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Generic Drugs – Essential for the Sustainability of Healthcare Systems with Numerous Strategies to Enhance their Use

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ABSTRACT

The increasing use of lower-cost multiple sourced medicines (generics) and biosimilars are essential to attain or retain universal healthcare in the face of continual pressure on available resources. Alongside this, reduce patient co-payments and enhance access to medicines in countries with high co-payments where affordability is an issue. Supply-side measures, including aggressive procurement practices and increased transparency in the manufacture and pricing of generics, can appreciably lower the price of generics. Such measures alongside demand-side measures can enhance savings versus originators as well as increase access to standard medicines. However, there needs to be trust in the generics to maximise savings. The same applies to biosimilars. Multiple demand-side measures can also appreciably enhance the preferential prescribing of multiple sourced medicines versus still patented medicines in a class or related class without compromising care. As a result, enhance utilisation at lower costs. Countries can learn from each other when planning or instigating reforms, and this will grow.

INTRODUCTION

We have seen global expenditure on medicines rising appreciably in recent years with estimates that expenditure will reach US$1.5 trillion globally by 2023 [1]. This growth in medicine expenditure represents an annual compounded growth rate of 3–6% (1), driven by many factors [2]. Key factors include the growing prevalence of Non-Communicable Chronic Diseases (NCDs), which include Coronary Vascular Disease (CVD) and diabetes, along with an associated increase in medicine use, increasing prices and expenditure on new medicines especially for orphan diseases and oncology, as well as changes in guidelines and clinical practice [3-9]. This increase in expenditure on medicines has ramifications for the sustainability of universal

healthcare in high-income countries, which have resulted in calls for new approaches to the pricing of new medicines [7,8,10,11]. Alongside this, concerns with the management of diseases among Lower- and Middle-Income Countries (LMICs) where expenditure on medicines can be as high as 60% of total healthcare expenditure [12,13]. In certain disease areas such as diabetes and associated complications, expenditure on medicines can be as high 90% of total costs [9,14,15]. An appreciable proportion of expenditure on medicines will be out-of-pocket in many of these countries with potentially catastrophic consequences on families when members become ill [12,16-18]. Consequently, the medicines' budget must be carefully managed with initiatives introduced to achieve sustainable development goals especially for NCDs [2,19,20].

One of the key initiatives to make savings available to fund increased volumes of medicines, enhance the affordability of medicines to patients, as well as fund new premium priced medicines to address unmet need, is through increased prescribing of multiple sourced medicines (generics) and biosimilars [4,21-25]. This includes encouraging the preferential prescribing of multiple sourced medicines versus originators as well as against still patented medicines in the class or related class without compromising care [4]. Numerous publications have demonstrated similar effectiveness and safety between originator and generic medicines provided bioequivalence has been demonstrated [26-32]. Consequently, patient care should not be compromised. However, there can be concerns where there are no strict regulations or enforcement surrounding the quality of generics within a country impacting on both physician and patient acceptance of generics, which is a major challenge in LMICs [33-36]. This needs to be addressed to enhance their use including strengthening healthcare systems [37].

Initiatives to enhance the prescribing and dispensing of generic medicines versus originators include voluntary or compulsory International Non-Proprietary Name (INN) prescribing coupled with education of key stakeholder groups, compulsory substitution, and/ or incentives to pharmacists to increase substitution [4,25,38,39]. This is apart from an agreed limited number of clinical situations where INN prescribing or compulsory substitution may cause concern. Disease areas and medicines of concern include long-acting calcium channel blockers and certain medicines for patients with epilepsy [40-43]. There have also been concerns with switching between originator and generic medicines in patients prescribed immunosuppressants following transplantation; however, this now appears to be less of an issue [44].

High voluntary INN prescribing rates in the United Kingdom, which can be up to 99% or more of prescription items dispensed in non-controversial clinical situations, are achieved by education and clinical practice starting in medical schools and continuing post-qualification via electronic reminders and other approaches [45-47]. High utilisation of generics in Sweden versus originators have been achieved by physician and patient acceptance of the regulations surrounding compulsory generic substitution apart from the limited number of disease areas or molecules where the Swedish Medicines Agency has concerns. In addition, patients having to cover the additional costs themselves if they still prefer an originator versus a generic [40,48]. This is reflected for instance by generic losartan and generic venlafaxine accounting for 97% to 99.6% of total losartan and venlafaxine respectively soon after their availability [49,50].

One potential advantage of INN prescribing is that possible confusion with different product names in the case of different names for each branded generic and the originator can be addressed by just having the INN name on packages of generic medicines. This is the situation in the United Kingdom, which is different to a number of European and other countries [2]. Different names on the packages of the same medicine can cause confusion among patients especially if different named medicines are being dispensed each time as a result of procurement and other practices [2]. The resultant confusion can potentially result in over- or under-dosing unless the dispensing pharmacist and/ or prescribing physician spends time with patients re-assuring them that the medicines are the same [51-53]. As mentioned though, there can be concerns with the quality of generics among LMICs challenging routine INN prescribing [33,34,54,55]. The World Health Organisation (WHO) pre-qualification scheme is one avenue for ensuring the quality of generic medicines among LMICs [56]. This scheme has been successful in helping to promote access to artemisin-based antimalarial therapies in many countries; however, there are still issues with the quality of multiple sourced medicines including among African countries because of issues with the

regulatory and market environment in some of these countries [57]. The Lomé initiative that has recently been launched in Africa to address falsified and substandard medicines is a major step forward to enhance patient and physician trust in generic medicines where there are concerns, building on earlier WHO initiatives [58-60]. We will continue to monitor these initiatives in view of their importance for patients.

There can be situations where companies try and influence the prescribing of generics as seen when Sanofi in France had concerns with generic clopidogrel [61,62]. Eventually though the Company were fined by the French health authorities for the level of misinformation [62]. We have also seen Companies threatening physicians with legal action in the UK if they prescribe medicines by their INN name rather than brand name for still patented indications [63]. However, this does not appear to be the case for generic cancer medicines in the UK, which is welcomed given ever increasing expenditures on oncology medicines [64].

The instigation of supply-side measures among countries has resulted in prices for generics becoming as low as 2% to 4% of pre-patent loss prices, which include medicines for NCDs and oncology [64,65]. Measures include regular procurement auctions in the Netherlands, compulsory generic substitution coupled with regular auctions in Sweden as well as increasing transparency in the manufacture and pricing of generics in the United Kingdom [45,47,49,66]. Increased transparency in the pricing of generics helped to reduce their costs by alleviating practices whereby generic companies sought to keep prices high and offer discounts to pharmacists to preferentially dispense their generics, which have been common in some countries despite legislation [47,67]. However, there are concerns that if the price of generics becomes too low, this will make their manufacture unprofitable. As a result, leading potentially to shortages; alternatively, other manufacturers becoming the new license holders appreciably increasing their price [64,68,69]. Low prices for generics are though not universal. Prices of generics typically depend on the regulations within a country [64]. As a result, there can be appreciable differences in the prices of generics among countries as seen in the case of prices for oral multiple sourced oncology medicines across Europe, with generally population sizes having limited impact on reimbursed prices despite earlier concerns [64,70].

We have seen situations where initiatives among countries to increase the prescribing and dispensing of generics have not achieved the desired result. Whilst the health authorities in Abu Dhabi sought to conserve resources by introducing compulsory INN prescribing, there were no simultaneous measures to encourage pharmacists to preferentially dispense the cheapest multiple sourced medicine. Alongside this, the authorities did not instigate any demand-side measures to encourage physicians to preferentially prescribe multiple sourced products first line as opposed to patented medicines in a class when care is not compromised. As a result, the desired savings were not achieved exacerbated by the manufacturers of patented medicines encouraging their preferential prescribing by questioning the quality of generics [71]. In South Korea, the Government introduced policies to try and increase pricing competition among generics and originators to increase savings from generic availability. However, the ratio of originator to generic prescribing actually increased without any concomitant demand-side measures to encourage physicians to preferentially prescribe multiple-sourced medicines [72]. Consequently, well thought out and complimentary measures are typically more likely to achieve desired outcomes than complex disparate measures [72,73].

We have also seen that multiple demand-side measures are typically needed to encourage the preferential prescribing of multiple-sourced medicines in a class or related class versus patent-protected medicines. Multiple demand-side measures in Sweden, which included physician education, prescribing targets and financial incentives, encouraged the preferential prescribing of generic omeprazole and generic simvastatin versus patented medicines in their classes when these first became available. These multiple demand-side measures, coupled with aggressive measures to lower the prices of generics in Sweden [74,75], produced considerable savings when compared with Ireland with more its limited demand-side measures [75,76]. In both countries, there was an appreciable increase in the prescribing of statins and Proton Pump Inhibitors (PPIs), with the increase in statin prescribing driven by increasing rates of coronary vascular disease and a greater understanding of their patient benefits [77,78]. However, expenditure for PPIs and statins was over ten times higher in Ireland in 2007 when adjusted for population size [75].

Low prices for generics in Scotland, coupled with multiple demand-side measures to preferentially prescribe multiple sourced medicines, have also resulted in appreciable savings alongside improvements in the quality of care [46,79]. In the case of lipid-lowering therapies, this meant initiatives to increase the dose of statins prescribed as more data became available demonstrating improved outcomes at higher doses [46,77]. These multiple measures resulted in a 50% reduction in expenditure on lipid-lowering therapies in Scotland between 2001 and 2015 despite a 412% increase in their utilization [46]. Similarly, total expenditure on PPIs fell by 66.7% in 2017 compared with 2001 despite a 3.06-fold increase in their utilization [79].

We have seen a similar situation regarding the impact of initiatives to encourage the preferential prescribing of generic Angiotensin Converting Enzyme Inhibitors (ACEIs) versus patented Angiotensin Receptor Blockers (ARBs) without compromising care. The instigation of prescribing restrictions for ARBs in Austria and Croatia, as well as multiple measures in Scotland to encourage the preferential prescribing of ACEIs including again physician education, prescribing targets and financial incentives, appreciably limited the prescribing of ARBs in these countries compared with Portugal with its limited demand-side measures [45,80]. As a result, expenditure on renin-angiotensin inhibitors was 2.4 times greater in Portugal in 2007 when adjusted for population size versus Scotland despite similar increases in utilisation of these medicines between 2001 and 2007 [45,80]. Of note was that the greater follow-up of prescribing restrictions by the authorities in Croatia versus Austria among GPs, which included access to patients' histories with the potential fines for physicians if abuse was suspected, resulted in more limited prescribing of ARBs in Croatia [45,80]. Encouragingly, the multiple demand-side measures introduced in Scotland appeared to be as effective with limiting ARB prescribing compared with the prescribing restrictions in Austria and Croatia [45]. This is important for countries that are unable to introduce prescribing restrictions as a potential demand-side measure to enhance the preferential prescribing of multiple sourced medicines versus patented medicines [2].

There was again appreciably variation among European countries regarding the extent of demand-side measures introduced to enhance the prescribing of losartan as the first ARB to lose its patent without compromising care [81]. The removal of patented ARBs from the reimbursement list in Denmark had the greatest impact, with the utilisation of losartan rapidly reaching 92.3% of total ARBs [82]. Multiple demand-side measures in Sweden including education, prescribing targets, switching and financial incentives, resulted in losartan rapidly reaching 37.6% of total losartan utilisation [50]. Lifting prescribing restrictions for losartan but not for other patented ARBs resulted in its increased prescribing in Austria and Belgium following generic availability; however, the extent of the increase was more limited compared with the multiple demand-side measures in Sweden and the delisting of patented ARBs in Denmark [81,83,84].

No specific demand-side measures were introduced in Scotland to enhance the prescribing of losartan first line versus still patented ARBs since the authorities believed other quality targets were more important and they did not want to overload physicians which resulted in little change in physician prescribing habits post generic losartan [85]. Alongside this, losartan was already the most prescribed ARB in Scotland and there was a belief that there could be mixed messaging away from just encouraging the preferential prescribing of ACEIs first line, which had been very successful in Scotland [45,85]. However, one regional primary care group in England instigated multiple measures to enhance the prescribing of losartan versus patented ARBs to necessarily save costs without compromising care [52]. Losartan rapidly accounted for 65% of all ARBs dispensed, up from 24% pre the initiatives, with total ARB expenditure 59% below pre-study levels [52]. Overall, annual net savings in this primary care group were estimated at over eight-times the cost of implementing these multiple measures [52] providing direction to others. These various studies demonstrate that multiple measures are typically needed to successfully change prescribing habits [4]. Without such measures, which typically means passive activities among health authorities, there can be limited change in prescribing habits as seen with losartan prescribing in Scotland [85]. We also saw this with limited impact of additional quality targets for the prescribing of ACEIs over ARBs in the UK with no appreciable broadcasting of these increased targets nor additional financial incentives [86].

We see a similar situation with respect to the impact of demand-side measures to enhance appropriate utilisation of antibiotics. The authorities in Azerbaijan, the Republic of Srpska, and Slovenia, successfully introduced multiple measures over a number of years to reduce inappropriate prescribing and dispensing of antibiotics, as well as limit increases where utilisation rates were already low, to address concerns with rising antimicrobial resistance rates [87-90]. Their successful approaches contrasted with limited activities in Poland to curb rising antibiotic utilisation rates [91]. Limited demand-side measures resulted in Poland continuing having one of the highest rates of antibiotic utilisation rates in Europe between 2007 and 2016 [91].

There are classes of medicines though where health authorities acknowledge it can be difficult to instigate demand-side measures to influence the preferential prescribing of lower cost multiple sourced products. Classes include the atypical antipsychotic medicines for treating schizophrenia and bipolar disease. Concerns with differences in patients' profiles and their needs, as well as the different profiles of the various anti-psychotic medicines, have resulted in growing acknowledgment that where possible treatment should be tailored to individual patients [92-95]. We see the same considerations generally for antidepressants [96]. However, demand-side measures have been successfully introduced in Scotland to switch patients from patented escitalopram to multiple sourced citalopram given perceived limited differences in effectiveness alongside considerable cost differences [97]. The combined activities, along with high INN prescribing rates, resulted in a 73.7% reduction in overall expenditure on Selective Serotonin Re-Uptake Inhibitors (SSRIs) between 2001 and 2017 in Scotland despite a 2.34-fold increase in their utilisation [97]. Prescribing restrictions were also successfully introduced for duloxetine in Sweden as the authorities were concerned with its effectiveness and costs versus other multiple-sourced anti-depressants. These restrictions resulted in significantly increased prescribing of multiple sourced venlafaxine, with 3 monthly expenditure on the newer anti-depressants 55% below expenditure prior to the availability of generic venlafaxine soon after the restrictions were introduced [49].

We have also seen similar issues regarding the biosimilars. There have been concerns with their effectiveness and safety leading to a nocebo affecting challenging their use versus originators [98-100]. However, landmark studies such as the NOR-SWITCH study with biosimilar infliximab in Norway as well as clinical studies demonstrating similar effectiveness and safety with biosimilars, combined with greater knowledge that originator companies can often change their manufacturing process, have enhanced their use [2,22,101-108]. The increasing use of biosimilars is important especially in LMICs where there are issues of access and affordability to biological medicines in the first place [109-111]. In high-income countries, increasing use of biosimilars can offset increasing expenditure on new high-priced medicines for oncology and orphan diseases as well as fund an increasing number of healthcare professionals in clinics to improve patient care where there are concerns [2,112]. Recent studies and reviews have again identified that multiple demand-side measures are necessary to enhance the use of biosimilars; otherwise, their uptake may be limited despite appreciable price reductions [2,9,21,113].

The increased availability of standard medicines for oncology as either lower cost biosimilars or generics should increasingly result in health authorities re-evaluating the prices and/ or discounts for still patented medicines that used these standard medicines for pricing purposes under value-based pricing principles [2,64,114]. We will be monitoring this development given the continued launch of new premium-priced medicines for oncology and orphan diseases and concerns with their impact on continuing to provide comprehensive and universal healthcare for patients with cancer.

In conclusion, we have shown that multiple-sourced medicines are essential to enhance access to standard medicines where co-payments are an issue as well as help fund increased medicine volumes and new premium priced medicines in countries seeking to attain or retain universal healthcare. This also increasingly includes biosimilars. We will continue to monitor ongoing developments to address barriers and concerns with the routine availability of low priced, good quality generics as well as biosimilars to provide direction to others.

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