescriptions are more likely to be presented at foreign pharmacies because people may take them on to their travels.

- **EU Prescription Recognised:** We assume problems are likely to occur more frequently in countries where EU prescriptions are not at all or only conditionally recognised.

- **Hand-Written Prescriptions:** Because legibility is more likely to be a problem with hand-written prescriptions, we assume that on average it is more difficult to have hand-written prescriptions dispensed.

- **Drug Availability:** Our selection of Member States been designed to include countries which have a higher number of licensed drugs available, increasing the likelihood that some commonly prescribed drugs will not be available in other Member States, as well as other countries with fewer licensed drugs available, which are likely to have difficulties in accessing the prescribed drugs. We have therefore suggested including Denmark and Poland as representatives of countries with relatively few drugs available, and Germany, France and the UK as representatives of countries with higher numbers of drugs available. Drug availability in Bulgaria was not identifiable for this report.

While all of the abovementioned selection criteria are relevant, we argue they are not equally so for the purpose of the study. To reflect varying degrees of relevance, we have weighted the selection criteria according to relevance:

- Structural Factors pertaining to prescribing/dispensing issues have received a weight of .5. These indicators are considered highly relevant, as they narrow in on potential problem cases.

- Indicators under the category of health tourism have received a weight of .3, as this population group as a whole is more likely to take a 'foreign prescription' to a pharmacy, either in the country of treatment, or back in the home country.

- Intra-EU migration and tourism more generally have received a weight of .2. While they provide an indication of cross-border movement, in comparison to the health tourists, they are not necessarily expected to seek dispensing of a foreign prescription in a pharmacy.

In every category, Member States received one point for each time they 'made it into the top six'. The overall ranking has been determined by the weighted sum of their performance across all three categories. The top six countries were automatically considered for selection: Germany, Italy, the UK, France, Poland, the Czech Republic, Denmark, Ireland and Luxembourg (due to identical scores, the top six places have been occupied by nine countries).

Table 14: Member State Ranking

	TOURISM		INTRA EU MIGRATION			HEALTH TOURISM			PRESCRIPTION PROBLEMS					
Member States	Hotel Nights by Non-Residents (2009) (indexed to reference country Spain (n=141,228))	Tourists Staying 4 Nights Minimum (2009) (indexed to reference country Germany (n=46,598))	Non-National EU Citizens per MS (2009) (indexed to reference country Germany (n=2,530,706))	Total EU27 Emigration (2009) (indexed to reference country Germany (n=501,158))	Total Intra EU Migration & Tourism (weighted at 0.2)	Medical Treatment Abroad (2006/2007) (percentage of respondents)	Willingness to Travel Abroad for Medical Treatment (percentage of respondents)	Total Health Tourism (weighted at 0.3)	EU Prescription Recognised (0=no, 1=conditional, 2=yes)	Paper Based/Hand Written Prescriptions (yes = 1, no = 0)	Prescription Duration (1 =months or less, 2= 3 months or more, 3 = 6 months or more, 4=12 months or more	Drug Availability (Top 4-H; Bottom 4 -L)	Total Prescription Problems (weighted at 0.5)	Weighted Total
Germany	30.8%	100.0%	100.0%	100.0%	4	4.6%	40.0%		2	1	4	276 (H)	3	2.30
Italy	75.1%	50.8%	44.7%	13.8%	4	3.1%	63.0%		2	0	3	265 (H)	2	1.80
UK*	45.5%	62.4%	70.9%	56.9%	4	3.0%	53.9%		2	1	4	n/a	2	1.80
France	45.2%	73.1%	51.5%	12.4%	3	3.5%	37.0%		1	1	4	247	2	1.60
Poland	5.3%	25.4%	0.7%	13.9%	2	3.5%	56.9%		1	1		194 (L)	2	1.40
Czech	11.3%	10.4%	5.8%	7.0%		7.6%	40.4%	1	0	0		251 (H)	2	1.30
Denmark*	3.0%	6.2%	4.3%	5.4%		6.0%	78.1%	2	1	0	1	195 (L)	1	1.10
Ireland	13.3%	n/a	14.4%	10.5%		5.4%	78.9%	2	1	1	2	207	1	1.10
Luxembourg	0.8%	0.7%	7.3%	1.8%		19.6%	75.6%	2	1	1	1	n/a	1	1.10
Belgium	7.3%	8.9%	27.3%	n/a	1	5.8%	52.7%	1	2	1		219	1	1.00
Bulgaria	6.6%	1.1%	0.1%	0.4%		2.4%	46.4%		0	1		n/a	2	1.00
Estonia	1.8%	1.0%	0.4%	0.8%		2.7%	29.3%		0	0	4	n/a	2	1.00
Finland*	3.0%	5.5%	2.1%	2.3%		2.4%	26.0%		1	1		182 (L)	2	1.00
Portugal*	16.4%	4.9%	3.3%	3.7%		4.3%	75.3%		1	1	1	256 (H)	2	1.00
Romania	1.8%	11.2%	0.2%	n/a		1.8%	56.6%		0	0	3	n/a	2	1.00
Spain	100.0%	34.9%	89.9%	14.1%	4	2.8%	67.3%		2	0	1	247		0.80
Cyprus	8.1%	1.3%	3.1%	0.3%		5.3%	87.9%	1	0	0	1	n/a	1	0.80
Malta	4.5%	n/a	0.3%	1.2%		2.9%	82.2%	1	0	0	2	n/a	1	0.80
Slovakia	2.1%	5.1%	1.3%	0.5%		6.9%	49.7%	1	2	1		n/a	1	0.80
Austria	40.9%	8.9%	12.5%	10.0%	1	4.4%	43.0%		2	0	4	239	1	0.70
Greece	32.5%	8.8%	6.4%	4.5%	1	2.1%	71.6%		1	1	2	227	1	0.70
Netherlands	10.2%	20.1%	11.5%	15.3%	1	3.7%	77.4%	1	1	0		219	0	0.50
Hungary	5.5%	8.2%	4.3%	1.6%		2.9%	45.0%		2	1	1	210	1	0.50
Latvia	1.1%	0.7%	0.4%	0.8%		2.2%	32.5%		0	0		n/a	1	0.50
Lithuania	0.9%	1.8%	0.1%	2.8%		4.3%	38.0%		2	1		n/a	1	0.50
Slovenia	2.4%	2.2%	0.2%	1.2%		3.5%	67.8%		2	1	1	n/a	1	0.50
Sweden*	4.3%	n/a	10.1%	7.4%		1.5%	60.8%		1	0	1	183 (L)	1	0.50

*Member States received one point in "Total" columns for each time they 'made it into the top six for related subitems

Secondary Qualitative Analysis

Our initial ranking has undergone two rounds of secondary analysis.

1. Following the first round of qualitative analysis, we suggested replacing Ireland and Italy with Bulgaria and Poland. In addition to a difference in alphabet, Bulgarian prescribers issue hand-written prescriptions. These are both factors making prescriptions from the country prone to dispensing errors. Poland scores low on drug availability data, which means that many drugs available in other Member States are not available in Poland – another potential for dispensing errors. By including Bulgaria and Poland, we also ensure that both EU12 and EU15 countries are included in the study.

   Since Italy received the same overall score as Germany, but Germany ranked top in some of the more important performance indicators (e.g. drug availability data), we suggest to exclude Italy from the country selection. Considering the linguistic similarities between the UK and Ireland, we propose to exclude Ireland from the countries in this study.

   We suggest including each of the countries in prescribing and dispensing capacity. That is to say, for instance, prescriptions from Bulgaria will be tested in all other Member States on the one hand, and Bulgarian pharmacies will be presented with prescriptions from each of the other Member States on the other hand.

2. The original study design had foreseen the inclusion of six Member States. However, as a result of discussions with the Pharmaceutical Group of the European Union (PGEU) we proposed to the Commission to increase the number of countries included in the study from six to seven and to replace Bulgaria with Greece.

6.2.2 Selecting Drugs and Devices

The identification of drugs/devices used in the dispenser survey has undergone a rigorous two-step selection process:

1. **Desk Research:** We relied on desk research and evidence review to answer questions on drug availability and drug use and constructed the selection of drug examples for each of the pathologies.
2. **Expert Consultation:** In order to confirm the individual regimens/dosages for our drugs/devices, we contacted representatives of the relevant national pharmacists associations (national members of the PGEU). Each of the seven members contacted, provided feedback on the list of proposed drugs/devices.

Drug Availability Data

We identified all drugs licensed for community use for one or more of the eight target conditions (that is, excluding those drugs that are administered only in a hospital setting) from the 36th edition of Martindale's drug reference (2009).[56] The results are illustrated in the table below.

Table 15: Number of Drugs Licensed for Use in 17 Member States for 8 Chronic Conditions

MS	Osteo/ rheumatoid arthritis	Depression	Diabetes	Epilepsy	Asthma	COPD	Hypertension	Ischaemic heart disease	Total[57]
AT	42	28	33	18	27	32	66	85	239
BE	37	27	36	18	20	25	59	74	219
CZ	38	29	52	21	26	30	60	79	251
DE	41	32	55	20	26	31	76	96	276
DK	37	23	33	16	18	22	50	63	195
EL	40	20	44	19	22	27	61	76	227
ES	51	27	37	18	24	30	64	82	247
FI	31	21	31	16	20	23	46	58	182
FR	43	28	42	19	21	29	67	85	247
HU	35	22	33	19	24	29	55	70	210
IE	36	24	36	17	21	24	54	68	207
IT	54	23	42	19	28	36	67	89	265
NL	36	21	49	18	19	22	59	71	219
PL	27	22	47	16	19	22	47	58	194

[56](https://www.medicinescomplete.com/mc/martindale/current/login.htm?uri=http%3A%2F%2Fwww.medicinescomplete.com%2Fmc%2Fmartindale%2Fcurrent%2F).
[57] Total number of drugs available (duplicates removed)

MS	Osteo/ rheumatoid arthritis	Depression	Diabetes	Epilepsy	Asthma	COPD	Hypertension	Ischaemic heart disease	Total[57]
PT	55	29	46	17	25	30	62	77	256
SE	32	21	33	16	20	23	42	57	183
UK	42	27	48	19	23	26	65	79	243
TOTAL	**104**	**45**	**169**	**27**	**53**	**62**	**110**	**141**	**549**

A total of 549 drugs were identified, of which 482 were licensed for use in one or more of the 17 EU Member States included in Martindale. Only 79 drugs (14%) were licensed in all 17 EU Member States; 69 (13%) were not available in any of the EU countries, and 198 (36%) were licensed in only one, two or three countries. Although there is still room for improvement, the situation is better than in 1999, when only 7% of drugs were available to all 14 of the then Member States (Mäkinen, 2007). This data contributed to the selection of the final seven Member States for the dispenser survey.

To confirm the availability of all drugs in each country, the results from Martindale were checked against the following relevant national databases.

Table 16: Sources of Data on Drug Availability for 7 Target Countries

Country	Type of Data	Source (all accessed March-April 2011)
All	Drug availability	Martindale: The complete drug reference. 36th edition. Pharmaceutical press, London, 2009.
France	Drug availability	Dictionnaire VIDAL: http://www.vidal.fr/fiches-medicaments; Doctissimo: http://www.doctissimo.fr/
Germany	Drug availability	http://www.farmacopedia.de/wirkstoffe-L.html
Greece	Drug availability	http://www.eof.gr/web/guest/search
Netherlands	Drug availability	Medicines Evaluation Board : http://www.cbg-meb.nl/CBG/en/human-medicines/geneesmiddeleninformatiebank/default.htm
Poland	Drug availability	Załącznik do obwieszczenia Prezesa Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych: http://www.mz.gov.pl/wwwfiles/ma_struktura/docs/zal_cza_10052011.pdf
UK	Drug availability	British National Formulary: http://bnf.org/bnf/index.htm
Denmark	Drug availability	Danish Medicines Agency:

Country	Type of Data	Source (all accessed March-April 2011)
		http://www.medstat.dk/MedStatDataViewer.php (accessed March-April 2011; site no longer available)

Drug Use Data

National sales or dispensing data for drugs across the EU is difficult to obtain, as many Member States do not publish such data. However, we have identified several sources of national data from five of our target countries, which we have used to identify those drugs that are most commonly prescribed for the eight chronic conditions. These sources are as follows:

Table 17: Sources of Data on Drug Use for 7 Target Countries

MS	Type of Data	Source (all accessed March-April 2011)
DK	Drug use	Danish Medicines Agency: http://www.medstat.dk/MedStatDataViewer.php (accessed March-April 2011; site no longer available)
FR	Drug use	Agence Francaise de securite sanitaire des produits de sante. Analyse des ventes de medicaments aux officines et aux hopitaux en France. 1998-2008. 10eme edition, mai 2010. http://www.afssaps.fr/var/afssaps_site/storage/original/application/3b13d02741902933e1f930db3d882603.pdf.
DE	Drug use	Bundeszentrale für politische Bildung: http://www.bpb.de/popup/popup_druckversion_sosi.html?guid=WZDR7I&sosi_guid=AAB620&sosi_lt=AAB779 Gesundheits-report 2004: http://www.tk.de/centaurus/servlet/contentblob/48744/Datei/3087/Gesundheitsreport-3.pdf Arzneiverordnungs-Report 2007: http://www.wido.de/fileadmin/wido/downloads/pdf_arzneimittel/wido_arz_pk_avr07_1007.pdf
NL	Drug use	Genees- en hulpmiddelen Informatie Project: http://www.gipdatabank.nl/
UK	Drug use	Department of Health Prescription Cost Analysis data from England and Wales in 2009-10: http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-england--2009)

Comparative drug use for these five Member States is presented below and standardised to show the number of doses or prescriptions dispensed or sold each year (in thousands). Note that the units of measurement vary for the different countries – in particular, the number of defined daily doses (DDD) is not reported for the UK and is not consistent per prescription, and the different subgroups included within each total may be different across the Member States.

	Denmark	Netherlands		France		Germany		England	
Pathology and drug class (ATC code)	Drug use for selected drugs, 1,000 DDD, community	1,000 DDD per year, 2009	% of all DDD/year	1,000 units prescribed per year, 2008 (primary care)	% of all units sold/year	1,000 units sold per year, 2006	% of all units sold/year, 2003	1,000 prescriptions dispensed per year, 2010	% of all prescriptions/year
Asthma/ COPD									
Antiasthmatics (R03)	75,394	347,950	4%	50,000	2%	1,173,300	3.99%	45,440	5%
Depression									
Antidepressants (N06A)	154,535	239,410	3%	66,000	2%	912400	3.10%	42,788	5%
Diabetes									
Antidiabetic drugs (A10)	68,488	393,164	5%	69,000	2%	1,698,700	5.77%	37,705	4%
Epilepsy									
Antiepileptic drugs (N03)	27,030	49,538	1%	25,000	1%	238900	0.81%	14,012	2%
Hypertension and IHD									
Antihypertensives (C02)	-	20,434	0%	13,000	0%	320700	1.09%	63,571	7%
Diuretics (C03)	115,305	328,647	4%	35,000	1%	1,810,900	6.15%	37,687	4%
Beta blockers (C07)	67,434	318,409	4%	52,000	2%	1983000	6.74%	29,686	3%
Calcium channel blockers (C08)	147,361	268,481	3%	34,000	1%	1,523,600	5.18%	32,007	3%
ACE inhibitors (C09)	227,773	790,701	10%	80,000	3%	4,815,700	16.37%	56,489	6%
Lipid lowering drugs (C10)	194,191	531,635	7%	71,000	2%	1,911,800	6.50%	59,550	6%
OA/RA									
Anti-inflammatory drugs (M01)	71,276	138,132	2%	69,000	2%	904100	3.07%	16,685	2%
Other analgesics (M02)	124,512	1,272	0%	37,000	1%	1,398,400	4.75%	39,265	4%

	Denmark	Netherlands		France		Germany		England	
Pathology and drug class (ATC code)	Drug use for selected drugs, 1,000 DDD, community	1,000 DDD per year, 2009	% of all DDD/year	1,000 units prescribed per year, 2008 (primary care)	% of all units sold/year	1,000 units sold per year, 2006	% of all units sold/year, 2003	1,000 prescriptions dispensed per year, 2010	% of all prescriptions/year
Total units prescribed for 8 conditions	1,273,299	3,427,773		601,000		18,691,500		474,885	
Total units prescribed, all conditions	**N/A**	**7,788,216**		**3,089,820**		29,426,400		926,657	
% of all prescriptions	N/A	44%		19%[58]		64%		51%	

[58] This figure presents an outlier. We are unable to provide a direct explanation, however, the French data was only available as prescription units, not DDDs – this may have had an effect. For example, if prescriptions for chronic diseases are each for 1 month, and other prescriptions are for 1 week, these will each count as 1 prescription but there will be 4 times the DDDs per prescription for the month-long prescription than the 1-week prescription.

Guidelines on Prescribing for the Eight Selected Pathologies

We identified national and international guidelines on the management of the eight selected pathologies, used by the seven target countries, to confirm that our drugs selected for the dispenser survey would reflect those most likely to be prescribed. These guidelines generally recommended drug classes or types, rather than specific members of a drug class. We therefore identified examples within recommended drug classes as follows:

- Drug A (unlikely to cause dispensing problems): commonly used and available in all 7 member states
- Drug B (more likely to cause dispensing problems): available in 3 or fewer member states and/or less frequently used.

Table 18: Guidelines Used to Guide Selection of Drugs

Asthma		
Astma: behandling. Dansk Lungemedicinsk Selskab 2009.	Denmark	1. Short acting beta agonists (salbutamol, terbutaline) 2. Montelukast 3. Inhaled corticosteroids (beclometasone, budesonide, flucticsone, mometasone), salmeterol, formoterol 4. omalizumab
Finnish Medical Society Duodecim. Long-term management of asthma. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007	Finland	1. short acting beta agonists (salbutamol, terbutaline, fenoterol) 2. inhaled corticosteroid (beclometasone, budesonide, fluticasone 100-400 mcg/d) pressurised aerosol + spacer or dry powder inhaler 3. leukotriene antagonist (montelukast 10 mg/d, zafirlukast 20 mg bd) 4. long acting beta agonist (salmeterol 50 mcg twice daily, formoterol 12-24 mcg twice daily) 5. long acting theophylline 200-300 mg at night
AFSSAPS, ANAES (2004). Medical follow-up of patients with asthma – Adults and adolescents. http://www.has-sante.fr/portail/upload/docs/application/pdf/asthma_follow-up_guidelines.pdf	France	1. short-acting beta agonist 2. inhaled corticosteroid (beclometasone, budesonide, fluticasone), long term beta agonist 3. theophylline

Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. (2010). Asthma. http://www.awmf.org/uploads/tx_szleitlinien/nvl-002k_S3_NVL_Asthma_kurz.pdf	Germany	1. Beta agonists (fenoterol, formoterol, salbutamol, terbutalin) 2. inhaled corticosteroids (beclometason, budesonid, fluticason), long acting beta agonists (formoterol, salmeterol), leukotriene receptor antagonists (montelukast) 3. systemic corticosteroids, omalizumab, theophyllin, oral beta agonists
Global Initiative for Asthma (2009). Global strategy for asthma management and prevention.	International	1. short acting beta agonists, inhaled anticholinergics (ipratropium) 2. inhaled corticosteroids (beclometasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone) 3. leukotriene modifiers, long acting beta agonists (formoterol, salmeterol), theophylline 4. cromoglycate, omalizumab
Nederlands Huisartsen Genootschap. Astma bij volwassenen M27 (november 2007). http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M27_svk.htm	Netherlands	1. Short-acting beta agonists (ipratropium 40 microg 4 times daily as inhaled powder, 20 microg 4 times daily by aerosol, max 320 microg/day; salbutamol 100-400 microg 4 times daily, max 1600 microg/day; terbutaline 250-500 microg 4 times daily, max 4000 microg/day). 2. Low-dose inhaled corticosteroids via inhalation chamber (beclometason 200-400 microg to 800-1600 microg per day; budesonide 200-400 microg to 800-1600 microg/day; fluticason 100-250 to 500-1000 microg/day) 3. Leukotriene antagonist (montelukast 10 mg daily), long-acting beta agonists (formoterol, 6-12 microg twice daily, max 48 microg/day; salmeterol 50 microg twice daily, max 100 microg/day)
SIGN 101 (2009). British guideline on the management of asthma. http://www.sign.ac.uk/guidelines/fulltext/101/index.html	UK	1. short acting beta agonist 2. inhaled corticosteroid (beclometasone, budesonide, fluticasone, mometasone, ciclesonide) 3. long acting beta agonists 4. leukotriene antagonist, theophylline, slow release oral beta agonist 5. omalizumab
Dolovich MB, Ahrens RC, Hess DR, Anderson P,	US	1. Short-acting beta agonists via metered dose inhaler + spacer or dry powdered inhaler

Dhand R, Rau JL, Smaldone GC, Guyatt G. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005 Jan;127(1):335-71.		2. Inhaled corticosteroids via metered dose inhaler + spacer or dry powdered inhaler Up to 70% of patients fail to use MDIs appropriately; dry powder inhalers need rapid rate of inhalation to trigger drug aerosolisation
Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of asthma. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010	US	1. short acting beta agonist 2. inhaled corticosteroids, leukotriene antagonists 3. long acting beta agonist 4. oral corticosteroid 5. omalizumab
Medications. In: National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 Aug. p. 213-76.	US	1. short-acting beta agonists 2. inhaled corticosteroids 3. long acting beta agonists 4. cromoglycate, nedocromil, theophylline 5. omalizumab
Management of Asthma Working Group. VA/DoD clinical practice guideline for management of asthma in children and adults. Washington (DC): Department of Veteran Affairs, Department of Defense; 2009.	US	1. short acting beta agonists 2. inhaled corticosteroids, long acting beta agonists 3. leukotriene antagonist, cromoglycate, theophylline
COPD		
Finnish Medical Society Duodecim. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley	Finland	1. Anticholinergics (ipratropium, oxitropium), short acting beta agonists (salbutamol, terbutaline, fenoterol) 2. Long acting anticholinergics (tiotropium)or beta agonists (formoterol, salmeterol) 3. Inhaled glucocorticoid 4. theophylline

Interscience. John Wiley & Sons; 2007		
HAS. (2006). Insuffisance respiratoire chronique grave de l'adulte secondaire à une bronchopneumopathie chronique obstructive. http://www.has-sante.fr/portail/upload/docs/application/pdf/07-009_insuf-bpco-guide_sans_lap.pdf	France	1. short-acting bronchodilators, long-acting bronchodilators, inhaled corticosteroids 2. theophylline, oral corticosteroids
AWMF (2010). Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD) http://www.awmf.org/uploads/tx_szleitlinien/020-006_S2_Diagnostik_und_Therapie_von_Patienten_mit_chronisch_obstruktiver_Bronchitis_und_Lungenemphysem__COPD__10-2005_10-2011.pdf	Germany	1. anticholinergics (tiotropium), beta agonists, ihnaled glucocorticoids 2. theophyllin, , mucolytics
American Thoracic Society, European Respiratory Society. (2004). Standards for the diagnosis and management of patients with COPD.	International	1. Short acting beta-agonist (salbutamol, albuterol), ipratropium, oxitropium 2. Long-acting bronchodilator (salmeterol, formoterol), tiotropium 3. Inhaled corticosteroid (beclometasone, budesonide, triamcinolone, fluticasone, flunisolide) 4. Oral theophylline 5. Mucolytics (ambroxol, erdosteine, carbocysteine, iodinated glycerol)
Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2009	International	1. Long acting bronchodilators 2. Short acting bronchodilators, inhaled corticosteroids
Nederlands Huisartsen Genootschap. COPD M26	Netherlan	1. Short-acting beta agonists or ipratropium (ipratropium 40 microg 4

(July 2007). http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M26_svk.htm	ds	times daily as inhaled powder, 20 microg 4 times daily by aerosol, max 320 microg/day; salbutamol 100-400 microg 4 times daily, max 1600 microg/day; terbutaline 250-500 microg 4 times daily, max 4000 microg/day). 2. Long-acting bronchodilator (tiotropium 18 microg daily; formoterol, 6-12 microg twice daily, max 48 microg/day; salmeterol 50 microg twice daily, max 100 microg/day) 3. High dose inhaled corticosteroids (budesonide or beclametasone 400 microg twice daily, max 1600 microg/day; fluticason 500 microg twice daily, max 1000 microg/day)
National Clinical Guideline Centre. (2010) Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical Guideline Centre. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English	UK	1. short-acting beta-agonist (salbutamol), short acting muscarinic antagonist (ipratropium) 2. long acting beta agonist (salmeterol formoterol), long acting muscarinic antagonist (tiotropium), inhaled corticosteroids
Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2007 Nov 6;147(9):633-8.	US	1. Long-acting beta-agonists, long-acting inhaled anticholinergic, inhaled corticosteroid 2. Combination inhaled therapies (salmeterol-fluticasone)
Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of chronic obstructive pulmonary disease (COPD). Bloomington (MN): Institute for Clinical Systems Improvement (ICSI);	US	Acute exacerbation 1. Albuterol, ipratropium 2. Oral corticosteroids Stable COPD 1. Short-acting bronchodilators (albuterol, ipratropium)

2009		2. Long-acting bronchodilators (beta agonist/anticholinergic: salmeterol, tiotropium) Metered-dose inhaler + spacer, dry powder inhaler 3. theophylline
Management of COPD Working Group. VA/DoD clinical practice guideline for the management of outpatient chronic obstructive pulmonary disease. Washington (DC): Department of Veterans Affairs, Department of Defense; 2007.	US	1. short acting beta agonist 2. short acting anticholinergic 3. inhaled glucocorticoid
Depression		
Kliniske retningslinier for medicinsk antidepressiv behandling af voksne. 2005	Denmark	1. SSRI (citalopram, sertraline) 2. Tricyclics (nortriptyline, clomipramine) venlafaxine, mirtazepine, mianserin 3. Lithium, anitpsychotics
Kliniske retningslinjer for biologisk behandling af bipolare affektive sindslidelser, 2010	Denmark	1. SSRI (citalopram, escitalopram, paroxetine, sertraline, fluoxetine) 2. Tricyclics (nortriptyline, clomipramine, amitriptyline), venlafaxine, duloxetine
Kristoffersen J. (2008). Behandling af psykotisk depression. Ugeskr Laeger 170: 3753	Denmark	1. ECT 2. Tricyclics 3. antipsychotics
ANAES (2002). Prise en charge d'un épisode dépressif isolé de l'adulte en ambulatoire http://www.has-sante.fr/portail/upload/docs/application/pdf/rpc_depression_2002_-_mel_2006_-_recommandations._2006_12_27__16_20_34_967.pdf	France	1. SSRI, SNRIs 2. Tricyclics, MAOIs
AWMF (2009). Unipolare Depression. http://www.awmf.org/uploads/tx_szleitlinien/nvl-	Germany	1. Tricyclics, SSRIs, venlafaxine

005_S3_NVL___DGPPN-S3_Unipolare_Depression_kurz_12-2009_05-2013.pdf		
Working Group on the Management of Major Depression in Adults. Clinical practice guideline on the management of major depression in adults. Madrid: Ministry of Health and Consumer Affairs, Galician Health Technology Assessment Agency (HTA) (avalia-t); 2008.	Spain	1. SSRIs 2. Tricyclics, venlafaxine, mirtazepine, mianserin 3. MAOIs
Nederlands Huisartsen Genootschap. Depressive stoornis M44 (October 2003). http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M44_svk.htm	Netherlands	1. Tricyclics (amitriptyline, imipramine, nortriptyline 75 mg at bedtime increasing to 150 mg); SSRIs (fluvoxamine 100 mg at bedtime, paroxetine 20 mg in the morning or sertraline 50 mg daily)
Anderson, I., Ferrier, IN., Baldwin, RC et al.(2008). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology XX, 1–54	UK	2. SSRI 3. Tricyclics, MAOIs, venlafaxine
NICE CG90 (2009). Depression. http://guidance.nice.org.uk/CG90	UK	1. Generic SSRI or CBT/IPT 2. SSRI plus CBT/IPT 3. tricyclics
American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. Arlington (VA): American Psychiatric Association; 2010 Oct.	US	1. SSRI, SNRI, mirtazepine, bupropion 2. MAOI (phenelzine, tranylcypromine, isocarboxid), St John's Wort

Institute for Clinical Systems Improvement (ICSI). Major depression in adults in primary care. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 May.	US	1. SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazepine, bupropion 2. Tricyclics, MAOIs
Bipolar		
Kliniske retningslinjer for biologisk behandling af bipolare affektive sindslidelser, 2010	Denmark	1. Lithium, valproate, atypical antipsychotics, lamotrigine
AWMF (2010). Manische und bipolare affektive Störungen. http://www.awmf.org/uploads/tx_szleitlinien/028-004_S1_Manische_und_bipolare_affektive_Stoerungen__F30__F31__11-2006_11-2011.pdf	Germany	1. Lithium 2. Carbamazepine, valproate
NICE CG 38 Bipolar disorder. http://guidance.nice.org.uk/CG38	UK	Hypomania 1. Lithium, olanzapine 2. Valproate (not women at risk of pregnancy), lamotrigine, carbamazepine Depression 1. SSRI (Not paroxetine if women at risk of pregnancy) 2. quetiapine
SIGN 82 (2005). Bipolar affective disorder. http://www.sign.ac.uk/guidelines/fulltext/82/index.html	UK	Acute mania 1. chlorpromazine, haloperidol, perphenazine, olanzepine, quetiapine, risperidone, valproate 2. lithium Depression 1. SSRI, lamotrigine 2. SNRI, tricyclics Maintenance 1. Lithium

		2. Carbamazepine, lamotrigine
Management of Bipolar Disorder Working Group. VA/DoD clinical practice guideline for management of bipolar disorder in adults. Washington (DC): Department of Veterans Affairs, Department of Defense; 2010	US	Mania 1. Antipsychotics (olanzapine, quetiapine, aripiprazole, risperidone), lithium, valproate 2. Ziprasidone, clozapine Mixed episode 1. Antipsychotics (olanzapine, haloperidol, aripiprazole, risperidone), lithium, valproate 2. Quetiapine, ziprasidone, clozapine Maintenance 1. Lithium, valproate, carbamazepine, aripiprazole, olanzepine, quetiapine, risperidone, ziprasidone 2. Clozapine, haloperidol, oxcarbazepine
Diabetes		
Type 1		
Canadian Optimal Medication Prescribing and Utilization Service (COMPUS). Optimal therapy recommendations for the prescribing and use of insulin analogues. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2009 May.	Canada	1. Insulin NPH is preferred long-acting for adults with type 1 and 2; regular human insulin, insulin aspart, insulin lispro are preferred rapid acting in adults including pregnant women 2. Insulin glargine, insulin detemir
Kliniske retningslinier for behandling af voksne med Type 1 diabetes	Denmark	1. Basal-bolus therapy: insulin NPH + human or analogue insulin
NICE CG15 (2010). Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults.	UK	1. Basal-bolus therapy – ispohane NPH insulin, insulin glargine, biphasic insulin premixes via pen or syringe/vial 2. Continuous subcutaneous insulin infusion
SIGN 116 (2010). Management of diabetes. http://www.sign.ac.uk/guidelines/fulltext/116/index.html	UK	1. Regular human insulin, rapid acting insulin analogues, basal insulin analogues (glargine, detemir), NPH insulin 2. Continuous subcutaneous insulin infusion
AACE Diabetes Mellitus Clinical Practice Guidelines	US	1. Basal-bolus therapy – long acting insulin + rapid-acting analogue

Task Force. AACE diabetes mellitus guidelines. Glycemic management. Endocr Pract 2007 May-Jun;13(Suppl 1):16-34.		or inhaled insulin 2. Continuous subcutaneous insulin infusion 3. Pramlintide
American Diabetes Association (ADA). Standards of medical care in diabetes. V. Diabetes care. Diabetes Care 2010 Jan;33(Suppl 1):S16-29.	US	1. Basal-bolus therapy, continuous subcutaneous insulin infusion 2. Insulin analogues
Type 2		
AFSSAPS, HAS (2006). TRAITEMENT MEDICAMENTEUX DU DIABETE DE TYPE 2. Recommandation de Bonne Pratique. http://www.has-sante.fr/portail/upload/docs/application/pdf/synthese_diabete-2006.pdf	France	1. Metformin, 2. Sulphonamides, glinides, glitazones 3. insulin
Matthaei, S., Bierwirth R., Fritsche A et al. (2008). Medikamentöse antihyperglykämische Therapie des Diabetes mellitus Typ 2. http://www.awmf.org/uploads/tx_szleitlinien/057-012_S3_Medikamentoese_antihyperglykaemische_Therapie_des_Diabetes_mellitus_Typ_2_10-2008_10-2013.pdf	Germany	1. Metformin 2000 mg/Tag 2. Alpha-glucosidease inhibitors (acarbose, miglitol, vogilbose), glitazones (pioglitazon), biguanides, sulfonylureas (glibenclamid, glibornurid, gliclazid, glimepirid, gliquidon, tolbutamid), repaglinid, nateglinid, DPP-4 inhibitors (sitagliptin, vildagliptin) 3. Exenatide, insulin
IDF Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2005.	International	1. Metformin 2. Generic sulfonylureas, 3. Thiazolidinediones, □-glucosidase inhibitors, insulin detemir, insulin glargine, NPH insulin via pen or syringe/vial
Nederlands Huisartsen Genootschap. Diabetes mellitus type 2 M01 (March 2006). http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M01_svk.htm	Netherlands	1. Metformin (500 mg daily, up to 100 mg 3 times daily) 2. Sulphonylurea (tolbutamide 500 mg daily) 3. Pioglitazone (15 mg once daily, max 45 mg daily) 4. NPH insulin or mix-insulin

NICE CG87 (2010). Type 2 diabetes. http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12165	UK	1. Metformin, sulfonylurea if not overweight 2. Rapid-acting insulin secretagogue, acarbose, DPP-4 inhibitor (sitagliptin, vildagliptin); thiazolidinedione (pioglitazone) 3. Exenatide, insulin NPH by pen 4. Insulin detemir, insulin glargine
SIGN 116 (2010). Management of diabetes. http://www.sign.ac.uk/guidelines/fulltext/116/index.html	UK	1. Metformin, sulphonylurea (chlorpropamide, glibenclamide) 2. Pioglitazone, DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin), insulin NPH, acarbose 3. GLP-1 agonist(exenatide, liraglutide) in obese with DM, basal and/or rapid-acting insulin
AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. AACE diabetes mellitus guidelines. Glycemic management. Endocr Pract 2007 May-Jun;13(Suppl 1):16-34.	US	1. Metformin, thiazolidinediones (pioglitazone, rosiglitazone), secretagogues (glyburide, glimepiride), dipeptidyl-peptidase 4 inhibitors, alpha-glucosidase inhibitors 2. Exenatide, insulins, pramlintide
American Diabetes Association (ADA). Standards of medical care in diabetes. V. Diabetes care. Diabetes Care 2010 Jan;33(Suppl 1):S16-29.	US	1. Metformin 2. insulin
Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of type 2 diabetes mellitus in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 Jul.	US	1. Metformin, 2. Sulfonylurea (glipizide, glimepiride), insulin, pioglitazone (NOT rosiglitazone)
Epilepsy		
NICE CG20 (2004). The epilepsies. http://guidance.nice.org.uk/CG20	UK	1. Carbamazepine, sodium valproate 2. Gabapentin, lamotrigine, levetiracetam, oxcarbazine, tiagabine, topiramate, vigabatrin (first-line in women at risk of pregnancy) Avoid valproate in women at risk of pregnancy First-line (generalised tonic-clonic, myoclonic, tonic, atonic): Carbamazepine, lamotrigine, sodium valproate, topiramate

SIGN 70 (2003). Diagnosis and management of epilepsy in adults. http://www.sign.ac.uk/guidelines/fulltext/70/index.html	UK	1. Sodium valproate, carbamazepine, lamotrigine, oxcarbazepine
Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009 Jul 14;73(2):133-41.	US	1. Carbamazepine 2. Lamotrigine – unknown risk of malformations 3. Phenytoin, phenobarbital Avoid valproate if risk of pregnancy
Hypertension		
Graham, I., Atar, D., Borch-Johnson, K., et al (2007). European guidelines on cardiovascular disease prevention in clinical practice: executive summary. European Journal of Cardiovascular Prevention and Rehabilitation 14(Supp 2): E1-E40.	EU	1. thiazides (chlorthalidone, indapamide), beta-blockers, calcium antagonists, ACE inhibitors, ARBs
Practice Guidelines For Primary Care Physicians: 2003 ESH/ESC Hypertension Guidelines. Journal of Hypertension 2003; 21:1011–1053.	EU	1. Diuretics, beta-blockers, CCB, ACE inhibitors, ARBs 2. Alpha-blockers
The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the management of arterial hypertension. European Heart Journal 28: 1462-1536.	EU	1. Thiazide diuretics, CCBs, ACE inhibitors, ARBs, beta-blockers 2. Alpha-blockers, aldosterone antagonists, loop diuretics
HAS (2005). Management of adults with essential hypertension. 2005 update. http://www.has-sante.fr/portail/upload/docs/application/pdf/Hypertensi	France	1. Thiazide diuretics, beta blockers, CCBs, ACE inhibitors, ARBs

on_guidelines.pdf		
Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. (2010). Chronische KHK. http://www.awmf.org/uploads/tx_szleitlinien/nvl-004k_S3_Chronische_Koronare_Herzkrankheit_Kurzfassung.pdf	Germany	1. Diuretics, beta blockers, ACE inhibitors, long acting CCBs, ARBs
Nederlands Huisartsen Genootschap. Cardiovasculair risicomanagement M84 (November 2006). http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M84_svk.htm	Netherlands	1. Diuretics, beta blockers, ACE-inhibitors, ARBs, CCBs
NICE CG34. Hypertension (2006). http://guidance.nice.org.uk/CG34	UK	1. People under 55: ACE inhibitor, ARB 2. Beta-blockers, CCBs 3. Thiazide diuretics, Selective alpha-blocker
SIGN 97 (2007). Risk estimation and the prevention of cardiovascular disease. http://www.sign.ac.uk/guidelines/fulltext/93-97/index.html	UK	1. ACE Inhibitor if <55years 2. CCB, thiazides 3. Beta-blockers
Mosca L, Banka CL, Benjamin EJ, et al. Expert Panel/Writing Group, American Heart Association, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American College of Cardiology Foundation, Society of Thoracic Surgeons, American Medical Women's Association, Centers for Disease Control and Prevention, Office of Research on Women's Health, Association of Black	US	1. Beta-blockers, ACE inhibitor/ARB 2. thiazides

Cardiologists, American College of Physicians, World Heart Federation, National Heart, Lung, and Blood Institute, American College of Nurse Practitioners. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007 Mar 20;115(11):1481-501.		
Institute for Clinical Systems Improvement (ICSI). Hypertension diagnosis and treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Oct.	US	1. Thiazide diuretic, Beta-blockers (in people <60) 2. ACE inhibitors, ARBs (diabetics) 3. CCBs
Michigan Quality Improvement Consortium. Medical management of adults with hypertension. Southfield (MI): Michigan Quality Improvement Consortium; 2009 Aug.	US	1. Thiazide diuretic, ACE inhibitor, long-acting CCB(amlodipine, felodipine) 2. Beta-blockers, ARBs
University of Michigan Health System. Essential hypertension. Ann Arbor (MI): University of Michigan Health System; 2009 Feb.	US	1. Thiazide diuretic, ACE inhibitor, long-acting CCB 2. Beta-blocker, ARB
IHD		
Iskæmisk hjertesygdom : Behandling. http://www.hjertedoktor.dk/?ug=1&aid=7	Denmark	1. Aspirin 75 mg/d, statin, beta blocker (carvedilol), CCB (diltiazem, verapamil), nitrate (ISMN, ISDN, GTN)
Fox, K., Garcia, MAA., Ardissino D., et al (2006). Guidelines on the management of stable angina pectoris: full text. European Heart Journal, doi:10.1093/eurheartj/ehl002	EU	1. Low dose aspirin, statin, ACE inhibitor, beta-blocker, GTN 2. Calcium channel blocker, long-acting nitrate, clopidogrel
Graham, I., Atar, D., Borch-Johnson, K., et al (2007). European guidelines on cardiovascular disease prevention in clinical practice: executive summary. European Journal of Cardiovascular Prevention and Rehabilitation 14(Supp 2): E1-E40.	EU	1. Statins, aspirin 2. Beta-blockers after MI, ACE inhibitors if LVD, DM; clopidogrel 3. CCB

Finnish Medical Society Duodecim. Coronary heart disease (CHD): symptoms, diagnosis and treatment. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2008	Finland	1. Statin, beta-blocker, aspirin, GTN 2. ACE Inhibitor if post MI or CHF 3. CCB, long acting nitrate
Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. (2010). Chronische KHK. http://www.awmf.org/uploads/tx_szleitlinien/nvl-004k_S3_Chronische_Koronare_Herzkrankheit_Kurzfassung.pdf	Germany	1. Nitrates, beta-blockers (bisoprolol, carvedilol, metoprolol), CCBs (amlodipin, verapamil), clopidogrel, aspirin, statins, ACE inhibitors, ARBs
Nederlands Huisartsen Genootschap. Stabiele angina pectoris M43 (February 2004). http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M43_svk.htm	Netherlands	1. Aspirin 80 mg daily; metoprolol 100-200 mg in 2 divided doses per day 2. Long acting nitrates (isosorbide mononitrate 50-60 mg daily) 3. Diltiazem 60 mg 3-4 times daily
NICE CG48 (2007). MI: secondary prevention. http://guidance.nice.org.uk/CG48	UK	1. Aspirin, ACE inhibitor, beta-blocker, statin 2. ARB, clopidogrel 3. CCB
SIGN 96 (2007). Management of stable angina. http://www.sign.ac.uk/guidelines/fulltext/93-97/index.html	UK	1. Beta-blockers, GTN, aspirin, ACE inhibitor 2. CCB, long acting nitrates, nicorandil
SIGN 97 (2007). Risk estimation and the prevention of cardiovascular disease. http://www.sign.ac.uk/guidelines/fulltext/93-97/index.html	UK	1. Aspirin 75 mg/d, simvastatin 40 mg/d 2. Clopidogrel, dipyridamole, fibrate, nicotinic acid

Mosca L, Banka CL, Benjamin EJ, et al. Expert Panel/Writing Group, American Heart Association, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American College of Cardiology Foundation, Society of Thoracic Surgeons, American Medical Women's Association, Centers for Disease Control and Prevention, Office of Research on Women's Health, Association of Black Cardiologists, American College of Physicians, World Heart Federation, National Heart, Lung, and Blood Institute, American College of Nurse Practitioners. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007 Mar 20;115(11):1481-501.	US	1. Aspirin, beta-blockers, ACE inhibitors/ ARBs
Arthritis		
HAS (2007). Rheumatoid arthritis. Treatment of established RA. http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-10/treatment_of_established_ra_-_guidelines.pdf	France	1. Methotrexate 10 to 25 mg/week 2. Leflunomide 20 mg/day, sulphasalazine 1 g/day 3. Anti-TNF-α (adalimumab, etanercept, infliximab) Pain control 1. NSAIDs 2. Oral corticosteroids
AWMF (2010). Koxarthrose. http://www.awmf.org/uploads/tx_szleitlinien/033-001_S3_Koxarthrose_11-2009_11-2014.pdf	Germany	1. Paracetamol 2. Metamizol, dipyrone, NSAIDs 3. Opioid analgesics, intra-articular corticosteroids, glucosamine, exaceprol, hyaluronic acid
GUIPCAR Group. Clinical practice guideline for the management of rheumatoid arthritis in Spain. Madrid: Spanish Society of Rheumatology; 2007 Mar. 301 p.	Spain	1. Methotrexate 2. Hydroxychloroquine, sulfasalazine, low dose oral glucocorticoid 3. Leflunomide, anti-TNFs Pain control 1. Paracteamol, NSAIDs
NICE CG59 (2008). Osteoarthritis.	UK	1. Paracetamol, topical NSAID

http://guidance.nice.org.uk/CG59		2. Oral NSAID, coxib (not etoricoxib 60 mg), topical capsaicin
NICE CG79 (2009). Rheumatoid arthritis. http://guidance.nice.org.uk/CG79	UK	1. Methotrexate + other DMARD + short term glucocorticoid 2. Rituximab NOT anakinra Pain control: 1. Paracetamol, codeine 2. Oral NSAID, coxibs
Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis. Edinburgh: SIGN; 2011. (SIGN publication no. 123). [cited February 2011]. http://www.sign.ac.uk/guidelines/fulltext/123/index.html	UK	1. Methotrexate, sulfasalazine 2. Low dose oral corticosteroids Pain control: 1. Paracetamol, codeine 2. NSAIDs, coxibs: low dose ibuprofen (1.2 g daily), naproxen (1g daily)
Schnitzer TJ (2002). Update of ACR guidelines for osteoarthritis: role of the coxibs. Journal of Pain and Symptom Management, 23: S24	US	1. Paracetamol 2. Coxibs 3. NSAIDs
Saag KG., Teng, GG., Patkar NM., et al. (2008). American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis and Rheumatism 59:762-784.	US	1. DMARDS: methotrexate, minocycline, leflunomide, hydroxychloroquine, sulfasalazine 2. Biologics: etanercept, infliximab, adalimumab
Michigan Quality Improvement Consortium. Medical management of adults with osteoarthritis. Southfield (MI): Michigan Quality Improvement Consortium; 2009 Aug. 1 p.	US	1. Paracetamol, topical capsaicin 2. NSAID: Naproxen 3. Coxib

Identification of Drugs for Dispenser Survey in 7 Target Countries

Using the data sources on drug availability and drug use, we identified a number of drugs as useful candidates for the dispenser survey: drugs that are available in the 17 relevant Member States, which are known to be popular choices in those Member States for which we have data, to be used as examples where few problems are expected (Drug A); and drugs that are available in only a small number of Member States but are frequently prescribed in all Member States for which we have data; to be used as examples where dispensing in another country is likely to cause problems (Drug B). We also identified drugs that have a high sensitivity and specificity for each of the target conditions to use for the dispenser study, and drugs that reflect national guidelines on appropriate management of the target pathologies. The drugs selected are listed below.

Table 19: Drugs Selected for all Pathologies and Prescribing Countries

Denmark	Asthma	Fluticason 250 mikrogram/dosis, take two puffs twice daily; 120 doser inhal.spray, susp	Bambuterol 10 mg; take one 20mg tablet once daily at bedtime orally; 100 stk. tabletter
France	Asthma	Fluticasone propionate 250µg/dose pdre p inhal; 2 fois par jour (matin et soir); flacon pressurisé de120 doses	Théophylline L.A. 200mg gél LP: 1 comprimé par jour; B/30
Germany	Asthma	Fluticason 250 µg pro Einzel-dosis Pulver- Inhalator; take two puffs twice daily; 120 Einzeldosen Pulver- Inhalatoren	Cholintheophyllinat 400 mg; take 1 tablet once a day; 30 Filmtbl
Greece	Asthma	Fluticasone proprionate Inh. Sus. P 250 mcg/dose (σταθερών δόσεων); take two puffs twice daily; 1 inhaler	Reproterol hydrochloride aer. Md. Inh. 0.5 mg/dose; 2 puffs three times daily; 1 inhaler
Netherlands	Asthma	Fluticasonpropionaat Volumatic CFK vrij, aerosol 250 microgram/dosis; 250 microgram tweemaal daags; 1 inhalator	Theolair Retard 250, tabletten met gereguleerde afgifte 250 mg; 4 tabletten per 24 uur; De tabletten dienen 's morgens en 's avonds na de maaltijd te worden ingenomen; 100 tabletten.
Poland	Asthma	Fluticasoni propionas aerozol wziewny 50 mcg/dawkę inh. take two puffs twice daily poj. 120 dawek	Zafirlukastum tabletki powlekane 20 mg; take 1 tablet twice a day, 1 hour before or 2 hours after a meal; 56 tabl.
UK	Asthma	Fluticasone proprionate Evohaler 250	Bambuterol 20 mg; take one 20mg tablet once daily at

		micrograms/metered inhalation, take two puffs twice daily, 1 x 120 dose unit	bedtime orally; 28 tablets
Denmark	COPD	Tiotropiumbromid 18 mikrogram; take one capsule once daily; 30 stk. (blister) + HandiHaler	Fenoterol og andre midler mod obstruktiv lungesygdom 100 + 40 mikrog/kaps 100 kapsler + inhalator inh.pulver i kapsler; 100 micrograms taken three or four times a day, maximum 8 puffs a day; 1 inhaler
France	COPD	Tiotropium 18µg pdre p inhal en gél : l'inhalation du contenu d'une gélule une fois par jour à heure fixe dans la journée à l'aide du dispositif Handihaler; Plq/30+Handihaler	Bamifylline 300mg cp enr: 2 comprimés par jour; Le comprimé sera avalé sans être croqué, avec un verre d'eau, de préférence en dehors des repa; Plq/40
Germany	COPD	Tiotropium 18 Mikrogramm Kapsel mit Inhalationspulver; take one capsule once daily; Hartkapseln m. Pulver z. Inhal	Tulobuterol hydrochloride 2 mg; one tablet taken twice daily orally; 100 tablets
Greece	COPD	Tiotropium bromide monohydrate Inhpd. ; take one capsule once daily; Cap. 18 mcg	Hexoprenaline sulphate tab 0.5 mg; take one tablet three times a day orally, 30 minutes before meals; 84 tablets
Netherlands	COPD	Tiotropium 18 microgram, inhalatiepoeder in harde capsules; éénmaal per dag de inhoud van één capsule (18 microgram tiotropium) te Inhaleren; 1 HandiHaler en 30 capsules (3 blister strips).	Ciclesonide 80 Inhalator, aërosol, oplossing 80 microgram/dosis; 160 microgram eenmaal daags; 1 inhalator met 60 nauwkeurig afgemeten pufjes.
Poland	COPD	Tiotropium proszek do inhalacji w kapsułkach twardych 18 mcg /dawkę inh. take one capsule once daily; 90 kaps.	Fenoteroli hydrobromidum aerozol inhalacyjny, 100 mcg/dawkę 1 poj. 10 ml (200 dawek); 100 micrograms taken three or four times a day, maximum 8 puffs a day; 1 inhaler
UK	COPD	Tiotropium 18 mcg inhalation powder; take one capsule once daily; 30 cap pack + HandiHaler	Ciclesonide 80 micrograms/metered inhalation; take 80 micrograms daily; 1 x 120-dose unit

Denmark	Depression	Citalopram 20 mg; take one tablet orally once daily; 56 stk. (blister) filmovertrukne	Isocarboxazid 10 mg; take 1 tablet three times a day; 56 stk. tabletter
France	Depression	Citalopram 20 mg cp pellic séc: 20 mg par jour; Plq/28	Iproniazide phosphate 50mg cp séc: un comprimés par jour; T/30
Germany	Depression	Citalopram 20 mg Filmtabletten; take one tablet orally once daily; 100 ST	Tranylcypromin 20 mg Filmtabletten; take 1 tablet twice a day; 100 Filmtbl.
Greece	Depression	Citalopram hydrobromide F.C. tab 20 mg; take one tablet orally once daily; 28 tab	Amoxapine tab 50 mg; take one tablet three times a day; 84 tablets
Netherlands	Depression	Citalopram 20 mg, filmomhulde tabletten 20 mg; 20 mg per dag; 28 tabletten	Fenelzine 15 mg tablet; take one tablet three times a day; 84 tabletten.
Poland	Depression	Citalopramum tabletki powlekane 20 mg; take one tablet orally once daily; 20 tabl.	Opipramolum tabletki powlekane 50 mg; take one 50 mg tablet in the morning and at midday, then two 50 mg tablets in the evening; take with meals; 112 tabl.
UK	Depression	Citalopram 20 mg; take one tablet orally once daily, 28 tablets	Nortriptyline hydrochloride 25 mg; take one tablet twice daily; 20 tablets
Denmark	Diabetes	Metformin 1000 mg; take one tablet with meals twice a day orally; 60 stk. (blister) filmovertrukne	Humulin NPH Pen 100 IE/ml, inject subcutaneously as directed; 5 penne a 3 ml injektionsvæske
France	Diabetes	Metformine 500mg cp pellic: un comprimé 2 à 3 fois par jour, administré au cours ou à la fin des repas; Plq/90	Umuline profil 30 100 UI/ml susp inj en cart: injectée par voie sous-cutanée; 5Cart/3ml
Germany	Diabetes	Metformin 1000 mg Filmtabletten; take one tablet with meals twice a day orally 180 ST	Actraphane 30 FlexPen 100 IE/ml; inject subcutaneously as directed; 5X3 ml
Greece	Diabetes	Metformin hydrochloride tab 500 mg; take one tablet with meals three times a day orally	Liprolog mix 25; inject subcutaneously as directed.
Netherlands	Diabetes	Metformine HCl 500 PCH, filmomhulde tabletten 500 mg; 2 keer daags 1 tablet; 50 tabletten	Insuline glargine 100 Eenheden/ml oplossing voor injectie in een injectieflacon; subcutaan gebruik; 1

			injectieflacon.
Poland	Diabetes	Metformini hydrochloridum tabletki powlekane 1000 mg; take one tablet with meals twice a day orally; 120 tabl.	Polhumin Mix-3 Insulinum humanum zawiesina do wstrzykiwań 100 j.m/ ml ; inject subcutaneously as directed ; 5 wkładów 3 ml
UK	Diabetes	Metformin 500 mg; take one tablet with meals three times a day orally; 84 tablets	Mixtard 30 100 units/mL; inject subcutaneously as directed; 1x 10 mL vial
Denmark	Epilepsy	Lamotrigin 100 mg 56 stk. tabletter	Rufinamid 200 mg; take one tablet twice a day; 60 stk. (blister) filmovertrukne
France	Epilepsy	Lamotrigine 100mg cp dispers; 100 mg/jour; croqués ou dissous dans un petit volume d'eau; Plaq/30	Felbamate 400mg cp : 1 200 mg/jour, administrée en 3 prises; B/80 comprimés
Germany	Epilepsy	Valproinsäure 300 mg magensaftresistente Filmtabletten **100 Filmtbl**	Mesuximid 150 mg Kapseln, take one capsule three times a day; 100 ST
Greece	Epileps	Lamotrigine tab 200 mg	Felbamate 400 mg; take one tablet twice a day (every 12 hours) with water; 60 tablets
Netherlands	Epilepsy	Lamotrigine CF 200 mg, dispergeerbare tabletten; 200 mg per dag; 30 tabletten.	Felbamaat TABS 400, tabletten 400 mg; elke dag twee keer (elke 12 uur) met water ingenomen; 60 Tabletten in blisterverpakking
Poland	Epilepsy	Lamotriginum abletki 25 mg 90 tabl.	Phenobarbitalum tabletki100 mg; one tablet to be taken orally once daily at night; 10 tabl.
UK	Epilepsy	Lamotrigine 50 mg tablet, take one tablet orally once daily; 28 tablets	Phenobarbital 60 mg; two tablets to be taken orally once daily at night; 56 tablets
Denmark	Hypertension	Ramipril 2,5 mg; take one capsule orally once daily; 28 stk. tabletter	Bendroflumethiazid 5 mg, take one tablet once daily in the morning; 100 stk. tabletter
France	Hypertension	Ramipril 2,5 mg; 2,5 mg par jour; B/30 comprimés	Tertatolol 5mg; Un comprimé par jour en une prise matinale; B/30 comprimés
Germany	Hypertension	Ramipril 2.5 mg; take one capsule orally once daily; Tabletten 50 ST	Penbutolol 40 mg Filmtabletten; take one tablet once daily; 100 Filmtbl.

Greece	Hypertension	Ramipril tab 5 mg; take one capsule orally once daily; 28 capsules	Barnidipine hydrochloride Mod. R. CA. H. 20 mg/cap; take one capsule once daily; 28 capsules
Netherlands	Hypertension	Ramipril 2.5 mg; take one capsule orally once daily; 28 capsules	Chloorthiazide 250 mg tablet; take two tablets once a day; 56 tablets
Poland	Hypertension	Ramiprilum tabletki 1,25 mg; take two tablets orally once daily; 30 tabl.	Chlortalidonum abletki 50 mg; take one tablet each day in the morning; 20 tabl.
UK	Hypertension	Ramipril 2.5 mg; take one capsule orally once daily; 28 capsules	Nisoldipine 10 mg; take two tablets once daily in the morning; 56 tablets
Denmark	IHT	Simvastatin 20 mg; take one tablet once daily at night orally; 100 stk. (blister) filmovertrukne	Labetalol 100 mg, take one tablet twice a day orally; 250 stk. Filmovertrukne tabl.
France	IHT	Simvastatine 20mg cp pellic séc; 20 mg/jour administrés par voie orale en une prise unique le soir: B/28 comprimés	Zofénopril 30mg cp pellic: 30 mg par jour; B/28 comprimés
Germany	IHT	Simvastatin 20mg Filmtabletten; take one tablet once daily at night orally; 100 Stück	Molsidomin 8 mg Tabletten; take one tablet once a day; 100 Retardtbl.
Greece	IHT	Simvastatin F.C. tab 20 mg; take one tablet once daily at night orally; 28 tablets	Spirapril hydrochloride tab 6 mg; take two tablets once a day orally; 56 tablets
Netherlands	IHT	Simvastatine 20 mg, filmomhulde tabletten; 20 mg één keer per dag 's avonds gebruikelijk; 28 tabletten	Barnidipine hydrochloride 10 mg, capsules met gereguleerde afgifte; eenmaal daags 1 capsule 10 mg; 28 capsules
Poland	IHT	Simvastatinum tabletki powlekane 20 mg; take one tablet once daily at night orally; 28 tabl. (2 x 14)	Torasemidum abletki 2,5 mg; take two tablets once a day; 60 tabl.
UK	IHT	Simvastatin 20 mg; take one tablet once daily at night orally; 28 tablets	Nadolol 80 mg; take one tablet once daily orally, 28 tablets
Denmark	Osteoarthritis/ Rheumatoid Arthritis	Naproxen 250 mg 100 stk. Tabletter; take one tablet orally twice daily; 56 tablets	Penicillamin 250 mg, take 250 mg once daily before food; 200 stk. Kapsler, hårde

France	Osteoarthritis/ Rheumatoid Arthritis	Naproxène sodique 275 mg; 2 comprimés à 275 mg, soit 550 mg par jour; Les comprimés sont à avaler tels quels, avec un grand verre d'eau; B/30 comprimés	Alminoprofène 300mg cp pellic : B/15; 2 à 3 comprimés à 300 mg par jour; B/56 comprimés
Germany	Osteoarthritis/ Rheumatoid Arthritis	Naproxen 250 V CT – 100 ST; take one tablet orally twice daily; 56 tablets	Metamizol natrium 500 mg als Einzelmenge 1-2 Tabletten 2 or 3 times a day; 50 tabletten
Greece	Osteoarthritis/ Rheumatoid Arthritis	Naproxen sodium C. Tab 220 mg; take one tablet orally twice daily; 56 tablets	Nimesulide 100 mg; take one tablet twice a day; 100 tabl.
Netherlands	Osteoarthritis/ Rheumatoid Arthritis	Naproxen 250 PCH, tabletten 250 mg; 250 mg om de 8 tot 12 uur; 56 tabletten	Tiaprofeenzuur capsules met gereguleerde afgifte 300 mg; 2 capsules à 300 mg 1 keer per dag, 's avonds voor het slapen gaan; 60 capsules
Poland	Osteoarthritis/ Rheumatoid Arthritis	Naproxenum natricum tabletki powlekane 220 mg; take one tablet orally twice daily; 40 tabl.	Nimesulidum tabletki 100 mg; take one tablet twice a day; 60 tabl.
UK	Osteoarthritis/ Rheumatoid Arthritis	Naproxen 250 mg tablets, take one tablet orally twice daily; 56 tablets	Penicillamine 250 mg; take 1 tablet twice daily orally; 56 tabs

A Note On Devices

A number of medical devices are also available on prescription from Member States. We tested the cross-border availability of such devices in two ways:

- Availability of diabetes pens, jet injectors, pumps, syringes and needles for administration of insulin by people with diabetes.
- Availability of specific inhaler devices for administration of medication for asthma and COPD.

These two examples tested the issues around mutual recognition of prescriptions for devices relevant to the eight pathologies included in this study. The syringes and needles commonly used by people with diabetes to self-administer insulin are also in demand by people who wish to inject controlled drugs, and therefore might be harder to obtain from pharmacies when confirming the validity of the prescriber and the patient's health status is difficult.

Issues around the use of different devices to administer insulin reflect problems patient may experience with measuring accurate doses, and problems in physically manipulating the device to administer the medication. For example, authors of a study funded by a manufacturer of an insulin pen concluded that, compared with traditional syringes and needles, patients may find insulin pens easier to use when they first start insulin therapy, the scales may be easier to read, dosing may be more accurate and adherence may be increased (Kroon 2009).

An observational study of 32 children with type 1 diabetes and 16 parents of such children in the US found that, at doses less than 5 units, a pen device was significantly more accurate than a syringe and needle (0.2 unit error with the pen compared with 0.4 unit error with syringe, $p<0.01$), even in children and parents who were familiar with both device types. At higher doses, there was no significant difference in accuracy between the pen and the syringe. The findings suggested that this reduced accuracy in drawing up the dose may be associated with an increased risk of hypoglycaemic events (Lteif and Schwenk 1999). Other studies have found that different insulin pens may have slightly different accuracy of dosing (Crowe 2009). Patients who are dispensed an insulin device that differs from their usual device may therefore both struggle to use the device, and may be exposed to a different actual dose of insulin, with adverse effects on the control of their blood glucose.

Similarly, patients with asthma or COPD may require training and practice to use devices such as metered-dose inhalers. A study of 120 patients attending outpatients at a tertiary teaching hospital in Brazil, half with asthma and half with COPD, found that almost all patients considered that they knew how to use their inhaled medication, but 94.2% of participants made at least one error when being observed using the inhaler device. Patients with COPD made more errors than patients with asthma who used the same type of inhaler device, $p<0.0001$ (de Moraes Souza et al. 2009).

A patient who is used to a different device but has the relevant drug dispensed in a metered-dose inhaler may struggle to use the unfamiliar device effectively. The type of device dispensed may therefore have an effect on how much of the drug they are able to absorb and therefore how well their asthma attacks can be controlled. A qualitative study of 19 patients with asthma in the UK who had had their inhaler device changed found that most had not been shown how to use the new device and struggled to actuate the new device as efficiently as the old one. Some patients failed to activate the new device and either returned to their GP, used their old inhaler, or went without treatment until someone explained how to us the new device. In some cases, patients used more medication than previously to ensure that they had successfully inhaled enough. The majority of participants in the study reported worsening symptoms and a sense of being less in control of their asthma, but some had better control with the new device (Doyle et al. 2010). However, patients in this study, funded by a pharmaceutical manufacturer, were respondents to an advertisement in the national media and were unlikely to be representative of all asthma patients.

Any difficulty in using a different inhaler device is likely to be short-term, however. A systematic review of randomised controlled trials and systematic reviews concluded that there is no evidence that any inhaler device or nebuliser for asthma or COPD has greater clinical benefit than metered dose inhalers, with or without a spacer device, for delivery of inhaled medication (Brocklebank et al. 2001).

6.3 Methodology: Evidence Review

In this appendix we describe our methodological approach to the various evidence reviews carried out as part of this study.

6.3.1 Evidence Review 1: Issues around Cross-Border Dispensing

Table 20: Review 1: Issues around Cross-Border Dispensing of Prescriptions

Search Strategy: Medline

Medline was searched using the EBSCO Discovery interface in February 2011, using the following strategy:

[international or cross-border]

AND

[MH "Prescription Drugs/AD/ST/SD"] OR [MH "Prescriptions"] OR [MH "Community Pharmacy Services"] OR [prescri* or dispens*]

(MH = MeSH term; other search terms were text words)

Search limited to date 1990 to February 2011; English language.

Inclusion Criteria

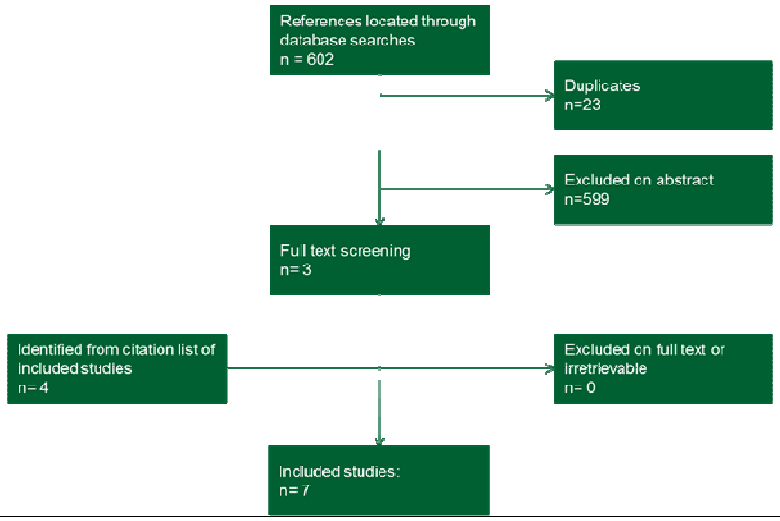
Studies were screened for inclusion according to the following criteria:

Was the study published in 1990 or later?	YES/UNCLEAR – go to Q2	NO – exclude **1_EX Date**
Was the study published in an OECD country?	YES/UNCLEAR – go to Q3	NO – exclude **2_EX OECD**
Was the study on the topic of cross-border dispensing or recognition of prescriptions?	YES/UNCLEAR – go to Q4	NO – exclude **3_EX TOPIC**
Does the study report data from primary research or a review of primary research studies?	YES/UNCLEAR – **5_INCLUDE**	NO – exclude **4_EX DATA**

OECD countries are taken to include: Australia; Austria; Belgium; Canada; Chile; Czech Republic; Denmark; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Israel; Italy; Japan; Luxembourg; Mexico; the Netherlands; New Zealand; Norway; Poland; Portugal; South Korea; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; the UK; and the USA.

Flow of Literature Diagram

We located 625 citations through our database search. Of these, 23 were duplicates, meaning that 602 unique references were screened on title and abstract, and 599 were excluded. The remaining 3 references proceeded to full text screening and were included in the review. An additional 4 studies were identified as relevant from the reference list of the 3 included studies and were also included in the review, giving a total of 7 included studies for the first review.



6.3.2 Evidence Review 2: Impact of Dispensing Errors

Table 21: Review 2: Impact of Dispensing Errors

Summary

We searched the following databases for relevant studies, selected to be the most relevant sources of such research on the harms that can result from a failure to dispense or administer prescribed medication accurately:

CINAHL (nursing and allied health professions)
Medline (Medicine and social care)
EconLit (economic analyses)
NHS EED (economic analyses)

Our first evidence review identified no studies that reported harms from dispensing drugs used for our eight selected pathologies in the community. We therefore broadened the search terms and screened the identified studies for examples of harm arising for patients who received the wrong drug, dose or formulation in either the community or hospital settings (as the harms are the same as for self-administered treatments).

We ran the search to identify studies published since 1990, as studies older than this were considered to have little relevance to the current policy and practice. We only included studies published in English and carried out in an OECD country. We included studies that reported

primary research, case reports, and narrative reviews or commentaries where the authors discussed the issues around erroneous prescribing, dispensing or administration of drugs and the consequences of such errors on patients or healthcare providers.

We identified 27 studies from this search that met the inclusion criteria for the review and could be retrieved. Most of these studies were case reports, and most could be mapped to the NCC MERP Index for categorising medication errors, as described below.

We found no studies that quantified the size of the problem of dispensing errors, or calculated the overall costs of such errors or of failure to dispense prescriptions. The studies we identified offer illustrations of the sort of harm that can arise from different types of drug prescribing or administration error, or are indicative of the sort of problem that may arise in terms of controlling a chronic disease if the patient fails to receive their medication in a timely way, via a device they are able to use.

Most of the examples we identified relate to incorrect administration of drugs such as insulin for diabetes, resulting in hypoglycaemic attacks and diabetic coma; and toxic effects of drugs such as antiepileptic drugs, antidepressants or methotrexate for rheumatoid arthritis, where the difference between a clinically effective dose and a toxic dose may be small.

Search Strategy: Medline

Medline was searched using the EBSCO Discovery interface in March 2011, using the following strategy. The search strategies used in CINAHL, EconLit and NHS EED followed the same structure as the Medline search.

Terms for epilepsy:

[MH “Epilepsy”] OR [MH “Epilepsy, absence”] OR [MH “Epilepsy, tonic-clonic”]

OR

[barbexaclone or carbamazepine or clobazam or clonazepam or ethosuximide or felbamate or fosphenytoin or gabapentin or lamotrigine or levetiracetam or mephenytoin or mesuximide or methylphenobarbital or oxcarbazepine or pheneturide or phenobarbital or phenytoin or pregabalin or primidone or rufinamide or sultiame or tiagabine or topiramate or valproate or valproic or vigabatrin or zonisamide or barbiturate or benzodiazepine]

Terms for hypertension or ischaemic heart disease:

[MH "Myocardial Ischemia+") OR [hypertension or ischaemic heart disease or angina or coronary heart disease]

OR

[benazepril or captopril or cilazapril or delapril or enalapril or fosinopril or imidapril or lisinopril or

moexipril or perindopril or quinapril or ramipril or spirapril or trandolapril or zofenopril or bunazosin or doxazosin or indoramin or moxisylyte or phenoxybenzamine or phentolamine or prazosin or terazosin or tolazoline or urapidil or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or acebutolol or atenolol or betaxolol or bisoprolol or bopindolol or bupranolol or carazolol or carteolol or carvedilol or celiprolol or esmolol or indenolol or labetalol or mepindolol or metoprolol or nadolol or nebivolol or oxprenolol or penbutolol or pindolol or propranolol or sotalol or talinolol or tertatolol or timolol or amlodipine or barnidipine or bepridil or cilnidipine or diltiazem or felodipine or gallopamil or israpidine or lacidipine or lercanidipine or manidipine or nicardipine or nifedipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or verapamil or amiloride or canrenone or eplerenone or potassium canreonate or spironolactone or triamterene or altizide or bemetizide or bendroflumethiazide or benzthiazide or butizide or chlortalidone or clopamide or cyclopenthiazide or hydrochlorothiazide or indapamide or mefruside or metolazone or polythiazide or xipamide or cilostazol or clopidogrel or cloricromen or dipyrindamole or ditazole or picotamide or ticlopidine or trapidil or bumetanide or etacrynic or etozolin or furosemide or piretanide or torasemide or glyceryl trinitrate or GTN or isosorbide dinitrate or isosorbide mononitrate or lindisomine or molsidomine or pentaerithrityl tetranitrate or sodium nitroprusside or tenitramine or atorvastatin or fluvastatin or lovastatin or pravastatin or rosuvastatin or simvastatin or ACE inhibitor or anticholinesterase inhibitor or alpha blocker or angiotensin II receptor antagonist or beta blocker or calcium channel blocker or diuretic or thiazide or antiplatelet or nitrate or statin]

Terms for asthma or COPD:

[MH "Lung Diseases, Obstructive+"] OR [Asthma or COPD or chronic obstructive pulmonary disease or chronic obstructive airways disease or chronic bronchitis or emphysema or obstructive airways disease]
OR

[amlexanox or montelukast or zafirlukast or ipratropium or oxitropium or tiotropium or bambuterol or clenbuterol or fenoterol or formoterol or hexoprenaline or orciprenaline or pirbuterol or procaterol or reproterol or salbutamol or salmeterol or terbutaline or tulobuterol or beclometasone or budesonide or ciclesonide or fluticasone or mometasone or triamcinolone or nedocromil or cromoglycate or ambroxol acefyllinate or aminophylline or bamifylline or caffeine or choline theophyllinate or diprophylline or doxofylline or etamiphylline or etophylline or heptaminol acefyllinate or proxyphylline or theobromine or theophylline or omalizumab or dornase or acetylcysteine or bromhexine or brovanexime or carbocysteine or erdosteine or letosteine or mecysteine or eprazinone or eprozinol or dacisteine or neltenexine or sobrerol or talniflumate or mucolytic or leukotriene antagonist or antimuscarinic or beta agonist or corticosteroid or mast cell stabiliser or xanthenes]

Terms for depression or bipolar disorder:

[MH “Depressive disorder+”] OR [MH “Bipolar disorder+”] OR manic depression

OR

[amineptine or amitriptyline or amoxapine or bupropion or citalopram or clomipramine or desipramine or dibenzapin or dosulepin or dothiepin or doxepin or duloxetine or escitalopram or fluoxetine or fluvoxamine or imipramine or iproniazid or isocarboxacid or lithium or lofepramine or maprotiline or melitracen or mianserin or milnacipran or mirtazepine or moclobemide or nefazodone or nortriptyline or opipramol or oxitriptan or paroxetine or phenelzine or pirindole or reboxetine or sertraline or st john's wort or tianeptine or tranylcypromine or trazodone or trimipramine or tryptophan or venlafaxine or viloxazine or tricyclic or selective serotonin reuptake inhibitor or SSRI or serotonin-norepinephrine reuptake inhibitor or SNRI or monoamine oxidase inhibitor or MAOI]

Terms for arthritis:

[MH “Osteoarthritis+”] OR [MH “Arthritis, rheumatoid+”]

OR

[aspirin or abatacept or adalimumab or anakinra or etanercept or infliximab or leflunomide or auranofin or aurothioglucose or aurotioprol or sodium aurothiomalate or sodium aurotiosulfate or aceclofenac or acemetacin or alminoprofen or aminophenazone or aminopropylone or amtolmetin or azapropazone or bendazac or benorilate or benzydamine or bufexamac or butibufen or celecoxib or clonixin or dexibuprofen or diclofenac or diflunisal or dipyrone or etodolac or etofenamate or etoricoxib or felbinac or fenbufen or fenoprofen or fentiazac or fepradinol or feprazone or floctafenine or flufenamic acid or flurbiprofen or furprofen or ibuprofen or ibuproxam or indometacin or indomethacin or isonixin or kebuzone or ketoprofen or ketorolac or lonazolac or lornoxicam or lumiracoxib or meclofenamic acid or mefenamic acid or meloxicam or mofebutazone or morniflumate or nabumetone or naproxen or nepafenac or niflumic acid or nimesulide or parecoxib or phenazone or phenylbutazone or piketoprofen or piroxicam or pranoprofen or proglumetacin or propyphenazone or proquazone or rofecoxib or sulindac or suxibuzone or tenoxicam or tiaprofenic acid or tolfenamic acid or tolmetin or valdecoxib or acetanilide or paracetamol or non-steroidal anti-inflammatory or NSAID or disease modifying antirheumatic drug or DMARD]

Terms for diabetes:

[MH “Diabetes mellitus+”]

OR

[acarbose or buformin or metformin or phenformin or sitagliptin or vildagliptin or nateglinide or repaglinide or carbutamide or chlorpropamide or glibenclamide or gliclazide or glimepiride or glipizide or gliquidone or glisentide or glisolamide or glisoxepide or glyclyclamide or tolbutamide or pioglitazone or rosiglitazone or guar gum or exenatide or insulin or actraphane or actrapid or apidra or berinsulin or bioinsulin or H-tronin or exubera or gensulin or humaject or humalog or

humaplus or huminsulin or humulin or humutard or hypurin or insulatard or insulinum or insuman or insuplant or isuhuman or lantus or levemir or lillypen or liprolog or mixtard or monotard or novomix or novorapid or optisulin or penmix or polhumin or protaphane or semilente or ultratard or umuline or velosulin or aldose reductase inhibitor or alpha-glucosidase inhibitor or biguanide or dipeptidylpeptidase-4 inhibitor or meglitinide or sulfonylurea or thiazolidinedione]

Terms for prescribing or dispensing:

[MH "Medication errors+"] OR [MH "Drug prescriptions"] OR [MH "Drug compounding"] OR [MH "Pharmacy+"] OR [error or dispens* or prescri*]

Strategy is:

Terms for epilepsy [1 OR 2] OR terms for hypertension or ischaemic heart disease [3 OR 4] OR terms for asthma or COPD [5 OR 6] OR terms for depression or bipolar disease [7 OR 8] OR terms for arthritis [9 OR 10] OR terms for diabetes [11 OR 12]

AND

Terms for prescribing or dispensing [13]

Search limited to date 1990 to March 2011; English language.

Inclusion Criteria

Studies were screened for inclusion according to the following criteria:

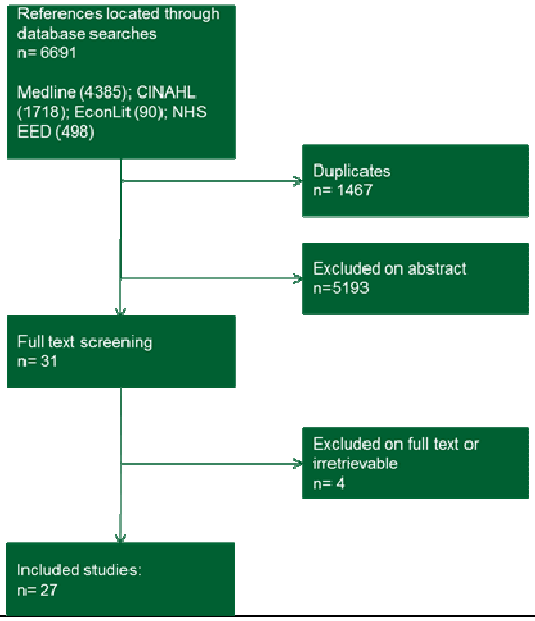
Q	Question	Hierarchy	Code
	Does the study have a focus on the harms of medication errors at the drug dispensing stage?	YES/ UNCLEAR – go to Q2	NO – exclude **EX.TOPIC**
	Was the study published in **1990 or later**?	YES/ UNCLEAR – go to Q3	NO – exclude **EX.DATE**
	Is the study report in **English**?	YES/ UNCLEAR – go to Q4	NO – exclude **EX.NON-ENG**
	Was the study conducted in an **OECD country**?	YES/ UNCLEAR – go to Q5	NO – exclude **EX.OECD**
	Does the study present any **data on harm**?	YES/ UNCLEAR – go to Q7	YES – **IN.EMP**

OECD countries are taken to include: Australia; Austria; Belgium; Canada; Chile; Czech Republic; Denmark; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Israel; Italy; Japan; Luxembourg; Mexico; the Netherlands; New Zealand; Norway; Poland; Portugal; South Korea; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey; the UK; and the USA.

Flow of Literature Diagram

We located 6,691 citations through our database search. Of these, 1,467 were duplicates,

meaning that 5,224 unique references were screened on title and abstract, and 5,193 were excluded. The remaining 31 references proceeded to full text screening. Four could not be retrieved, so 27 were included in this review.



6.3.3 Evidence Review 3: Impact of Medication Gap on Patient Harm

- **Time Scales:** In terms of time-scales we differentiated between short-term (less than 1 month), short to medium term (between 1 month and 6 months), medium term (6 to 12 months) and long-term (above 12 months).

- **Level of Harm**: We distinguished between the following five levels of harm: Level 1 (mild increase in symptoms requiring a consult with a physician); Level 2 (increase in symptoms requiring hospitalisation); Level 3 (acute and severe symptoms requiring emergency surgery), Level 4 ((likely) death).

Pathology	Drug	Impact of not taking drug	Citation	Time Scale	Level of Harm
Any	Any essential medication for chronic disease	Cost-sharing in the US led to a 9% decrease in use of essential drugs by elderly people. This was associated with a 14.2/10,000 person-months increase in ED visits related to non-use of essential drug; and a 6.8/10,000 person-month increase in serious adverse events	Tamblyn et al. 2001	2	
Any	Any medication for chronic disease	People who experienced interruption of medication were more likely to have deteriorated health status one month after the event (OR = 4.5; 95% CI = 1.2-17.6).	Tomio et al. 2010	2	
Asthma	Inhaled corticosteroids or leukotriene inhibitors	ED visits: 80/1000 patient-years with lowest compliance quartile vs 36/1000 with highest compliance quartile; Hospital admissions: 34/1000 patient-years with lowest compliance vs 13/1000 for highest compliance	Mattke et al. 2010	3	
Asthma	Inhaled corticosteroids	24% of asthma exacerbations were attributable to non-adherence with ICS	Williams et al. 2011		
Asthma	Combined or concurrent ICS and long-acting beta 2 agonists (LABA)	Patients taking combined medication were 17% less likely to stop their treatment than concurrent medication users, and were 17% less likely to have a moderate to severe exacerbation of asthma.	Marceau et al. 2006		
Asthma	fluticasone propionate/salmeterol combination inhaler	Each 25% improvement in adherence was associated with a 10% reduction in the odds of asthma-related ED visit or hospitalization ($p < 0.001$), and 23% increase in total asthma-related costs	Delea et al. 2008		
Asthma	ICS	Each 25% increase in the proportion of time without ICS medication resulted in a doubling of the rate of asthma-related hospitalization (relative rate, 2.01; 95% CI, 1.06-3.79). During the study period, there were 80 asthma-related hospitalizations; an estimated 32 hospitalizations would have occurred were there no gaps in medication use (60% reduction).	Williams et al. 2004		
Asthma	Inhaled corticosteroids (ICS)	Asthma treatment days: 2.9 average for high compliance vs 3.9 days for low compliance, $p<0.0001$; Asthma treatment charges: $2655 for high compliance vs $3345 for low compliance	Navaratnam et al. 2010		
Asthma (children)	ICS	The median compliance with inhaled corticosteroids was 13.7% for those who experienced exacerbations and 68.2% for those who did not.	Milgrom et al. 1996		
COPD	Tiotropium	Sudden withdrawal of therapy after a clinical trial led to an increase in shortness of breath, lung function and worse health status over the following 3 weeks.	Adams et al. 2009	1	1
COPD	Inhaled medication	For 1000 COPD patients, a 5% point increase in proportion of days with access to medication reduced the annual number of inpatient visits (-2.5%) and emergency room visits (-1.8%) and slightly increased outpatient visits (+.2%); the net reduction in annual cost was approximately $300,000.	Toy et al. 2011	3	
COPD	ICS	Withdrawal of ICS led to a significant fall in lung function (FEV1 4.1 decrease from baseline, $p<0.001$). Annual moderate to severe exacerbations did not increase significantly (1.6 per year vs 1.3 per year with continued therapy, $p=0.15$) but mild exacerbations did increase significantly (1.3 per year vs 0.6 per year with continued therapy, $p=0.02$).	Wouters et al. 2005	3	
COPD	Inhalation therapy	Significant correlations were found between the overall mean adherence score and the health-related quality of life score (St George's Respiratory Questionnaire: total, $r = -0.35$, $P = 0.023$; symptoms, $r = -0.43$, $P = 0.002$; impacts, $r = -0.35$, $P = 0.011$).	Takemura et al. 2011		

Pathology	Drug	Impact of not taking drug	Citation	Time Scale	Level of Harm
COPD (moderate to severe)	Inhaled medication (ICS + salmeterol)	Mortality (3 year): 11.3% in group with good adherence (>80% use of prescribed medication) vs 26.4% in group with poor adherence; Hospital admissions: 0.15/year with good adherence vs 0.27/year with poor adherence	Vestbo et al. 2009	3	
Depression	SSRIs	A 10-day gap between finishing one prescription and getting the next prescription filled meant that antidepressant therapy was needed for twice as long	Gardarsdottir et al. 2010	1	1
Depression	Tricyclics, MAOIs, SSRIs	Discontinuation syndromes start within a few days of stopping the medication. Most require no treatment but some can be serious	Haddad 2001	1	1
Depression	SSRIs	Annual medical costs: were between $423 and $511 less for people who adhered with medication vs those who had poor adherence	Cantrell et al. 2006	3	
Depression (adolescents)	Antidepressants (SSRI, venlafaxine)	Adherence was not related to suicidal events or suicidal ideation.	Woldu et al. 2011		
Depression (after bipolar depressive episode)	Antidepressants	Antidepressant continuation did not significantly decrease severity of depressive symptoms compared with discontinuation (mean difference in DSM-IV depression criteria = -1.84 [95% CI, -0.08 to 3.77]) or mildly delayed depressive episode relapse (HR = 2.13 [1.00-4.56]), without increased manic symptoms (mean difference in DSM-IV mania criteria = +0.23 [-0.73 to 1.20]).	Ghaemi et al. 2010		
Depression (bipolar)	Antidepressants	Relapse of depression (1 year): 70% if antidepressants discontinued; 36% if antidepressants continued	Altshuler et al. 2003	3	
Diabetes	Any antidiabetic drug	Increasing diabetic drug adherence from 50% to 100% reduces the hospitalization rate by 23.3% (from 15% to 11.5%). ER visits reduce by 46.2% (from 17.3% to 9.3%). Although such an increase in adherence increases diabetic drug spending by $776 a year per diabetic, the cost savings for averted hospitalizations and ER visits are $886 per diabetic, a cost offset of $1.14 per $1.00 spent on diabetic drugs	Encinosa et al. 2010	3	
Diabetes	Oral antidiabetic drugs +/- insulin	Adherence measured as taking 80% or more of prescribed doses. Probability of events over 2 years: Acute MI: 4% in nonadherent vs 1.8% in adherent, p<0.01; leg amputation or ulcer: 8% in nonadherent vs 4% in adherent, p<0.01; cerebrovascular disease: 10.1% nonadherent vs 7.8% adherent, p<0.05; neuropathy: 15.9% nonadherent vs 11.8% adherent, p<0.01; peripheral vascular disease: 8.1% nonadherent vs 6.3% adherent (NS); renal events: 10.8% nonadherent vs 5.8 adherent, p<0.01; retinopathy: 15.7% nonadherent vs 13% adherent, p<0.05.	Gibson et al. 2010	4	
Diabetes	Any antidiabetic drug	Cost-related medication underuse was associated with significantly higher HbA1c levels, more symptoms, and worse physical and mental functioning	Piette et al. 2004		
Diabetes	Metformin	A 10% increase in nonadherence was associated with an increase in HbA1c of 0.14%	Pladevall et al. 2004		
Diabetes	Any antidiabetic drug	Total medical costs decrease as adherence with medication increases above a threshold of 20-39% adherence, and diabetes-related medical costs reduce after a threshold of 40-59% adherence; Hospital admission rates were 16-17% with 1-39% adherence, vs 11% for 100% adherence; ED presentation rates were 21% for 1-39% adherence vs 14% for 100% adherence.	Hepke et al. 2004		
Diabetes	Oral antidiabetic drugs, antihypertensives and statins	In unadjusted analyses, nonadherent patients had higher all-cause hospitalization (23.2% vs 19.2%, P<.001) and higher all-cause mortality (5.9% vs 4.0%, P<.001).	Ho et al. 2006		

Pathology	Drug	Impact of not taking drug	Citation	Time Scale	Level of Harm
Diabetes	Oral antidiabetic drug	Complete adherence improves control of diabetes (reduces HbA1c by 0.88%) compared with no adherence	Horswell et al. 2008		
Diabetes (type 2)	Oral antidiabetic drugs	Non-adherence over 2 years significantly increased the risk of hospitalisation (odds ratio 1.26, 95% CI 1.08 to 1.47) and of mortality (odds ratio 1.40, 95%CI 1.01 to 1.95)	Hong & Kang 2011	4	
Epilepsy	Lamotrigine	Immediately following the abrupt discontinuation of lamotrigine in a 68 year old man, disordered sleep symptomatology was severely aggravated, with dreams becoming more vivid and frightening and occurring almost every night.	Economou et al. 2011	1	1
Epilepsy	Antiepileptic drug	Discontinuation showed a trend towards an increased risk of hospitalisation (OR: 2.57; 95%CI: 0.81-8.17) among patients admitted to hospital, comparing medication use in the 28 days before the admission with medication use in four earlier 28-day periods.	Handoko et al. 2007	1	3
Epilepsy	Gabapentin	A 76 year old woman was unable to get her prescription filled. 4 days later she was admitted to hospital with agitation and restlessness. The symptoms resolved when gabapentin was restarted.	See et al. 2011	1	3
Epilepsy	Entiepileptic drugs	Nonadherence was associated with significantly higher hospitalisation rate (incident rate ratio [IRR] 1.76, 95%CI 1.75 to 1.78); inpatient days (IRR = 1.76, 95% CI = 1.75-1.78), and ED visits (IRR = 1.19, 95% CI = 1.18-1.21). Nonadherence was associated with US$4320 higher inpatient costs per quarter and $303 higher ED costs per quarter, but lower outpatient and pharmacy costs	Faught et al. 2009	2	
Epilepsy	Entiepileptic drugs	Nonadherence was associated with an increased likelihood of hospitalization (odds ratio [OR]= 1.110, p = 0.013) and emergency room (ER) admission (OR = 1.479, p < 0.0001), as well as increased inpatient and ER costs of $1,799 and $260 (both p = 0.001), respectively, per patient per year.	Davis et al. 2008	3	
Epilepsy	Antiepileptic drugs	Noncompliance increases the risk of sudden unexplained death in epilepsy (SUDEP)	Ryvlin et al. 2009	1*	
Epilepsy	Antiepileptic drugs	Immediately following treatment withdrawal, the seizure recurrence risk in the next 12 months was 30% (95% CI 25% to 35%) and at 3 months after withdrawal was 15% (95% CI 10% to 19%).	Bonnett et al. 2011	2*	
Epilepsy	Patients switching between bioequivalent antiepileptic drugs	The odds of an epilepsy-related event were 1.78-fold higher for switchers (95% CI 1.35 to 2.36) and, when adjusted for gender and total number of AED prescriptions filled, 1.57-fold higher (95% CI=1.17-2.10).	Hansen et al. 2009		
Epilepsy	Antiepileptic drugs	Seizure risk was 21% higher among nonadherers (hazard ratio=1.205, P=0.0002) than adherers.	Manjunath et al. 2009		
Epilepsy	Antiepileptic drugs	On average, one in three patients who were seizure-free has a seizure recurrence after discontinuation of antiepileptic drugs, though the range can go up to 66% (34%, range 12-66%, 95% CI: 27-43).	Schmidt 2011		
Epilepsy	Antiepileptic drugs	Nonadherence was associated with an over threefold increased risk of mortality compared to adherence (hazard ratio = 3.32, 95% CI = 3.11-3.54) after multivariate adjustments. Periods of nonadherence were also associated with a significantly higher incidence of ED visits (IRR = 1.50, 95% CI = 1.49-1.52), hospital admissions (IRR = 1.86, 95% CI = 1.84-1.88), MVA injuries (IRR = 2.08, 95% CI = 1.81-2.39), and fractures (IRR = 1.21, 95% CI = 1.18-1.23) than periods of adherence.	Faught et al. 2008 b		

Pathology	Drug	Impact of not taking drug	Citation	Time Scale	Level of Harm
Epilepsy (in children)	Antiepileptic drugs	Early withdrawal of antiepileptic drugs was associated with an increased risk of seizure, relative risk 1.32 (95% confidence interval 1.02 to 1.70). For every 10 children who withdraw from medication, one will have a seizure.	Sirven et al. 2001		
Hypertension	Antihypertensives	BP following 7 days of excellent adherence was between 12/7 mm Hg and 15/8 mm Hg lower than after 7 days of poor adherence.	Rose et al. 2011	1	1
Hypertension	Antihypertensives	Patients with interrupted antihypertensive drug therapy consumed an additional $873 per patient (P < .0001) in health care during the first year, not counting a reduction in prescription drug cost of $281 (P < .0001). Increased costs were primarily due to increased hospital expenditures of $637 (P < .0002).	McCombs et al. 1994	3	
Hypertension	Antihypertensives	No significant difference in crude cardiovascular event rate with high adherence, 7.5/1000 patient-years vs 7.4/1000 for low adherence. After weighting for propensity for adherence, high adherence was associated with significantly fewer cardiovascular events than low adherence, hazard ratio 0.62, 95%CI 0.40 to 0.96, p=0.032.	Mazzaglia et al. 2009	3	
Hypertension	Antihypertensives	Mean total healthcare costs were significantly lower in year 2 for patients with 80% or more adherence with antihypertensive medication, $7182 vs $7995 for less than 60% adherence. Moderate or low adherence was also associated with a significantly higher risk of cardiovascular related hospitalisation (Odds ratio 1.33, 95%CI 1.25 to 1.41) and ED visits (OR 1.45, 95%CI 1.33 to 1.58).	Pittman et al. 2010	4	
Hypertension	Antihypertensives	Patients with low adherence were more likely to have coronary disease (OR, 1.07; 95% confidence interval [CI], 1.00-1.13), cerebrovascular disease (OR, 1.13; 95% CI, 1.03-1.25), and chronic heart failure (OR, 1.42; 95% CI, 1.27-1.58)within the 3-year follow-up period.	Dragomir et al. 2010	4	
Hypertension	Antihypertensives	Approximately 270 (43%) of high adherence patients achieved BP control compared with 56 (34%) and 15 (33%) patients with medium and low adherence, respectively. High-adherence patients were 45% more likely to achieve BP control than those with medium or low compliance after controlling for age, gender, and comorbidities (odds ratio=1.45; P =0.026).	Bramley et al. 2006		
Hypertension	Antihypertensives	Adherence was associated with lower odds of having elevated SBP (eg, odds ratio = 0.87 [95% CI, 0.84-0.89] for adherence to the full antihypertensive regimen).	Fung et al. 2007		
Hypertension	Antihypertensives	A 15% increase in adherence was associated with a significantly reduced risk of stroke (hazard ratio 0.91, 95%CI 0.86 to 0.97) and death (HR 0.93, 95%CI 0.90 to 0.96).	Bailey et al. 2010		
Hypertension	Antihypertensives	People with 80% or higher adherence to antihypertensives had a 22% reduced risk of cerebrovascular disease (eg stroke) compared with lower adherence (rate ratio 0.78, 95%CI 0.70 to 0.87)	Kettani et al. 2009		
Hypertension	Antihypertensives	Compared with patients who experienced at least one episode of treatment discontinuation, those who continued treatment had a 37%reduced risk of cardiovascular outcomes (95% confidence interval 34-40%).	Corrao et al. 2011		
Hypertension	ACE inhibitors	Non-adherence to ACE inhibitors was not associated with an increase in blood pressure	Pladevall et al. 2004		
IHD	Antithrombotic drugs	A 68 year old lady who had a drug-eluting coronary stent had an acute MI 2 days after stopping her antithrombotic therapy (aspirin plus clopidogrel)	Cardona et al. 2011	1	3
IHD	Any medication for cardiovascular disease	Hospital admission (2 year): 47% of people who underuse medication because of cost vs 38% in people who did not underuse medication, p<0.001.	Heisler et al. 2010	4	

Pathology	Drug	Impact of not taking drug	Citation	Time Scale	Level of Harm
IHD	Statins	A 10% increase in nonadherence was associated with an increase in LDL cholesterol of 4.9 mg/dL	Pladevall et al. 2004		
IHD	Statins	Patients with low, intermediate, or high statin coverage had hazard ratios for ischaemic heart disease hospitalisation (95% CI) values of 0.85 (0.72-0.98), 0.82 (0.71-0.95), and 0.81 (0.71-0.94), respectively, compared with patients with very low coverage.	Corrao et al. 2010		
IHD	statins	People with 80% or more adherence to statins had a significantly lower risk of recurrent MI (adjusted relative risk 0.19; 95%CI 0.08 to 0.47) and total mortality (RR 0.47, 95%CI 0.22 to 0.99) compared with people who were not taking statins. Lower adherence rates did not significantly reduce MI or mortality rates.	Wei et al. 2002		
IHD	Any medication	Respondents with cardiovascular disease who restricted medications reported higher rates of angina (11.9% vs. 8.2%; adjusted odds ratio, 1.50; CI, 1.09-2.07) and experienced higher rates of nonfatal heart attacks or strokes (7.8% vs. 5.3%; AOR, 1.51; CI, 1.02-2.25).	Heisler et al. 2004		
IHD	statins	People at high risk of cardiovascular disease who had high adherence to statins had significantly lower risk of developing heart failure (RR 0.81, 95%CI 0.71 to 0.91).	Perreault et al. 2008		
IHD	Beta-blockers, ACE inhibitors and statins	Nonadherence was significantly associated with increased all-cause mortality risk for beta-blockers (hazard ratio [HR] 1.50, 95% CI 1.33-1.71), ACE inhibitors (HR 1.74, 95% CI 1.52-1.98), and statins (HR 1.85, 95% CI 1.63-2.09). In addition, nonadherence remained significantly associated with higher risk of cardiovascular mortality for beta-blockers (HR 1.53, 95% CI 1.16-2.01), ACE inhibitors (HR 1.66, 95% CI 1.26-2.20), and statins (HR 1.62, 95% CI 1.124-2.13).	Ho et al. 2008		
IHD	Statins	Good statin adherence was associated with a reduced incidence of major coronary events in those with prior CHD [OR 0.84 (95% CI 0.74-0.95)]	Ruokonie mi et al. 2011		
Rheumatoid arthritis	Infliximab, adalimumab, etanercept	75% of patients who stopped medication once they were in remission suffered a relapse within 12 months; mean time to relapse was 14.7 weeks.	Brocq et al. 2009	2*	
Rheumatoid arthritis	Disease modifying drugs	Patients who persisted with medication had significantly lower disease activity and symptom scores than those who did not take medication consistently.	Contreras-Yáñez et al. 2010		
Rheumatoid arthritis	Disease modifying drugs	Adherent patients reached sustained remission significantly more often (82.8% versus 46.5%, P = 0.003) and earlier (7.7 +/- 4.6 versus 13.6 +/- 5.7 months, P = 0.001) than non-adherent. Risk of erosive disease (causing joint damage) was not significantly different, 26.8% of non-adherent vs 17.9% of adherent patients, p=0.56.	Pascual-Ramos et al. 2009		
Rheumatoid arthritis	Statins to prevent IHD	There was a 2% increase in risk of Acute MI with each 1-month increase in the duration of discontinuation of statins (adjusted HR 1.02; 95% CI 1.01 to 1.03).	De Vera et al. 2011	2	

Table 22: Detailed Overview of Eight Relevant Studies

Study 1	Evaluation of withdrawal of maintenance tiotropium in COPD
Author, year	**Adams et al. 2009**
Pathology	COPD
Type of study	Placebo-controlled study; patients randomly assigned in 3:2 ratio to receive either tiotropium or placebo; over three weeks. Health was then assessed during a three-week follow-up period, during which both groups received no medication.
Sample size	921 patients, of which **713** completed 3-weeks post-withdrawal evaluation.
Independent variable	Withdrawal of tiotropium.
Dependent variable	Dyspnea (transition dyspnea index [TDI]), Peak Expiratory Flow Rate (PEFR), health status (St George's Respiratory Questionnaire [SGRQ]) and rescue β_2-agonist use.
Control variables	Two groups were selected to have similar characteristics; along the dimensions of gender, age, body mass index, duration of COPD, smoker/ex-smoker, smoking history, forced expiratory volume, morning/evening peak expiratory flow rate, baseline dyspnea index, St George's Respiratory Questionnaire scores.
Summary of results	Sudden withdrawal of therapy after a clinical trial led to an increase in shortness of breath, lung function and worse health status over the following 3 weeks, as opposed to those who previously received no treatment and continued to receive no treatment.
Drug	Tiotropium
Reason for medication gap	Study-induced withdrawal of treatment
Harm occurred after...	3 weeks
Level of harm	1

Study 2	Very late coronary stent thrombosis after discontinuation of antiplatelet therapy
Author, year	**Cardona et al. 2011**
Pathology	IHD
Type of study	Case study
Sample size	**1** person
Independent variable	Discontinuation of antiplatelet therapy.
Dependent variable	Anterior ST-elevation MI; in-stent occlusion of the left anterior descending (LAD) and an 80% lesion of the proximal right coronary artery (RCA).
Control variables	N/A
Summary of results	A 68 year old lady who had a drug-eluting coronary stent had an acute MI 2 days after stopping her antithrombotic therapy (aspirin plus clopidogrel).
Drug	Antiplatelet therapy
Reason for medication gap	Self-induced non-adherence
Harm occurred after...	3 days
Level of harm	3

Study 3	Lamotrigine Withdrawal may Worsen RBD Symptoms
Author, year	**Economou et al. 2011**
Pathology	Epilepsy
Type of study	Case study
Sample size	1 person
Independent variable	Rapid eye movement behaviour disorder (RBD) symptomatology intensified, reoccurring, vivid, frightening dreams.
Dependent variable	Abrupt discontinuation of lamotrigine

Study 3	Lamotrigine Withdrawal may Worsen RBD Symptoms
Control variables	N/A
Summary of results	Immediately following the abrupt discontinuation of lamotrigine in a 68 year old man, disordered sleep symptomatology was severely aggravated, with dreams becoming more vivid and frightening and occurring almost every night.
Drug	Lamotrigine
Reason for medication gap	Abrupt discontinuation of treatment following lengthy period of lamotrigine not significantly *reducing* RBD symptomatology.
Harm occurred after...	Immediate – 1 day
Level of harm	1

Study 4	Akathisia Induced by Gabapentin Withdrawal
Author, year	**See et al 2011**
Pathology	Epilepsy
Type of study	Case study
Sample size	**1** person
Independent variable	Medication gap due to prescriptions not being refilled.
Dependent variable	Mental status, agitation and restless limb movements
Control variables	N/A
Summary of results	A 76 year old woman was unable to get her prescription filled. 4 days later she was admitted to hospital with agitation and restlessness. The symptoms resolved when gabapentin was restarted.
Drug	Gabapentin
Reason for medication gap	Unable to have prescriptions refilled.
Harm occurred after...	4 days
Level of harm	3

Study 5	Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length
Author, year	**Gardarsdottir et al. 2010**
Pathology	Depression
Type of study	Pharmacy prescription data analysis
Sample size	Source population from Dutch PHARMO database 1999-2003 (220,964); of which 149,555 received a selective serotonin reuptake inhibitor (SSRI); of which 56,046 over the age of 18 and started SSRI in 2001; of which 20,796 had not used antidepressants in the 24 months before the start date; of which **16,053** had received more than one antidepressant prescription and not received two antidepressants on the same date.
Independent variable	Gap between finishing one prescription and obtaining the next prescription.
Dependent variable	Median antidepressant treatment episode length.
Control variables	None (correlationary study primarily focused on finding methodology with which to calculate antidepressant treatment episodes).
Summary of results	A 10-day gap between finishing one prescription and getting the next prescription filled meant that antidepressant therapy was needed for twice as long.
Drug	Selective serotonin reuptake inhibitors, most commonly paroxetine (66.9%).
Reason for medication gap	Not specified – merely noted that there is a prescription gap.
Harm occurred	Flexible relative measure, headline example given of 10 days.

Study 5	Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length
after...	
Level of harm	1

Study 6	Antidepressant Discontinuation Syndromes: Clinical Relevance, Prevention and Management
Author, year	**Haddad 2001**
Pathology	Depression
Type of study	Survey review of anecdotal reports and the opinion of experts in the field.
Sample size	N/A, survey of many different opinions and anecdotal reports
Independent variable	Various forms of discontinuation, including trial-induced treatment interruption, random medication trials, placebo-controlled efficacy studies.
Dependent variable	Most common syndromes after SSRI discontinuation include dizziness, nausea, lethargy and headache. After TCA discontinuation, most common syndromes include general somatic symptoms, sleep disturbance, gastrointestinal symptoms and affective symptoms. Rare effects of discontinuation of antidepressants include akathisia, parkinsonism, cardiac arrhythmias, panic attacks and delirium. A worsening of depression, or seizures, very rare.
Control variables	N/A, survey of many different opinions and anecdotal reports.
Summary of results	Discontinuation syndromes start within a few days of stopping the medication. Most require no treatment but some can be serious.
Drug	Some antidepressants that have been reported as causing discontinuation symptoms: **- Tricyclics and related compounds (TCA):** amineptine, amitriptyline, amoxapine, clomipramin, desipramine, doxepin, imipramine, nortripyline, protriptyline, trazodone. **- Monoamine oxidase inhibitors:** isocarboxazid, phenelzine, tranylcypromine. **- Selective serotonin reuptake inhibitors (SSRI):** citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline. **- Miscellaneous antidepressants:** venlafaxine, nefazodone, mirtazapine.
Reason for medication gap	Various forms of discontinuation, including trial-induced treatment interruption, random medication trials, placebo-controlled efficacy studies.
Harm occurred after...	Surveyed studies generally looked at a medication gap of around a week.
Level of harm	1

Study 7	Changes in medication associated with epilepsy-related hospitalisation: a case-crossover study
Author, year	**Handoko et al 2007**
Pathology	Epilepsy
Type of study	Case-crossover study, using a conditional logistic regression analysis
Sample size	1185 patients with a first epilepsy-related hospitalisation (from Dutch PHARMO Record Linkage System between 1998 and 2002); of which 352 had used at least one antiepileptic drug before hospitalisation, of which **217** met the 'continuous use' criteria.
Independent variable	Changes in antiepileptic drugs, changes in interacting co-medication and changes in non-interacting co-medication.
Dependent variable	Risk of epilepsy-related hospitalisation.
Control variables	Because each patient served as his/her own control (a patient's outcomes were compared to his/her outcomes in previous periods), there was no need to control for factors such as education, lifestyle, etc. Control moments were introduced for hospital admissions for cerebrovascular diseases, neurological diseases and trauma, because recent hospitalisation with potential seizure-related events were considered a possible confounding factor.
Summary of results	Discontinuation showed a trend towards an increased risk of hospitalisation (OR: 2.57; 95%CI: 0.81-8.17) among patients admitted to hospital, comparing medication use in the 28 days before the admission with medication use in four earlier 28-day periods.
Drug	Antiepileptic drugs.
Reason for medication gap	Any form of discontinuation of medication.

Study 7	Changes in medication associated with epilepsy-related hospitalisation: a case-crossover study
Harm occurred after...	28 days
Level of harm	3

Study 8	Effects of Daily Adherence to Antihypersensitive Medication on Blood Pressure Control
Author, year	**Rose et al. 2011**
Pathology	Hypertension
Type of study	Randomised trial; comparing blood pressure readings using a Medication Events Monitoring System (MEMS). Blood pressure of those with seven days of excellent adherence (100%) was compared with those with seven days of poor adherence (60%).
Sample size	869 patients; of which 689 completed the study; of which 249 had at least 2 clinic visits with blood pressure readings; of which 210 consistently took one dose a day for the first 90 days of the study; of which **200** were not excluded for not understanding the MEMS.
Independent variable	Adherence to therapy (as measured by number of times MEMS cap on bottle has been opened)
Dependent variable	Clinical blood pressure measurements (at irregular intervals)
Control variables	Sex, self-reported race and age at study inception. Whether the patient had cerebrovascular disease, congestive heart failure, chronic kidney disease, coronary artery disease, diabetes mellitus, hyperlipidemia, obesity or peripheral vascular disease (all of which could impact on blood pressure, the use of antihypersensitive medication or the perceived urgency of controlling hypertension).
Summary of results	BP following 7 days of excellent adherence was between 12/7 mm Hg and 15/8 mm Hg lower than after 7 days of poor adherence.
Drug	Antihypertensive medication
Reason for medication gap	Self-induced non-adherence.
Harm occurred after...	7 days
Level of harm	1

6.4 Methodology: Dispenser Survey

Considering the limited evidence base, the dispenser survey, aimed at pharmacists across the seven Member States, has been an important tool to better understand the potential problems and underlying problem drivers associated with dispensing foreign prescriptions. Considering the importance of this part of the study and the fact that survey work traditionally suffers from poor response rates we have taken a number of steps to mitigate potential problems.

- **Survey Length:** In total the survey encompasses 56 questions (8 pathologies, 7 countries, 2 prescriptions per pathology and country – one commonly prescribed and one rarely prescribed.) To keep the length of the survey manageable for individual respondents, each pharmacist receives a shorter and tailored version with only a few background questions and a total of six prescriptions (one from each other Member State).

Table 23: Pathology/Country Constellation for Dispenser Survey

		Prescriber						
		DE	DK	EL	FR	NL	PL	UK
Dispenser	DE		Asthma	COPD	Depression	Diabetes	Epilepsy	Hypertension
	DK	COPD		Depression	Diabetes	Epilepsy	Hypertension	IHD
	EL	Depression	Diabetes		Epilepsy	Hypertension	IHD	RHEUM
	FR	Diabetes	Epilepsy	Hypertension		IHD	RHEUM	Asthma
	NL	Epilepsy	Hypertension	IHD	RHEUM		Asthma	COPD
	PL	Hypertension	IHD	RHEUM	Asthma	COPD		Depression
	UK	IHD	RHEUM	Asthma	COPD	Depression	Diabetes	

- **Questionnaire Design:** Following consultations with the PGEU and its national associations of countries included in this study, the research team made a conscious decision not to engage in any form of 'mystery shopping'. The concern was that pharmacists would be reluctant to engage with the research in such a way that could raise questions of professional liability. The research team thus opted to engage with pharmacists in their capacity as experts rather than as practitioners. To this end we ask pharmacists to what extent they would expect a variety of factors to cause problems as regards dispensing the prescription. Furthermore, we include a text box at the end of each multiple-choice question to allow respondents space to elaborate on their answers.

- **Stakeholder Buy-In:** The project manager presented the study at the Annual General Assembly of the PGEU in Berlin on 21 June 2011. With the aim to talk to each of the relevant national representatives individually at the side-lines of the conference, the purpose of this exercise was to maximise stakeholder buy-in and facilitate access to national pharmacists.

- **Validation of the Questionnaire:** Key representatives of the national pharmacists associations were provided with information packs during the abovementioned PGEU General Assembly. The information packs included a copy of the survey questionnaire. Representatives were asked to validate and/or provide comments on the content of the questionnaire to ensure that the information that appears in the survey is correct.

- **Translation:** The survey has been translated into the official language of each of the seven Member States to make it more accessible to local pharmacists who may not speak English.

The survey ran between July and August 2011; with several reminders sent out by the national associations.

Survey Responses

Each individual survey answ ered by pharmacists consisted of general questions on place of employment, profession and experience with foreign[59] prescriptions. Furthermore, each survey asked about possible dispensing problems associated with twelve different drugs (with one drug perceived to be commonly available across the EU (A) and one drug perceived to be less commonly available across the EU (B) for each of six pathologies). Each survey thus corresponded to twelve possible prescription responses. Across the seven targeted countries, 996 pharmacies responded to the survey. This amounts to 11,952 prescription observations.[60]

Table 24: Pharmacists responding; corresponding prescription numbers; prescriptions by drug type and pathology

Dispensing Country	Responses	Prescriptions	Common drug (A)	Uncommon drug (B)	Arthritis	Asthma	COPD	Depression	Diabetes	Epilepsy	Hypertension	IHD
DE	20	240	120	120		40	40	40	40	40	40	
DK	54	648	324	324			108	108	108	108	108	108
EL	1	12	6	6	2			2	2	2	2	2
FR	122	1464	732	732	244	244			244	244	244	244
NL	390	4680	2340	2340	780	780	780			780	780	780
PL	383	4596	2298	2298	766	766	766	766			766	766
UK	26	312	156	156	52	52	52	52	52			52
Total	996	11952	5976	5976	1844	1882	1746	968	446	1174	1940	1952

In order to encourage more responses, not all pharmacists were given questions on all eight pathologies – the pathologies were divided up between countries. Because of this, the **number**

[59] Note that 'foreign' refers to 'from another EU Member State' throughout this section.
[60] One additional response, targeted at the Netherlands but answered by a pharmacist working in Belgium, was omitted from the sample due to Belgium not being a country of interest here. There were generally very few occasions of respondents stating a different country of work than the country the questionnaire was targeted towards (e.g. some Poles working in the UK, some Dutch working in France). These observations were included in the country of work's sample, rather than in the target country's.

of prescription responses varies by country and by pathology, with the fewest prescription responses obtained on Diabetes (446, primarily because of low response rates in Germany, the UK and Germany), and the most prescription responses obtained for IHD (1952). Nevertheless, the prescription numbers for all pathologies represent **sample sizes sufficient for a degree of statistical inference.**

Whilst the vast majority of pharmacists responded to questions related to place of work, profession and experience with foreign prescriptions (see below), some chose not to answer questions on the dispensing of a certain drug type, and some chose only to answer some questions on certain drug types (see below for an explanation of the seven questions). A prescription response was only useful for our study if one or more dispensing questions were answered on that drug. **Of the 11952 prescription responses, 4512 (38%) were not suitable, because all seven questions were left blank for that drug**. The sample size for the evaluation of whether drugs are dispensed or not therefore consists of the **7440 suitable prescription responses.**

The proportion of suitable responses does vary by pathology, but barely varies by A/B drug type. The fact that many fewer pharmacists commented on the dispensing of depression versus asthma drugs many in itself be an indication of less knowledge associated with dispensing depression drugs, rather than asthma drugs and thus a lower propensity to dispense. Therefore, estimates of non-dispensing probabilities based on suitable responses may be **biased downwards:** those who did not respond are probably more likely to *not* dispense a drug than to be happy with dispensing drugs prescribed by foreign prescriptions. This hypothesised effect, however, unfortunately cannot be quantified to a meaningful degree or taken into consideration in the systematic analysis.

Table 25: Percentage of responses suitable, by drug type and pathology

	Total	A drugs	B drugs	Arthritis	Asthma	COPD	Depression	Diabetes	Epilepsy	Hypertension	IHD
% of responses suitable	62%	62%	62%	57%	73%	68%	52%	57%	69%	59%	58%

These numbers must be regarded in the context of how many pharmacists were originally contacted. According to estimates provided by the national pharmacy organisations, which were given responsibility for circulating the surveys, the following number of organisations was contacted:

Table 26: Absolute response rate, by dispensing country[61]

Dispensing Member State	Pharmacists contacted (approx.)	Approximate Response Rate
DE	17 state pharmacy chambers and 17	N/A

[61] Still awaiting responses for Denmark.

Dispensing Member State	Pharmacists contacted (approx.)	Approximate Response Rate
	state pharmacy associations[62]	
DK	N/A	N/A
EL	none	N/A
FR	Community Pharmacist Owners, Employed Community Pharmacists, Pharmacists working overseas[63].	N/A
NL	3000	13%
PL	5000	8%
UK	1000[64]	2.6%

Survey Evaluation Methodology

As outlined above, survey participants were asked the same seven questions about whether any particular action or circumstance would 'definitely not' (0), 'unlikely' (1), 'likely' (2) or 'definitely' (3) cause a problem in dispensing a particular drug.[65] These were:

- Verifying the authenticity of the prescription
- Verifying the prescribing physician
- Language in which the prescription is written
- Prescription written by hand
- Not all the information you need is written on the prescription
- Access to the correct drug/device
- Access to alternative drug or device if the one on the prescription is unavailable

These answers were coded from 0 to 3, respectively. In order to obtain a measure for general availability of any one medicinal product via a prescription from another EU country, a mean average of these codes was taken for each prescription response (any of the seven questions not answered were disregarded for the average, if all seven questions were not answered, the mean average was not calculated at all for that prescription response – as highlighted above, this was the case for 38% of all prescription responses), with a higher average denoting a higher probability of the drug not being dispensed due to problems associated with parts of the dispensing process. This was a value judgment which effectively considers **each of the seven criteria equally important in determining dispensing a drug.**

Alternative Methodologies

Note that this continuous probability measure is essentially **equivalent to a discrete threshold probability measure**. In the latter case, a binary 'dispensed' or 'not dispensed' conclusion could be reached for each prescription response, according to the proportion of 'definitely not'

[62] The German pharmacy organisation was not able to provide an estimate of how many pharmacists it contacted exactly, because this was up to the discretion of the heads of the named groups.
[63] The French pharmacy organisation was not able to provide an estimate of how many pharmacists it contacted exactly, because this was up to the discretion of the heads of the named groups.
[64] Emails to 6000 addresses were sent, but many of these are old or un-used. The pharmacy association estimated that for any given mailing, around 1000 emails were actually opened.
[65] Note that the codes referred to throughout this report have been rescaled from the original coding mechanism (0 – 4, where 0 represented 'don't know'). This was in order to use the codes to calculate a continuous probability measure and to remove confusion over whether a 'don't know' answer was different from a blank response. This initial coding mechanism is not mentioned elsewhere in the report, and all references to codes or a 0-3 scale solely apply to the new coding system.

(0), 'unlikely' (1), 'likely' (2) or 'definitely' (3) responses. If the proportion of each of the four responses is multiplied by the 0-3 value of the response, this is just an alternative way of obtaining the average code. If a **threshold level** is set, above which the average code is deemed to be high enough to justify a 'not dispensed' conclusion and below which 'dispensed' is concluded, the proportion of 'not dispensed' should signify the overall probability of not being dispensed. Setting this threshold at 1.5 (half-way through the code range, which is reasonable) means 56% of all prescription responses are deemed 'not dispensed', which is essentially the same figure as the continuous measure.

Importantly, as the below section outlines, because of the clustering of scores and probabilities around the middle, **assuming that only the extremely high scores imply non-dispensing is an inaccurate way of depicting the actual probability, skewing the estimate towards a higher probability of being dispensed**. A continuous probability measure, which takes into account the fact that many of the responses clustered around the middle of the distribution lead to drugs **not** being dispensed, is therefore a **more accurate method of finding the probability.**

6.5 Methodology: Foreign Prescription Extrapolations

The quantitative analysis highlighted two headline results approximating pharmacists' experience with foreign prescriptions:

- A **point estimate** of 1.46 foreign prescriptions per pharmacy per month; and
- A **range estimate** of between 50,206 and 351,762 foreign prescriptions across the six targeted countries per month.

The different methodologies leading to these two results are outlined above. The below table provides a detailed arithmetic overview of how these monthly results for six countries were:

- Extrapolated across the EU; and
- Calculated on an annual basis.

Table 27: Overview of calculation of EU and annual foreign prescription results

Point Estimate, targeted countries			
	Monthly Foreign Prescriptions per Pharmacy	**EU6 Monthly Foreign Prescriptions**	**EU6 Annual Foreign Prescriptions**
Transformation	*from earlier analysis*	*multiply by 69,778 (number of pharmacies)*	*multiply by 12 (months in a year)*
Result	**1.4632**	**102,096.14**	**1,225,153.63**
Point Estimate, EU			
	EU6 Monthly Foreign Prescriptions	**EU27 Monthly Foreign Prescriptions**	**EU12 Annual Foreign Prescriptions**
Transformation	*multiply by 69,778 (number of pharmacies)*	*divide by 52.5749, multiply by 100 (52.5749% of all prescriptions in EU6)*	*multiply by 12 (months in a year)*
Result	**102,096.14**	**194,191.78**	**2,330,301.39**

Range Estimate, targeted countries			
		EU6 Monthly Foreign Prescriptions	**EU6 Annual Foreign Prescriptions**
Transformation		*from earlier analysis*	*multiply by 12 (months in a year)*
Lower Bound		**50,206.27**	**602,475.28**
Upper Bound		**351,762.03**	**4,221,144.33**
Range Estimate, EU			
	EU6 Monthly Foreign Prescriptions	**EU27 Monthly Foreign Prescriptions**	**EU12 Annual Foreign Prescriptions**
Transformation	*from earlier analysis*	*divide by 52.5749, multiply by 100 (52.5749% of all prescriptions in EU6)*	*multiply by 12 (months in a year)*
Lower Bound	**50,206.27**	**95,494.76**	**1,145,937.10**
Upper Bound	**351,762.03**	**669,068.37**	**8,028,820.46**

6.6 Methodology: Additional Stakeholder Consultation

In addition to the dispenser survey and several discussions with members of the PGEU, we also actively sought the input of prescribers on this issue – with varying degrees of success. We invited representatives of relevant organisations (e.g. European Medical Association) to a workshop at the end of September. The objective of the workshop was to discuss the following questions:

- **Validation of Research Findings (Problem Definition):** We would like to discuss the survey outcome with the participants to see whether the results resonate with them.

- **Discussing Possible Impacts of Medication Errors (Impact Analysis):** We would like to use this forum to explore questions on possible implications of medication errors for patient safety and therapeutic effectiveness with medical experts in break-out sessions.

- **Testing Model Assumptions (Impact Analysis):** We would like to present and discuss our assumptions surrounding the economic model for estimating the impact of medication errors on therapeutic effectiveness and patient safety.

Because of the low number of participants who registered for the workshop, we have decided to cancel it. In its place and as a sign of gratitude for all the help PGEU and its members had provided with the survey, we organised a breakfast meeting to discuss and reflect on the survey results. Prescriber views were sought during individual discussions.

6.7 Methodology: Economic Modelling

To attain the economic model which combines the estimates on non-dispensing with the estimates on foreign and total prescriptions and attempts to estimate harm costs, we required the following further information:

- Number of total foreign prescriptions
- Cost of visiting local practitioner

Cost of Visiting Local Practitioner

Assumptions

- It was assumed that every patient who does not receive his/her drug dispensed subsequently goes to a local GP to receive a domestic prescription within three days.
- The main component of GP visit costs is the GP's salary.
- Average GP salaries across 8 EU Member States correspond to average salaries across the entire EU.

Because of this assumption, the cost of a GP visit needed to be factored into the total harm costs of non-dispensing. There is no systematic EU-wide evidence on the cost of an average GP visit. Whilst a widely-used figure within the UK is £36 for a 12 minute consultation (estimated by PSSRU, http://www.pssru.ac.uk/pdf/uc/uc2011/uc2011.pdf), this is likely to be above the EU average, i.e. not implementable as a reliable EU estimate.

Because the main component of GP visit costs is GP's salaries, a way in which to proxy a more reliable EU-wide estimate for GP visit costs is to weight the £36 according to how far above the EU average UK GP salaries are. The below table depicts OECD data on GP salaries in 8 Member States[66] and WHO 'Health for All' Database data[67] on the number of GPs across the EU.

Table 28: Calculation of weighted EU8 Average Salary

Country	Number of GPs	Proportion of total	Average salary (1000 US$, PPP)	Proportion * Salary = Weight
AT	12979	0.05	108	5.75
CZ	7366	0.03	39	1.18
FI	5453	0.02	56	1.25
FR	103349	0.42	84	35.59
DE	53549	0.22	112	24.59
LU	286	0.00	108	0.13
NL	11741	0.05	120	5.78

[66] http://www.oecd.org/dataoecd/51/48/41925333.pdf. Data for other member states were not available.
[67] http://data.euro.who.int/hfadb/

UK	49184	0.20	121	24.40
EU8 Total	243907			
Weighted EU8 Average Salary (1000 US $ PPS)				98.66

In order to calculate the average salary across the countries for which data were available, the individual average salaries were weighted according to each country's proportion of total GPs The weighted average EU8 average salary was $98,660, implying that the average UK GP earns around 125% of the average EU GP (if we consider the average EU8 salary to be applicable to the entire EU). Consequently, the EU GP visit cost estimate was weighted down by 25%, to £28.80, or around €34[68].

Model Calculation

The above-mentioned assumptions, calculations and estimates were consolidated into an economic model for the six member states (which was based on the 102,096 foreign prescriptions a month figure) and for the EU as a whole (which was based on the 194,192 foreign prescriptions figure). The steps for the 6 Member State model are outlined in detail below.

1. Calculate number of cases in which foreign prescription is not dispensed (.55 * 104,096)
2. Multiply by unit cost per visit to a local physician (€34)
3. Extrapolate to EU27 based on the number of pharmacies and associated prescriptions for six Member States.

[68] Exchange rate 1 GBP = 1.18 EUR, 22 December 2011

6.8 Explanation and Justification for Adjustments in Methodology

Project Steps	Original Tender	Our Suggestions	Justification for Adjustment (March 2011)	Justification for Adjustment (November 2011)
Scoping (especially on drugs/devices)	Delphi I	Evidence Review Expert/Client Consultation	As is illustrated in the report, we were able to obtain the information on drugs/devices through evidence review guided by our in-house health experts. We will test our findings in the 1st round of prescriber survey. From experience we know how difficult it can be to have stakeholders engage in a Delphi survey. Delphi surveys tend to suffer from low response rates. Since this information is reliably available elsewhere, we suggested saving the stakeholder engagement in Delphi form for other parts of the study.	
Problem Definition	Dispenser Survey	Prescriber Survey (2 Rounds) Dispenser Survey (Dispensers)	In addition to the dispenser survey, we suggest to include two rounds of prescriber surveys to seek stakeholder engagement on the problem definition. As part of the 1st round of the prescriber survey we will ask respondents to validate our shortlist of drugs and devices (see section above).	Despite numerous attempts (initial prescriber survey launched in March and workshop planned for the end of September); prescribers have been exceptionally reluctant to engage with this study. We encountered two problems; firstly, most of the specialists we contacted were not willing to participate in the interview. Secondly, those prescribers that we had a chance to talk to were unable to provide us with any reliable answers, specifically as regards the impact analysis, leaving us concerned how this might affect the robustness of the economic model on health effects. We thus consulted with our in-house economics team, specialising in health economics. They recommended basing the model on established research in the area of 'possible health effects of a delay in treatment' instead. The reviews team carried out a targeted evidence review and managed to find several academic studies - for all individual pathologies! The adjusted approach to the economic modelling has provided more credible and robust results. We are still able to feed the results of our discussions with the prescribers into the narrative of the study.
Impact Analysis	Delphi II	Expert Workshop Economic Modelling	There should not be any variation in medical opinion as to the expected effect of using a drug (i.e. a doctor from Poland should come to the same conclusion as a doctor from the UK what the expected effect of x dosage of y drug would be on person, all else equal). We therefore propose to explore question on possible implications of medication errors for patient safety and therapeutic effectiveness with medical experts in a workshop in Brussels, rather than a Delphi Survey. Following the workshop, we will write-up the results and send these to all participants, asking them whether they would like to review their opinion in light of the aggregate findings. This methodology in essence keeps the notion of a three-round Delphi.	

6.9 Overview Workplan

	Phase I: Scoping	Phase II: Problem Definition	Phase III: Impact Analysis
Tasks/Activities	**Internal Kick-Off Meeting** **Finalising Methodology** **Evidence Review/Desk Research (Study Scope)** **Initial Survey Preparations**	**Evidence Review (Problem Definition)** **Survey Preparations** **Prescriber Survey** **Presentation at PGEU General Assembly (June 2011)** **Dispenser Survey** **Analysis of Survey Results** **Economic Modelling Problem Size**	**Evidence Review (Impact of Medication Errors)** **Preparation Breakfast Meeting** **Economic Modelling (Cost of Medication Error)** **Final Analysis/Report Writing**
Client Interaction	**External Kick-Off Meeting;** **Inception Report Review meeting**	**Several Informal Meetings** **Interim Report Review Meeting**	**Breakfast Meeting** **Draft Final Report Review Meeting**
Deliverables	**Inception Report (late February)** **Revised Inception Report (late March)**	**Interim Report (early August)**	**Draft Final Report (mid- November)** **Final Report (mid/late December)**
Timing	2 months	8 months	12 months