Initiatives to increase the prescribing of low cost generics; the case of Scotland in the international context

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Abstract

Getting the most out of the pharmaceutical budget is critical across all countries as the financial pressures on healthcare systems intensify. In this paper, we review global practice on encouraging the use of low costs generics versus branded pharmaceuticals, including patented products in the same class where care is not compromised, across countries to guide future practice. Our review ranges widely across European countries as well as other high income countries, including Abu Dhabi, Japan and the USA, and other low and middle income countries. There is a particular focus on Scotland, building on previous publications. We conclude based on multiple publications, including several case studies, that achieving efficiency in pharmaceutical spending is possible in virtually all environments, although there are examples of technologies where generic or therapeutic substitution should not be encouraged. However, there is no magic bullet to achieving full and appropriate use of generics. Countries have to be prepared to use a number of different education, economic, engineering and enforcement methods including prescribing restrictions to achieve success. Similarly, different approaches to achieve low prices for good quality generics given the considerable price differences that currently exist. The combination of low prices and increased use of generics will help achieve or attain universal healthcare, benefiting all key stakeholder groups. We conclude with a call for greater cross-country learning in pursuit of what should be a common goal for all health systems.

Keywords: Co-payments, compulsory substitution, generics, prescribing restrictions, prices, reforms, Scotland

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1. Introduction

Increasing the prescribing and dispensing of generics versus originators, or patented products in a class where care is not compromised, is essential to enhance access to medicines as well as, maintain or attain comprehensive healthcare given ever increasing resource pressures (1-3). We are now seeing even high income countries struggling to fund new valued premium priced medicines (2, 4). As the population ages, this phenomenon will worsen unless adequately addressed (1, 5). Increasing the prescribing and dispensing of generics is particularly important in lower and middle income countries (LMICs) where up to 70% of total healthcare costs are spent on medicines; a significant proportion of which can be out-of-pocket, and where considerable savings can be made (6-9). Lowering the prices of generics among Central and Eastern European countries can also be beneficial, especially where co-payments are high and a barrier to appropriate care (10).

The availability of generic antiretroviral (ARVs) medicines are of particular importance in LMICs, especially in sub-Saharan countries, where up to 69% of the 34 million worldwide cases of HIV currently reside and where 41% of the population currently live on less than US$1.25 per day (11-15). Studies have shown that the availability of generic ARVs not only decreases the costs of treatment, but has a positive impact on treatment compliance, leading to decreased morbidity, mortality and rates of transmission (16-19). The cost of highly active antiretroviral therapy (HAART) decreased 20-fold after generic HAART in India, with a 5 fold reduction in mortality (20). Increased access to generic antibiotics has also helped combat infection in many LMICs (21); however, increasing antibiotic availability has increased resistance rates (22).

The increasing availability of low cost generics for patients with cancer, including novel cancer medicines such as the tyrosine kinase inhibitors, will also increase the number of patients that can be effectively treated (23, 24). In addition, help address health authority concerns with ever increasing prices for new cancer medicines, which are now threatening access for patients and the sustainability of healthcare systems (23, 25-27). However, the availability of sub-standard generic cancer medicines is a concern to physicians, patients and health service managers, which needs to be addressed (24).

Low cost generics can also help increase adherence to medicines, with adherence critical for the effective treatment of chronic diseases including HIV as well as non-communicable diseases (NCDs) such as diabetes, hypercholesterolaemia and arterial hypertension (28-34). Adherence is negatively affected not only by the complexity of prescribed drug regimens, their safety or tolerability, but also by issues of co-payments in a number of countries as well as health care systems (35-46).

Recent publications have demonstrated similar effectiveness between generics and originators across a range of molecules and disease areas (46-60), and addressed concerns even where different salts have been used for generics, e.g. generic clopidogrel (61). However, concerns still exist about the quality of generics and their effectiveness, especially in some classes and countries, as well as issues with substitution impacting on potential savings (3, 8, 24, 62-77). This includes concerns with generic lopinavir/ ritonavir in recent years, which is the cornerstone of second-line ARVs (11), resulting in suggestions for dynamic ongoing surveillance. Concerns with the quality of generics has also resulted in suggestions for better monitoring of the

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ingredients as seen recently in Pakistan (78). Key stakeholder concerns with substitution with a limited number of molecules has resulted in countries, including Sweden and the United Kingdom (UK), issuing guidance on which molecules should not be substituted (Box 1 Section 3.2.2), with the Royal Dutch Pharmacists Association issuing similar guidance to their members (79-82). There is now less concern with substituting generic immunosuppressive medicines than originally thought (83, 84). However, care is needed regarding potential strategies and their outcome with a recent systematic review on generic substitution demonstrating that that while health outcomes appear similar following substitution, the full extent of potential savings are not guaranteed (85).

There have been concerns among health authorities if pharmaceutical companies heavily discount prices of their branded medicines in hospitals with the expectation that patients will be discharged on more expensive medicines, greatly increasing costs in ambulatory care (86-88). In addition, if companies launch patented follow-on products just before patent expiry of the initial molecule to limit revenue loss, referred to as „evergreening strategies" (89). There are also concerns if pharmaceutical companies pay generic companies to delay launching their generics, as well as instigating other tactics such as product hopping, to try and reduce generic use (41, 65, 90-93). These strategies are all potentially counter-productive especially if pharmaceutical companies wish public monies to fund their new more expensive medicines with increasing pressure on resources (4,94).

Some studies suggest that there can be confusion among patients if they are dispensed different branded generics with different names without explanation, leading potentially to under- and over-dosing (95), although others did not find such problems (96). In any event, concerns with generics need to be addressed to maximise potential savings from their availability.

There have been varying measures across countries to lower the price of generics (2, 75, 97-102) as well as enhance their use versus originators (1, 2, 9, 99, 103-107). There have also been multiple initiatives across countries to enhance the use of generics in a class versus patented products to conserve resources where this does not compromise care. Classes include the proton pump inhibitors (PPIs), renin-angiotensin inhibitors and the statins (10, 102, 108-111). There have also been initiatives among health authorities to influence the prescribing of generic versus patented anti-depressants, although recognising that there can be inter-patient variation (101, 112, 113).

Consequently, the aim of this paper is to review ongoing measures among health authorities across countries to enhance the prescribing of low cost generics, whether successful or not, and the implications to guide future activities. We will also perform a deeper analysis outlining recent changes in prescribing behaviour in Scotland and the outcomes to anchor key discussion points.

2. Methods

2.1 General measures regarding pricing and utilisation of generics

This is principally a descriptive review of regulations, meta analyses and other relevant papers known to the co-authors rather than an extensive literature search of peer-reviewed publications regarding attitudes and policies towards generics as these have already been published (1, 9, 67, 77, 85, 94, 97-99, 103, 104, 106, 107, 114-119). In addition, a history of time lines

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surrounding the regulations for medicines including generics has also recently been published (71).

Demand-side measures discussed in this paper will again be collated under the 4Es, namely education, engineering, economics and enforcement (120). These include (81, 88, 97, 100, 111, 112, 120-131):

- **Education** - activities range from recommended medicines such as the „Wise List" in Stockholm, Sweden, to printed guidelines as well as more intensive strategies including academic detailing and benchmarking physician prescribing habits.
- **Economics** – initiatives falling under this category include financial incentives for physicians, patients or pharmacists. These include additional co-payments if patients want a more expensive medicine than the referenced price generic.
- **Engineering** – this typically refers to managerial or organisational interventions such as prescribing targets and switching initiatives as seen with losartan versus other angiotensin receptor blockers (ARBs) once generics became available in England and Sweden.
- **Enforcement** – includes regulations by law such as compulsory generic substitution or compulsory international non-proprietary name (INN) prescribing in Abu Dhabi, Lithuania, South Africa and Sweden as well as prescribing restrictions for angiotensin receptor blockers (ARBs) in Austria, Belgium, the Republic of Srpska (Bosnia and Herzegovina) and Sweden.

We will first review strategies to achieve low prices for generics before reviewing different strategies to influence their prescribing versus originators and patented products in a class.

2.2 Scotland

We will also include an update on the influence of multiple measures in Scotland to enhance the prescribing of low cost generics versus originators and patented products in a class to provide a focus in the discussion. This builds on previous publications (101, 108, 132).

Data from the National Health Services Scotland Warehouse has again been used to analyse trends in the utilisation and expenditure of key products and classes in Scotland. This again includes the PPIs, selective serotonin reuptake inhibitors (SSRIs), and statins. Items dispensed, which is typically 28 days, has been used as the utilisation metric in this update instead of defined daily doses (DDDs), which is the internationally recognised standard for drug utilisation studies (133, 134). This is because, items dispensed is the usual metric used in the United Kingdom when evaluatingphysician prescribing(129).

3. Results

3.1 Prices ofgenerics

3.1.1 Prices of generics – Europe

Prices of generics can vary 36 fold or more across countries depending on the molecule and the price setting mechanisms for generics in that country (2, 97, 115). European countries also have different approaches to the pricing of generics (10, 97, 108, 116). However, they can be typically categorised under three headings (97, 116, 135) including:

- **Price regulated systems** (prescriptive pricing) – where there are established rules for the pricing of generics, e.g. Croatia, France, Norway and Poland (136-139)
- **Free pricing** - where manufacturers are (relatively) free to set the prices of

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generics, e.g. Germany, Netherlands, Sweden and the UK. However, there are typically programmes in place to lower prices which include compulsory generic substitution in Sweden linked to monthly tendering, 3-monthly preference pricing policies in the Netherlands linked to tendering and 3-monthly review of prices in the UK (81, 102, 119, 132,140)

- **Mixed approach** – where a combination of approaches are used, e.g. Austria (141,142)

The various approaches can result in substantial differences in the prices of generics among different European countries. In European countries with aggressive measures to lower generic prices, generic prices can be as low as 2% to 4% of the pre-patent loss prices, e.g. Netherlands, Sweden and the UK for generic simvastatin and the Netherlands for generic omeprazole (81, 102,132).

The preference pricing policy was instigated in the Netherlands in 2008 whereby only the cheapest generics would be reimbursed, with patients covering the costs for a non-preferred drug (94, 102). Tenders were subsequently conducted for high volume generics resulting in further price reductions of between 76% to 93% for the 10 largest generics by volume (94). *Dylst et al* calculated that without aggressive pricing policies to lower the price of generic omeprazole, and increase its utilisation versus the originator, the Dutch government would have spent an additional €3.723 billion on omeprazole between 2002 and 2013, assuming similar utilisation rates and prices remained at pre-patent loss prices (41). Overall, it is estimated that the introduction of these policies in the Netherlands reduced pharmaceutical expenditure by €0.75-€0.90bn per year over the past five years (2).

Prices for high-volume generics fell to 4 to 13% of originator pre-patent loss prices in Sweden by 2009, helped by compulsory substitution introduced in 2002 and a comprehensive technical support system enabling pharmacies to continually stock the cheapest product, with prices reviewed at least twice a month (81). Overall savings from generic substitution were estimated at €700 million (>6.97 billion SEK) from 2002 to the end of 2005 (81, 94). Savings are greater following the introduction of the monthly tendering process at 8 billion SEK/year from 2011 onwards (94).

The situation regarding generic pricing is different in Belgium. The prices of generic drugs have to be lowered at least to the reference price to be reimbursed in Belgium, which was a 16% reduction versus pre-patent loss prices until 2002, 20% until 2003, 26% until 2005, and currently 31%, with the potential for further lowering after that (109, 131). The only major exception was the statins where as a result of a public tendering system in January 2008, prices for simvastatin were further lowered by on average 40% (109). As a result, generic losartan in 2011 was only 46% below pre-patent loss prices and generic omeprazole in 2009 was only 70% below pre-patent loss prices, whilst generic simvastatin was 85% below pre-patent loss prices (109, 131). This compares with the price of generic losartan in Sweden in 2011 at 90% below pre-patent loss prices (expenditure/ DDD) (128), with a similar low price in Scotland (Table 1).

Prices of generics in Poland are regulated through price negotiations and reimbursement decisions issued by the Minister of Health (143). The price of the first generic has to be at least 25% lower than the solitary product (usually the originator) which is already included in the reimbursement list. Prices of all other generic equivalents, which subsequently apply for reimbursement, cannot be higher

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than the reference price in a given reference group (usually one of the cheapest products but not always). These policies are in place together with the typical practice of granting reimbursement status to a wide spectrum of applying equivalent products (144). In many cases, this results in groups containing a number of generics and their originator, where prices do not appear to be the major factor in the prescribing decision. When coupled with insufficient educational activities, and a lack of promotion of generics, this can result in a high market share of expensive branded generics or originators to the detriment of cheaper generics.

The size of the European country does not appear to be a barrier to obtaining low prices for generics as seen in Lithuania and the Republic of Srpska (122, 125) despite comments to the contrary (145). Overall, prices of generics in Europe typically fall further from pre-patent loss prices in high versus low volume generic markets (117). In European countries with high volume generic markets, *Dylst et al* showed prices among 35 active substances that had lost their patents dropped by 43.2% by the end of the study period; this compares with only 21.6% in low volume generic markets (117).

The differences in the approaches to the pricing of generics among European countries can also lead to substantial differences between originator and generic prices (98), with for instance Greece, Ireland and Spain displaying lower price differences that Denmark, Finland and Sweden (98). For example, sumatriptan saw a price decrease in Greece of 5.8% when compared to the originator, while in Denmark the variation was 95%.

3.1.2 Prices of generics – Other countries

There are concerns with high prices of generics in a number of non-European countries including Australia, African countries such as Nigeria, and Malaysia (74, 146-149). Prices in Malaysia are not helped by the lack of any established pricing policy compared with European countries (Section 3.1.1) (74). Prices of generics in the private healthcare sector in South Africa were also high with no formal pricing system, e.g. generic PPIs in 2010 were only 32% to 64% lower than originator prices with generic statins only 33% to 51% below originator prices in 2011 (100, 150).

Recently, „Novartis Access" was launched in Kenya, which is a portfolio of 15 principally oral medicines for patients with NCDs, part of Essential Medicine Lists, at a cost of US$1/ treatment/ month (151). This programme will be extended to other countries as it is envisaged to be commercially sustainable over the long term (151). Such initiatives should help to substantially lower generic prices in Africa and other LMICs enhancing medicine access.

Care is needed though when introducing new pricing policies for generics as seen in South Korea. The Korean government implemented a new pricing policy in 2012 in order to try and make the generic market more competitive through setting the same maximum reimbursement price between originators and generics (75). It was envisaged this would increase competition among generic manufacturers to lower their prices. However given the concerns that still exist regarding generics among physicians in Korea, the opposite was achieved. The price dispersion between different generics significantly decreased, and originator-to-generic utilization significantly increased (75).

3.1.3. Prices of generics – Scotland

The combination of high voluntary INN prescribing (see section 3.2.2), coupled with

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measures to lower the prices of generics every 3 months through increased transparency (see *Bennie et al* 2012 and *Godman et al 2013* for details (101, 132)), has resulted in typically low prices for a range of generics in Scotland (Table 1).

Table 1 – Prices of generics as a percentage of pre-patent loss originator prices (amended from (101, 132, 152, 153))

	% of prepatent loss prices in the designated year
Antipsychotics	
Risperidone	16% in 2010
ARBs	
Losartan	12% in 2012
PPIs	
Lansoprazole	8% in 2015
Omeprazole	9% in 2010, 7% in 2015
Pantoprazole	10% in 2015
SSRIs	
Citalopram	8% in 2015
Paroxetine	16% in 2015
Statins	
Atorvastatin	8% in 2015
Simvastatin	3% in 2010, 4% in 2015

NB: ARB = angiotensin receptor blocker, **PPI** = proton pump inhibitor, **SSRI** = selective serotonin reuptake inhibitor

3.2 Enhancing the utilisation of generics versus originators

3.2.1 Europe

Health authorities across Europe use a variety of measures to encourage the prescribing of generics versus originators (brand name products), some of which are described in Table 2. Overall, multiple initiatives typically have a greater influence on future prescribing habits than more limited measures, in accordance with previous publications (10, 108, 154, 155).

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Table 2 – Examples of measures used by health authorities across Europe to encourage the prescribing and dispensing of generics vs. originators (brand name molecules)

Initiatives and countries	**Description**
Education - encouraging high voluntary international non-proprietary name (INN) prescribing – education - **UK** (9, 80, 101, 132, 156, 157)	• Multiple educational activities among physicians in the UK during training and post qualification, including decision support software and monitoring, has resulted in high INN prescribing • INN prescribing averages over 84% across all products, rising to over 98% for most generics (Table 3) • There are a recognised limited number of medicines where INN prescribing is not encouraged (Box 1)
Education and economics – **Austria**	• Several initiatives nationally to educate key stakeholders regarding generics, including dispelling myths such as the myths that existed with generic clopidogrel (61, 158) • The Sickness Funds in Austria also use a variety of approaches to enhance the prescribing of generics among physicians. These include training, monthly newsletters on changes in the reimbursement list, information events, personal visits to discuss prescribing habits, analysis of prescriptions and feedback/ benchmarking and software systems(105) • Physicians in Austria receive financial incentives for increased prescribing of generics versus originators (105, 141) • Despite these initiatives, generic losartan accounted for only 46% of total losartan on a DDD basis in 2011 (142)
Education, economics and engineering – **France** (94, 103, 116, 136)	• The French authorities regularly publish and update the list of available generics • Health Insurance Funds provide regular feedback to physicians on their generic prescribing rates • This combined with quality targets for physicians, substitution targets and incentives for pharmacists, financial incentives for patients as well as a prescriptive pricing policy for generics, led to estimated annual savings of €1bn in 2007, €0.905bn in 2008 and €1.01bn in 2009 • The financial incentives for pharmacists are for reaching national/ regional agreed substitution targets
Economics - financial incentives for patients (various countries)	• There is internal reference pricing (97, 99) in the majority of European countries • Under this system, patients typically pay the additional cost themselves for a more expensive medicine than the referenced priced generic medicine to encourage the prescribing of cheaper generics • This includes the Netherlands with its preference pricing policy (see section 3.1.1)
Economics – **Germany**	• Physician prescribing costs regularly benchmarked, with

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(116)	potential financial sanctions for continued over budget costs • Abolishing patient co-payments if reimbursed prices of the generic is at least 30% below current reference prices • Potentially reducing or abolishing co-payments if physicians prescribe drugs where the Sickness Funds have successfully negotiated contracts. The rebates, included those for patented drugs, resulted in estimated savings of €1.3bn in 2010 • Despite these measures, reimbursed prices for generics can be appreciably higher in Germany than e.g. Netherlands or the UK
Enforcement - Compulsory INN prescribing - **Lithuania** (116, 125)	• There is compulsory INN prescribing in Lithuania unless prior approval from the Hospital or Polyclinic Therapeutic Committee • Pharmacists in Lithuania are obliged to stock the cheapest generics with financial penalties if they do not comply • Overall, INN prescribing is mandatory in at least 5 European countries (99)
Enforcement - Compulsory substitution - **Sweden** (81, 112, 128, 159-162)	• There has been mandatory generic substitution in pharmacies in Sweden from 2002 onwards apart from a minority of situations (similar to the UK – Box 1), with patients covering the additional costs themselves for a higher cost medicine including the originator • Key stakeholder groups were typically supportive of this, although concerns if patients are not fully informed that their medicine could have a different name • As a result, 96% of risperidone by volume was generic, 97.4% of total losartan was generic and 99.6% of venlafaxine was generic in 2011 • Overall, generic substitution is mandatory in at least 6 European countries (99)
Education, economics and enforcement – **Poland** (143)	• Price ceiling established by the reference product in a given reference group (Section 3.1.1) • The retail margin at the pharmacy level is currently based on the reference price instead of a given product‟s retail price • This can result in pharmacist‟s price indifference when filling a prescription for reimbursed products which have generic equivalents • This is despite compulsory informing patients (pharmacist obligation) on the possibility of receiving a cheaper reimbursed generic equivalent, whose price does not exceed the reimbursement limit. As a result, potentially reducing co-payments

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3.2.2 UKincluding Scotland

Alongside high INN prescribing rates inthe UK (Table 3), there are a small number of products and classes where substitution is not encouraged (Box 1).

Box 1 – Examples where concerns with INN prescribing in the UK based on recommendations in the British National Formulary (BNF), the Council of the Royal Pharmaceutical Society and the Medicines and Healthcare Products Regulatory Agency (adapted from (79, 80, 84, 163))

- Amphotericin intravenous - prescribe by brand name as doses depend on the formulation
- Asthma treatments:
    - Theophylline modified release preparations – typically not seen as interchangeable due to concerns with the clinical implications of switchingbetweeninequivalentpreparations
    - Beclometasone dipropionate CFC-free inhalers - care where administration approaches differ with different instructions
- Calcium antagonists – care with modified release preparations as typically not seen as interchangeable
- Drugs for rejection – relatively small number of eligible studies with hard to compare methods make recommendations difficult. However generic immunosuppressants such as generic cyclosporine have been on the market in Europe for more than 10 years with no identified serious safety signals among the many doses prescribed and dispensed
- Epilepsy – in view of the different publications, the Medicine Agency recently issued the following advice:
    - **Category 1** – phenytoin, carbamazepine, phenobarbital, and primidone – Physicians are advised to ensure that patients are maintained on a specific manufacturer‟s product
    - **Category 2** – valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, and topiramate - the need for continued supply of a particular product should be based on clinical judgement and consultation with patients taking into account considerations such as seizure frequency
    - **Category 3** - levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, and vigabatrin - usually unnecessary to ensure that patients are maintained on a specific manufacturer‟s product
- Lithium – concerns with differences in bioavailability between different formulations suggesting care when considering any substitution.
- Morphine sulphate slow release tablets – doses prescribed should be reviewed if the brand is changed as there may be different release patterns between the different formulations – similar situation regarding fentanyl transdermal formulations

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Typically rates of generic prescribing across high volume classes including antidepressants, antipsychotics, PPIs,renin-angiotensin inhibitors and statins were 98% or more in recent years (Table 3).

Table 3 - Percentage of generics as a percent of total molecules dispensed (DDDs or items dispensed) in Scotland (adapted from (101))

Class	% of generic utilisation in defined daily doses (before 2015) and items dispensed (2015)
Atypical antipsychotics	
Risperidone	98% in 2009
PPIs	
Omeprazole	98% in 2010, 99.1% in 2015
Lanzoprazole	98.8% in 2015
Pantoprazole	99.9% in 2015
Statins	
Simvastatin	98% in 2010, 99.1% 2015
Atorvastatin	99.7% in 2015
Renin-angiotensin inhibitors	
ACEIs	
Enalapril	99% in 2007
Lisinopril	98% in 2007
ARBs	
Losartan	99% in 2011
SSRIs	
Citalopram	99% in 2007, 99.9% in 2015
Fluoxetine	98% in 2007, 99.6% in 2015
Sertraline	98% in 2007, 99.7% in 2015

NB: ACEI = angiotensin converting enzyme inhibitor, **ARB** = angiotensin receptor blocker, **PPI** = proton pump inhibitor, **SSRI** = selective serotonin reuptake inhibitor

3.2.3 Lower and Middle Income Countries (LMICs)

The WHO proposes that optimally all medicines (100%) should be prescribed by their generic (INN) name (164). However, there is room for considerable improvement with a recent meta-analysis by *Ofori-Asenso et al* showing that the percentage of medicines prescribed by generic name across Africa was only 68.0 % (IQR 55.4–80.3)(165).

This is important with *Cameron et al* demonstrating that substantial savings could be made among 17 LMICs from switching from originator brands to the lowest-priced generic equivalent (7). As an example in Thailand, implementation of generic substitution policies with the lowest priced generic would yield average annual potential savings of US$ 3.997million for seven medicines alone (7, 9). Suggested strategies to enhance generic uptake, that could be incorporated into national medicine policies, included substitution by pharmacists as well as increasing

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confidence in generics among key stakeholder groups (7).

In Mexico, generics and interchangeable generics are currently seen as different products. Here, there are not only patented medicines and generics, but also "similar" and "interchangeable" medicines. This can confuse patients and affects how they perceive the safety and efficacy of generics overall since similar products are marketed as bio-equivalent, when they are not. Consequently, there can be mistrust in generics by patients and physicians (166). This is despite the fact that it is mandatory for physicians to prescribe by generic name; however, they can prescribe a brand name if the recommendation is placed between parenthesis. In this way, patients have the right tochoose.

A generic drug policy were established in Brazil in 1999, which includes a generics preference policy in public purchases, mandatory generic substitution in public pharmacies, availability of generic drugs lists published by the regulatory agency (ANVISA), and educational activities among health professionals. Generics were typically introduced on average 40% lower than the price of the patented medicine, with this difference increasing to 68% lower in recent years. Brazil is a "pharmemerging" country with domestic companies marketing low cost generics. Despite these various initiatives though, generics only accounted for 27.3% of Brazilian pharmaceutical sales in 2013. The main barrier being the low confidence that physicians have in the quality of generics (167-169).

In their recent comprehensive review, *Hassali et al* also found physicians from LMICs tend to have mixed views regarding generic medicines. The authors believed this may be due to differences in the health care systems and medicine policies, including how medicines are funded, as well as differences in income levels. In addition, the extent of educational initiatives among key stakeholder groups as well as available drug information sources (67). Concerns with therapeutic failure among physicians in Nigeria, especially among locally produced generics, also potentially discourages their use (63). There are also concerns between the perceived and actual quality of generics in South Africa, again potentially affecting their use(3).

Having said this, there have been only a limited number of policy evaluations to date to determine which of the potential policies and measures LMICs could introduce to increase the utilisation of generic medicines in their countries (106). Ensuring a functioning medicines regulation system for marketing authorisation, creating a robust market as well as aligning incentives for all key stakeholder groups appear necessary prerequisites for increasing the utilisation of generics in LMICs (106).

Truter in her recent study found increasing use of generic meprobamate analgesic combination in a retrospective study of a medical health insurance claims database. There is compulsory generic substitution in South Africa unless otherwise specified by the physician or the patient prefers to pay for the more expensive originator. This is unlikely in this case in view of the price difference (170, 171). Her study found that the originator constituted only 3.7% of the analgesics prescribed (average cost was R30.42) compared to 70.6% for the most popular branded generic, with a cost of R11.65 (170, 171).

However, there has been low use of generics versus originators among hospitals in China, where most medicines are dispensed, when compared to a number of European countries (172-174), e.g. generic statins accounted for only 9% to 10 % of total statins in recent years in hospitals in China

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(175). The low use of generics is exacerbated by the need for hospitals to make money from drug procurement for their sustainability and physicians to supplement their income, with this incentive system also stimulating overuse of injections (174, 176-178). Having said this, *Li et al* recently demonstrated that patients could be successfully switched from imported originator anti-depressants to locally produced generics following education and psychological support without affecting subsequent care (179).

In recent publications from Malaysia, *Chua et al* demonstrated that private GPs in Malaysia have largely accepted generic medicines. However, they still have concerns regarding their reliability and quality necessitating further education and reassurance (72). *Kumar et al* also recently demonstrated that the majority of the physicians among private medical centres in Malaysia had negative perceptions about the safety and efficacy of generic medicines, impacting on their use (74). Similar approaches are needed to address this including reassurance of the quality of generics as well as physician education (74). There are also still concerns with generic substitution in Malaysia, enhanced by fears regarding the efficacy and safety of generics (74). This resulted in *Hassali et al* developing a list of requirements that should be met to enhance successful generic substitution (Box 2).

Box 2 – Potential requirements to successfully implement a generic substitution policy (adapted from (118)).

- Pharmacists and patients should communicate with each other to understand the safety and suitability of the alternate brands to improve patient acceptability of generics
- A formulary of interchangeable medicines must be developed as well as medicines that should not be substituted (Box 1)
- Requirements for marketing authorization must include (i) a license for manufacturing and marketing; (ii) the factory must have a license or accreditation for manufacturing the generic, which must comply with the country's GMP. As a result, strict quality standards for generics
- The length of the supply chain should be reduced to avoid unnecessary distribution costs to ensure affordable prices
- Education is important with the government and physicians responsible for disseminating appropriate information about generics. Pharmacists and physicians should have positive perceptions toward generic substitution
- Labelling by INN to avoid patient confusion – as seen in the UK
- Pharmacists should have a system where they can access relevant information about generic medicines before dispensing them as well as have the authority to change to a generic unless the patient demands the originator and/or the physician indicates do not substitute

3.2.4 Other countries

In 2012, Japan modified its prescription format to allow generic substitution for individual medicines to encourage greater generic prescribing, although physicians can also indicate „no substitution" if concerns (24). Generic substitution is encouraged as it is estimated successful implementation would result in estimated savings of

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Japanese Yen (JPY) 1.3 trillion per year. This is coupled with financial incentives for physicians and pharmacists to enhance their generic prescribing and dispensing (9). However despite these moves, the utilisation of generics remains low in Japan. This is because there are still negative perceptions towards generics, pharmacists are reluctant to recommend them, and there is currently limited cost differences between generics and originators in practice (9).

However, care is needed when introducing policies such as compulsory INN prescribing as recently seen in Abu Dhabi (130). Compulsory INN prescribing was not backed up by multiple policies among physicians to enhance the preferential prescribing of multiple-sourced medicines in the class. In addition, pharmacists could still dispense different brands of the same product and be reimbursed in full. As a result, there was increased utilisation of patent protected products and the envisaged savings were not attained (130).

3.2.5 Addressing concerns with the efficacy and safety of generics

As seen, education and effective regulatory systems are key to addressing concerns with generics, where these exist, given the extensive number of publications that have demonstrated similar effectiveness between generics and originators for generics meeting agreed quality standards (3, 24, 67, 106).

Concerns with the complexity, production, and distribution of generics has highlighted the need for convergence of regulations. This has resulted in the instigation of the „International Generic Drug Regulators Programme", which comprises regulatory bodies from several countries as well as the WHO (24).

To help address concerns in the US, the FDA in 2014 issued 18 warning letters to generic manufacturers oversees, and in 2015 undertook multiple inspections in for instance in India as well as increasing its office staff there (24). The FDA has also banned generics manufactured at several facilities in India until improvements, as well as fined manufacturers for selling adulterated generics. The EMA has also recommended countries to withdraw a large number of generic medicines whose pivotal trials were performed fraudulently with GCP variations by one Indian contract research organisation, leading to concerns with data quality (24). Such initiatives will continue through steadily enlarging authorities" inspection activities. In addition, the Central Drugs Standard Control Organization (CDSCO) in India will soon start making surprise inspections among manufacturing sites to improve the quality (24).

Khan et al recently suggested ways to improve the quality of generics in Pakistan in view of concerns with the quality of the active ingredient (78). Concerns with their quality resulted in some manufacturers increasing the quantity of the active ingredient in the manufacturing process, which is not in the best interest of any key stakeholder group as this could lead to over-dosing.

It should be borne in mind though that efficacy and safety concerns have also arisen with different batches of patented products (71).

3.3 Increasing the prescribing of generics (multiple sourced products) vs patented products in a class

There are also a variety of measures that health authorities have used to encourage physicians to increase their prescribing of generics versus patented products in a class

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to save resources without compromising care (53, 55, 59, 180-182). These measures are more prevalent in countries with high volumes of generics (117) and involve (i) educational initiatives among physicians including guidelines, academic detailing and benchmarking physician prescribing habits; (ii) incentive schemes (financial incentives); (iii) encouraging switching as well as prescribing targets (engineering) and (iv) prescribing restrictions (enforcement) (59, 77, 103, 108, 110, 111, 128, 129, 136, 138, 158, 183, 184). Classes include the proton pump inhibitors (PPIs), renin-angiotensin inhibitors and the statins (1, 59, 110, 111, 124, 185, 186). In addition, antidepressants in certain countries (101, 112). However, there are classes where health authorities are not active with influencing prescribing patterns. These include the antipsychotics (Section 3.3.4). Again, multiple initiatives typically have a greater influence on future prescribing habits than a more limited number of measures (10, 108, 154, 155).

In the US in 2005, it was estimated that US$20billion could be saved annually in 8 medicine classes among the commercially insured patients if there was therapeutic interchange to guideline adherent medicines (46). More recently, it was estimated by *Gellad et al* that Medicare could save US$1.4billion alone each year for patients with diabetes if prescribing mirrored the VA (Veterans Administration) system combining generic substitution and therapeuticinterchange(187).

3.3.1 PPIs across Europe excluding Scotland

Multiple demand-side initiatives were instigated in a number of European countries to increase the prescribing of generic versus patented PPIs, combined with measures to lower generic prices (Section 3.1), to enhance prescribing efficiency as no perceived difference in effectiveness between the different PPIs (10, 46, 108). Typically, countries that instigated multiple policies limited the prescribing of patented PPIs versus those countries with more limited demand-side measures (1, 10, 108). This is illustrated by:

- Sweden versus Ireland (10, 108)
    - Multiple demand side measures, including education, economics, and engineering, appreciably increased the prescribing of omeprazole in Sweden once generics became available and limited the utilisation of esomeprazole to less than 20% on a DDD basis by the end of 2007
    - There was limited demand-side measures in Ireland. As a result of commercial activities, utilisation of omeprazole decreased following generic avaialbility with esomeprazole increasing, with the utilisation of both approximately 30% of total PPI utilisation in 2007
    - These activities, combined with the measures to lower the prices of generics in Sweden (Section 3.1), resulted in reimbursed expenditure for the PPIs in Sweden decreasing by 49% in 2007 vs. 2001 despite utilisation increasing by 53%. In Ireland (GMS population – greater co-morbidity than the normal population), utilisation increased by 2.4 fold during this period and expenditure increased 2.6 fold
    - Consequently, reimbursed expenditure (Euros/ 1000 inhabitants/ year) in Ireland in 2007 was over 10 fold greater at over €60,000 versus €5832 for Sweden

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- Netherlands (102)
  - Aggressive measures to lower generic prices coupled with multiple demand side measures in the Netherlands, including education, economic and engineering initiatives, (Section 3.1), led to low utilisation of esomeprazole stabilising at 15% of total PPI utilisation in 2010
  - As a result, reimbursed expenditure for the PPIs fell by 58% in 2010 compared with 2000 despite a 3 fold increase in utilisation

The situation in Ireland compares with Norway where esomeprazole dominated PPI prescribing shortly after its launch with limited demand-side measures (138). There was though increasing utilisation of pantoprazole especially after the introduction of prescribing restrictions for esomeprazole and the preferred product status for pantoprazole in February 2007. The utilisation of esomeprazole fell after this although rose again in 2009 compared with 2008 (Table 4). This was perhaps not surprising as specialists in Norway have to verify the diagnosis and recommend therapy before PPIs can be reimbursed, and they were not subject to these restrictions. In addition, prescribing by physicians in ambulatory care is principally on trust, with limited follow by the health authorities, and they are reluctant to change prescriptions emanating from specialists (138).

Table 4 – Utilisation of PPIs in Norway 2001 to 2009 (DDDs/ 1000 inhabitants/ day-138)

	2001	2003	2005	2007	2008	2009
Omeprazole	8.98	5.03	4.38	5.61	6.42	6.67
Esomeprazole	3.6	10.17	13.64	13.73	13.4	14.34
Pantoprazole	0.25	0.5	0.8	4.32	6.77	8.18
Lanzoprazole	4.04	4.75	5.66	6.13	6.49	6.53
Total PPIs	16.87	20.45	24.48	29.79	33.08	35.72

3.3.2 Renin-angiotensin inhibitors across Europe

3.3.2.1 Angiotensin converting enzyme inhibitors (ACEIs)

ACEIs can produce a cough in some patients, which can be bothersome. This argument has been used as the main justification for increasing the prescribing of ARBs (188, 189), which are typically substantially more expensive than generic ACEIs although the effectiveness and safety of both are similar (111, 190). Nevertheless, prospective clinical studies had shown coughing only occurs in approximately 10% of patients, and only 2% to 3% of patients in ACEI clinical trials actually discontinued treatment due to coughing (111, 189). As a result, considerable resources can be conserved with limiting the prescribing of patented angiotensin receptor blockers (ARBs) versus generic ACEIs as seen for instance in Austria, Croatia and Scotland (111).

The introduction of prescribing restrictions for patented ARBs in Austria and Croatia restricting their prescribing to patients intolerant to ACEIs, such as those with excessive coughing, limited their utilisation in practice (111). This compares with Portugal with appreciably higher utilisation of ARBs in 2007 with limited demand-side measures combating ARB manufacturers' marketing activities (Table 5). Low ARB

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utilisation was also seen in Scotland with multiple initiatives to encourage the prescribing of low cost generic ACEIs first line (111). There was greater follow-up of prescribing restrictions in Croatia compared with Austria, which included access to patients‟ histories to check for abuse coupled with potential fines for physicians if this was seen. As a result, more limited utilisation of ARBs in Croatia compared with Austria between 2001 and 2007 (Table 5) (101, 111).

Table 5 – ARB utilisation as a percentage of total renin-angiotensin utilisation (in DDDs) 2001 to 2007 (adapted from (101, 111)).

	2001	2002	2003	2004	2005	2006	2007
Austria	15.3	17.9	18.9	20.7	22.4	23.6	24.8
Scotland	11.6	12.9	14.5	16.1	17.2	18.2	18.8
Croatia	2.1	2.5	5.8	9.2	11.8	14.0	13.2
Portugal	19.8	24.7	29.1	33.3	36.4	40.2	44.5

These various measures resulted in reimbursed expenditure (Euros/ 1000 inhabitants/ year) remaining relatively stable in Austria, Croatia and Scotland for the renin-angiotensin inhibitor drugs during this period despite increasing volumes (111), e.g. the utilisation of renin-angiotensin inhibitors increased 159% from 2001 to 2007 in Scotland during this period (101, 111). This compares with Portugal where expenditure increased by 155% during this period (111).

Prescribing restrictions for ARBs were also introduced in the Republic of Srpska (122). These included patients experiencing unwanted side-effects with ACEIs, specialist recommendation for switching, monitoring of restrictions by pharmacists before dispensing and a 50% co-payment for selected ARBs otherwise 100% co-payment. These combined activities limited ARB prescribing in practice in the Republic to 2% of total renin-angiotensin inhibitors in 2010 (122). Similarly, appreciably higher co-payments for the ARBs in Serbia (50%) due to higher requested acquisition costs than generic ACEIs, compared with a co-payment of 50 cents/ pack for ACEIs, resulted in ARBs again only accounting for 2% of total renin-angiotensin inhibitor drugs in Serbia in 2011 (190).

3.3.2.1 Angiotensin receptor blockers (ARBs)

There were considerable activities in Austria, Belgium, Denmark, and Sweden, to enhance the prescribing of generic losartan versus patented ARBs following their availability, with limited measures in countries such as Scotland (110). Activities included (110, 128, 131, 142, 191):

- **Austria** - economics and enforcement including prescribing restrictions removed for losartan but not the other ARBs with potential financial sanctions for physicians for abuse
- **Belgium** - economics and enforcement – physician prior approval needed to prescribe patented ARBs else 100% co-payment; prescribing restrictions lifted for losartan
- **Denmark** - enforcement - delisting of all ARBs other than losartan from the reimbursedlist
- **Sweden** - education, engineering, economics and enforcement including academic detailing, prescribing targets, therapeutic switching, financial

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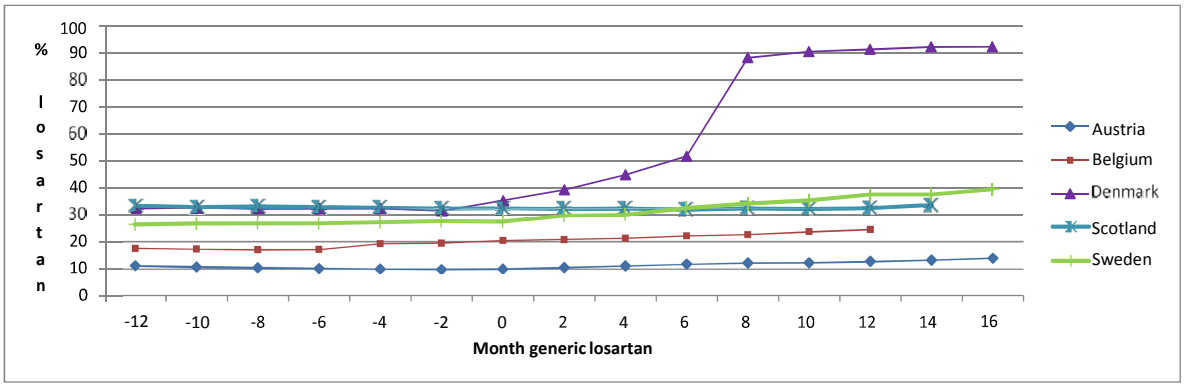
incentives, and prescribing restrictions lifted for losartan but not patented ARBs

These initiatives resulted in ARB expenditure in Sweden falling by 26% by August 2011 (accumulated 6-monthly basis) despite a 16% increase in overall utilisation versus the pre-patent loss situation (128).

However, there were limited demand-side measures in countries such as Scotland (152). This is because the Health Boards already had a number of quality initiatives in place, they did not want to confuse physicians from encouraging ACEIs first line, they would obtain appreciable savings from generic losartan with high INN use and associated low prices (Tables 1 and 3), and other ARBs would shortly lose their patent (152). As a result, there was no change in the prescribing of losartan as a percentage of total ARB in Scotland versus the other European countries with active measures in place, which were all significant (110, 128, 131, 142, 191) (Figure 1).

Figure 1 – Prescribing of losartan as a percentage of total ARBs (DDD basis) before and after the availability of generic losartan (Month 0) (adapted from (110))



A similar situation was seen in England to Scotland until active switching policies were instigated (129).

3.3.3 Statins across Europe excluding Scotland

Again, multiple demand-side initiatives were instigated by a number of European countries to increase the prescribing of generic versus patented statins, combined with measures to lower generic prices (Section 3.1), to enhance prescribing efficiency. This was because the various statins were seen as essentially similar by health authorities at therapeutic doses (10, 108, 186, 192).

Typically, countries that again instigated multiple policies limited the prescribing of patented statins versus those countries with more limited demand-side measures (1, 10, 108). This is illustrated by:

- Sweden versus Ireland (10, 108)
  - Multiple demand-side measures in Sweden (Education, economics and engineering) resulted in simvastatin utilisation increasing to 74% of total statin utilisation by the end of 2007 with patented statins (atorvastatin and rosuvastatin) limited to 21% totalutilisation
  - Again limited demand-side measures in Ireland resulted in the utilisation of atorvastatin and rosuvastatin rising appreciably in Ireland

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following generic simvastatin. These two statins combined accounted for nearly 80% of total statin utilisation (DDD basis) in Ireland in 2007 (GMS population)
    - This resulted in reimbursed expenditure in Ireland increasing 4.9 fold between 2001 and 2007 with utilisation increasing 7.3 fold, compared with a 39% reduction in reimbursed expenditure in Sweden alongside a 3.2 fold increase in utilisation
    - As a result, reimbursed expenditure (Euros/ 1000 inhabitants/ year) in Ireland in 2007 for the statins was again over €60,000 versus €5,192 for Sweden
- Netherlands (102)
    - Again multiple demand side measures to limit the prescribing of patented statins, with atorvastatin comprising only 27% of total statin utilisation (DDD basis) in 2010
    - This coupled with supply side measures to lower generic prices (Section 3.1.1) resulted in reimbursed expenditure for the statins falling by 14% in 2010 vs. 2000 in the Netherlands despite a 3.8 fold increase in utilisation
- Austria and Norway (59, 138, 193)
    - Prescribing restrictions were introduced for patented statins in both Austria and Norway to limit the prescribing of patented statins following the availability of generic simvastatin
    - In Austria, physicians needed the permission of the Chief Medical Officer of their Social Insurance Fund for atorvastatin to be reimbursed, otherwise 100% co-payment
    - In Norway, active therapeutic switching was encouraged alongside prescribing restrictions. However, this was principally on trust as again limited follow up of physician prescribing by the health authorities. However, physicians needed health authority permission if they wished to prescribe lower strength atorvastatin (10 and 20mg) and patients be reimbursed
    - As a result of the differences in the follow-up of the restrictions, utilisation of patented statins fell from 31.6% of total statins in 2003 (year before restrictions – DDD based) in Austria to 10.9% in 2007, a 66% reduction. In Norway, their utilisation fell from 46.2% of total statins (full year before restrictions) in 2004 to 26.2% in 2008, a reduction of 44%

3.3.4 Atypical antipsychotics

It is generally recognised by health authorities that there are classes where it can be difficult for them to instigate demand-side measures to try and increase the prescribing of generics versus patented products in a class. One such class is the atypical antipsychotic drugs for treating schizophrenia and bipolar disease. Experts, as well as health authorities, suggest treatment should be tailored to individual patients (194-196).

This was seen in practice in a recent study, which showed a consistent decrease in risperidone utilisation among European countries as a percentage of selected atypical antipsychotics (DDD basis) following the availability of generic risperidone (113, 153, 161, 196, 197). Consequently, health authorities generally need to wait until more atypical antipsychotics lose their patents before they see significant reductions in expenditure, which is already happening (196). The only exceptions to this are initiatives to enhance the prescribing of different formulations

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where generic availability changes their value. This was seen in Belgium where there has been greater scrutiny over the prescribing of more expensive long-acting risperidone injections following oral generic risperidone at appreciably lower costs (197). This resulted in its reduced utilisation in recent years versus other formulations of risperidone, which is continuing (197).

3.3.5 Prescribing restrictions

As seen in Table 5 and Section 3.3.2.1, restricting the prescribing of ARBs in Austria, Croatia, and the Republic of Srpska, appreciably limited their prescribing versus countries with limited demand-side measures, e.g. Portugal. The prescribing restrictions for patented statins in Austria also appreciably reduced their utilisation (Section 3.3.3).

However, the greater intensity of follow-up of ARB prescribing restrictions in Croatia and the Republic of Srpska, resulted in greater utilisation of generic ACEIs in Croatia and the Republic of Srpska versus Austria. Similarly greater follow-up of prescribing restrictions for patented statins in Austria compared with Norway resulted in appreciably lower utilisation of patented statins in Austria (111, 122, 138). Limited follow-up of prescribing restrictions for esomeprazole in Norway (Section 3.3.1) also resulted in greater utilisation of esomeprazole than initially envisaged (138).

A similar situation was seen in Sweden where the authorities restricted the prescribing of patented duloxetine following the availability of generic venlafaxine as its effectiveness and cost could not justify first line use (112). However, there was limited follow-up of the prescribing restrictions among the authorities in practice. This resulted in no change in duloxetine utilisation (DDD basis). However, there was a significant increase in the utilisation of venlafaxine post duloxetine restrictions (112).

The timing of prescribing restrictions is also important. Prescribing restrictions were recently introduced for patented statins in Sweden. However, they had limited influence on subsequent utilisation patterns in practice (198). This may be due to the fact that they were introduced some six years after intensive activities to encourage the preferential prescribing of generic statins (Section 3.3.3) (108).

3.3.6 Scotland

- **PPIs**

There was typically limited prescribing of patented esomeprazole in Scotland in recent years with multiple demand-side measures, which included formularies, academic detailing, prescribing targets and financial incentives (132). As a result, esomeprazole comprised only 5.3% to 7.1% of total PPI utilisation (DDD basis) between 2002 and 2010 compared with omeprazole, which comprised 67% of total PPI utilisation in 2010 (132).

This has continued with esomeprazole comprising 7.7% in 2011 and 6.4% in 2012 of total omeprazole and esomeprazole, i.e. before generic esomeprazole utilisation became available, versus 6.29% in 2002 (items dispensed).

As a result of these initiatives, coupled with measures to lower the price of generics (Table 1) and ensure high INN prescribing (Table 3), PPI expenditure fell from GB£56.49 million in 2001 in Scotland to GB£18.06 million in 2015, a drop of 68%. At the same time, utilisation increased 2.91 fold to 5.23 million items dispensed in 2015. Reimbursed expenditure for the PPIs in 2015 would have been GB£146.18 million greater assuming no generic PPIs

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and the average cost/item dispensed in 2015 remained at 2001 levels.

- **SSRIs**

Multiple demand side initiatives in Scotland between 2001 and 2007 limited the prescribing of escitalopram compared with countries with less demand side measures (101). For example, escitalopram comprised 27.1% of total SSRI prescribing in Ireland by the end of 2007 versus only 7.0% in Scotland. As a result, SSRI expenditure fell by 59% in Scotland in 2007 compared with 2001 but increased by 72% in Ireland. This was despite a 2.37 fold increase in SSRI utilisation during this period in Scotland (101).

The same prescribing patterns have continued with anything a reduction in the utilisation of escitalopram over time from 15.6% of total citalopram and escitalopram use in 2007 to 7.3% in 2012, 6.4% in 2013 and 5.8% in 2014. As a result of these initiatives, coupled with measures to lower the price of generics (Table 1) and ensure high INN prescribing (Table 3), SSRI expenditure fell from GB£28.937 million in 2011 to GB£11.551 million in 2015, a drop of 60.1%. During this time, utilisation (items dispensed) increased from 1.3 9million in 2001 to 2.95 million in 2015, and increase of 112%.

- **Statins**

There again were multiple measures to increase the prescribing of multiple sourced (generic) statins. This resulted in simvastatin dominating statin utilisation, e.g. 57% to 58% of total statin utilisation (DDD basis) from 2007 to 2010. Concurrent with this, there was stabilisation of atorvastatin and rosuvastatin utilisation at 40% of total statin utilisation (132).

Since the availability of generic atorvastatin in 2012, its prescribing has appreciably increased as a result of initiatives to switch patients from rosuvastatin to atorvastatin as well as encourage the prescribing of simvastatin and atorvastatin first line, particularly higher strength atorvastatin (199-203). This led to the utilisation of rosuvastatin falling from 262,409 items dispensed in 2011 to 217,791 in 2015 in Scotland, a 16. 8% fall, whilst the utilisation of atorvastatin rose from 1,149,459 items dispensed in 2011 to 1,637,000 in 2015. As a result, the utilisation of rosuvstatin fell from 5.7% of total statins (items dispensed) in 2011 to 4.5% in 2015.

Following the variety of initiatives to increase the prescribing of low cost generic statins (Tables 1 and 3), statin expenditure in Scotland fell from GB£43.39 million in 2001 to GB£19.10 million in 2015, a drop of 56%. At the same time, utilisation increased 4.03 fold to 4.89 million items dispensed in 2015. Reimbursed expenditure for the statins in 2015 would have been GB£155.80 million more assuming no generic statins and the average cost/ item dispensed in 2015 remained at 2001 levels.

4 Discussionandconclusions

Increasing the use of generics is essential to maintain equitable and comprehensive health care in Europe given increasing pressure on resources, with case histories demonstrating the extent of potential savings that can be achieved. Countries are learning from each other, and this will continue (1).

The first step in this process is ensuring good quality generics for patients as seen in Europe and the US. This can be achieved through strengthening the registration system, including factory inspections, and the tests performed in accordance with *Kaplan et al* and others (106). Regulations

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and initiatives supporting the production of good quality generics can also help countries with exports, which is a concern currently in countries such as Pakistan (78). Concurrent with this is education of all key stakeholder groups that there should be no difference in patient care once the quality of generics is assured. The ultimate aim is to achieve high INN prescribing rates as seen in the UK (Table 3) for the ARBs, PPIs, SSRIs and statins, which are very close to the 100% target set by the WHO (165). Encouraging INN prescribing is seen as beneficial to reduce patient confusion if different branded generics are dispensed at each occasion (95, 129). However, in some countries this will take time as current IT systems are based around branded generics, e.g. Sweden. Once instigated, apart from a small minority of clinically justified situations (Box 1), the focus should be on efficient registration and reimbursement systems as well as quality control.

The pricing of generics is also a key consideration to sustainability and affordability especially in LMICs, with companies now showing the way on potential low costs for producing oral generics with economies of scale (Section 3.1). The Netherlands, Scotland (Table 1) and Sweden (Section 3.1) provide examples of ways to lower prices of generics when linked to increased utilisation. However in a number of countries, this has to be balanced against supporting the development of local manufacturing facilities which can add to costs. In addition, low prices for generics have to be balanced against their availability (2). If prices of generics become too low, they become uneconomical making drug shortages more likely (38, 204).

Pricing policies for generics have to be thought through, and coupled with demand-side measures, to ensure expectations are met. Otherwise there could be disappointment as seen in China with its current incentive systems (Section 3.2.3). Price cuts can bring about substantial savings; however, these are short lived without also looking at demand-side measures (75).

There are multiple ways that health authorities can increase the prescribing of generics versus originators (Table 2). As mentioned, encouraging INN prescribing is advocated by the WHO and others (165). This includes encouraging INN prescribing voluntarily through education of both health professionals and patients, and follow-up apart from a limited number of cases (Box 1), as seen in the UK (Table 1). Alternatively, mandating this as seen in Abu Dhabi and Lithuania (125, 130). However care is needed as seen in Abu Dhabi else again the envisaged goals will not be achieved (Section 3.2.4). A number of countries have also instigated compulsory generic substitution, including South Africa and Sweden (140, 159, 170); alternatively encouraged pharmacists to substitute, e.g. France (Table 1) (136). *Hasseli et al* provide guidance (Box 2) for countries contemplating such measures.

There are also multiple initiatives that can be introduced by health authorities to encourage the prescribing of multiple sourced products in a class versus patented ones (Section 3.3). As seen (Sections 3.1, 3.2 and 3.3), both supply as well as multiple demand-side reforms are essential to maximise prescribing efficiency. The multiple supply- and demand-side measures in Scotland have resulted in considerable savings (Section 3.2.6) for the various classes despite appreciably increased utilisation, providing direction to others. The multiple measures in Scotland also stabilised renin-angiotensin inhibitor expenditure between 2001 and 2007 despite a 159% increase in utilisation (Section 3.3.2.1).

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Demand-side measures appear to be complementary. Countries that have instigated only a limited number of demand-side measures typically fail to combat pharmaceutical company pressure. This was seen in Ireland with the PPIs, SSRIs and statins versus Scotland and Sweden (3.3.1, 3.3.3, 3.3.6), Norway with esomeprazole even with prescribing restrictions (Table 4) and Portugal with the ARBs (Table 5). In Scotland, where there was no change in ARB prescribing patterns following generic losartan, with no specific activities encouraging its preferential prescribing versus patented ARBs (Figure 1) (152), suggests no „spill over" effect of health authority activities across classes even if they are closely related such as the renin-angiotensin inhibitors. Physicians in Scotland were good at preferentially prescribing generic ACEIs versus patented ARBs (Table 5); however, this did not translate into increased prescribing of generic losartan versus patented ARBs when it became available. Overall, the multiple demand-side measures in Scotland to limit ARB prescribing appeared just as effective as prescribing restrictions with follow-up in Croatia (Table 5).

There are similar considerations when it comes to prescribing restrictions. These need to be followed up by health authorities to maximise their impact, else health authorities could be disappointed in the outcomes (Section 3.5). However, it is acknowledged there are some classes where it is difficult for health authorities to introduce multiple measures such as the atypical antipsychotics (Section 3.3.4)

Concentrating on one reform, i.e. either supply or demand side measures, but not both, can also reduce potential efficiency gains from the availability of generics. This was seen with price cuts in Korea for medicines to treat patients with hypercholesterolaemia which failed to achieve the desired results with appreciably increased use of atorvastatin following generics as well as more expensive lipid lowering drugs (205). In Germany in 2007, there was very limited utilisation of atorvastatin following reference pricing for the class in 2003 at just 2% of overall statin utilisation (185). This compares with 21% and 33% respectively on a DDD basis for atorvastatin and rosuvastatin in Sweden and England in 2007 (108). However, expenditures were similar or greater in Germany when adjusted for population sizes due to higher expenditure/ DDD for simvastatin.

Above all, the commitment of health authorities to promote the appropriate use of medicines including generics, coupled with the political will to pursue changes in existing pharmaceutical policies, is very important to achieve desired savings and medicine access.

We accept there are limitations with this paper. This includes the fact that we did not undertake a systematic review of published studies as many such reviews and meta analyses have already been performed. However in view of the consistency of our findings, we believe our findings are robust and provide direction to others.

In conclusion, multiple measures and initiatives are needed to ensure low cost for generics and enhance their utilisation versus originators and patented products in a class. This is essential to attain or ensure universal health care as well as increase affordability of medicines. Countries are learning from each other, and this will continue.

Conflicts of interest

Alec Morton is PI for his institution on a work package of a European project DRIVE-AB (Driving Re-Investment for R&D on Antibiotics) under the Innovative

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Medicines Initiative (IMI) https://www.imi.europa.eu/. DRIVE-AB is funded by the European Commission but receives in-kind support from pharmaceutical companies. He has no other conflicts of interest. The other authors have no other conflicts of interest to declare.

Acknowledgements

Alec Morton and Axel Leporowski would like to thank that New Professor‟s Fund of Strathclyde University for its financial support.

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