



Patient Safety and Comfort

The Challenges of Switching Medicines

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Executive Summary

Health technologies and medicines are today more advanced and sophisticated than ever before. Highly targeted and even personalised therapies (particularly biologic drugs) are revolutionising the treatment of many life-threatening and chronic illnesses such as diabetes, cardiovascular conditions, cancer and autoimmune diseases. This greater utilisation of pharmaceuticals (and longer periods of use) means that more patients in North America and the EU are, in one way or another, dependent on medicines and medical treatments. Indeed, by most estimates the global use of prescription drugs is set to increase rapidly, with more patients taking more medicines for longer periods of time. In the US, for instance, prescription drug spending is set to almost double by 2017. While the health benefits of this are undeniable, the cost and the therapeutic and safety implications raised by this rise in demand, choice and utilisation are quite serious. One important issue this raises is the practice of switching patients between different medicines or medical therapies and/or using different therapies interchangeably. The introduction of biosimilar drugs – and whether or not regulators should treat these in the same way as they do chemically-based generic drugs – further complicates matters for prescribers and patients alike.

This paper outlines how therapeutic switching and interchange has gained traction in many countries and is becoming a key tactic for local and national healthcare bodies in implementing more cost-effective prescription policies. In the five surveyed countries – the US, Canada, the UK, Spain and Sweden – switching and substitution policies are being actively used to limit rises in pharmaceutical expenditure and to streamline prescription practices. The way in which switching policies are being implemented varies a great deal between the surveyed countries and depends largely on the design of their respective healthcare systems. For example, the fragmentary nature of the American healthcare system means that a variety of healthcare actors, ranging from the central government and state governments to private health insurers, all, in one form or another, shape the formulation and implementation of therapeutic interchange policies. In the UK the decentralised nature of healthcare delivery (largely in the hands of local Primary Care Trusts) and the lack of clear national guidelines has resulted in a virtual postcode lottery in how switching takes place.

Whether switching takes place as part of a formal protocol or based on the discretion of a patient's physician, it has many benefits and risks. It may help identify more effective and sometimes more cost-effective treatments, improving the quality of life for patients dealing with chronic conditions. But therapeutic switching may also result in undue medical risks and jeopardise the independence and preference of patients if it is not done cautiously and with the appropriate information. This is especially the case for risky patients and those that are already stabilised on a treatment regime.

In addition to switching for chemical-based medicines this paper also examines how biological drugs and, in particular, biosimilars have figured within switching and substitution policies. By and large, this paper has found that, in the surveyed countries, regulators and health policymakers have taken a much more active role with regard to formulating switching policies for biologics and biosimilars than they have with chemical-based drugs. While this finding does not mean that all surveyed countries have embraced the same policies, it suggests that

policymakers have real concerns over the switching and substitution policies for biologics and biosimilars. Indeed, many experts highlight the immunogenic potential of biologic agents, saying that this factor makes finding the most appropriate therapy a risky process. Once the best treatment is identified, switching to another biologic – whether a biologic or biosimilar – carries an unjustified risk, and thus involves a decision that must be taken carefully and based on as much information as possible. For this reason, many healthcare authorities recommend or mandate that the decision to switch a biologic must be taken by the patient's physician and many EU countries actively prohibit the automatic substitution of a biologic drug with a biosimilar.

Based on these findings, the following recommendations are intended to give policymakers an overview of how to design and implement effective and safe switching policies:

- **Patients should be made aware of any switch to their medication.** When a switch is to take place, both the advantages and disadvantages of this switch should be explained clearly. This is especially true for balanced patients, those with chronic illnesses and comorbidities, and where the switch involves a biologic or biosimilar drug. In such cases where the patient and/or physician disagree with the proposed switch, scope must be left for the patient to either appeal the decision or be allowed to make a co-payment and keep his or her original prescription.
- **The benefits and risks of therapeutic switching need to be better understood at all levels of medical practice.** This should help eliminate the wide variations in how switching is understood and implemented on the ground. For example, in the UK individual PCTs largely set switching policies themselves. This can create a postcode lottery for patients as to which medicines and treatments they can access. Information should also be improved for patients.
- **Healthcare practitioners and policymakers understand the significant risks involved with switching biologic medicines.** They must be made aware that biologics and biosimilars are a fundamentally different set of medicines from chemical-based drugs. Biosimilars are not the same as generic drugs and should be treated differently. Regulations, guidelines and educational information should be clear regarding this difference. Policymakers at all levels of health care should take caution in listing biologics as therapeutically equivalent or therapeutically interchangeable.
- **A distinction should be made between those patients who are on medication for shorter periods of time and whose medical condition requires less invasive treatment versus balanced patients whose conditions are long-term (including chronic) and require prescriptions on a daily basis over long period of time (even for life).** For the latter group establishing an effective, safe and comfortable prescription regime – i.e. achieving the objective of "balancing" the patient - is a time-consuming and arduous task. In these cases switching should only take place with the full knowledge and consent of the prescribing physician in consultation with the affected patient.

Taking these recommendations as general principles, countries and regions can form positive policies on the selection of medicines, which will help balance future medical innovation, financial pressures and patient safety and choice.

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Introduction

Health technologies and medicines are today more advanced and sophisticated than ever before. Highly targeted and even personalised therapies (particularly biologic drugs¹) are revolutionising the treatment of many life-threatening and chronic illnesses such as diabetes, cardiovascular conditions, cancer and autoimmune diseases. Indeed, patients across North America and the European Union (EU) are today making use of an increasing array of medicines and medical therapies for longer periods of time. Patients have access to a wide range of treatment options, including more effective and, in some cases, cheaper therapies. This is particularly helpful for treating chronic or long-term illnesses and those coupled with multiple conditions. Prescribers can find the right combinations, or “cocktails”, of therapies to fit the needs of individual patients. By and large, this development is a good thing. The greater utilisation of pharmaceutical drugs and treatments means that patients can live more fulfilling and productive lives than would otherwise be possible. Access to medicines has also improved. The development of a robust generics market in both North America and within the EU (as well as greater access to branded medicines for many patients) means that increasing numbers of patients are able to access pharmaceutical treatments whether they are in branded or generic form. The market for generic drugs has grown substantially over the past two decades and today generic products account for over half of all prescriptions in the United States (US) and in many European countries.

This greater utilisation (and longer periods of use) means that more patients in North America and the EU are, in one way or another, dependent on medicines and medical treatments. Indeed, by most estimates the global use of prescription drugs is set to increase rapidly, with more patients taking more medicines for longer periods of time. In the US, for instance, prescription drug spending is set to almost double by 2017. While the health benefits of this are undeniable, the cost and the therapeutic and safety implications raised by this rise in demand, choice and utilisation are quite serious. One important issue this raises is the practice of switching patients between different medicines or medical therapies and/or using different therapies interchangeably. The introduction of biosimilar drugs – and whether or not regulators should treat these in the same way as they do chemically-based generic drugs – further complicates matters for prescribers and patients alike.

Switching medicines

For most medicines and medical treatments there tend to exist several similar or alternative products. These are available either in generic or branded form and can be broken down into two distinct categories:

- i) Generic drugs, which are chemically very similar to a referenced drug², using the same active ingredient but, generally, different excipients; and

¹ The latest biologic technologies are able to move beyond merely treating the symptoms of illnesses to instead slow the progress of or even prevent disease. They are also highly selective and are familiar to the body, so that they avoid affecting healthy cells and tend to have fewer side effects than synthesised drugs.

² A referenced drug is the drug to which the generic is compared to during regulatory approval. A drug cannot receive market authorisation and call itself a generic drug unless there is an already existing treatment, a reference drug, which uses the same active ingredient and has received prior market and regulatory approval.

- ii) Therapeutically equivalent drugs, that is, those medicines and treatments which contain a different chemical structure but are viewed as having therapeutic equivalence and producing similar patient outcomes as a reference drug or treatment.

A generic product will, by definition, contain the same active ingredient as its referenced (and often branded) counterpart. Indeed, to gain market approval as a generic product, in both the US and the EU a proposed medicine or pharmaceutical treatment must contain the same active ingredient and also prove bioequivalence to an already approved reference drug.³ Generic drugs are often prescribed by physicians and health insurers as a replacement for a referenced medicine. This happens in public as well as private healthcare systems. The purpose of generic prescription is to reduce the cost of the treatment to patient and/or health provider, whether it be a private health insurer or publicly supported body.

This paper will focus on the second category of products used in switching: those deemed to have therapeutic equivalence with an originally prescribed medicine or therapy. As described above, these products can be either innovative drugs (often branded) or therapeutically equivalent generic drugs. Regardless, these products (whether they be stand-alone branded medicines or generic versions of an alternative branded drug) will have a different chemical composition and use a different active ingredient than the originally prescribed drug. By and large, these products will be viewed by prescribing physicians, health insurers or pharmacists, as being therapeutically equivalent and producing similar patient outcomes as the original prescription. The specific reasons for switching patients from one medicine or line of therapy to another that is considered therapeutically similar are varied and will be discussed in more detail below. They include the following: attempts to reduce negative side effects experienced with a baseline therapy; cost-containment (as a second therapy may appear to be cheaper than the first); or, finally, because a new, potentially more effective or comfortable version of a treatment or drug has been introduced to the market. Currently, a medical consensus exists that patients who have derived a therapeutic benefit and are physically and mentally comfortable with their medications should not be switched unnecessarily from one medicine or medical treatment to another unless there is a clear therapeutic rationale. However, the steady growth in the cost of medical care and of prescription drugs (to public healthcare systems, health insurers and patients) and the growing use of highly specific and expensive biological drugs, presents health and clinical policymakers with a new set of challenges when it comes to finding the most appropriate therapy mix.

In addition, a third category of drugs have been introduced to world markets: biosimilars. Biosimilars are neither generic drugs nor completely new biological drugs and their existence raises a host of regulatory and patient safety concerns. This paper will describe some of the key issues relating to biosimilars and how regulators in North America and the EU are incorporating them into their national switching, substitution and prescribing practices.

This paper will introduce the practice of therapeutic switching to a public policy audience. The purpose is to describe what this practice is; what its benefits are to patients, insurers and health policymakers; and what

³ Bioequivalence is a testing procedure measuring the rate at which a medicine is taken up into the blood stream following intake.

some of the consequences (actual and potential) are to patients in North America and the EU. The paper will describe the practice of switching, discuss the different contexts in which the practice may occur and analyse associated benefits and risks. In addition, it will explain the different approaches and guidelines existing in North America and in the EU. Currently, there are very few centralised national guidelines for therapeutic switching issued by a government, except for biosimilars for which there are mostly clear national and even supra-national standards and guidelines. Instead, there is a mix of individual best-practice models and policy guidelines issued by physicians, hospitals, health insurers, patient associations, local and regional healthcare providers, and national health services. From this overview of the existing guidelines in North America and a sample of EU countries, the paper will provide guidance on how patient safety and comfort can be balanced with medical innovation and sustainable healthcare systems. Finally, this paper will explore how policymakers can best understand and shape drug policies that accommodate future medical innovation (particularly in the field of biotechnology), which ensure maximum patient comfort and safety, and which are financially sustainable over the longer-term.

Section I: Introducing and defining therapeutic switching

Therapeutic switching encompasses a host of different medical practices and decisions. For the purposes of this paper, it will generally refer to practices that involve switching patients between therapeutic alternates. That is, those medicines and pharmaceutical treatments which are chemically distinct – and may also have different structures and mechanisms of action – but which can usually be expected to have similar therapeutic effects and risks, that is, toxicity and drug reaction.⁴ (Therapeutic alternates are also sometimes known as therapeutic equivalents.) The following section will not focus on the practice of switching patients from a branded drug or treatment to its generic counterpart, also known as therapeutic substitution. While this is a common form of switching implemented by many public health bodies in Europe, North America and beyond, switching between a branded drug and its generic counterpart still involves administering a medicine or treatment that contains the same active ingredient. Instead, the following section – and this paper – concentrates on the switching that involves therapeutically equivalent products, that is, those products which contain *different* active ingredients. Apart from purposes of definition, generic drugs will be included in the analysis only when they are categorised as a therapeutically equivalent treatment.

1.1 Introducing the topic: defining therapeutic interchange and switching

The following extract, from a 2007 article in *Managed Care Magazine* on the use of therapeutic interchange with biologics, provides a good working definition of switching or, as it is known in the US, therapeutic interchange:

Therapeutic interchange is the practice of switching or dispensing drugs that are chemically distinct but therapeutically similar in terms of their efficacy, safety, and tolerability profiles. The stated goal of therapeutic interchange is to achieve an improved or neutral outcome with the new agent while reducing overall treatment costs.⁵

Definitions used by professional healthcare bodies, like the American Medical Association (AMA) and the American College of Clinical Pharmacy (ACCP), are similar to the above. The ACCP views therapeutic interchange as “the dispensing of a drug that is therapeutically equivalent to but chemically different from the drug originally prescribed by a physician or other authorized prescriber”.⁶ These drugs “may differ in chemistry or pharmacokinetic properties, and may possess different mechanism of action, adverse-reaction toxicity, and drug reaction profiles”, but in most cases the interchanged drugs have “close similarity in efficacy and safety profiles.”⁷

⁴ American Medical Association (AMA), “Impact of Drug Formularies and Therapeutic Interchange on Health Outcomes: Report 2 of the Council on Scientific Affairs”, 2004, <http://www.ama-assn.org/ama/no-index/about-ama/13675.shtml> (Accessed 4 December 2009).

⁵ Flood, J., Mihalik, C., Fleming, R., Strober, B., Zucker, D. & Burgoyne, D., “The Use of Therapeutic Interchange for Biologic Therapies”, *Managed Care Magazine*, January 2007, p. 51. http://www.managedcaremag.com/archives/0701/0701_peer_switch.html (Accessed 8 April 2010).

⁶ American College of Clinical Pharmacy (ACCP), “ACCP Position Statement, Guidelines for Therapeutic Interchange 2004”, p. 1667, http://www.accp.com/docs/positions/guidelines/Pharm2511_ACCP-TherapIntchg.pdf (Accessed 8 April 2010).

⁷ Ibid.

As mentioned above, therapeutic substitution, on the other hand, involves the switching and substitution of medicines that are “chemically equivalent products”.⁸ For example, cases in which pharmacists automatically interchange a therapeutic alternate with another, without consulting the physician, are known as therapeutic or automatic substitution.⁹ Automatic substitution tends to occur as part of the protocol of third-party payers for ambulatory (not hospitalised or bedridden) patients. It commonly involves substituting a generic drug for a branded drug, also known as generic substitution.¹⁰ Indeed, the most common example of therapeutic substitution would be the substitution of a branded product with its generic counterpart. This can involve automatic substitution, that is, a policy of automatically substituting branded pharmaceutical drugs with their generic counterparts once a generic is made available and has passed all relevant market approval requirements. Such a policy of automatically substituting a prescribed medicine for its cheapest counterpart – unless explicitly negated by the prescribing physician – exists in Denmark’s public healthcare system, and is currently being reviewed for implementation by the Department of Health in the UK.¹¹ It is important to note this difference between therapeutic or automatic substitution and therapeutic interchange. The AMA, in a 2004 report on the impact of drug formularies and therapeutic interchange on health outcomes, drew a clear distinction between therapeutic interchange and therapeutic substitution, viewing the former as the “authorized exchange of therapeutic alternates in accordance with previously established and approved written guidelines or protocols within a formulary system”.¹² As these examples suggest, most definitions of therapeutic interchange do not include the practice of therapeutic substitution, that is, of switching patients between products that use the same active ingredient.

1.2 Therapeutic switching in North America and Europe – a brief overview

In the United States therapeutic interchange is a very common practice. One study found that, on average, close to 90% of hospitals – including teaching, non-teaching and investor institutions – had established therapeutic interchanges in their drug formularies.¹³ This survey of 463 hospitals – all of which were major institutions with a bed capacity at or above 100 beds – found that 88% of teaching, 89% of nonteaching, and 100% of investor-owned hospitals had established therapeutic interchange policies and procedures.¹⁴ Furthermore, 88% of these hospitals reported the use of therapeutic interchange as a means of formulary management.¹⁵

In Canada, the use of therapeutic interchange and substitutions mainly takes place at the provincial level. For example, in 2003 British Columbia implemented a program of therapeutic interchange (confusingly called Therapeutic Substitution) which restricted coverage for three widely used proton pump inhibitors (PPIs); PPIs

⁸ Flood, J. et al (2007), p. 53.

⁹ AMA (2004).

¹⁰ National Consumers League (NCL), “Therapeutic Substitution”, 2008, <http://www.nclnet.org/health/switching/index.htm> (Accessed 7 December 2009).

¹¹ For the particulars on Denmark’s system of automatic substitution see: Laegemiddel Styrelsen (Danish Medicines Agency) webpages <http://www.laegemiddelstyrelsen.dk/1024/visLSArtikel.asp?artikelID=645>. For further details about the Department of Health’s review of automatic substitution see: http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_110517 (Accessed 8 April 2010).

¹² AMA (2004).

¹³ Schachtner, J., Guharoy, R., Medicis J., Newman N. & Speizer R., “Prevalence and cost savings of therapeutic interchange among US hospitals”, *American Journal of Health System Pharmacists*, Vol. 59, No. 6, 2002, Abstract.

¹⁴ Ibid.

¹⁵ Ibid.

are used for the treatment of gastric-related illnesses such as dyspepsia and peptic ulcer disease. The project restricted medical coverage to just one PPI, rabeprazole, and imposed a mandatory out-of-pocket expenditure for patients' continued use of the more expensive and more widely used PPIs omeprazole, pantoprazole and lansoprazole.¹⁶ This program resulted in a broad shift away from the more expensive PPIs, with patients making increased use of rabeprazole. Whether or not this resulted in an actual overall cost-saving for the healthcare system and better patient outcomes is still being debated. Some commentators have argued that the project actually increased overall healthcare utilization by the patients who were switched and thus resulted in an overall rise in health costs.¹⁷

Within the EU, therapeutic interchange is often referred to simply as drug switching. In the UK, local health authorities known as Primary Care Trusts (PCTs), are largely responsible for designing drug switching schemes. PCTs play a crucial role in both the delivery and commissioning of healthcare services for the UK's National Health Service.¹⁸ Currently, there are 150 Primary Care Trusts and collectively they spend 80% of the NHS's annual budget, which now exceeds £100billion. Over the last few years PCTs have increasingly promoted drug switching policies as a way of reducing local healthcare expenditure and overall cost. Local general practitioners (GPs) – the gatekeepers and first point of contact for patients within the UK's system of health care – have been pressurised to change their prescribing practices to include more switching. In this regard switching does not necessarily include generic substitution or prescribing, but simply the switching of one drug to another that is viewed as therapeutically equivalent. Recent examples include wide-spread switching of statins from atorvastatin to simvastatin.¹⁹ Switching is also quite common in Spain, particularly at the local hospital level. As with the UK, Spanish switching policy is heavily influenced by the nature and design of its overall healthcare system. Thus switching policy is largely in the hands of regional governments, hospitals and providers. In other parts of the EU, switching is relatively common, but, as Section 2 will illustrate, switching programs and policies vary from country to country as there are currently no EU-wide guidelines.

1.3 Therapeutic switching in practice

As therapeutic interchange and switching involves the switching from one chemically distinct medication to another chemically distinct medication or pharmaceutical treatment, it is often the result of a change in pharmaceutical formularies. Indeed, switching often involves the redesign of a pharmaceutical formulary to either replace an existing preferred medication or pharmaceutical treatment or rearrange an existing tiered list of treatments. Pharmaceutical formularies are lists of what medicines and treatments are to be prescribed and used for specific illnesses and diseases. Drug formularies, which often include therapeutic switching systems, are used firstly to manage complex drug therapies used in hospitals and other healthcare organisations; secondly, to address the multiplicity of therapy options; and, finally, to control drug costs.²⁰ They are used

¹⁶ Schneeweiss, S., Maclure, M., Dormuth, C., Glynn, R., Canning, C. & Avorn, J., "A therapeutic substitution policy for proton pump inhibitors: clinical and economic consequences", *Clinical Pharmacology and Therapeutics*, Vol. 79, No. 4, April 2006, pp. 379-88, Abstract.

¹⁷ Skinner, B., Gray, J. & Attara, G., "Increased health costs from mandated therapeutic substitution of proton pump inhibitors in British Columbia", *Alimentary Pharmacology and Therapeutics*, Vol. 29, No. 8, pp. 882-891, Abstract.

¹⁸ For details of the role of PCTs see: <http://www.nhs.uk/NHSEngland/thenhs/about/Pages/authoritiesandtrusts.aspx> (Accessed 8 April 2010).

¹⁹ See: Wadehra, R., "PCTs widen scope of drug switch scheme", *Pulse Magazine*, 6 September 2007, <http://www.pulsetoday.co.uk/story.asp?storycode=4114383> (Accessed 8 April 2010).

²⁰ AMA (2004).

frequently by hospitals, healthcare trusts, health insurers, and any final payer of healthcare services. These include hospitals, local or regional healthcare trusts, health insurers or publicly operated healthcare payers and providers such as the Veterans Health Administration (VHA) in the United States. Depending on the type of healthcare organisation, the onus to interchange one drug for another may be on physicians or on pharmacists, the latter being based on protocols developed and overseen by internal or external pharmaceutical and therapeutics committees. While there are distinct national and regional variations in place (which will be explored in more detail in Section 2) generally, therapeutic interchange and switching policies are developed and implemented within each individual healthcare organization by specific committees, such as a pharmacy and therapeutics committee or, as in the UK, by PCTs.²¹

Formulary changes and decisions on drug switching take place both in hospital settings (affecting the treatment of patients needing immediate or emergency care) and within the primary care sector and more long-term based care. Therapeutic interchange and switching can involve healthcare providers recommending a switch in treatment based on individual patient requirements, such as an adverse reaction or emerging evidence on the risks of the baseline treatment, in which case the patients' feedback and relationship to his or her physician plays a key part in the switch. But the most common and institutionalised forms of therapeutic interchange and switching involve the collaboration of medical staff – often including pharmacists, physicians and other health professionals – who develop guidelines or lists of preferred drugs.²² These guidelines and lists are based on drugs that are found to work most effectively for a given population or are the most cost-effective among other therapeutically equivalent drugs. Such formularies are a relatively straightforward way for healthcare bodies to manage their drug costs. For instance, formulary systems, particularly tiered plans, are commonly used by many third-party payers, such as managed care organisations to help manage healthcare costs. Critics of drug switching and therapeutic interchange warn that quality of care and patient outcomes can suffer under an extensive use of either policy. In their view, the use of switching and therapeutic interchange risk over-emphasising cost-containment at the expense of quality of care and patient-physician contact. This is especially the case if pharmacists have the authority to interchange a prescribed drug with a preferred or generic drug. (These concerns over the risks with switching and therapeutic interchange will be discussed below in a separate section on the risks and benefits of switching and therapeutic interchange.) Whether or not a given switch of drugs or therapeutic interchange is pursued primarily because of cost or clinical considerations will vary from case to case and provider to provider. What is clear is that the increase in the number of therapeutically equivalent drugs and therapies available for prescription, combined with the steady growth in health expenditure and demand across most of North America and the EU, helps to explain the increased use of therapeutic interchange and switching in both North America and among many EU Member States.²³

Different healthcare providers will use therapeutic switching in different ways. For example, under a formulary-based system, the level of flexibility given in the decision to interchange a medication differs from one system to another. Closed formulary systems restrict drugs provided by the hospital or under the plan to those on

²¹ ACCP (2004), p 1667.

²² Preferred drugs are often less expensive brands with no generic alternative. It is often the case that a payer will have negotiated a large discount from the manufacturer (in return for the payer's role in increasing the drug's market share).

²³ ACCP (2004).

the list. Prescribing physicians are thus left with a very restricted set of medicines from which to choose from. This may, or may not, be a bad thing depending on the individual patients' need and the drugs included in the particular formulary. Open formulary systems will cover drugs that are not labelled as preferred, that is, those drugs that are not on the formulary list. Many open formularies include an incentive-based system, in which formularies are tiered, with varying levels of co-payments. Tiered formularies generally seek to incentivise choices within the lists of preferred or generic drugs by charging more for non-preferred drugs. For instance, in the US many employer-based health insurers²⁴ have three-tiered formularies. According to the Kaiser Family Foundation, 89% of workers in the US covered by employer-sponsored health plans use a tiered cost-sharing formula for prescription drugs. Out of these workers, 77% had plans with three or more tiers.²⁵ Under these formularies the three most common tiers are: i) Generic Drugs, which has the lowest co-payment; ii) Preferred Branded Drugs, which has a mid level co-payment; and iii) Non-preferred Branded Drugs, which has the highest co-payment.²⁶ Moreover, the single biggest US provider of health care – the federally administered and funded social insurance program Medicare – also operates a system of tiered co-payments for its own drug plans.²⁷

1.4 Why switch?

The practice of switching patients between different therapies is a relatively recent medical development. The increase in the number of new drug therapies available and of alternatives within therapeutic classes now provides physicians with a wide variety of sophisticated pharmaceutical drugs from which to choose from. In many cases, several different classes of drugs are now available to treat the same effects or symptoms of an illness. This means that treatments can become more individualised and that combinations, or cocktails, of drugs can be tailored to minimise side effects and maximise patient outcomes. This is of particular significance to patients with long-term illnesses, such as cardiovascular diseases, gastrointestinal conditions, epilepsy and mental illness. These populations require a sustainable treatment regimen, in which symptoms are able to be stabilised and side effects minimised over long periods. Indeed, patients with long-term conditions often face the need or possibility to switch between alternate therapies. If a baseline treatment is shown to be ineffective or to cause undue discomfort in a particular patient, or if new evidence emerges that supports a new treatment or suggests that the baseline treatment should not be used by a given patient population, there are now generally several other therapeutic alternatives available. Under these circumstances therapeutic switching can improve actual outcomes and also provide relief from any unwanted side effects.

Still, patients with chronic illnesses often face a tricky process of finding the best fit among similar therapies, especially since modern treatment regimens for chronic illnesses often involve a combination of drugs. This is a real problem when it comes to switching these patients with multiple, chronic conditions. Doctors and pharmacists need to find the right mix of medicines not only to treat a patients' underlying illness, but also to

²⁴ These insurers are the most common in the US with almost 6 of every 10 Americans receiving their health insurance through their employers or the employers of their spouses or family.

²⁵ Kaiser Family Foundation, "Kaiser/HRET Employer Health Benefit Survey", September 2009, Section 9, p.1, <http://ehbs.kff.org/?page=charts&id=2&sn=24&p=1> (Accessed 7 December 2009).

²⁶ AMA (2004).

²⁷ Kaiser Family Foundation, "The Medicare Prescription Drug Benefit Fact Sheet", November 2009, <http://www.kff.org/medicare/upload/7044-10.pdf> (Accessed 7 December 2009).

minimise the risk of any potential side effects. Drugs frequently interact with one another and the effect of drug interaction may range from a neutral response to one that reduces the effectiveness of one or more drugs or elicits life-threatening side effects. In a few cases, it is also possible that drug interaction may have a positive effect, that is, to increase the effectiveness of one or more drugs, in which case it would be prescribed with that result in mind.

Identifying the safest and most effective treatment mix is a difficult process requiring a great deal of caution and attentiveness. Indeed, once a patient is stabilised on a comfortable and effective regimen, prescribers and patients are often reluctant to modify any aspect of it. Changes to one type of medication may not be possible without altering other drug prescriptions. The risk of unwanted side effects in patients with chronic illnesses is also based on the fact that these patients often have co-morbidities, or multiple conditions or diseases affecting them at one time. Thus, the complexity of managing their treatment is further compounded by balancing treatments for the different diseases. Furthermore, the patients are often difficult to manage and may be very sick, so that symptoms and side effects are amplified. The most common population in this category are the elderly. Overall, the decision about whether to switch between different therapies often arises among populations that represent the greatest risk of doing so.

As the following sub-section suggests, even at its most basic level, getting a switch right is a difficult process which requires medical supervision and lengthy monitoring.

1.5 The risks and benefits of therapeutic switching

Aside from the positive medical impact which therapeutic switching can have at the individual patient level, switching is also viewed as a potent tool for health systems and payers to cut costs and improve efficiency. Indeed, the cost-saving benefits of successfully implemented therapeutic interchange and switching policies are seen by many as being as important as their clinical effects. What are the types of cost-savings that can be made through these policies and how are they implemented?

The basic idea is that either by replacing existing drug prescribing habits or by creating specific lists of preferred medicines, payers can streamline which medicines are prescribed and cut the cost of prescriptions. By switching large numbers of patients from one drug to another which is both therapeutically equivalent and less expensive, payers can make large savings theoretically without compromising on patient outcomes. Given the extent to which healthcare spending and demand has risen (and is projected to continue to rise) in both North America and in the EU, health authorities and insurers are increasingly looking for legitimate ways to find savings where they can.

While many health trusts, hospitals and insurers have implemented switching schemes, there are relatively few academic studies on either the actual cost-savings or on patient outcomes. In 2004, the American Medical Association carried out a review of the existing literature and found that there were relatively few studies of

health outcomes caused by restrictive drug formularies.²⁸ A sample of some of those studies that do exist does not point conclusively in either direction. For example, a 1999 paper on a local Veteran Affairs Medical Center based in Long Beach, California, found that switching patients from one form of statins to another proved to be, on the whole, a positive move.²⁹ The study evaluated the impact of switching from pravastatin to lovastatin and covered the impact on treatment outcomes, quality of life, patient satisfaction and costs. It found that medically the switch had little negative impact on patients as all their major values and treatment outcomes were similar to what they were before the switch. And financially the switch was projected to provide an annual cost-saving of \$211,000.³⁰ But other studies contradict these findings. For instance, a 2009 American study of the impact of therapeutic switching in long-term care found that in about 75% of the case histories collected there was a negative clinical impact.³¹ Almost half of survey respondents said side effects typically increased after a non-medical switch and in many cases patients had to start taking a supplemental medication to deal with the side effects of their new medication. In addition, many of the nurses, doctors and pharmacists surveyed pointed out that in many cases the switch of medicines had not decreased costs. Instead, costs had actually increased as more clinical and administrative time was taken up by switched patients.³² In light of these two studies, generalisations about the positive or negative impact of switching are difficult to make. One way of better understanding the potential clinical risks of therapeutic switching is by looking at its impact in the context of particular illnesses and individual patients.

Over the years, clinical experience has suggested that a number of therapies can be successfully switched in certain (lower risk) populations. However, evidence also suggests that switching in higher risk populations, such as elderly patients and those with co-morbidities, and higher risk therapies, such as biologics, must be done cautiously. The process of finding the best therapy for long-term conditions is generating a growing body of clinical evidence on the risks and benefits of switching. Most therapeutic interchange takes place within specific drug classes such as angiotensin-converting enzyme (ACE) inhibitors, proton pump inhibitors, and HMG-CoA reductase inhibitors (statins). In the case of some common chronic conditions, including mental illnesses, cardiovascular disease, epilepsy and gastrointestinal conditions, several different classes of drugs may be used to treat it. For instance, SSRIs (selective serotonin re-uptake inhibitors), tricyclics and MAOIs (monoamine oxidase inhibitors) have all been commonly used to treat depression. ACE (angiotensin-converting enzyme) inhibitors, calcium channel blockers (CCBs) and statins are commonly used to treat cardiovascular disease. Much of the clinical evidence seems to suggest that despite being structurally different, these therapies are similar in terms of their clinical benefits and potential risks. As a result, they are frequently switched in patients.³³ However, there is an important caveat: some studies also indicate that these switches do not always have a neutral impact on patients' treatment³⁴ and may, in many cases, actually fail.

²⁸ AMA (2004).

²⁹ Patel, R., Gray, D., Pierce, R. & Jafari, M., "Impact of Therapeutic Interchange from Pravastatin to Lovastatin in a Veteran Affairs Medical Center", *The American Journal of Managed Care*, Vol. 5, No. 4, 1999, pp. 465-474.

³⁰ *Ibid.* p. 465.

³¹ Cote, B. & Petersen, E., "Impact of Therapeutic Switching in Long-term Care", *The American Journal of Managed Care*, Special Issue, Vol. 14, No. 11, November 2008, pp. 23-8.

³² *Ibid.*

³³ Flood, et al (2007), p.52.

³⁴ For instance, Hensley and Nurnberg indicate that switching between different antidepressants on the whole has negative outcomes in patients. See Hensley, P. & Nurnberg, H., "Formulary restriction of selective serotonin reuptake inhibitors for depression: potential pitfalls", *Pharmacoeconomics*, Vol. 19, 2001, pp. 973-982.

For instance, failed switching has been observed involving SSRIs, CCBs and proton pump inhibitors (which treat acid reflux).³⁵ Not only the process of starting the new medication, but also of stopping the old medication was shown to exacerbate symptoms or elicit new side effects as a result of the switch. Similarly, a 2009 academic survey of epilepsy patients and community pharmacists found that an overwhelming majority of both the patients (92%) and the pharmacists (85%) sampled “agreed that switching between forms of the same AEDs may cause an increase in seizures or adverse effects”.³⁶ More than two-thirds of the patients surveyed reported that they had personally had problems with formulation switching or knew someone that had. Moreover, just over half, 51%, of pharmacists also reported knowing of patients who had experienced problems when switching medicines.³⁷ Unsurprisingly, the study concluded that a clear majority of patients, 62%, did not regard formulation switching as safe.³⁸

As a consequence of the lack of clarity on the safety and efficiency of switching, many patient interest groups oppose therapeutic switching or at least have very deep reservations about the practice, especially if it is implemented without the approval of either the patient or prescribing physician. For example, the American Psychiatric Association, American Heart Association and the National Kidney Foundation all – as recently as 2005 – opposed therapeutic interchange without the approval of the treating physician and/or patient.³⁹

Indeed, despite documented therapeutic similarities for many illnesses, the above and other clinical evidence suggests that in many cases therapeutic switching still involves a risk that prescribers, physicians and patients must evaluate carefully. This is particularly true for a new and exciting class of medicines: biologics.

1.6 Switching and biologics

In addition to chemical-based drugs (or new chemical entities, NCEs), automatic substitution and therapeutic switching are now being discussed – and in some cases implemented – for biological drugs, especially for chronic conditions such as rheumatoid arthritis and psoriasis (a skin condition) and in some cases, for rare genetic diseases. This has raised debates about how biologics and biosimilars should be utilised by health practitioners and policymakers. Should substitution and switching between biologics and biosimilars take place?

Over the past fifteen years, biologic drugs have revolutionised the treatment of many life-threatening and rare illnesses, such as cancer and autoimmune diseases. Biologics refer broadly to substances produced by living cells which are used in the treatment, diagnosis or prevention of diseases. They include a wide range of substances, including genetic material, antibodies and vaccines. Biologics work by influencing cellular processes that lead to, or block, a disease or affect diseased cells themselves. Consequently, biologics are able to move beyond merely treating the symptoms of illnesses – which is what drugs based on new chemical entities

³⁵ Carroll, N., “How effectively do managed care organizations influence prescribing and dispensing decisions?”, *American Journal of Managed Care*, Vol. 8, 2002, pp.1041-1054.

³⁶ McAuley, J., Chen, A., Elliott, J. & Schneker, B., “An assessment of patient and pharmacist knowledge of and attitudes toward reporting adverse drug events due to formulation switching in patients with epilepsy”, *Epilepsy & Behaviour*, Vol. 14, 2009, pp. 113-117, Summary.

³⁷ *Ibid.*

³⁸ *Ibid.*, p. 114.

³⁹ ACCP (2004), p.1678.

(NCEs) generally seek to do – and instead slow the progress of, or even prevent, disease. Over time biologics have become an attractive treatment option and the size of this drug market has grown rapidly. Between 1992 and 2007, biologic sales grew six-fold and now represent around 20% of global pharmaceutical sales.

But biologics are not chemical-based drugs and biosimilars are not generics. Substitution between biologics and biosimilars as well as biological switching – and the individual decision to switch a patient from one biologic to another – involves added layers of risk on top of those already associated with therapeutic switching and chemical-based drugs. To begin with, biologics are completely different in nature, size and complexity from chemical-based drugs: NCE-based drugs are chemically synthesised, while biologics are made in living systems. Also, NCE-based drugs are mostly small and generally have well-defined structures and characteristics. Conversely, although some biologics are more straightforward than others, most are large and heterogeneous molecules. As such, it is very difficult, if not impossible, to duplicate biologics in a predictable way.⁴⁰ Even when a biologic drug makes use of the same active ingredient, factors like the source cell, secondary molecules and the manufacturing process can all have an impact or alter the intended behaviour and effect of a drug. In particular, since biologics commonly elicit an immune response in patients (or are “immunogenic”) some of these changes may heighten the intensity of the immune response. Current available technology is not able to analyse and understand biologic molecules to know for certain how each one will perform in different patients and what responses each one may induce.

As a result, the risks associated with both automatic substitution of biologics for biosimilars and therapeutic switching policies for biologics – in which a biologic drug can be interchanged with one that is deemed therapeutically equivalent – are substantial. Indeed, studies that exist on this subject suggest that therapeutic switching policies should only be used for biologics after very careful consideration of the possible negative outcomes. A 2007 *Managed Care* article on therapeutic switching for biologics treating psoriasis and rheumatoid arthritis argues that because variations in patient reaction can be so large when it comes to biologics – despite the fact that on a macro population level variations may seem normal – switching guidelines for biologics must be made on a case-by-case basis:

Disparities in clinical pharmacology among the biologic agents used to treat RA, psoriasis, or PsA are more pronounced than those among the aforementioned classes of traditional drug therapies, but the underlying principles of therapeutic interchange are essentially the same in either case. Because of differences in chemical structure, clinical pharmacology and pharmacokinetics, mode of administration, safety and long term experience, black-box warnings, drug interactions, immunogenicity, and points of impact in the inflammatory, **therapeutic interchange of biologic agents for RA, PsA, and psoriasis should be thought through carefully; these differences may be significant.**⁴¹ [Emphasis added]

⁴⁰ The following Stockholm Network paper provides a full discussion of biosimilars and their potential role in modern medicine: Stockholm Network. *Biogenerics or Biosimilars? Discussing the Present, Considering the Future*, 2009, http://www.stockholm-network.org/downloads/publications/Biosimilars_FINAL.pdf (Accessed 8 April 2010).

⁴¹ Flood, et al, (2007), p. 52.

From this it seems that labelling a product as “therapeutically equivalent” or as a “therapeutic alternate” to another biologic product in the same way that chemical-based entities are labelled could be misleading for healthcare practitioners.

The switching and substitution of biologics has become more of a burning issue with the entry of follow-on substitutes to original biologics known as biosimilars. With many biologics currently facing patent expiration, the ability to introduce biosimilars presents patients and providers with new, and perhaps cheaper, treatment options.

Yet biosimilars present significant regulatory and safety challenges, compared with generic equivalents of NCE-based drugs. Most importantly, while generic drugs are sometimes referred to as “carbon copies” of an original drug (based on having the same active substance and proven bioequivalence), a biosimilar does not have the same active ingredient and cannot be referred to as the generic version of the original biologic drug. As a result, a consensus seems to have emerged among different health authorities and regulators that biosimilars should be approved and utilised differently from generic drugs.

As will be discussed in more detail below, regulatory frameworks in place for the review and approval of biosimilars reflect the fact that biosimilar and generic drugs are distinct and have different safety profiles. Since generic drugs are understood to have the same active ingredient as the original drug and are thus expected to perform identically, they face a considerably abbreviated approval process as compared with new drug applications. While NCE applications must include a lengthy and costly series of non-clinical and clinical trials, the generic application usually amounts to submitting bioequivalence tests demonstrating that its chemical and biologic effects are statistically similar to the original drug. Biosimilar applications tend to include much more than the generic application. They generally involve the submission of at least one clinical test to prove how the biosimilar performs in different groups of patients; such studies can cost several million dollars more than bioequivalence tests. Even if a biosimilar is approved, experts say that much more post-marketing observation of its performance in a wide range of patients is needed before the drug can be sufficiently understood.

This is the case with the biosimilar pathway in the EU – which is the most established pathway and has been in use since 2003. EU legislation establishing the biosimilar pathway (Directive 2004/27/EC) requires a stringent non-clinical and clinical comparison of the biosimilar and original biologic. To realise this comparison, the Committee for Medicinal Products for Human Use (CHMP) of the EMEA has developed several product-specific guidelines covering different biologics. These guidelines explicitly require the results of preclinical and clinical tests; although the requirements vary depending on the molecule, at least one or two clinical tests are compulsory. The CHMP has also introduced special guidelines for assessing immunogenicity and for cases in which changes are made to the manufacturing process after the biosimilar is authorised. Furthermore, all biosimilars are subject to pharmacovigilance monitoring (i.e. further testing of the drug as it is used in the market). From this, it is clear that the treatment of biosimilars is more comparable to new biologic products than generic ones.

Increasingly, experts and many health authorities are saying that biosimilars should be utilised in the same way as biologics are, i.e. switching from a biologic to a biosimilar – whether it be the biosimilar of one biologic or the biosimilar of a separate biologic from the same therapeutic class – should be treated with the same caution that is given to switching between two original biologics. Although the idea of interchangeability or automatic substitution with biosimilars is still being discussed and debated in different forums, many national regulatory bodies are prohibiting or discouraging the substitution of biosimilars by pharmacists. Instead, many are saying that the decision to switch to a biosimilar or to another biologic should be taken by a patient’s physician (this will be discussed in greater detail in the next section).

As the prescription rates and clinical usage of biologics and biosimilars increase, health policymakers, physicians and patients will have to think more about how biologics can be utilised, including in the case of switching them, in a way that maintains a minimum risk for patient safety and comfort.

1.7 Summary of Section I

This section has provided an introduction to therapeutic switching. It has outlined what switching is; defined it in relation to other forms of drug substitution policies; examined how switching policies are implemented; explain what is the clinical and economic rationale underpinning therapeutic switching policies; and discussed some of the major risks and benefits of switching, with a special focus on biologic medicines. The following section will look at how therapeutic switching actually works in practice in North America and within the EU.

Section 2: Regulations, guidelines and best-practice models in North America and the European Union

2.1 Introduction

The purpose of the following section is to provide an overview of how therapeutic switching works in some of the biggest and most advanced medical and pharmaceutical markets in the world: the United States, Canada, and a sample of EU Member States, namely the United Kingdom, Spain and Sweden.

While all of these countries share a number of important characteristics – they are all economically and medically advanced states with rapidly rising healthcare costs – the differences between individual countries' healthcare systems are actually more significant than their similarities. This is an important point and worth stressing. Indeed, given that therapeutic switching policies (as well as policies regarding biologics and biosimilars) are the result of the design and implementation of medical and healthcare regulation (whether it be national, regional or individual providers and payers) the country-specific sections below will all begin with an introductory discussion of the key characteristics of existing healthcare systems.

It is important to note that this section will examine guidelines which are aimed at or which impact on balanced patients (i.e. those with chronic conditions and using medications over a long period of time), and that discuss practices involving switching or interchange between therapeutic equivalents. Switching or substitution of branded for generic medicines falls outside of the scope of this analysis. In addition, the guidelines analysed here generally involve either policies that directly address therapeutic interchange or switching, or those that include pressures or incentives that could lead to interchange or switching - for instance, guidelines on utilising tiered formulary systems.

2.2 United States

Healthcare in the US is based on a health insurance model, principally managed via private funding, and on private delivery. Private insurance is primarily arranged and sponsored by employers. According to the Kaiser Family Foundation, around 52% of the American population are covered by employer-sponsored insurance. About 5% are covered by individual insurance.⁴² Healthcare facilities, including hospitals and clinics, are mainly privately owned and operated.

The elderly, low income, military personnel and those publically-employed are eligible for public coverage of healthcare (either full or subsidised) via Medicare, Medicaid and other programs that are run by both the

⁴² Kaiser Commission on Medicaid and the Uninsured, "Health Insurance Coverage in the US, 2008", Kaiser Family Foundation, 2009, <http://facts.kff.org/chart.aspx?ch=477> (Accessed 22 January 2010).

federal and state governments. Around 14% of the population qualify for Medicare and 13% for Medicaid or other public programs. In addition, the federal government operates healthcare services for military servicemen, veterans and Native Americans.

In the US, the responsibility for regulating healthcare is shared between the federal government and the states. The federal government controls the safety of medicines (via the Food and Drug Administration), Medicare and a few other public healthcare programs. Regulation of health insurance, Medicaid and children's services is shared between these two levels. The balance of healthcare, especially as it relates to day to day services for the majority of Americans, is managed at the state level.

Given this set-up, the US healthcare system is complex, decentralised and involves a large number of players that in many ways operate autonomously (within the boundaries of federal and state regulations, which will be discussed below). This is underscored by the fact that with so many independent players in the market, and due to the American tradition of having a robust civil society, many interest groups and professional associations have a strong voice when it comes to patient interests and best medical practices.

2.2.1 Pharmaceutical policy

The US pharmaceutical market is predominantly market-based. Private payers, including insurers, managed care organisations and pharmaceutical benefit managers, aggregate various health plans and purchase pharmaceuticals on behalf of the members. Private payers often employ formularies (including therapeutic interchange), differential cost-sharing (including tiered copayments) and other methods to influence prescribing practices. In doing so, they are able to negotiate discounted prices from pharmaceutical manufacturers and pharmacies.⁴³ Individual hospitals and other healthcare institutions are also increasingly using formularies to manage costs.

2.2.2 Therapeutic switching policies

Federal law does not address the practice of therapeutic switching or interchange. Furthermore, the Food and Drug Administration (FDA)'s role in the practice of therapeutic switching is limited and indirect – it ensures the integrity of marketed medicines,⁴⁴ but does not regulate their use.

States have a more direct influence over therapeutic switching, at least from the perspective of professional medical practice. They oversee healthcare practitioners via state licensing boards, such as those regulating physicians, pharmacists, nurses, etc. In this light, state boards, particularly state pharmacy boards, control therapeutic interchange (and therapeutic substitution) practices. Often these practices are regulated as components of a formulary system, falling under guidelines and rules governing formulary systems existing within the state.

⁴³ Pharmaceutical Research and Manufacturers of America (PhRMA), "Foreign Government Pharmaceutical Price and Access Controls", Dept of Commerce, 2004, pp.14, <http://www.trade.gov/td/health/phRMA/phRMA%20Response.pdf> (Accessed 27 January 2010).

⁴⁴ Brushwood, D., "Legal issues surrounding therapeutic interchange in institutional settings: An update", *Formulary*, Vol. 36, 2001, p.797, <http://formularyjournal.modernmedicine.com/formulary/data/articlestandard/formulary/462001/2016/article.pdf> (Accessed 15 February 2010).

The practice of therapeutic interchange is commonly accepted and recognised in pharmacy practice standards.⁴⁵ By and large, it is viewed as a way of ensuring that patients receive the most appropriate drug therapy⁴⁶ and state protocols generally establish a set of protocols that allow therapeutic interchange by pharmacists in various practice settings.⁴⁷ Although certain aspects may differ from state to state,⁴⁸ these protocols are often similar to the prescribing and dispensing standards advocated by professional organizations, such as the AMA and the American Society for Health-System Pharmacists (ASHP).⁴⁹ For instance, Florida state law requires that:

A facility...which is operating under the formulary system shall establish policies and procedures for the development of the system in accordance with the joint standards of the American Hospital Association and American Society of Hospital Pharmacists for the utilisation of a hospital formulary system, which formulary shall be approved by the medical staff.⁵⁰

As discussed below, professional practice guidelines generally give a large role to healthcare providers, in many cases physicians, and patients in therapeutic switching decisions.

Nevertheless, state board regulations are often broad and the responsibility for forming drug policies is generally delegated to oversight committees (e.g. pharmacy and therapeutics committees) for individual health plans and healthcare bodies.⁵¹ Taking a sample of different healthcare organisations and programs, it is clear that different practice settings implement these guidelines to different degrees.

2.2.3 Therapeutic switching in practice

Practices of health insurers, such as the use of tiered formularies, which affects the majority of Americans, may rely on economic incentives to encourage switches to the lowest tiered medicine among therapeutic equivalents with varying prices. In many cases, patients are notified of the switch and can choose to stay on a higher tiered drug by paying a higher co-pay, but this is not true for all plans.

For example, the Veterans Health Administration (VHA) plan does not afford physicians and patients this kind of option. A relatively large system in the US, covering 8 million US veterans⁵² and consisting of 172 hospitals and over 700 other facilities,⁵³ the VHA is publicly funded and delivered.⁵⁴ It is known for having a highly rigid formulary system and strict therapeutic interchange policies. The VHA makes usage-driven agreements with drug manufacturers, in which it agrees to use a determined volume of medicines and in turn, the VHA receives

⁴⁵ American Medical Association (AMA), Council on Ethical and Judicial Affairs. "Managed care cost containment involving prescription drugs", p. 1, <http://www.ama-assn.org/ama/pub/upload/mm/code-medical-ethics/8135a.pdf> (Accessed 8 April 2010).

⁴⁶ Online Sunshine, "Regulation of Professions and Occupations, 465.019 Institutional pharmacies; permits", 2009, http://www.leg.state.fl.us/statutes/index.cfm?mode=View%20Statutes&SubMenu=I&App_mode=Display_Statute&Search_String=465.019&URL=CH0465/Sec019.HTM (Accessed 15 February 2010).

⁴⁷ Ibid.

⁴⁸ ACCP (2007), p.1676.

⁴⁹ Ibid.

⁵⁰ Online Sunshine (2009).

⁵¹ ACCP (2007), p.1676.

⁵² US Congressional Budget Office, "Quality Initiatives Undertaken by the Veterans Health Administration", 2009.

⁵³ Blumenthal, D. & Herdman, R. (Eds), "Description and Analysis of the VA National Formulary", Institute of Medicine: VA Pharmacy Formulary Analysis Committee, 2000, p. viii, http://www.nap.edu/catalog.php?record_id=9879 (Accessed 15 February 2010).

⁵⁴ Medicare, Medicaid and the State Children's Health Insurance Program all deal mainly with funding healthcare, which is then provided by various private sources.

a lower price for that set of medicines. With the purpose of achieving the promised volume, if patients are already using non-formulary drugs, providers must switch them to the preferred or formulary medicines.⁵⁵ VHA pharmacists are also permitted to switch patients to formulary drugs, according to the protocol developed by local pharmacy and therapeutics committees, without consulting the prescriber.⁵⁶ The National Formulary does not contain a mechanism for making exceptions, and a study by the Institute of Medicine has not found concrete evidence that such flexibility exists at the local level either.⁵⁷ Furthermore, the national guidelines lack provisions for educating and consulting patients and providers concerning when and how therapeutic interchange occurs. In particular, the Institute of Medicine has found that from veterans' perspectives, therapeutic interchanges occur involuntarily and are not well understood by patients.⁵⁸

From this, it does not appear that the VHA system addresses the potential risks involved with switching as well as the impact that it may have on patients who have achieved a stable drug treatment regime. This is particularly relevant in light of the fact that VHA drug contracts are often re-examined annually; as a result, the list of preferred drugs may change frequently, likely making switching a common occurrence (at least from the perspective of patients who are taking a medicine or medicines over the long-term).

In many cases, state-run health insurance plans approach formulary switches in a similar way to some private health insurers. A state pharmacy and therapeutics committee often exists to manage formularies and therapeutic interchange policies for the state. Residents using state insurance include mainly state employees and Medicaid or Medicare recipients. It can be said that although state pharmaceutical therapeutics committees (P&T committees) follow state board protocols, they are more distanced from actual patients and perhaps more intimate with state budgetary restrictions. Therefore, interests in managing healthcare costs can encourage widespread switching without the patient's – and in many cases the physician's – permission.

Washington State's Therapeutic Interchange Program (TIP) is a case in point.⁵⁹ The TIP mainly applies to people qualifying for Medicaid (around 1.2 million residents, or 19% of the state population⁶⁰) and to people enrolled in the state-run Uniform Medical Plan (including most state employees, or around 180,000 people⁶¹). By registering with TIP, providers agree that a pharmacist will automatically switch preferred drugs for non-preferred ones, unless the provider directs to dispense as written.⁶² This is comparable to many private insurance plans – it is fairly flexible, but relies on the physician to step in when a switch is unsafe. (The key exception is with very risky drugs, such as antipsychotics or immunosuppressants, which must be dispensed as prescribed.) However, the system is much less flexible for patients whose providers do not endorse the policy. Patients on the Uniform Medical Plan may pay a higher co-payment in the event that they do not want to

⁵⁵ Blumenthal and Herdman (2000), p. 61.

⁵⁶ *Ibid.* It is interesting to note that VHA policies pre-empt state laws governing therapeutic interchange, i.e. those requiring the physician to approve an interchange. See *Ibid.*, p. 63.

⁵⁷ *Ibid.*, p.64.

⁵⁸ *Ibid.*

⁵⁹ Marshall, D., Mai, J., Childs, S. & Thompson, J., "Endorsing Practitioner Therapeutic Interchange Program", RxWashington, <http://www.rx.wa.gov/documents/TIPhandout042004.pdf> (Accessed 15 February 2010).

⁶⁰ Kaiser Foundation, "Washington: Medicaid Enrollment, FY 2006", <http://www.statehealthfacts.org/profileind.jsp?cat=4&sub=52&rgn=49> (Accessed 15 February 2010).

⁶¹ Shannon, B., "State will break Aetna contract", *The Olympian*, 18 September 2009.

⁶² Washington Prescription Drug Program, "Washington State Preferred Drug List and the Therapeutic Interchange Program", 2009, <http://www.rx.wa.gov/tip.html> (Accessed 15 February 2010).

switch, but Medicaid patients, especially those who do not have a strictly medical reason for refusing to switch, will have to pay the full price of the medicine out-of-pocket. The financial incentive to go ahead with the switch is thus very strong, even if it will cause discomfort or other problems for the patient.

Ultimately, hospitals and healthcare networks are the bodies which most directly determine switching practices, whether it be via compulsory protocols or via incentives that encourage switching. Hospitals are given substantial room to make their own policy, since regulatory and advisory bodies only involve general guidelines.

Hence, the role of physicians and patients in switches will differ from hospital to hospital. However, it is worth noting that the use of automatic substitution protocols (i.e. in which the pharmacist makes a switch without contacting the physician or patient) is quite prevalent – an *American Journal of Health System Pharmacists* article finds that most American hospitals utilise some form of them. There are also many examples of hospitals which do not utilise automatic interchange or substitution. For instance, several hospitals within the Texas Medical Center (the largest medical centre in the world⁶³) require that if a physician's order specifies "dispense as written", the non-formulary medication must be dispensed.

In other cases, making an exception to a switch is more complicated. Take, for example, Intermountain Healthcare, a network of hospitals and clinics in Utah and Idaho. When physicians refuse a switch as part of the organisation's standardisation protocol, they are required to explain the medical rationale for doing so and if the reasoning (whether it be with regards to the patient's safety or based on the patient's own decision) does not convince the pharmacy and therapeutics committee, the physician is often the target of "naming and shaming". At times, physicians are under pressure to conform to the standards and are compelled to ask patients to agree to an interchange. Indeed, Intermountain is not the only group of hospitals taking this approach – many hospitals are increasingly moving towards standardisation in order to find optimum treatments (to improve health outcomes) and to cut costs.⁶⁴

The Group Health Cooperative, a system of hospitals that manages both care and coverage of its enrollees in Washington State and Idaho, demonstrates an even less flexible interchange system. It is reputed to be a patient-managed organisation as well as having extremely streamlined care (even becoming a prototype in Congressional debates on US healthcare reform).⁶⁵ However, its therapeutic interchange system is still quite burdensome and rigid for physicians wishing to refuse an interchange. In order to receive a non-formulary medicine, the doctor must ask for a review by the pharmacy and therapeutics committee. If the request is not deemed "medically necessary", the patient must pay the full cost of the medicine (not only a higher co-pay).⁶⁶ Having to go through the review process may drive physicians to prescribe formulary medicines in cases

⁶³ Texas Medical Center, "2009 Facts and Figures"

<http://www.texasmedicalcenter.org/root/en/GetToKnow/FactsandFigures/Facts+and+Figures.htm> (Accessed 15 February 2010).

⁶⁴ Leonhardt, D. "Making Health Care Better", *New York Times*, 3 November 2009,

<http://www.nytimes.com/2009/11/08/magazine/08Healthcare-t.html?pagewanted=1&r=2> (Accessed 20 January 2010).

⁶⁵ Sack, K. "Health co-op offers model for overhaul", *New York Times*, 6 July 2009,

<http://www.nytimes.com/2009/07/07/health/policy/07coop.html> (Accessed 20 January 2010).

⁶⁶ Group Health, "About our Drug Formulary", 2010, <http://www.ghc.org/pharmacy/formulary/about-formulary.jhtml> (Accessed 20 January 2010).

where the switch is only borderline risky or where the patient has non-medical reasons for not wanting to switch.

2.2.4 Biologic, biosimilars, switching and automatic substitution policies

Switching of biologics is still a somewhat nascent practice in the US. But due to the development of an approval pathway for biosimilars (which is still ongoing) as well as the increasing set of biologic medicines available to treat chronic illnesses, they are becoming a component of debate on therapeutic switching and substitution policies.

In this context, the FDA has had the most substantial voice, much more than with the switching of chemical-based drugs. The debate on the right regulatory pathway for biosimilars has given the FDA a platform on which to discuss the use of biologics in general. Given the potential risks associated with biologics, the FDA's response to an inquiry by the House and Energy Committee (as part of creating a legislative pathway for the approval of biosimilars) recommends that only the physician in charge of the patient's care should authorise switching of biologics.

...[W]ithout clinical evidence that patients can be switched back and forth between two [biologic] products without any detrimental effect, such changes should not be made unless directed by a physician, and legislation should not allow for determinations of interchangeability at this time.⁶⁷

Hence, the FDA's position is that physicians, who know the patient's condition and specific risks best, should make any decisions on switching biologic products, implying that the decision should be taken cautiously and vigilantly.

Prior to this recommendation, no formal guidelines or recommendations seem to have been in place in the US on the practice of switching biologics, even though many European countries have advised against it at least since 2007. A *Managed Care* article from 2007 suggests that especially with chronic conditions, interchange of biologics was a common practice, at least at that time. For instance, it cites a Managed Care Organisation that changed its formulary for biologics treating rheumatoid arthritis and mandated that all patients switch to the new medicine. The order applied to unstable as well as controlled patients. Physicians who tried to block the switch for controlled patients were refused. As a result, there were instances in which patients experienced strong recurrences of their symptoms, with one having to undergo surgery subsequently.⁶⁸

2.2.5 Professional organisations and patient groups

It is very common for professional and public interest groups to develop position or policy statements on therapeutic interchange. In 2000, six organisations,⁶⁹ including the American Medical Association – the largest association of physicians in the US and probably one of the most influential organisations with regard to

⁶⁷ Torti, F. "Letter to Honorable Frank Pallone, Jr of the House Committee on Energy and Commerce", FDA, 18 September 2008, p.10.

⁶⁸ Flood, et al (2007), pp. 56-7.

⁶⁹ These were: the Academy of Managed Care Pharmacy, Alliance of Community Health Plans, American Society of Health-System Pharmacists, Department of Veterans Affairs, National Business Coalition on Health and United States Pharmacopeia.

therapeutic interchange – developed and endorsed a set of principles on the practice of drug formulary systems and therapeutic interchange.⁷⁰ The basis of the document is that the safety and therapeutic need of individual patients should be addressed ahead of cost factors. It holds that the system should include a well-defined, straightforward process for the physician to use a non-formulary drug when medically indicated and physicians should not be penalised for doing so. These points are important because even if a physician has the flexibility to refuse an interchange, an onerous process to do so may incentivise him to agree to or promote the switch; the process must be feasible and acceptable for the physician to request a non-formulary drug. Also, the formulary system should include adequate education and communication among physicians, pharmacists and patients, including full disclosure of formularies, any changes to the formulary and rationale of the change.

A 2004 report by the AMA reiterates and expands these principles.⁷¹ In particular, AMA states that therapeutic interchange would be acceptable in both inpatient hospitals and outpatient settings, as long as the principles discussed in the 2000 document are followed, along with several new criteria. First, the practice should be based on a formal system (rather than merely a list of drugs), which is transparent, based on policies agreed upon by the institution's medical staff and managed by a committee of pharmacy and therapeutics experts. Second, prescribers must always be consulted before an interchange occurs. Although a patient's ability to oppose a switch is not mentioned explicitly, having mechanisms in place by which physicians can do so is a huge priority of the AMA's policy. With regards to outpatient settings, the AMA adds that the switching of therapeutic equivalents in patients with chronic diseases who are stabilised on a drug therapy regimen should be discouraged.

Not surprisingly, pharmacist organisations in the US are universally supportive of therapeutic interchange involving pharmacists. However, they generally support many of the same principles governing the practice, such as including a process for prescribers to opt out of an interchange when medically indicated. They also attach importance to patients' interests. For instance, the American College of Clinical Pharmacy (ACCP) recommends that pharmacists directly responsible for a patient's care advocate for him (and his safety and choice) in relating to insurers or pharmacy benefit companies.⁷²

Many US patient organisations have publicised position statements or recommendations on the practice of therapeutic interchange. As can be expected, these generally advocate that patient's safety and individual choice be prioritised when providers decide to switch a medicine or in the development of formulary systems involving therapeutic interchange protocols. For instance, the National Consumers League (NCL), an advocacy group for American consumers on a range of issues including health and product safety, encourages patient education concerning their treatment regime as well as active communication between providers,

⁷⁰ AMA, "Principles of a Sound Drug Formulary System", 2000, <http://www.ama-assn.org/ama/pub/upload/mm/443/drugformularyprincip.pdf> (Accessed 15 February 2010).

⁷¹ AMA (2004).

⁷² ACCP (2004).

patients, pharmacists and insurers, in order to prevent interchanges occurring without the patient or provider's knowledge or assent.⁷³

Many disease-specific patient organisations also have very patient-focused positions on the practice of therapeutic interchange, especially those involved with more serious chronic diseases, such as epilepsy or certain neuropsychiatric conditions. These bodies generally recommend avoiding switching medications prescribed for these types of indications, especially without the physician and patient's express consent, since negative side effects or adverse reactions are more risky in these patients than others.⁷⁴

2.2.6 Summary

Bearing in mind that huge variation exists within the US, there is a great deal of support for patient safety and rights in the policy world when it comes to the use of therapeutic switching. However, the way in which different practice settings implement these policies (for both chemical-based and biologic medicines) differs extensively among federal and state-run systems, as well as among hospitals. In many cases, the tension between the rising costs of medicines and the spirit of medical practice codes is evident. Individual physician practices of switching are difficult to gauge, given the dearth of studies on the subject. However, their practice probably depends a lot on the different prescribing incentives or pressures present in a given healthcare organisation.

2.3 Canada

The Canadian healthcare system is based on the publically funded model of a single-payer system for primary care, with most healthcare services delivered through a private physician or medical provider. Public healthcare funding is divided into a federal and a provincial level.⁷⁵ Most of the funding is provided in the form of block grants from the Canadian Federal Government, but the actual healthcare provision is run and implemented by each individual province. As a result, a relatively large degree of independence and control is left in the hands of the provinces; the only proviso being that the provincial health care delivered complies with federal law, in particular the Canada Health Act. Each province has a public health insurance program covering primary care, including care in hospitals and by physicians.

2.3.1 Pharmaceutical policy

As a result of the structure of the Canadian healthcare system, out-patient prescription drugs are often not covered by public health insurance. Most provinces have added public coverage programs for elderly or low-income residents (although this differs from province to province). However, the majority of residents (65%) have private health insurance, mainly offered through employers, that covers most of the cost of outpatient medicines.⁷⁶

⁷³ NCL (2009).

⁷⁴ American Psychiatric Association, "Medication Substitutions Position Statement", Approved by the Board of Trustees, December 1995, Reaffirmed, September 2009. See also: the American Epilepsy Association and the American Heart Association's respective positions in ACCP (2004), p.1678.

⁷⁵ All primary health care is funded by the federal and provincial governments; private provision of primary medical care is not allowed in Canada.

⁷⁶ Organisation for Economic Cooperation and Development (OECD), "Private Health Insurance in OECD Countries", 2004, pp. 11, 13.

A price control and reimbursement system involving both federal and provincial health bodies is used to manage pharmaceutical policy. Canada's central Patented Medicines Prices Review Board (PMPRB) sets a maximum allowable price that manufacturers may charge.⁷⁷ On top of this, the provinces establish the maximum price that provincial health plans will reimburse pharmaceutical manufacturers (typically these are significantly lower than the maximum established by the PMPRB).⁷⁸ This is often based on the recommendations of the central body, Common Drug Review, which undertakes cost-effectiveness analyses on new drugs.⁷⁹ Generic medicines have traditionally been prescribed over branded medicines,⁸⁰ and although this trend has slowed somewhat, it is still active.

2.3.2 Therapeutic switching policies

As in the US, federal legislation and regulators do not directly address therapeutic switching. In particular, the guidelines of Health Canada, the federal body responsible for public health including the safety of medicines, do not generally advise on switching, except between specific products.

Also like the US, provincial bodies managing the regulation of medical practice deal more with the practice and the process of therapeutic switching. The College of Physicians and Surgeons and the College of Pharmacists in each province are responsible for licensing medical practitioners and for setting practice standards. These bodies generally have a position on therapeutic switching (sometimes known as therapeutic substitution),⁸¹ or at least provide broad standards on physician-pharmacist and patient-provider relationships that can apply to therapeutic switching.

For instance, in its practice guide the College of Physicians and Surgeons of Ontario requires physicians to

work with the patient in order to understand the patient's healthcare needs, to formulate treatments that are optimal for the patient, to ensure that the patient remains informed about his or her care, and to address patient questions and concerns...All communication with patients should recognise an individual patient's autonomy and demonstrate a collaborative approach to patient decision-making.⁸²

With respect to therapeutic switching, such standards can be taken to mean that physicians should make patients' safety, comfort and any other interests their main concern when faced with a decision or opportunity to switch a medication, and should ensure that patients are aware of the possibility of a switch. The Canadian Medical Association, the largest professional organisation for physicians, partly contradicts this by recommending that doctors and patients should equally take into account cost and clinical suitability when

⁷⁷ US Dept of Commerce, "Pharmaceutical Price Controls in OECD Countries", 2004, p. 4, <http://www.trade.gov/td/health/DrugPricingStudy.pdf> (Accessed 27 January 2010).

⁷⁸ PhRMA (2004), pp.10-11.

⁷⁹ Ibid., p.32.

⁸⁰ Stockholm Network, *Courting Confusing? Where is Canada's Intellectual Property Policy Heading?*, 2008, p.7, http://www.stockholm-network.org/downloads/publications/Courting_Confusion.pdf (Accessed 27 January 2010).

⁸¹ In Canada, switching is frequently referred to as therapeutic substitution. For the sake of clarity, this paper will continue to label this practice as switching.

⁸² College of Physicians and Surgeons of Ontario, "The Practice Guide: Medical Professionalism and College Policies", 2008, pp.10-11, http://www.cpso.on.ca/uploadedFiles/policies/guides/PracticeGuideExtract_08.pdf (Accessed 26 January 2010).

making decisions about drug treatment.⁸³ This position can be seen as adding the practical dimension of cost pressures to the clinical setting and corresponds more with what actually occurs in practice (discussed below) in the selection of medicines.

The College of Pharmacists of British Columbia's standards suggest that pharmacists should view therapeutic switching somewhat more liberally. The College of Pharmacists allow the practice of automatic substitution in acute or long-term institutions, according to provincial standards and unless protocols established by the institution indicate differently. Still, it limits the practice to a few classes of medicines (including H2 blockers, NSAIDs, ACE inhibitors, CCBs and PPIs).⁸⁴ In addition, in community practice settings pharmacists should not make changes to a prescription regimen for particularly vulnerable patients, i.e. those with cancer, cardiovascular disease, asthma, seizures or psychiatric conditions.⁸⁵ Furthermore, pharmacists must honour requests by prescribers to not adapt the prescription.⁸⁶ On the whole, though, the practice of switching without patient and in some cases, physician involvement seems to be established in pharmacist practice standards. The Canadian Pharmacists Association has even said that "pharmacists are in a better position to assess whether patients are getting the best drug or not".⁸⁷ Therefore, from the perspective of pharmacy policy, the onus is really on physicians if they want to be consulted about a switch taking place in the pharmacy.

There is not a strong voice from patient organisations to promote more patient involvement in decisions on switching. In fact, a study of several prominent Canadian patient organisations suggests that these bodies are not advocating sufficiently that healthcare practitioners consider the risks of different treatments as well as patients' values and preferences in therapeutic decision-making, including whether to switch between medications.⁸⁸

2.3.3 Therapeutic switching in practice

Provincial formulary guidelines – which manage prescription drugs in primary care settings and in some cases, other clinical settings – offer a good picture of the practice of therapeutic switching taking place in Canada. The guidelines and practice can vary extensively from province to province. Still, provincial formularies are much more far reaching than formularies utilised in US state-run programs – they cover all recipients of in-patient medicines as well as several other patient groups receiving out-patient medicines, depending on the province.

⁸³ Howell, E. "Prescribing patterns drive up health care costs", *Canadian Medical Association Journal*, Vol. 177, No. 12, 2007, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2096495/> (Accessed 26 January 2010).

⁸⁴ College of Pharmacists of British Columbia (CPBC), "Quick Reference to Prescription Adaptation: Amendment to PPP-58 Orientation Guide (December 2008)", 2009, http://www.bcpharmacists.org/library/D-Legislation_Standards/D-2_Provincial_Legislation/PPP58_QuickReference.pdf (Accessed 26 January 2010).

⁸⁵ CPBC, "Frequently Asked Questions, PPP-58", http://www.bcpharmacists.org/library/A-About_Us/A-8_Key_Initiatives/PPP58_FAQs.pdf (Accessed 26 January 2010).

⁸⁶ CPBC, (2009).

⁸⁷ Howell, E. "Prescribing patterns drive up health care costs", *Canadian Medical Association Journal*, Vol. 177, No. 12, 2007, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2096495/> (Accessed 26 January 2010).

⁸⁸ McCormack, J. & Loewen, P. "Adding value to clinical practice guidelines", *Canadian Family Physician*, Vol. 53, 2007.

For example, the Ontario Drug Benefit program covers out-patient (i.e. not given in primary care settings) drugs for residents 65 years and older, those in long-term care and any individual or family for which private insurance does not cover 100% of their prescription drug costs⁸⁹ And, since 2006, aspects of the provincial formulary also affect patients covered by employer-funded private insurance plans and cash patients.⁹⁰ One of these is the protocol on automatic substitution, which the provincial formulary uses at length. Hence, in Ontario pharmacists are universally permitted to switch a patient's medication in out-patient setting without consulting the physician in charge of the patient. The Exceptional Access Program is another notable aspect of the Ontario formulary – in order to get an exception to a switch, the physician must request a review by a provincial expert advisory committee and provide extensive medical documentation backing up the rationale for the review.⁹¹

The formulary used in British Columbia (BC) involves greater flexibility. This formulary has a tiered reference pricing system for several product classes, with patients paying the difference of a higher tiered medicine if they choose it over the cheaper one. Patients with medical reasons for not switching do not have to pay to stay on a higher tiered medicine. This is demonstrated in a therapeutic interchange program for ACE inhibitors, which exempts a range of patients from paying, including any patient receiving the prescription from a cardiovascular specialist, anyone with a history of diabetes or asthma (or other complicating conditions) and anyone considered “frail” or having previously failed a trial of the preferred drug. In a study of the program, over half of patients using this class of medicine were exempted from switching (mostly on the basis of “frailty”).

Within the framework of the provincial health system, hospitals and healthcare networks create their own specific protocols on the use of medicines. Since they face tight operating budgets from provinces, these protocols often involve policies like therapeutic switching in order to manage drug costs. For instance, among acute care hospitals in Ontario, 85% use therapeutic interchange protocols, and over half allow these protocols to apply to medicines with higher risk profiles such as cardiovascular medications.⁹²

2.3.4 Biologic, biosimilars, switching and automatic substitution policies

From a regulatory perspective, biologics are considered to fall under the remit of provinces and provincial formularies. Accordingly, Health Canada does not make any recommendations regarding the interchangeability of biologics (and biosimilars), save from saying that its approval of biologic products does not equate to a determination of interchangeability and that bodies addressing the matter should do so based on scientific and clinical data.⁹³ As of yet provinces have not made any general statements with regard to switching of biologics and have not made switching biologics an explicit policy. Indeed, the availability of biologics via provincial

⁸⁹ DrugCoverage.ca, “The Ontario Drug Benefit Program and the Trillium Drug Program”, Plasmid Biocommunications, 2009, http://www.drugcoverage.ca/p_benefit_on.asp#2 (Accessed 26 January 2010).

⁹⁰ Ogilvy Renault, “A Short-Sighted Approach to Reducing Drug Costs in Ontario”, 2006, http://www.ogilvyrenault.com/en/resourceCentre_1114.htm (Accessed 26 January 2010).

⁹¹ Ontario Ministry of Health and Long-Term Care, “Exceptional Access Program”, 2009, http://www.health.gov.on.ca/english/providers/program/drugs/eap_mn.html (Accessed 26 January 2010).

⁹² Bell, C., Telio, D., Goldberg, A., Margulies, A. & Booth, G. “Selective Therapeutic Interchange Practices in Ontario Acute Care Hospitals”, *Canadian Journal of Hospital Pharmacy*, Vol. 60, No. 5, 2007.

⁹³ Nyarko, K. “Regulatory Approach for Subsequent Entry Biologics in Canada”, Health Canada, 2009, [http://www.pmda.go.jp/2009bio-sympo/file/IV-2_Nyarko_\(Health%20Canada\).pdf](http://www.pmda.go.jp/2009bio-sympo/file/IV-2_Nyarko_(Health%20Canada).pdf) (Accessed 15 February 2010).

formularies is still limited in Canada. For example, biologic treatments for rheumatoid arthritis (RA) and other forms of autoimmune arthritis, treatments that are by now fairly common, have only recently been approved for reimbursement in some provinces. And not all provinces reimburse the same treatments. Several provinces including Ontario and Nova Scotia have approved only two biologics treating psoriatic arthritis, while others have approved at least three and a few have not approved any.⁹⁴

Evidence does not yet exist to suggest that switching between biologics is a widespread practice. Practitioners are limited by the few biologics that are reimbursed in their province. The disparity in reimbursement policies between provinces may make switching more prevalent – if a patient moves between provinces, he or she may be forced to switch if he is not taking the preferred biologic. Biosimilars are still very new and it is too early to study switching practices in this field; only one has been approved so far, Omnitrope, and the general regulatory pathway and guidelines are still not finalised.

2.3.5 Summary

Overall, the various authorities in Canada seem to be relatively more permissive regarding therapeutic switching than in the US, perhaps reflecting the strong tradition of switching and substitution there. The use of switching by practitioners seems to follow these standards, although practice really varies from province to province. The best example of this is BC, which exhibits a relatively more conservative practice. The use of biologics, especially of potentially alternate treatments, is relatively new and uncharted territory in Canada, particularly with regard to biosimilars where substitution policies have not been finalised. Both policy and practice does not seem to have caught up with the US and many European countries, which will be discussed next.

2.4 The EU

To begin with, it is worth pointing out the obvious but important fact that Europe – and the EU – is a continent and association of states, rather than a country. Unlike the United States and Canada, the European Union is not a federation of states or provinces bound together and governed by a centralised federal government. Instead, the EU is a political and economic union of independent Member States which retain their sovereignty and national characteristics in a number of key areas. One of these areas is health care. (There are some areas, such as the market authorisation of pharmaceuticals, which Member States have ceded to a centralised pan-European institution – in this case, the European Medicines Agency (EMA) – but overall these are very few and far between. Still, they are important and will be discussed in more detail below.)

The 27 Member States that make up the European Union all have their own individual healthcare systems. Today there are no European-wide regulations or laws that govern or standardise the provision of health care throughout the Union. There have been discussions and some movement toward harmonising health care and investing the Union with some authority in health policy, but these are currently quite limited. For example, while the EU Commission has developed a number of public health programmes, it still does not have any

⁹⁴ Arthritic Consumer Experts, "Report card on provincial formulary reimbursement listings for biologic response modifiers", *Joint Health*, 2010, <http://www.jointhealth.org/programs-jhreportcard.cfm> (Accessed 15 February 2010).

authority over the organisation and execution of individual Member State's systems of care.⁹⁵ Instead, each country's healthcare system is the result of national political and cultural traditions and decisions. As a result, the type of healthcare systems in place vary from completely nationalised systems of care, such as the UK's National Health Service (NHS) (which is a publicly funded and provided health service, free at the point of use), to Bismarckian social insurance systems (currently in place in Germany and across Central and Eastern Europe), to a range of more hybrid models. This variation in design means that the role and influence of health policymakers, health insurers, patients and health professionals will vary from country to country and system to system. But before turning to this issue, it is worth discussing the policy areas where Member States have delegated authority to an EU institution. The most important of these is in the medical and pharmaceutical field: the European Medicines Agency (EMA).

2.4.1 The European Medicines Agency

For a pharmaceutical drug or treatment to become available within the EU it must go through a process of market authorisation. This process is meant to test and ensure the safety of the treatment and is a prerequisite for bringing a new drug to market. Over the last fifteen years this process has largely been transferred from the national, Member State level to the pan-European level with the creation of EMA. Since its inception in the mid 1990s, EMA and its precursor have increased the efficiency and speed at which medicines and pharmaceutical treatments are brought to the European market. EMA is responsible for coordinating the scientific evaluation of the safety, quality and efficacy of medicinal products for humans and animals. Most patients, policymakers, and other stakeholders would agree that EMA's procedures of drug authorisation have proven to be a success.

Crucially, EMA's remit does not extend beyond either market approval procedures or pharmacovigilance. Specifically, when it comes to therapeutic switching, EMA is not charged with regulating or issuing guidelines. Therapeutic switching does not fall under the remit of pharmacovigilance or post-marketing monitoring of drug safety. EMA does produce warnings and alerts when certain combinations of medicines and medical treatments have been found to be dangerous or unsafe for patients. But such alerts are part of its general pharmacovigilance remit and do not make up a pan-European policy on therapeutic switching. Instead, and as mentioned above, policies on therapeutic switching are designed and implemented at the national, and the regional or sub-national level.

Although no formal policies exist for biologics at the European level, it is important to note that EMA has voiced particular warnings on the practice of switching biologic medicines and substituting biologics with biosimilars. Indeed, this issue has become especially pertinent in the last several years with the emergence of biosimilar medicines; since biosimilars are not considered to be exact copies of a reference biologic, switching between biosimilar and biologics is often viewed not as a form of generic substitution, but rather as a switch between therapeutic alternatives. In this context, EMA states in a 2008 document, "Questions and Answers on biosimilar medicines", that:

⁹⁵ Gerlinger, T. & Urban, H., "From heterogeneity to harmonization? Recent trends in European Health policy", *Cadernos de Saude Publica* (Reports in Public Health), online, Vol. 23, 2, 2007, pp. S133-S142, p. S133. http://www.scielo.br/scielo.php?pid=S0102-311X2007001400003&script=sci_abstract (Accessed 8 April 2010).

Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.⁹⁶

In addition, EMEA's Executive Director, Thomas Lönngrén, has in public stated that EMEA would "not guarantee" that a biosimilar is interchangeable with its originator drug.⁹⁷ In essence, EMEA's position is that whether they are reference (or original) medicines or biosimilars, biologics should be dispensed according to the exact prescription written by the patient's physician. In other words, physicians should have full control over the decision to switch between biologics. This indicates that biologics are risky medicines that, if switched, should only be done on an individual patient basis, with caution and under physician supervision.

Nevertheless, the most relevant standards and guidance on therapeutic switching in Europe is found at the national or sub-national level. When it comes to biologic and biosimilar medicines, many European countries have heeded EMEA's recommendations and either banned the automatic substitution of biologic medicines at the national level via legislative measures or have published regulatory guidelines on the use of biologics.⁹⁸ For instance, some countries, such as the Netherlands, Norway and Slovenia, prohibit outright the automatic substitution of biosimilars. Others, including Spain and Slovakia, list products that cannot be substituted which include biologics. Still others, such as Austria and the Czech Republic, require physicians to prescribe biologics by brand name, rather than by the non-proprietary name (known as the INN). In addition, some countries lack guidelines that explicitly address the use of biologics and biosimilars, including Poland and Latvia.⁹⁹

It would seem that many countries are in agreement concerning the risks associated with switching biologics and treating biosimilars like generics. In general, however, standards and guidance on therapeutic switching – even with biologics – can vary considerably among EU countries. Illustrating these points with some examples, the following pages will outline and discuss the healthcare systems and therapeutic switching policies and practices (for both NCEs and biologic medicines) of three EU Member States: the UK, Sweden and Spain.

2.5 The UK

The UK's healthcare system provides universal coverage to all British residents. This is achieved through a system of nationalised care, free at the point of use, funded almost entirely through taxation. Currently, the UK spends a total of 8.4% of its GDP on health, which is slightly below the OECD average of 8.9%.¹⁰⁰ Out of this approximately 80% comes entirely from public sources.¹⁰¹ The main provider of care is the NHS, which is not only the largest employer in the UK, but one of the biggest employers in the world with a staff of over 1 million people.

⁹⁶ EMEA, "Questions and Answers on biosimilar medicines", Doc. Ref. EMEA/74562/2006 Rev. 1, London, 22 October 2002.

⁹⁷ APM Health Europe, "EMEA 'will not guarantee' that biosimilars are interchangeable with originator", 21 July 2006, <http://www.apmhealthurope.com/story.php?searchMode=0&mots=&searchScope=0&rubrique=&profil=&country=&ddebut=21%2F07%2F2006&dfin=21%2F07%2F2006&searchType=0&depsPage=2&numero=3250&ctx=9b587be41a1126ad8fc68f5a8c576c05> (Accessed 8 April 2010).

⁹⁸ See the Appendix for a table detailing the positions on biosimilars and substitution of a sample of EU Member States.

⁹⁹ Bialik, V. "Some problems associated with chemical substitution of original and biotechnological medicines to their equivalents", *Okol. Practice. Klin.* Vol. 5, No. 4, 2009, pp. 148-156.

¹⁰⁰ OECD, *Health at a Glance 2009 OECD Indicators*, Released on 8 December 2009.

¹⁰¹ OECD Health Data 2009 – Selected Data, "Health Expenditure".

Organisationally, the NHS is divided into three main layers:

- i) local Primary Care Trusts (PCTs) responsible for the provision and management of primary care in a given geographical area¹⁰²;
- ii) Strategic Health Authorities (SHAs) which oversee local PCTs and provides strategic direction for local care; and
- iii) the Department of Health which sets the broad direction for the NHS and provides national political leadership on health policy.¹⁰³

A clear majority of the NHS's budget, over 80%, is spent by local PCTs. These PCTs are the real nuts and bolts of the national healthcare system. GP surgeries, walk-in clinics and most hospitals all fall under the purview of local PCTs. Primary Care Trusts make decisions on what health services are to be provided in a local area and are also charged with ensuring that adequate levels of healthcare capacity are maintained for that area.¹⁰⁴ As for SHAs, there are currently 10 Strategic Health Authorities covering England. These bodies are charged with improving health services, monitoring the quality of care being provided by PCTs, ensuring national policies are implemented locally, and providing the link between central decision-making in the Department of Health and local healthcare bodies. The final organisational layer in NHS England is the Department of Health which provides the overall national leadership and sets the direction for national health policy.

2.5.1 Pharmaceutical policy

Prescription drugs are provided on a subsidised basis with a capped payment. Some medications and classes of drugs are provided free of charge to all patients, examples include contraceptives and medicines provided in a hospital or by a treating physician. All drugs which are subsidised are approved for reimbursement by the Department of Health. Since 1999 the National Institute for Health and Clinical Excellence (NICE) has been performing health technology assessments of new and existing medicines and medical technologies. NICE offers guidelines and guidance to local PCTs, general practitioners and all UK medical professionals. While NICE's guidance is non-binding, its influence on prescription policies and procedures is significant. Indeed, rising health expenditure has added to the influence of NICE's recommendations. Like many other developed countries, the UK has been struggling to cope with an ageing population and the accompanying steep rise in overall healthcare costs. Overall spending – public and private – has increased substantially over the last decade with 1.2% more of GDP being devoted to health today than in 2000.¹⁰⁵ While much of this increase has been the result of a conscious long-term effort on part of the British Labour government to increase levels of

¹⁰² In addition to PCTs there are also NHS hospital trusts and foundation hospitals. These trusts and hospitals differ from PCTs in that they are, in the case of hospital trusts, contracted out to provide secondary care for PCTs. Foundation hospitals are hospital trusts which have been found to be of excellent quality and allowed to achieve a certain degree of budgetary and practical independence from NHS guidelines and procedures.

¹⁰³ National Health Service (NHS), "What are Strategic Health Authorities?", <http://www.nhs.uk/chq/Pages/1075.aspx> (Accessed 8 April 2010).

¹⁰⁴ NHS, "What are Primary Care Trusts (PCTs)?", <http://www.nhs.uk/chq/Pages/1078.aspx?CategoryID=68&SubCategoryID=153> (Accessed 8 April 2010).

¹⁰⁵ OECD Health Data 2009 – Selected Data, "Health Expenditure".

UK health spending to European continental averages, over the same period of time numerous cost-containment policies have also been implemented. Many of these measures have concentrated on pharmaceutical spending.

As mentioned, NICE and health technology assessment (HTA) was introduced in 1999 and its scope and use has consistently widened and expanded. For instance, since 2005 NICE's technology appraisals – that is, its assessment of the cost effectiveness of a particular medicine or medical technology – are legally binding and the NHS in England and Wales must provide the funding for recommended medicines and treatments. NICE exists in addition to older cost-containment strategies such as the Pharmaceutical Price Regulation Scheme (PPRS). The PPRS is a negotiated agreement between the Department of Health and the British Pharmaceutical Industry. It seeks to control the price of branded drugs sold to the NHS by regulating the profits made on these drugs.¹⁰⁶ The PPRS is a long standing cost-containment initiative with the first agreement having been signed as early as 1957. As elsewhere in the developed world, the NHS has also focused much of its pharmaceutical cost-containment efforts on widening the pool of drugs available to patients and, in particular, prescribing more generic drugs. Overall this policy has been successful: currently, 83% of prescriptions in England within the primary care sector are for generic drugs. Seeking to improve even further on this number, the NHS and the Department of Health recently launched a full consultation on implementing generic substitution for the relatively small number of cases in which a generic is available but where branded drugs are being prescribed.¹⁰⁷ The proposed changes would authorise pharmacists to substitute a branded prescription with a generic equivalent. Tied to this growth in the use of generic drug prescribing has been an increase in the use of therapeutic switching.

2.5.2 Therapeutic switching policies

Current UK prescribing practices as outlined in the Medicines Act 1968 and the NHS Act 2006 prohibit pharmacists from automatically substituting one prescription drug for another, if a prescribing doctor has stated a product by brand name on the prescription.¹⁰⁸ Prescriptions made with only the name of the generic – its International Nonproprietary Name (INN) – may be substituted by a pharmacist without the knowledge or consent of the prescribing physician. Still, within the NHS there are prescribing restrictions on relatively few drugs and the rationing of drugs is not permitted. Those medicines that are restricted are either black-listed or are restricted due to the particular condition of a patient. Apart from these drugs, it is at the discretion of the individual physician to consider what is appropriate for his or her patients. The wider point being that, in fact, it is not legal for PCTs to restrict the prescribing of certain drugs simply based on cost. However, in an age of ever rising costs and demand for more and more health care, it is not always clear what PCTs are allowed to do and what they are not.

¹⁰⁶ Department of Health, "Introduction to pharmaceutical price regulation", http://www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/DH_4071841 (Accessed 8 April 2010).

¹⁰⁷ Department of Health, "The proposals to implement 'Generic Substitution' in primary care, further to the Pharmaceutical Price Regulation Scheme (PPRS) 2009", pp. 5-6, http://www.dh.gov.uk/dr_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_110511.pdf (Accessed 8 April 2010).

¹⁰⁸ *Ibid.*, p. 9.

The national guidelines that do exist reflect this ambiguity of the benefits of switching and the difficulties in finding a coherent best-practice model. Specifically, this is reflected in the General Medical Services (GMS) contract between general practices and primary care organisations. The GMS amounts to the equivalent of official guidelines regulating and setting the playing field for local primary care providers. This contract outlines what is expected from local practices in terms of medical quality and clinical standards, as well as what services practices can charge to PCTs. The GMS is consequently an important document in shaping local care policies and reflects wider national concerns over rising costs. But the GMS does not make it clear under which circumstances GPs should make use of switching. The most recent revisions to the GMS from 2006/7, Annex 8 – “Excessive or inappropriate prescribing: guidance for health professionals on prescribing NHS medicines” – is somewhat ambiguous about therapeutic switching. It begins by stating that:

As a guiding principle it is appropriate to prescribe the most cost effective medication for a patient. It follows that switching patients to less expensive drugs usually within a therapeutic class is generally appropriate where there is no contra-indication and where there is evidence of equal or greater efficacy.¹⁰⁹

Yet the document does express some clear reservations about this general principle. For instance, the next paragraph cautions that switching the drugs of a significant numbers of patients should only be undertaken where “predicted NHS savings is expected to be sustained and provided there is no clinical disadvantage for the patient”.¹¹⁰ A similar logic is applied where there is concern over a new drug’s effect on bio-availability levels.¹¹¹ Finally, paragraph 2.6 reassures prescribers and doctors that they still have the freedom to switch patients to higher cost drugs, where clinically appropriate. The cumulative effect of these exceptions is one of confusion and raises questions about the applicability of the above cited “guiding principle”. Indeed, the confusion in the GMS illustrates just how difficult it is to establish any “guiding principle” on therapeutic switching and how British health policymakers and practitioners are still grappling with this issue. As will be illustrated below, there is great variation in how PCTs and individual physicians interpret these guidelines and in how switching is implemented locally.

2.5.3 Therapeutic switching in practice

Formularies and prescription guidance are set at the local, PCT level. Here, therapeutic switching policies are becoming more and more common. In many parts of the UK, PCTs are implementing switching policies and patients are being moved from one drug to another. A 2007 survey found that 83% of PCTs surveyed in England had implemented a scheme for therapeutic switching.¹¹² This shift has largely focused on statins, and specifically on moving patients from pravastatin and atorvastatin to simvastatin, but over the past few years more and more PCTs have begun switching patients on proton pump inhibitors (PPIs). In fact, some sources

¹⁰⁹ British Medical Association and NHS Employers, “Revisions to the GMS contract 2006/7, Delivering investment in general practice”, p. 228, paragraph 2.3, http://www.nhsemployers.org/SiteCollectionDocuments/Revisions_to_the_GMS_contract_-_full_CD_120209.pdf (Accessed 8 April 2010).

¹¹⁰ *Ibid.*, paragraph 2.4.

¹¹¹ *Ibid.*, paragraph 2.5.

¹¹² Docherty, K. “Performance Management of Branded Medicines, PDIG Award”, Procurement & Distribution Interest Group, Autumn Symposium 2007, Guild of Healthcare Pharmacists, slide presentation, slide 26, www.pdig.org.uk (Accessed 8 April 2010).

suggest that the cost-savings realised from PPI switching actually exceeds that for statins; 11.2% versus 8.1%.¹¹³ These switching policies are largely in the hands of local PCTs and prescribing physicians which make the ultimate decisions on which patients to switch. While the intensity of switching policies varies from trust to trust and doctor to doctor, given the overall pressure locally and nationally to cut costs where possible, switching policies look set to increase in popularity. Still, there are real reservations about switching with many doctors questioning both the clinical basis for switching as well as the financial gains. For example, Professor Roger Jones (founding president of the Primary Care Society for Gastroenterology) has stated that switching may not be suitable for all therapeutic classes: “There is a good deal of anecdotal evidence, some of which might well have a basis in pharmacogenomics, of patients feeling much better on one agent than another very similar one.”¹¹⁴ Other physicians have questioned the economic benefits of switching. One GP from Middlesex has said that:

Drug switching is a cost-effective method for PCTs to liberate resources. If the drugs are of equal efficacy and are of no clinical detriment to patients, then the scope for switching will widen even further. But what seems to be overlooked is the administrative costs. Switching has increased the number of visits to GPs, nurse time and reception time.¹¹⁵

These reservations and the ambiguities surrounding the clinical and economic effectiveness of therapeutic switching policies were on full display in a 2007 panel debate organised by *Pulse Magazine*, a weekly magazine for general practitioners. This debate entitled “Drug switching: unacceptable pressure or essential cost control?” – included representatives from general practice, PCTs, NICE, academia and the pharmaceutical industry. In the transcripts of this debate it is clear how difficult it is to separate the clinical considerations from the economic and how much of a problem this is for prescribing physicians, healthcare trusts and patients.¹¹⁶ For example, on the issue of PCTs following different switching procedures – and thus indirectly establishing a nation-wide postcode lottery for what medicines are available to patients – it was pointed out that, as mentioned above, this is, in fact, not legal.¹¹⁷

2.5.4 Biologics, biosimilars, switching and automatic substitution policies

As elsewhere in Europe, biological drugs are becoming more widely used in the UK, particularly for patients with psoriasis, rheumatoid arthritis and those suffering from cancer. Currently, biological drugs are not allowed to be switched or substituted. The official guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) is that biosimilars should not be treated as other generic drugs and that automatic generic substitution should not take place. Instead, biosimilars should receive their own branded name so that prescription through INN is not possible and, as a result, automatic substitution cannot take place. In a document outlining the issues facing the MHRA (and recommending a Ministerial forum (MISG) meeting on it), the MHRA were quite clear that biosimilars were not generics and should therefore not be treated as such:

¹¹³ Wadhwa, R., “PCTs widen scope of drug switch scheme”, *Pulse Magazine*, 6 September 2007, <http://www.pulsetoday.co.uk/story.asp?storycode=4114383> (Accessed 8 April 2010).

¹¹⁴ *Ibid.*

¹¹⁵ *Ibid.*

¹¹⁶ *Pulse Magazine*, Pulse Debate, “Drug switching: unacceptable pressure or essential cost control?”, 3-part edition, 19, 20, and 22 November 2007, <http://www.pulsetoday.co.uk/feature.asp?featurecode=73> (Accessed 8 April 2010).

¹¹⁷ *Ibid.*, 19 November 2007.

The introduction of similar biological products (biosimilars) into clinical practice presents new challenges that are not ordinarily presented by small-molecule generic medicines. This is because a biosimilar can only be proven to be similar and not identical to its reference product...As biosimilars are not generics, the generic substitution rules...for small-molecules should not apply to biosimilars. Any decision to substitute one biotechnology medicine with another should only ever be made with the knowledge and explicit prior consent of the physician, regardless of how the prescription is written.¹¹⁸

With regards to biological switching, the guidance is less clear – as with therapeutic switching the formularies and rules are largely set at the PCT level – yet most factors point to biologics not being switched. Anecdotal evidence shows that therapeutic switching for biologics is something that does not take place. In an interview with the Stockholm Network, a London-based pharmacist at one of the UK's biggest research-based hospitals confirmed that formularies and stock purchasing tend to determine which biological agents are prescribed.¹¹⁹ The only scenario in which a patient could conceivably be switched would be if the patient came in from a different trust which operated a different formulary system and thus prescribed a different biologic. But even under these circumstances a switch would not be carried out by the pharmacy based on the risks of immunological reactions.¹²⁰

2.5.5 Professional organisations and patient rights groups

The British Medical Association (BMA) is the professional body and trade union for UK doctors. Given the nature of the healthcare system and dominance of the NHS in healthcare provision, the BMA is heavily involved in health policy making and has close interaction with government ministers, NHS officials and in setting official medical guidance. For example, the BMA is co-author with the NHS of the General Medical Services contract. As described above, this document is ambiguous on therapeutic switching.

On the issue of substitution and biosimilars many patient rights groups and professional organisations have been very active in response to the Department of Health's decision in April 2009 to implement Automatic Generic Substitution (AGS) from January 2010. Indeed, this caused real concern among patients, doctors and pharmacists. The result was an open letter to the government calling for a consultation on this issue.¹²¹ This letter was signed by a number of physicians and senior medical figures including the former president of the European Parkinson's Disease Association (EPDA), The Cure Parkinson's Trust and a number of leading medical figures. In support of this initiative the Joint Epilepsy Council of the UK and Ireland (JEC – an umbrella group representing 24 epilepsy organisations) created a petition on the British Prime Minister's website, <http://www.number10.gov.uk/>. In this the JEC, together with over 12,000 signatories, called on the government to exempt epilepsy from the proposals of generic prescribing.¹²² Following the publication of this letter and the launch of the petition, the DH opened a consultation which is set to close in the spring of 2010.

¹¹⁸ Medical and Healthcare Products Regulatory Agency, "Substitution of biosimilars", 9 March 2007, <http://www.mhra.gov.uk/home/groups/es-policy/documents/websitesresources/con2030475.pdf> (Accessed 8 April 2010).

¹¹⁹ Stockholm Network interview; available from the Stockholm Network, 35 Britannia Row, London N1 8QH.

¹²⁰ Ibid.

¹²¹ Baker, M., Candy, D., Kownacki, S., McCoig, A., Mossman, J. & Solanki, T., "Automatic Generic Substitution – Clinical implications for patients", <http://www.bps.ac.uk/uploadedfiles/clinicalsection/AutomaticGenericSubstitutionClinicalImplicationsForPatientsJuly09.pdf> (Accessed 8 April 2010).

¹²² Number10.gov.uk, "E-Petitions", 2010, <http://petitions.number10.gov.uk/epilepsygenerics/> (Accessed 8 April 2010).

2.5.6 Summary

The state of therapeutic switching in the UK is heavily influenced by the shape of the British healthcare system. The combination of a nationalised system of care with decentralised administration has resulted in switching policies being adopted and treated differently in different parts of the country. The lack of clear national guidelines – as well as the inherent complexity of shaping a workable and ethical policy of therapeutic switching – has complicated matters further. Discussions among GPs and health professionals also seem to suggest that switching is a complicated topic on which, in the UK, there is no clear policy guidance. For patients the result is a lack of clarity and knowledge of what switching policies are in place in their local PCT. This can potentially lead to a postcode lottery in the kind of prescription services that are provided.

With regards to biologics and biosimilars, switching rules and practices are a lot clearer. UK regulators do not treat or view biosimilars as generics. Consequently, automatic substitution is not allowed. Manufacturers of biosimilars are similarly encouraged to acquire a branded name so that there can be no confusion among pharmacists and substitution cannot mistakenly take place. While not as clear-cut from a regulatory point of view, switching between different biologics does not seem that common and through anecdotal evidence gathered it would seem that clinical considerations always come first.

The following section on Spain also shows how the adoption and implementation of therapeutic switching policies is dependent on existing healthcare policy and system design.

2.6 Spain

Similar to the UK and Sweden, the Spanish healthcare system provides universal coverage and is mainly publicly financed and delivered. Spain currently spends around 8.4% of its GDP on health, and around 70% of this is covered publicly.¹²³ Health care is one of several policies that have been devolved to the regional level over the last 30 years; it is now devolved to all 17 Autonomous Communities (ACs). The central government still has a broad but nonetheless important role, including introducing general healthcare legislation, evaluating and authorising new medicines (via the Spanish Medicines Agency or AEMPS) and coordinating the overall healthcare system via the Inter-territorial Council. In particular, the chief remaining bastion of the central government lies in finance – it is responsible for collecting healthcare funding and transferring it to ACs based on a capitation formula. Having said this, the bulk of health care, especially healthcare budgets and day-to-day services, is managed by the AC through regional healthcare services (SNS). ACs often further decentralise the delivery of healthcare services to provincial¹²⁴ or local governments or to “health areas” – geographic districts based on a range of factors such as population and socioeconomic levels.¹²⁵ Health areas can provide both primary and specialist (i.e. in-patient) services. However, the role of health areas and local governments differs from region to region.

¹²³ OECD, Country Statistics: Spain, 2007.

¹²⁴ Spain is composed of 50 provinces. Provincial delineations are much more long-standing than the ACs and are centred around cities. Some ACs are composed of only one province, but most have several provinces.

¹²⁵ Duran, A., Lara, J. & van Waveren, M., “Spain: Health System Review”, European Health Observatory *Health Systems in Transition*, Vol. 8, No. 4, 2006, p.31.

2.6.1 Pharmaceutical policy

In Spain, pharmaceutical policy can differ substantially among ACs and within them, due to the autonomy of the ACs and to the substantial role of private and hospital pharmacies. The private sector manages the entire supply chain of pharmaceuticals – the distribution, wholesale and retail – and correspondingly, the process of purchasing or procurement. Under the Spanish Pharmaceuticals Act, the central government establishes national drug prices and reimbursement lists. But regional health services¹²⁶ and individual hospitals set specific agreements with pharmacies (and manufacturers, in the case of hospitals) and determine the nuts and bolts of pharmaceutical benefits.¹²⁷ Regional health services reimburse pharmacies (through their professional colleges) the balance of drug costs on a monthly basis. Expert committees in ACs generally establish therapeutic guidelines, which are informed by regional HTA bodies. Regional health services develop therapeutic guidelines for hospitals, based on which pharmacy, and therapeutics committees within hospitals develop localised guidelines. It is worth noting that under the Law of Rights and Rational Use of Medicines, pharmacists (particularly hospital pharmacists) are often given a large role in the evaluation and selection of medicines, both in determining guidelines and in day-to-day practice.¹²⁸

In the last two decades, pharmaceutical expenditure as a percentage of total health expenditure has steadily increased, even more than in other developed countries. The ratio of pharmaceutical expenditure to total regional healthcare expenditure varies from region to region, but to illustrate, in 2002 pharmaceutical expenditure made up 23% of total national healthcare expenditure.¹²⁹ Among OECD countries, Spain has some of the highest pharmaceutical consumption, spending around \$824 on pharmaceuticals per capita in 2005.¹³⁰ This is partly because new drugs account for the largest market share in Spain.¹³¹ Responding to this, the central health administration has introduced measures to reduce costs and raise awareness of pharmaceutical expenditure, including a negative list of pharmaceuticals, price ceilings and drug “budgets” assigned to individual physicians. In addition, user co-payments are high – around 40% of the price of medicines – although in-patients, pensioners and handicapped persons receive prescription medicines for free and some chronic medicines have a 10% cap on the co-pay.¹³² Furthermore, most ACs have taken additional cost-containment measures, i.e. treatment protocols, reference pricing and generic substitution, which seek to change prescribing patterns, lower costs and improve treatment success.

2.6.2 Therapeutic switching policies

In this context of cost-containment and rising pharmaceutical costs, therapeutic switching policies are very common within ACs and individual hospitals. As discussed above, regional health services create therapeutic guidelines that are used in primary care and are the basis for more specific guidelines developed by hospitals.

¹²⁶ Regional health services manage pharmacy agreements for primary care services, excluding hospital care. Individual hospitals manage their own pharmaceutical policies and agreements.

¹²⁷ Duran, et al (2006), p. 95.

¹²⁸ Fundación Abbott, “Especialistas en Farmacia Hospitalaria analizan el desarrollo de los programas de intercambio terapéutico”, 18 June 2007, http://www.fundacionabbott.es/formacion_actividades_realizadas09_prensa01.html (Accessed 8 February 2010).

¹²⁹ Lauridsen, J., Bech, M., Lopez, F., Mate Sanchez, M. “Geographic and dynamic heterogeneity of public pharmaceutical expenditure”, University of South Denmark Health Economic Papers 2007, p.4,

<http://www.sdu.dk/~media/28A9727E8F0D4B53B98ADBA03C448878.ashx> (Accessed 5 February 2010).

¹³⁰ OECD, *Pharmaceutical Pricing Policies in a Global Market*, 2008, p. 35.

¹³¹ Costa-Font, J. & Puig-Junoy, J., “Regulatory Ambivalence and the Limitations of Pharmaceutical Policy in Spain”, Working Paper No. 762, Faculty of Economics and Business, Universitat Pompeu Fabra.

¹³² Duran, et al (2006), p.35.

These guidelines commonly include therapeutic interchange protocols and other programs aimed at improving the rational use of medicines. For instance, the Central Committee of Hospital Pharmacies in Andalusia – which is the largest AC in terms of population and also one of the poorest – implements a therapeutic interchange programme based on its determination of “therapeutically equivalent alternates”; this is used primarily for PPIs and a few other classes (including classes of biologic medicines, which will be discussed below). However, among regional health services the idea is that hospitals and individual physicians would have the ultimate responsibility in selecting treatments for their patients. This is certainly the case among hospitals – hospital-specific therapeutic interchange protocols are now quite widespread, probably due to the growing number of in-house pharmacy and therapeutics committees. Therapeutic interchange programmes are generally implemented with the said aim of improving the success of treatments (i.e. identifying and using the best therapies for a given condition) and containing pharmaceutical expenditure. This is confirmed by the Genesis Group (*Grupo de Evaluación de Novedades, Estandarización e Investigación en Selección de Medicamentos*), a project of the Spanish Society of Hospital Pharmacies (SEFH) aimed at compiling and assessing existing therapeutic guidelines. The project has found that there is considerable variation in protocols and selection of medicines in switching programs from hospital to hospital.¹³³

In Spain there are numerous physician and pharmacist organisations, which can also influence hospital protocols and switching decisions by individual physicians, although most of these bodies do not seem to make recommendations regarding therapeutic switching. Medical practice guidelines, which are administered by provincial medical colleges,¹³⁴ do address relevant aspects of the use of medicines in a general way. For example, the Official College of Physicians of Barcelona requires doctors to make treatment decisions based on clinical and medical rationale, that is, what is in the best interest of the patient, and not to be influenced by other incentives.¹³⁵ In addition, a doctor must inform patients fully regarding treatments, including risks and side effects, and the patient has the right to refuse a treatment (or a switch to another treatment). Among other professional organisations, the Spanish Society of Hospital Pharmacists (SEFH) appears to have the strongest focus on therapeutic practices, having published a manual on therapeutic interchange programs.¹³⁶ When it comes to making a therapeutic switch, SEFH recommends that pharmacists and physicians consider the current and future clinical needs of patients carefully, ensuring that the switch is without any risk to the patient. Furthermore, if a patient has a chronic illness that is difficult to control and is stabilised on a medicine, SEFH advises against modifying the treatment.

2.6.3 Therapeutic switching in practice

Some evidence from individual hospitals suggests that these or similar standards for therapeutic switching are practiced in Spain. For instance, a hospital in Alicante and one in Palma de Majorca emphasise careful

¹³³ Santos Ramos, B. “Experiencia española en selección y evaluación de medicamentos”, Grupo Génesis de la SEFH, 2007, http://www.connmed.com.ar/instituciones2/aafhospitalaria.org.ar/capacitacion/7congreso_jujuy/20-A.ppt (Accessed 8 February 2010).

¹³⁴ See Consejo General de Colegios Oficiales de Médicos de España, “Colegios Oficiales de Médicos de España”, 2008, <http://www.cgcom.es/colegios> (Accessed 8 February 2010).

¹³⁵ Consell de Col·legis de Metges de Catalunya, “Código de Deontología”, 2005, p.12, http://www.comb.cat/cast/comb/normativa/codi_deontologic/home.htm# (Accessed 8 February 2010).

¹³⁶ Grupo GENESIS, “Programa de Intercambio Terapéutico: Manual de procedimientos para su redacción”, 2005, p.5, http://genesis.sefh.es/Documents/PIT_VersionPreliminarI.doc (Accessed 7 February 2010).

consideration of patients and their treatment regime before introducing a therapeutic switch.¹³⁷ Particular attention is paid to patients on medications that are not advisable to change, such as antiepileptics, antidepressants or medicines treating very specific indications. In cases like these, practitioners are encouraged to make an exception to the therapeutic interchange protocol, simply by indicating the reason on the prescription. In one hospital in Valencia physicians can reject a switch by speaking with the pharmacist.¹³⁸ The reasons for not switching can include an allergy or other contraindication, or purely because the patient wishes to continue on his established medication.

However, in contrast to these findings, the SEFH's own evidence indicates that in many other cases patients who are stabilised on a treatment are often automatically switched to the hospital's preferred therapeutic equivalent upon being admitted. Furthermore, the SEFH finds that mechanisms are often not in place to adapt switching protocols when a switch is unsuitable.¹³⁹ A second hospital in Palma de Majorca confirms this.¹⁴⁰ Its therapeutic interchange programme was initiated because patients were entering the hospital (i.e. were stabilised) on medicines that were not on its preferred list. The express purpose of the programme was to switch patients to preferred drugs or to suspend the use of a non-preferred drug during the patient's hospitalisation. Although the intention of the hospital is to give patients the most pharmacologically-effective and cost-effective treatment, the programme requires a switch of medications for patients who are stabilised on a treatment. The protocol requires doctors to choose the preferred therapeutic alternative on a case by case basis, to carefully consider the patient, but there is no explicit mechanism for rejecting the switch.

2.6.4 Biologics, biosimilars, switching and automatic substitution policies

When it comes to biologic medicines, the practice of therapeutic switching is regulated more stringently and explicitly than chemical-based drugs, although some confusion still exists as to the scope of the regulations. In 2007, the Spanish Medical Agency (AEMPS) modified the list of medicines that should not be automatically substituted by a pharmacist¹⁴¹; the Ministerial Order SCO/2874/2007 adds biologic medicines to this list and requires such medicines to be under special physician control. In large part, this measure was a response to the introduction of biosimilars onto the European market. This order – and other Spanish regulations – does not use the term biosimilar, instead biosimilars are included under the broader category of biologics.

The 2007 modification states that it should be applied universally to automatic substitution in hospital as well as community pharmacies.¹⁴² However, some ambiguity purportedly exists as to the use of automatic substitution in hospitals – SCO/2874/2007 states that the modification to the list of non-substitutable medicines should be “in accordance with” the 2006 Law of Rights and Rational Use of Medicines, which

¹³⁷ Hospital General Universitario de Alicante, “Guía de Intercambio Terapéutico”, 2009.

¹³⁸ Navarro de Lara, S., Font Noguera, I., Lerma Gaude, V., Lopez Briz, E., Martínez Pascual, M.J., & Poveda Andres, J.L., “Programa de calidad aplicado a la sustitución de medicamentos no incluidos en la Guía Farmacoterapéutica del hospital”, *Farmacia Hospitalaria*, Vol. 28, No. 4, 2004.

¹³⁹ Santos Ramos (2007).

¹⁴⁰ Ventayol, P., Puigventós, F., Delgado, O., Martínez, I., Maroto, A., Comas, F., Crespi, M. & Serna, J., “Programas de intercambio terapéutico en el hospital: la evidencia en favor del paciente”, *El Farmacéutico Hospitalares*. No. 131. Monográfico, 2002.

¹⁴¹ See: Artículo 86.4 of Ley 29/2006.

¹⁴² Galduf, Cabanas, J. & Gil Aguirre, A., “Excepciones a la sustitución automática de medicamentos: el caso de los medicamentos biotecnológicos”, *Revista Española de Economía de la Salud*, Vol. 61, No. 8, p. 429.

promotes the practice of therapeutic switching by hospital pharmacists.¹⁴³ An ongoing debate on the remit of the regulation has ensued among experts and hospitals. Some experts maintain that the 2007 regulation should be understood as impacting all pharmacies, given its strong emphasis on the role of physicians in switching biologics and the patient safety concerns raised. However, the AEMPS itself has privately questioned the applicability of the regulation to hospital pharmacies,¹⁴⁴ reinforcing the uncertainty surrounding how biologics should be treated in hospital therapeutic practices.

If the 2007 regulation's intention is to make healthcare practitioners aware of the safety concerns associated with switching biologics and to shift therapeutic practices, the evidence indicates that this has not been very effective in practice. Rather, physicians, hospitals and even ACs continue to give pharmacists a large role in making switching decisions involving biologic medicines and are making these switches on a general, rather than individual patient, basis. For instance, in Andalusia it is common for pharmacy and therapeutics committees in hospitals to list in their therapeutic guidelines "therapeutically equivalent alternatives" among several classes of biologics, including erythropoietins, interferons and low-molecular weight heparins.¹⁴⁵ This would seem to indicate to physicians and pharmacists that they can switch patients between alternate biologics in the same way that they switch between NCEs – without considering the patient or medicine on a case by case basis. Fundamentally, it appears that biologic medicines are not treated any differently in therapeutic guidelines than NCEs and that practitioners are not made sufficiently aware of the safety risks associated with switching biologics. Moreover, conventional standard-setting institutions, such as national legislation and the AEMPS, do not aid in educating or guiding physicians and pharmacists concerning biologic medicines and their safe use.

2.6.5 Summary

The practice of therapeutic switching is extremely common in Spain, but the highly decentralised healthcare system there means that both guidelines and practice vary significantly across the country. On the whole, regulatory and expert bodies advocate for the safety of patients and their ability to have a voice in treatment decisions, especially in the case of patients who are established on a long-term treatment regime. While some examples of practice along these lines exist, there is also substantial evidence suggesting that these standards are not fully implemented. Importantly, when it comes to biologic medicines, regulatory standards do not go far enough to inform and guide practitioners on safe therapeutic practice and the evidence suggest that actual practice is far from cautious in ensuring patients' safety.

2.7 Sweden

In Sweden, health care is viewed as a universal right and was a foundational element of the Swedish welfare state with universal access to health and social care being enshrined in national legislation. At 9.1% of GDP, Sweden's spending on health care is slightly higher than the OECD average of 8.9%.¹⁴⁶ The public share of this

¹⁴³ Dorantes Calderón, B. 'Controversias sobre medicamentos biosimilares y su intercambio terapéutico', *Farmacia Hospitalaria*, Vol. 33, No. 4, 2009.

¹⁴⁴ Ibid.

¹⁴⁵ Ibid. Also see, Santos Ramos (2007).

¹⁴⁶ OECD Health Data 2009, 'How Does Sweden Compare', <http://www.oecd.org/dataoecd/46/6/38980334.pdf>

expenditure is just over four-fifths, at 81.7%.¹⁴⁷ Overall political responsibility for health and social policy is vested with the national government while county council and municipal bodies are charged with the implementation, contracting and actual provision of care. Specifically, Sweden's 18 county councils (*landsting*), 2 Regions (*regioner*) and one independent municipality are charged with the actual responsibility of healthcare delivery in their given area. This includes primary care, hospitals, public health and preventative care. The decentralisation of healthcare delivery to regions and county councils has resulted in some regional variation in the kind and quality of care that is provided. Although not as pronounced as in other parts of Europe (like Spain and the UK) these variations in care can be significant. For example, when it comes to patient waiting times there are substantial differences between the best and worst performing county councils. A survey carried out in the spring of 2009 by the Swedish Association of Municipalities and County Councils found that over 95% of patients in the top-performing county council, Halland, saw a doctor within days of attempting to make an appointment.¹⁴⁸ The figure for the worst performing council, Dalarna, was 83%.

County councils also have broad budgetary and revenue raising powers in the area of health care. In 1997 this budgetary responsibility was expanded with councils being made responsible for also covering pharmaceutical expenditure. As will be seen below, this has resulted in significant variation as to what types of pharmaceutical prescribing policies have been implemented and the use of policies like therapeutic switching. The main tool used by county councils to influence pharmaceutical prescribing lists and prescribing practices is pharmaceutical committees (*läkemedelskommittéer*).

2.7.1 Pharmaceutical policy

Pharmaceutical policy is largely set at the national level through three different government entities¹⁴⁹:

- ii) the Medical Products Agency (MPA, *Läkemedelsverket*), a government agency responsible for the market authorisation, regulation and safety of medicines and medical treatments;
- iii) the Dental and Pharmaceutical Benefits Agency (TLV *Tandvårds- och Läkemedelsförmånsverket*), a government agency which determines reimbursement levels and what medicines should be publicly subsidized; and
- iv) the National Corporation of Swedish Pharmacies (*Apoteket AB*), until recently¹⁵⁰, a wholly state owned chain of pharmacies representing a state sanctioned monopoly on the sale of prescription and over the counter (OTC) pharmaceuticals.

For the purposes of this paper, the MPA is the most important as it sets national prescribing and substitution lists for pharmaceuticals.

¹⁴⁷ OECD Health Data 2009, Selected Data, Health Expenditure, "Public expenditure on health, % total expenditure on health", 2007.

¹⁴⁸ Sveriges Kommuner och Landsting, *Hälsa- och sjukvård ur olika perspektiv, Jämförelse mellan landsting 2009*, 2009, p. 51.

¹⁴⁹ http://www.skl.se/web/Okad_produkativitet_i_landstingen.aspx (Accessed 8 April 2010).

¹⁴⁹ In addition, the Swedish National Board of Health and Welfare (*Socialstyrelsen*) has some responsibilities for medicines and pharmaceuticals, but these are from a public health point of view and not budgetary or safety related. For example, since 2005 this body has collected information on all prescriptions dispensed.

¹⁵⁰ From January 2010 this state monopoly will cease to exist with private pharmacists allowed to take over and run state-run outlets. While this is a massive shift in Swedish pharmaceutical policy, these changes in ownership structure does not change the basic regulations guiding prescription and dispensing policies which are still shaped centrally by the MPA. The move is thought to bring about greater competition and efficiencies in the pharmaceutical market.

Since 2002, Sweden has had a system of generic substitution, whereby pharmacists (most of which work for, or within, the state-run National Corporation of Swedish Pharmacies) are charged with substituting and dispensing a prescribed drug for the cheapest equivalent.¹⁵¹ Exceptions to this rule can only be made either if a prescribing physician has indicated on the prescription that the drug must not be substituted, or if the patient is willing to pay the difference in price between the substituted medicine and the prescribed. The MPA determines which medicines qualify as being exchangeable and can be included on the national substitution list. Since 2007 medicines can be approved for substitution and included on the MPA's substitution list even before they have been approved for reimbursement by the pharmaceutical benefits agency TLV. Medicines are only included on this list if they have been judged as medically equivalent in terms of efficacy and safety. Each medical product is subject to a separate evaluation. The following are the most important criteria the MPA uses to evaluate the interchangeability of a medicine:

- the product should be approved as a medicine or medical treatment;
- it should contain the same active ingredient(s);
- it should contain the same amount of the active ingredient(s);
- it should have the same method/means of delivery; and
- the product should be judged to be bioequivalent/therapeutically equivalent.¹⁵²

While these criteria include therapeutic equivalence as a form of evaluation, it is clear from the emphasis on similarity of active ingredients that therapeutic equivalence in itself is not enough for a medicine to be deemed interchangeable and placed on the MPA's national list of interchangeable medicines. Indeed, the MPA's work on the national substitution list **does not** include medicines or recommendations for therapeutic switching. This list is what is used by pharmacists across the country to substitute prescribed medicines. Pharmacists are not allowed to change or substitute any medicines which are not included on the MPA's national substitution list. Specifically, pharmacists are not allowed to carry out therapeutic switching which is, as will be discussed in the next section, mostly in the hands of individual physicians, local healthcare centres and county councils. As for the MPA's policies on biologics they will be outlined in more detail below, but suffice it to say that since March 2007 biosimilars have not been deemed as being interchangeable or substituted for an already approved medicine. Consequently, they are not included on the national substitution list.

2.7.2 Therapeutic switching policies

Compared to generic substitution, Sweden's switching policies are not particularly widespread or well publicised. While in-depth and transparent rules exist for generic substitution – with the MPA and national government having since 2002 made a clear push towards increasing the use of generic drugs in an effort to lower spending on pharmaceuticals – similar guidance does not exist for switching. Just as in the UK, switching policies are much less transparent and, apart from pharmacists not being allowed to substitute therapeutically

¹⁵¹ Medical Products Agency (MPA, Läkemedelsverket), "Generisk förskrivning [Generic prescription]", January 2007. This study is an outline of the agency's views on generic prescribing; it includes a detailed history of the effects of generic substitution reforms in 2002.

¹⁵² MPA, "Kriterier för utbytbarhet" (Criteria for Substitution), Original in Swedish; translated into English by Stockholm Network. <http://www.lakemedelsverket.se/malgrupp/Halso--sjukvard/Forskrivning/Utbytbara-lakemedel-/Kriterier-for-utbytbarhet/> (Accessed 8 April 2010).

equivalent medicines, the onus on switching is largely confined to individual physicians, healthcare centres, hospitals and, most importantly, county councils. This is true for primary care, in-patient care, and drugs dispensed in hospitals. In large measure, this is due to pharmaceutical budgetary responsibilities having been decentralised to county councils. Not surprisingly, councils now have a budgetary interest in keeping expenditure as low as possible. Indeed, policies aimed towards achieving cost-effective use of pharmaceuticals are chiefly promulgated at the county council level. Even in those county councils where individual health centres are being given more individual budgetary responsibility, county councils still retain overall budgetary responsibility. Designing and implementing therapeutic switching is chiefly carried out through, firstly, pharmaceutical formularies and active county council guidance and, secondly, through individual decisions and pharmaceutical lists made at the hospital level. To understand how the Swedish equivalent of therapeutic switching works, one needs to examine in detail how pharmaceutical budgets are set at the county council level and how individual prescribers are incentivised to prescribe certain types of drugs and drug classes.

2.7.3 Therapeutic switching in practice

County councils use a range of tools to control their health and pharmaceutical costs. For example, many county councils have begun to decentralise parts of their budgets down to the local health centre level. In the county council of Uppsala, local health centres (the equivalent of the UK's GP surgeries and proposed polyclinics) were in 2009 given greater budgetary responsibility for pharmaceuticals.¹⁵³ Under these new responsibilities health centres in Uppsala were instructed to devote a maximum of 20% of their pharmaceutical budgets to medicines and treatments classified by the county council as expensive. If this maximum of 20% were breached, health centres would see cuts in their individual budgets for the following fiscal year, 2010. The purpose of the initiative was to pressurise health centres into following county council guidelines on pharmaceuticals and, specifically, centrally set formularies. Only one health centre managed to meet these requirements and, consequently, many others saw their budgets cut drastically. Other county councils have implemented different types of budgetary mechanisms, but still retaining the overall goal of decentralising budgetary responsibility. This move towards greater budgetary control at the health centre level has been indirectly incentivised by the Swedish central government which, since 2002, has pre-defined its annual block grants to county councils for pharmaceutical expenditure. Under this scheme councils are allowed to keep a proportion of unused funds but are similarly obliged to make up for any shortfalls.

As mentioned above, all county councils are legally obliged to set up pharmaceutical committees which offer advice and guidance to all healthcare practitioners – and in particular prescribers – within the county. Their main instrument of doing this is through drug formularies (*läkemedelslistan*). The main purpose of these committees (and hence of their formularies) is: “through recommendations to health and care practitioners...contribute to a reliable and rational use of pharmaceutical drugs within and by the county council.”¹⁵⁴ Ensuring that such recommendations and the work of the committees is based on “science and tried and tested experience”,¹⁵⁵ these committees are also charged with having their activities informed and/or

¹⁵³ *Dagens Medicin*, ‘Vårdcentraler i Uppsala län lyckades inte spara på läkemedel’, 27 Januray 2010, <http://www.dagensmedicin.se/dagensapotek/nyheter/2010/01/27/varidcentraler-lyckades-int/index.xml> (Accessed 8 April 2010).

¹⁵⁴ Statutory Law: Lag (1996:1157) om läkemedelskommittéer, paragraph 3, <https://lagen.nu/1996:1157> (Accessed 8 April 2010).

¹⁵⁵ *Ibid.*, Paragraph 5.

coordinated with academic institutions, public bodies and other pharmaceutical committees. While not legally obliged to follow these lists, practitioners and hospitals are subject to a number of actions if they are viewed as failing to sufficiently implement the guidance issued by a pharmaceutical committee. The relevant legislation states that if a committee finds that there are “deficiencies in the use of pharmaceuticals”, the committee should point this out and offer health practitioners the relevant “education to correct [these] deficiencies”.¹⁵⁶ In addition to these educational sanctions, hospitals and individual health practitioners who do not follow committee guidelines and run over their budgets are likely to face budgetary cuts from the county council.

Most county councils have specific goals for how much of a medicine or within a therapeutic class they wish to have prescribed.¹⁵⁷ Each county council’s pharmaceutical committee sets prescription targets to therapeutic quotas which are then passed on to prescribers. These targets and quotas are based on prescribing information and statistics collected from the National Corporation of Swedish Pharmacies. These targets are specific to certain medicines and most of them measure a level of usage of a group of medicines or a specific drugs rate of prescription within a therapeutic class. One example would be that 80% of statins prescribed should be simvastatin, an off-patent and thus cheaper version of the many existing statins.¹⁵⁸ When asked about these quotas in a 2008 survey, county councils responded that it is their expectation that these quotas should be followed.¹⁵⁹ Sörmland county council currently lists a number of targets for several different therapeutic classes.¹⁶⁰ For instance, in addition to the 80% requirement for simvastatin, there is also a requirement that omeprazol should be prescribed 80% of the time for PPI prescriptions.¹⁶¹ Similarly, generic gabapentin is targeted to make up 90% of all gabapentin prescribed in its therapeutic class.

Various incentive-based systems of reward are used to push local health centres and prescribers to follow these formularies and targets set by pharmaceutical committees. For example, the county councils of Kalmar, Stockholm, Sörmland and Västra Götaland have all implemented some system of incentive-based rewards system.¹⁶² Under these systems health centres and prescribers (both public and privately contracted) can receive additional funds if they, for instance, meet all or most of the targets set by their respective council’s pharmaceutical committee.

2.7.4 Biologics, biosimilars, switching and automatic substitution policies

Just like many other EU Member States, Sweden has over the past decade seen the introduction of biological medicines into its medical lexicon. While these drugs are becoming more widespread, they are still a minority of medicines used and, as explained above, they are so far only used to treat certain conditions like psoriasis, rheumatoid arthritis, cancer and certain rare diseases. Because of their relatively high cost (these drugs are

¹⁵⁶ Ibid., Paragraph 4.

¹⁵⁷ Levin, L.A., Andersson, D., Anell, A., Heintz, E., Hoffman, M., Schmidt, A. & Carlsson, P., *Styrformer för effektiv läkemedelsanvändning*, (Translation: Policies for effective use of pharmaceutical drugs), University of Linköping, University of Lund, and Nätverk för läkemedelsepidemiologi (National Network for pharmaceutical epidemiology; a government research foundation), 2010, p. 28, <http://www.nepi.net/Artiklar.htm> (Accessed 8 April 2010).

¹⁵⁸ Ibid.

¹⁵⁹ Ibid.

¹⁶⁰ Sörmland County Council, “Läkemedelsribbor 2010”, (Pharmaceutical targets), http://www.landstinget.sormland.se/Sidans_katalog/5343/L%C3%A4kemedelsribbor%202010.pdf (Accessed 8 April 2010).

¹⁶¹ Ibid.

¹⁶² Levin, et al (2010), p. 23.

predicted to substantially increase future overall public expenditure on pharmaceuticals and medicines¹⁶³) Swedish regulators and health policymakers have issued detailed guidelines to prescribers on when biological drugs can and should be prescribed. As this is primarily a cost and not a safety issue – deciding whether or not a biological drug is safe enough to be taken to market is taken by EMEA and/or the Swedish MPA – the regulation and oversight of prescription practices for biologicals is largely a consequence of decisions taken by the Dental and Pharmaceutical Benefits Agency TLV. For example, in 2007 when TLV decided to include Raptiva (a psoriasis drug which was eventually withdrawn in 2009 over safety concerns) on its list of reimbursable drugs, the agency stated clearly that the drug could only be used by certain patients under certain circumstances. Specifically, the medicine was only to be used in the treatment of patients with “medium to serious forms of chronic plaque psoriasis where other systematic treatment (including TNF inhibitors) was unsuitable” [Original in Swedish].¹⁶⁴

On the issue of biosimilars, automatic substitution and inter-changeability Swedish regulations are quite clear. Just like most other EU Member States, automatic substitution with biosimilars is not allowed. The MPA in 2007 made a clear decision that currently EMEA approved biosimilars were not deemed as interchangeable.¹⁶⁵ The basis for this decision was the evaluation of the two CHMP approved growth hormones: Omnitrope and Valtropin. With regards to Omnitrope the MPA stated that while it was not aware of any differences in activity between Omnitrope and its biological counterpart Genotropin, the agency still had reservations regarding the possible negative immunological effect of the drug on patients.¹⁶⁶ Similarly, with Valtropin the MPA stated that the clinical data did not support or show conclusively that it could be substituted for its biological counterpart, Humatrope. Taking this logic even further, the agency stated that it did not see how more complex biosimilars, such as erythropoietin and even insulins – which would be up for evaluation in the foreseeable future – could be approved for automatic substitution. The MPA said that such approval was “doubtful”.¹⁶⁷

2.7.5 Professional organisations and patient groups

Unlike North America, Sweden does not have a strong culture of patient rights group or health professionals being publicly involved in the policy making process on therapeutic switching either at the national or local level. Still, many groups exert a good deal of influence on overall health policy, particularly those that are unionised. In this regard the Swedish Medical Association (*Sveriges läkarförbund*, SLF), the professional organisation and union for medical practitioners, is quite influential. For example, on the issue of both generic substitution and generic prescribing (currently Sweden only runs a system of substitution not prescribing) the SLF were asked by the MPA to give their opinion. In their public responses the SLF have been critical of generic substitution making it clear that their preference was generic prescribing.¹⁶⁸

¹⁶³ Sweden's National Board of Health and Welfare (Socialstyrelsen), *Läkemedelsförsäljningen i Sverige – analys och prognos*, (Pharmaceutical drug sales in Sweden – analysis and predictions), September 2007, National Board of Health and Welfare, Stockholm, p. 27.

¹⁶⁴ Dental and Pharmaceutical Benefits Agency TLV, Decision on Raptiva, 30 March 2007, http://www.tlv.se/Upload/Beslut_2007/BES_070330_raptiva.pdf (Accessed 8 April 2010).

¹⁶⁵ MPA, “Biosimilars’ bedöms inte vara utbytbara” (Biosimilars judged not to be interchangeable), 15 March 2007, <http://www.lakemedelsverket.se/malgrupp/Halso---sjukvard/Artikelsamlingar/Lista/Lakemedelsformanerna-och-utbytbarhet/Biosimilars-bedoms-inte-vara-utbytbara/> (Accessed 8 April 2010).

¹⁶⁶ Ibid.

¹⁶⁷ Ibid.

¹⁶⁸ Läkarförbundet, “Läkarförbundets syn på generisk förskrivning” (the Swedish Medical Association's view on generic prescription), 26 August 2005, <http://www.slf.se/Vi-tycker/Remisser/Remissvar/Lakarforbundets-syn-pa-generisk-forskrivning/> (Accessed 8 April 2010).

At the county council level the interaction between pharmaceutical committees and patients rights organisations is relatively limited. Östergötland is the only county council whose pharmaceutical committee includes a permanent representative from a patients' rights group. It is also the only council in which the representative is actively engaged in the work of the committee. As of 2008 this representative was from the regional disabled patients' rights organisation, *Handikappföreningarna Östergötland*.

2.7.6 Summary

Just like the other countries examined in this study, the design of the Swedish healthcare system has heavily influenced its policies on therapeutic switching and biologics. The decentralisation of healthcare provision and funding to the regional, county council level has resulted in a good deal of variation in how pharmaceutical formularies are designed and in what manner switching takes place. County councils make their own decisions – chiefly through pharmaceutical committees and set formularies – on how medicines are to be prescribed in different therapeutic classes. While this has resulted in different councils using varying mechanisms for implementing their prescribing policies – chiefly through incentivisation schemes – overall there seems to be a good deal of overlap in the goals and targets set for many drugs and therapeutic classes. For instance, most county councils have set targets for the prescription rates of statins. By and large, for patients, it would seem that despite the scope for variation inherent in the structure of the healthcare system, switching policies overall have tended to focus on similar areas of drugs. With regard to biosimilars the Swedish authorities have put patient safety first by taking a very hard line and not allowing automatic substitution.

In terms of national regulation, like the UK, national guidance on general therapeutic switching is not detailed and has mainly been *de facto* confined to the county council and individual practice level. However, for biologics the opposite is true. For biological drugs as well as biosimilars, reimbursement decisions as well as substitution rules are quite clear: biosimilars are not allowed to be substituted for their biological counterpart. Similarly, the reimbursement agency TLV is quite clear on when and how approved biological drugs can be prescribed.

Summary of Section 2

Table 1: Summary of Section 2

	Therapeutic switching policies	Therapeutic switching in practice	Biologics, biosimilars, switching and automatic substitution policies
US	<p>Switching is not federally regulated.</p> <p>States sets medical and prescribing guidelines and regulate health insurers.</p> <p>Public interest groups (physician, pharmacist, patient) have powerful influence on switching policies, ranging from AMA to ACCP.</p>	<p>Health insurers are used by the majority of Americans; widespread use of tiered formularies, can include biologics.</p> <p>Federal programs such as the VHA and Medicare run their own national switching policies.</p> <p>States operate switching policies for state-run health providers (Medicaid, SCHIP, general insurance).</p> <p>Individual hospitals often set switching policies through pharmacy and therapeutics committees.</p>	<p>FDA recommends against switching without consent of physician. No regulatory pathway exists for biosimilars.</p> <p>Switching of biologics may be mandated by some private payers such as managed care organisations.</p>
Canada	<p>Switching is not federally regulated.</p> <p>Individual provinces set medical practice guidelines.</p> <p>Public interest and professional groups are less influential but still have important voice.</p>	<p>Individual provinces fund primary healthcare and run switching policies for primary care and in some provinces, non-primary prescription drugs.</p> <p>Individual hospitals set more detailed switching policies; many allow automatic substitution and ability to make exceptions varies.</p>	<p>Product approval by Health Canada does not mean it endorses automatic substitution; provinces set switching standards for biologics but most have not published any; pathway for biosimilars not yet finalised.</p>
EU	<p>Switching is not regulated on a pan-European basis.</p>	<p>Not applicable.</p>	<p>EMA has no regulatory mandate but recommends that physicians make the decision to switch a biologic or biosimilar. Recommends against substitution for biosimilars. EU Member States may set standards for switching biologics.</p>
UK	<p>Centrally formulated guidelines (GMS) exist but they are unclear.</p>	<p>PCTs make and implement switching policies; large variation in prescription policies.</p>	<p>UK regulators do not treat or view biosimilars as generics. Consequently, automatic substitution is not allowed. Manufacturers of biosimilars are similarly encouraged to acquire a branded name so that there can be no confusion among pharmacists and substitution cannot mistakenly take place.</p>

Spain	Switching is not centrally regulated. Autonomous Communities (ACs; regional governments, e.g. Catalonia) regulate medical practice standards.	ACs provide healthcare and set general standards for switching; most implement therapeutic interchange for common medicines, e.g. PPIs, statins, etc. Hospitals set more detailed switching policies.	Central legislation prohibits automatic substitution of biologics, however scope of application to include hospital pharmacies is under debate. Some ACs and hospitals designate therapeutic alternatives among biologics in guidelines.
Sweden	In terms of national regulation, like the UK, national guidance on general therapeutic switching is not detailed and has mainly been <i>de facto</i> confined to the county council and individual practice level.	Different councils use varying mechanisms for implementing their prescribing policies – chiefly through incentivisation schemes – but overall there seems to be a good deal of overlap in the goals and targets set for many drugs and therapeutic classes. Most county councils have set targets for the prescription rates of statins.	For biological drugs as well as biosimilars, reimbursement decisions as well as substitution rules are quite clear: biosimilars are not allowed to be substituted for their biological counterpart. Similarly, the reimbursement agency TLV is quite clear on when and how approved biological drugs can be prescribed.

Section 3: Conclusions and policy recommendations

The rising cost and increased demand for more health care is placing a serious burden on healthcare systems around the developed world. Over the last decade health expenditure in all major OECD countries, including the countries surveyed in this paper, has risen dramatically. In the US spending has gone up from 13.4% of GDP in 1997 to 16% in 2007.¹⁶⁹ In Canada, during the same period, expenditure rose from 8.8% of GDP to 10.1%.¹⁷⁰ In the UK the figures are 6.6% to 8.4%.¹⁷¹ And Spain and Sweden saw rises from 7.3% to 8.5% and 8.1% to 9.1%, respectively.¹⁷² In response to this both public and private bodies are implementing a variety of cost-containment measures and reforms. On pharmaceuticals, these range from limiting reimbursement rates, introducing generic prescription and/or substitution, and implementing therapeutic switching and interchange policies.

As this paper has outlined, therapeutic switching and interchange has gained traction in many countries and is becoming a key tactic for local and national healthcare bodies in implementing more cost-effective prescription policies. In the five surveyed countries – the US, Canada, the UK, Spain and Sweden – switching and substitution policies are being actively used to limit rises in pharmaceutical expenditure and to streamline prescription practices. The way in which switching policies are being implemented varies a great deal between the surveyed countries and depends largely on the design of their respective healthcare systems. For example, the fragmentary nature of the American healthcare system means that a variety of healthcare actors, ranging from the central government and state governments to private health insurers, all, in one form or another, shape the formulation and implementation of therapeutic interchange policies. In the UK the decentralised nature of healthcare delivery (largely in the hands of local Primary Care Trusts) and the lack of clear national guidelines has resulted in a virtual postcode lottery in how switching takes place.

Whether switching takes place as part of a formal protocol or based on the discretion of a patient's physician, it has many benefits and risks. It may help identify more effective and sometimes more cost-effective treatments, improving the quality of life for patients dealing with chronic conditions. But therapeutic switching may also result in undue medical risks and jeopardise the independence and preference of patients if it is not done cautiously and with the appropriate information. This is especially the case for risky patients and those that are already stabilised on a treatment regime.

In addition to switching for chemical-based medicines this paper has also examined how biological drugs and, in particular, biosimilars have figured within switching and substitution policies. By and large, this paper has found that, in the surveyed countries, regulators and health policymakers have taken a much more active role with

¹⁶⁹ OECD Health Data 2009, Frequently requested Data, Internet update version November 09, "Total expenditure, % of GDP", http://www.oecd.org/document/16/0,3343,en_2649_33929_2085200_1_1_1_1,00.html (Accessed 8 April 2010).

¹⁷⁰ Ibid.

¹⁷¹ Ibid.

¹⁷² Ibid.

regard to formulating switching policies for biologics and biosimilars than they have with chemical-based drugs. While this finding does not mean that all surveyed countries have embraced the same policies, it suggests that policymakers have real concerns over the switching and substitution policies for biologics and biosimilars. Indeed, many experts highlight the immunogenic potential of biologic agents, saying that this factor makes finding the most appropriate therapy a risky process. Once the best treatment is identified, switching to another biologic – whether a biologic or biosimilar – carries an unjustified risk, and thus involves a decision that must be taken carefully and based on as much information as possible. For this reason, many healthcare authorities recommend or mandate that the decision to switch a biologic must be taken by the patient's physician and many EU countries actively prohibit the automatic substitution of a biologic drug with a biosimilar.

Based on these findings, the following recommendations are intended to give policymakers an overview of how to design and implement effective and safe switching policies:

- **Patients should be made aware of any switch to their medication.** When a switch is to take place, both the advantages and disadvantages of this switch should be explained clearly. This is especially true for balanced patients, those with chronic illnesses and comorbidities, and where the switch involves a biologic or biosimilar drug. In such cases where the patient and/or physician disagree with the proposed switch, scope must be left for the patient to either appeal the decision or be allowed to make a co-payment and keep his or her original prescription.
- **The benefits and risks of therapeutic switching need to be better understood at all levels of medical practice.** This should help eliminate the wide variations in how switching is understood and implemented on the ground. For example, in the UK individual PCTs largely set switching policies themselves. This can create a postcode lottery for patients as to which medicines and treatments they can access. Information should also be improved for patients.
- **Healthcare practitioners and policymakers understand the significant risks involved with switching biologic medicines.** They must be made aware that biologics and biosimilars are a fundamentally different set of medicines from chemical-based drugs. Biosimilars are not the same as generic drugs and should be treated differently. Regulations, guidelines and educational information should be clear regarding this difference. Policymakers at all levels of health care should take caution in listing biologics as therapeutically equivalent or therapeutically interchangeable.
- **A distinction should be made between those patients who are on medication for shorter periods of time and whose medical condition requires less invasive treatment versus balanced patients whose conditions are long-term (including chronic) and require prescriptions on a daily basis over long period of time (even for life).** For the latter group establishing an effective, safe and comfortable prescription regime – i.e. achieving the objective of "balancing" the patient - is a time-consuming and

arduous task. In these cases switching should only take place with the full knowledge and consent of the prescribing physician in consultation with the affected patient.

Taking these recommendations as general principles, countries and regions can form positive policies on the selection of medicines, which will help balance future medical innovation, financial pressures and patient safety and choice.

Appendix

The following table is taken from a submission by the Biotechnology Industry Organisation (BIO) to the Federal Trade Commission's (FTC) 2008 roundtable, "Competition Issues Involving Follow-on Biologic Drugs". The table was initially published in the Morgan Stanley Report "Follow-on Biologics: Expect a Slow Start" (November 2008). It has been widely cited by experts in both the US and the EU, including by the FTC.¹⁷³ However, it is important to note that no key was provided defining the values, so there is some ambiguity in the exact difference between different rulings, i.e. "guidelines against substitution" versus "no automatic substitution". For that reason the table has not been included in the main body of this paper and is instead made available in the Appendix.

Sample of EU Member States' Position on Biosimilars and Substitution – Policies in place 2008¹⁷⁴

Country	Ruling
Austria	Physician obliged to prescribe by brand name
Czech Republic	Physician obliged to prescribe by brand name
Denmark	Guidelines against substitution
Finland	No injectable drug may be substituted
France	Automatic substitution prohibited without physician consent
Germany	No automatic substitution
Greece	Physician obliged to prescribe by brand name
Hungary	No automatic substitution
Italy	No automatic substitution
The Netherlands	No automatic substitution
Norway	No automatic substitution
Slovakia	Official list stating which products cannot be substituted
Slovenia	No automatic substitution
Spain	No automatic substitution
Sweden	No automatic substitution
UK	No automatic substitution

¹⁷³ Horton, L. "The European Experience With Follow-on Biologics Legislation", Federal Trade Commission, 2008, <http://www.ftc.gov/bc/workshops/hcbio/docs/fob/lhortonly.pdf> (Accessed 25 February 2010).

¹⁷⁴ Copied verbatim from Taylor, J. "Re: Emerging Competition and Consumer Issues – Comment, Project No. P083901", BIO, 2008, p.15, http://bio.org/letters/20081222_to_FTC.pdf (Accessed 25 February 2010).