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GENERIC PRESCRIBING

-  A generic medicine contains the same qualitative and quantitative composition of active substance as the proprietary (“reference”) version of that drug
-  Use of the generic name when prescribing reduces the potential for confusion and error
-  Generic prescribing is cost-effective and safe for the patient
-  Generic prescribing is recommended for all drugs except modified-release preparations, some combination products and drugs with a narrow therapeutic index.

INTRODUCTION

In Ireland, several community drug schemes are available by which prescription medicines are provided to patients. They include the General Medical Services (GMS) scheme, the Drug Payment (DP) and Longterm Illness (LTI) schemes and the High Tech Drugs (HTD) scheme, which facilitates the supply of specific high cost, specialist medicines.¹ In 2007, the overall expenditure for the provision of medicines under these various community drugs schemes (which covers approximately 85% of total drug expenditure) was €1.74 billion, a greater than five-fold increase over the decade 1997 to 2007.² The year on year increase in pharmaceutical expenditure in Ireland is amongst the highest in Europe with medicines now accounting for approximately 13.5% of total healthcare spending.² One of the recommendations of the recent Barry report, which looked at potential economies in drug usage in Ireland, was to encourage and facilitate the use of generic prescribing by general practitioners, which was estimated could achieve significant savings in the drug budget.³

This bulletin will outline the background to generic medicines and address some frequently asked questions regarding their use in clinical practice.

What is meant by the term “generic medicine”?

During research and development (R & D), a pharmaceutical substance is given an international nonproprietary name (INN) or a generic name.⁴ This INN is generated by the World Health Organisation (WHO) for all pharmaceuticals worldwide, using a procedure adopted by the WHO executive board.⁴ **Each INN is a unique name that is globally recognised and is public property.**⁵ An important feature of the INN system is that the names of pharmacologically-related substances demonstrate their relationship by using a common “stem”.⁴ This enables healthcare professionals dealing with pharmaceutical products to recognize that the substance belongs to a specific group of substances, having similar pharmacological activity. For example, all β -adrenoreceptor antagonists contain the suffix *-olol* in their INN (metoprolol, atenolol); *-azepam* denotes the benzodiazepine family (diazepam, temazepam); *-vir* denotes antiviral agents (oseltamivir, ritonavir).⁵

When a novel pharmaceutical substance is first authorised as a medicine, the pharmaceutical company, holding the marketing authorisation (licence), usually assigns a brand name to that medicine. For a specific time period thereafter, no other pharmaceutical company is allowed to market this medicine – the so-called period of exclusivity (usually 10 years from the date of first licence) +/- patent protection.⁶ This is to enable the originator company recoup the costs of R&D (now estimated at €1 billion).⁷ The INN of each medicine is normally found in the Summary of Product Characteristics under section 2.⁸

Once the period of exclusivity expires and the patent runs out, it is possible for other manufacturers to market generic forms of the “brand leader” or proprietary medicine. **A generic medicine has the same qualitative and quantitative composition in active substance(s) as a medicine that has already been authorised (the “reference” / proprietary medicine).**⁹ That means that the INN of the pharmaceutical product contained within the proprietary and generic medicines is the same. In practical terms, this means that these drugs are usually interchangeable, although there are some exceptions (see later).

Generic medicines can only be placed on the market if they are authorised by the relevant regulatory authority (i.e. the Irish Medicines Board in Ireland). In order to achieve a marketing authorisation the manufacturer must prove that the generic medicine is “essentially similar” to the proprietary medicine.⁹ This involves undertaking a series of *in-vitro* and usually *in-vivo* bioequivalence studies against the proprietary medicine, according to specific EU guidelines.¹⁰ Generic

and proprietary medicines therefore can be used at the same dose to treat the same disease.¹¹ Of importance, the manufacturers of these generic medicines do not have the same R & D costs and therefore can market these medicines at a lower cost compared with the proprietary medicine and still return a profit.¹²

What are the benefits of generic prescribing in clinical practice?

Patient safety

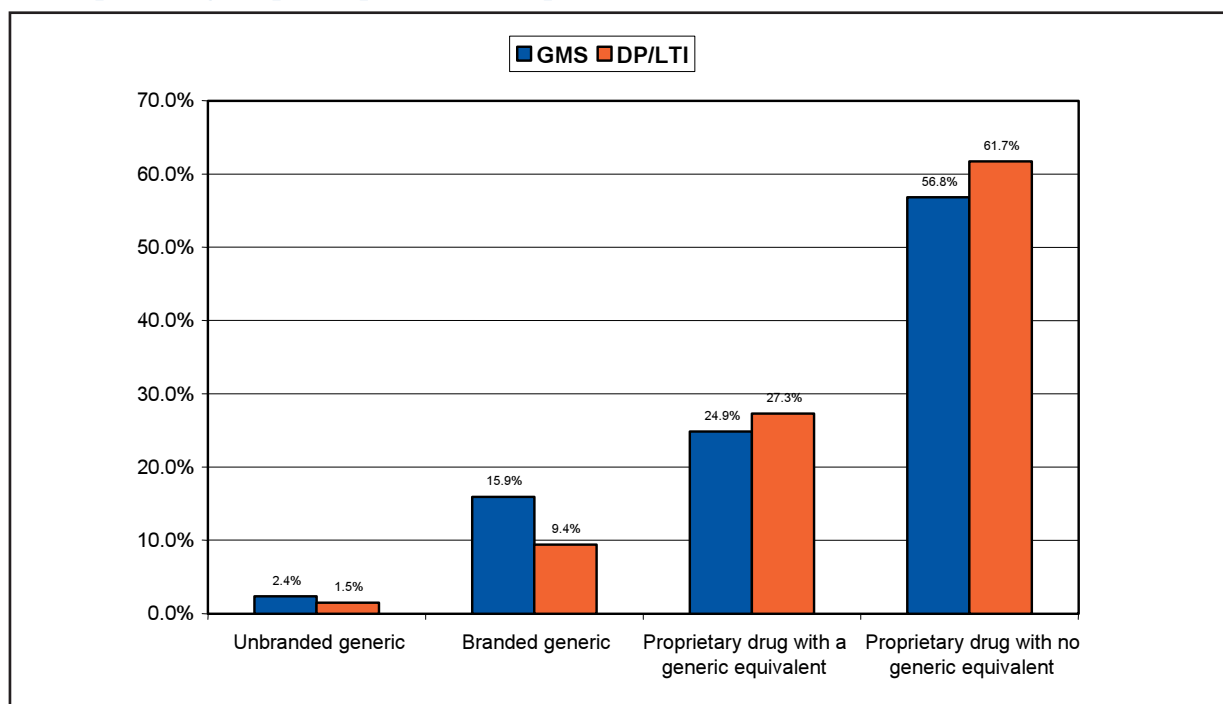
As mentioned previously, the INN for a specific pharmaceutical substance is a unique name that is globally recognised and the method used for assigning each INN promotes the identification of the drug class by use of common stems for medicines within the same class.^{4,5} These factors reduce the potential for confusion when prescribing a medicine or when seeking to identify a drug that the patient has been taking.¹³ As a rule, undergraduate training in pharmacology and therapeutics, and scientific publications dealing with medicines use the WHO approved generic name, therefore the prescriber's scientific knowledge base is centered around this name. Routine use of the generic name when prescribing ensures that the prescriber is able to use his/her knowledge of the underlying pharmacological action of the medicine to optimise prescribing.¹³

In Ireland, there are several instances where many "branded generic" medicines (i.e. a generic medicine licensed under a brand name) are available on the market for the same INN (e.g. some proton pump inhibitors and non-steroidal anti-inflammatory agents).^{14,15} It may prove difficult to identify quickly what is the active pharmaceutical substance, especially if the patient is unaware of the precise nature of the treatment; this raises the potential for incorrect management of drug toxicity or for drug interactions if further medicines are being co-prescribed. In addition, if a prescription specifies a brand name, there may be a delay in dispensing to the patient if that brand is not in stock; use of the generic name prevents such an occurrence.¹⁶

Cost-effectiveness

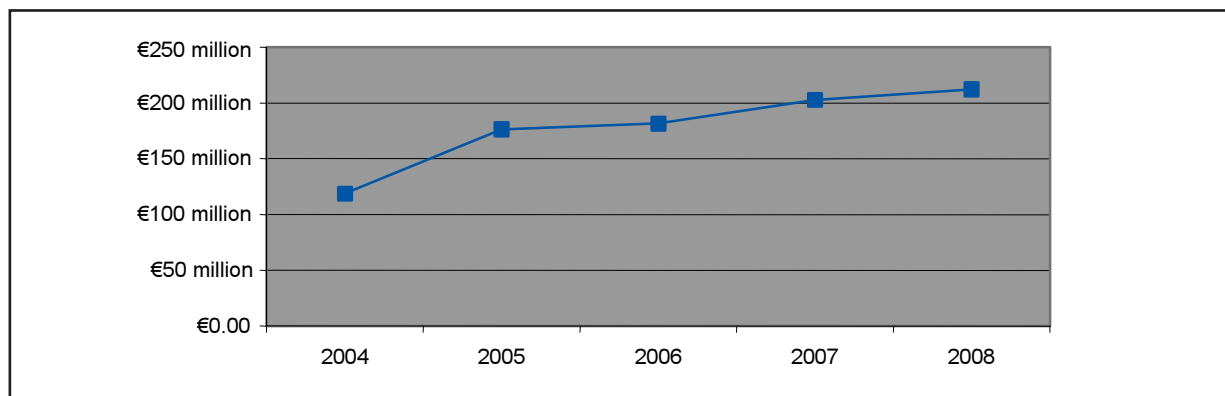
A generic medicine can only be marketed if it has shown that it is similar to the proprietary medicine, therefore its use will have the same beneficial effect expected from the proprietary medicine but with a lower cost. This helps to reduce the overall drugs bill in a healthcare system, without compromising the efficacy or safety of the treatment that the patient receives.¹² In many EU countries cost containment policies have included incentives and regulations to encourage prescription and/or substitution of cheaper generic medicines for more expensive proprietary medicines and in countries such as Denmark, Finland and the UK, generic prescribing (i.e. using the INN on the prescription) exceeds 50%.³ In Ireland during 2008, 18% of drugs were dispensed generically on the GMS and 11% on the DP/LTI schemes. (see figure 1).¹⁷

Figure 1. The percentage of prescription items dispensed on the GMS and DP/LTI schemes in 2008¹⁷



Generic prescribing in Ireland comprises both unbranded generics (use of INN) and branded generics. Of note approximately one quarter of prescription items were dispensed as a proprietary medicine when a generic equivalent was available (Figure 1). This translates into 19% (€163.36 million) of the total ingredient cost of medicines, spent on proprietary medicines where there was an equivalent generic product available for the GMS scheme and 17% (€64.40 million) of the total ingredient cost of medicines, spent on proprietary medicines where there was an equivalent generic product available for the DP/LTI schemes during 2008.¹⁷ Moreover the total expenditure (includes ingredient cost, dispensing fees and VAT) on these proprietary medicines has risen from €120 million in 2004 to more than €200 million on the GMS scheme in 2008 (see Figure 2).¹⁸

Figure 2. Total annual expenditure on proprietary medicines with a generic equivalent in the GMS, 2004 – 2008¹⁸



These figures highlight the potential for significant savings on drug costs if generic prescribing were implemented in Ireland and in fact the recent Barry report recommended that general practitioners should be “encouraged and facilitated (to do so) by the provision of prescription software systems, prescription data analysis and professional prescribing advice”.³

Why are generic medicines not identical to the brand leader?

Pharmaceutical products formulated by different manufacturers are unlikely to be identical in every respect.¹³ Therefore a generic medicine may have a different appearance (such as colour or shape) and different excipients (inactive ingredients) compared with the proprietary medicine.¹¹ The current legislation states that the manufacturer must show that a **generic medicine has (1) the same qualitative and quantitative composition in active substances as the proprietary medicine (2) the same pharmaceutical form (tablet / liquid) as the proprietary medicine and (3) demonstrated bioequivalence with the proprietary medicine using the appropriate bioavailability studies (in vitro +/- in vivo studies)**⁶ in order to be granted a marketing authorisation. In those cases where a different salt or ester of an active substance is proposed, additional information providing proof that there is no change in the safety or efficacy of the end product must be supplied.⁶

Once the generic medicine is authorised, it is subject to the same ongoing evaluation in terms of safety and efficacy that applies to all medicines, under the terms of the marketing authorisation.⁹ Each company is required to set up a system to monitor the safety of the medicines that it markets. The regulatory authorities may also perform an inspection of this monitoring system.¹¹ All specific precautions relating to the use of the proprietary medicine, will also apply to the generic medicine. In addition, any precautions relating to the excipients will be described both on the product labelling and in the package leaflet.¹¹

Patients may become familiar with the name, shape, colour and taste of the proprietary medicine (especially if on long-term treatment) and may become concerned if a generic version is substituted.¹³ **Patients may need reassurance from the prescriber and/or dispensing pharmacist that the medicines are similar in terms of risk and benefit** and the reasons for generic substitution, especially in terms of cost savings to the healthcare system should be explained.^{3,13}

Are all medicines suitable for generic substitution?

Although generic prescribing is encouraged, there are some circumstances in which it is preferable to prescribe by brand name.¹⁹ Table 1 outlines the main instances where generic substitution may not be suitable.

Table 1. Circumstances in which generic substitution may not be suitable¹⁹⁻²³

Circumstance	Examples
Differing bioavailability between formulations (drugs with narrow therapeutic index)	Carbamazepine, lithium phenytoin, ciclosporin, theophylline
Modified-release preparations	Nifedipine; diltiazem; morphine
Medicines with multiple ingredients	Pancreatic preparations; HRT; COCs
Similar medicines with different administration devices	Inhalers; adrenaline pre-filled syringes
Different preparations of same medicine with different indication(s)	Duloxetine (Cymbalta®; Yentreve®) Bisoprolol (Emcor®; Cardicor®)
Medicines of biological origin	Growth hormone; erythropoietin

As a rule, generic substitution is not suitable where continuity of the same brand is important due to potential differences in bioavailability between medicines.¹⁹ This is especially important if the medicine has a narrow therapeutic index where

the efficacy and/or toxicity are critically dependent on the drug's plasma concentration (see Table 1).¹³ The recommendation is that the patient should be prescribed the same formulation (either the brand leader or specified generic formulation) on each occasion.

A modified release preparation is one in which the active substance is released at a slower rate or is delayed compared with an immediate release dosage form of the same active substance.²⁴ Generic modified release preparations are required to undertake bioequivalence studies in line with current EU guidance.^{10,24} However, for certain modified preparations, especially those with a narrow therapeutic index, (see Table 1), current best practice recommends not to interchange between different preparations, but rather to prescribe the same formulation (either the brand leader or specified generic formulation) for the patient.^{13,19,20} In the case of medicines that contain multiple ingredients, the use of a specific product name aids identification of the exact content of each medicine that is being given to the patient. Where a medicine is administered via a device, it is advisable not to change between different devices as this may lead to confusion in the patient with resultant difficulties in administering the correct dose (see Table 1). Similarly, where there are special registration programmes associated with use of a medicine (e.g. clozapine), it may be preferable, from a logistical perspective, to prescribe the same formulation.²⁵

A “biosimilar medicine” is one that is similar to a medicine of biological origin (e.g. growth hormone; erythropoietin) that has already been authorised (known as the biological reference medicine).²³ As with other generic medicines a biosimilar medicine undergoes testing to ensure that it is as safe and effective as the reference product. However, due to the complex method of production of biological medicines, the active substance may differ slightly between the two medicines, therefore additional studies on safety and efficacy may be required on a case-by-case basis. Since biosimilar and biological reference (proprietary) medicines are similar but not identical, the current recommendation is that the patient should be prescribed the same formulation (either the proprietary or biosimilar formulation) on each occasion.¹⁹

Prescribing initiatives in Ireland

Of all the activities that take place in general practice, prescribing has the greatest potential to produce health benefits or to cause harm.²⁶ The majority of doctor-patient encounters result in the writing of a prescription, therefore the quality of prescribing in general practice is an important issue.²⁷ A recent survey, undertaken in general practice in Ireland identified a high rate of generic prescribing as a prescribing quality indicator, however a review of prescribing on the HSE prescribing database noted that this opinion did not translate into practice. Table 2 outlines the top 10 prescription medicines (in terms of ingredient cost) from January – March 2009 on the GMS prescription database, where there are generic equivalents available.

Table 2. GMS top 10 prescription drugs (by cost)* where generic equivalents are available²⁸

Pharmaceutical substance	Proprietary cost** €	Generic cost** €
Lansoprazole 30mg/day	36.29	23.30
Omeprazole 20mg/day	27.41	21.23
Pravastatin 40mg/day	30.00	27.00
Donepezil 10mg/day	113.27	70.66
Venlafaxine prolonged release 75mg/day	28.54	17.47
Alendronic acid 70mg once weekly	29.97	20.30
Amlodipine 5mg/day	9.21	7.54
Doxazosin prolonged release 4mg/day	18.87	12.66
Bisoprolol 10mg/day (angina indication)	6.68	6.65
Perindopril 4 - 5mg/day (~salt)	15.69***	13.64***

*Listing from January – March 2009 from GMS prescription database

Costs based on 28-day supply of defined daily dose / recommended dosage regimen for proprietary and cheapest generic brands available (as listed in MIMS Ireland March 2009); * 30 days' supply

As seen in Table 2, savings can be made if generic preparations are prescribed whenever available. These savings would be even greater if changes to the existing system of reimbursement for generic medicines in Ireland, as recommended in the recent Barry report on “Economies in Drug Usage in the Irish Healthcare Setting” were implemented.³ This report also recommended the promotion of quality and cost-effective prescribing and the development of continuity across hospital and community prescribing. Already, generic substitution initiatives for specific medicines are being introduced at hospital level and it is hoped that this will result in savings, not only in the secondary care sector but also carry over into primary care.^{29,30} It is anticipated that similar schemes will be implemented in primary care in the very near future. Taken together, these various initiatives should result in significant reduction in the cost of medicines supply to the patient without compromising efficacy or safety, or impacting on the prescribing rights of physicians.

List of references available on request. Date of preparation: July 2009

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue.

Prescribers are recommended to refer to the individual Summary of Product Characteristics (SPC) for specific information on a drug

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