

Generic drugs

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Sometimes it seems as though generic drugs are one of those things that everybody likes as an idea, but they wouldn't want to take one themselves. Ireland is at the bottom of the European market by value, and second from bottom by volume. Exports of generics make up a significant proportion of total finished product pharmaceutical exports. So we don't consume them, but we're happy to make money from them. By 2012 the patents of another 19 major drugs and combinations will have expired, such as fluticasone + salmeterol, losartan, clopidogrel, olanzapine, montelukast and docetaxel. In the next five years, the range of frequently prescribed drugs available as generics will probably grow faster than the number of major new patented drugs, producing an interesting shift in the balance between the generic companies and the patent-lead companies. Since the HSE is heading towards a deficit, and economic growth has slowed, how best to use generics will become an increasingly important and frequently discussed topic both for practitioners and for policy-makers.

In the USA where medicines cost more than they do in Ireland, and where patients contribute more towards the cost of their medicines than they do in Ireland, the quality of generics, and the best strategy to use when shopping around for a low price product, are major concerns for patients and newsworthy material for the media. One patient, who was taking a sustained release form of bupropion for depression switched to a generic sustained release form and saved \$197 per month. But she also began to experience symptoms of her depression and after six months she reverted back to her original brand. However, she was not alone, and patients from many States wrote to the authors of a newspaper column, The People's Pharmacy, that is published widely in newspapers across the USA. An independent testing laboratory that specialises in health and nutrition products, ConsumerLab.com, performed comparative tests on the branded product and the generic version. Significant differences were found, with the generic preparation releasing its drug much more quickly than the branded product. The results surprised everyone directly involved with the case and everyone involved with the sector who was asked to comment. This case highlights several issues about generics, the process of approval of generics and the actual and potential problems that face patients and practitioners.

Quality Issues

Once the patent that provides protection from competition for a manufacturer of an original drug product comes to an end, generic products can be marketed. Although there are some differences in the policies and requirements of Medicines Regulatory Bodies (MRBs) around the world, the principles of the approval process are essentially similar. It is not necessary for the manufacturer of the generic to repeat all of the work of the originator to gain a marketing authorisation. Two aspects are required, however. First of all, the product must be 'pharmaceutically equivalent'; in other words, its active ingredient must be equivalent in amount and quality and it must be in the same dosage form. Generic drug producers are subject to the same standards of good manufacturing practice and inspection as other pharmaceutical manufacturers. The excipients in their products must also be of equivalent quality and are selected from the same range of approved excipients as any other pharmaceutical product. Suitable analytical chemistry tests and rigorously maintained manufacturing quality standards can ensure pharmaceutical equivalence. Documentation and periodic inspection can be used to verify the robustness and integrity of these processes.

The second requirement is that the products be bioequivalent, based upon the plasma concentrations of the drug. If the drug is released into the gastro-intestinal juices at a similar rate to the original product and in the same region of the gastro-intestinal tract, it usually appears in the plasma at a similar rate and at a similar concentration. Dissolution testing can be used to check this, and for immediate release products, these procedures have been shown to be consistent and have been standardised to a considerable extent.

A bioequivalence clinical study is used to compare the plasma levels achieved by the two products. In practice these use a small group of healthy volunteers (24-36 in the USA; 18-24 in the WHO protocol and 12 in Canada) in a cross-over design (each patient receives each drug in turn). The area under the concentration curve over time (AUC) is used to estimate the amount absorbed, and the peak plasma concentration (C_{max}) is used as the measure of the rate of absorption. The test compares the performance of the two products under idealised conditions and sets a statistical standard (90% confidence interval of the geometric mean) for equivalence. For some preparations, such as inhalers, the amount absorbed is not relevant and an alternative, surrogate measure is used. Once again, the

provider of the clinical data must also work to defined set of high standards under good clinical practice.

Consequently, generic drugs that have been produced and tested in this way are of high quality, and are as equivalent as they can be, given the limits of the testing methods. And yet, as the case above shows, sometimes the system breaks down.

MRBs face a considerable burden of inspection in their own state. The number and capacity of generic manufacturers and the number of generic products are growing. For the MRBs to inspect as frequently as they would wish, they need to increase the resources that they devote to this quite quickly. In the USA, the Food and Drug Administration has an entire division committed to this work and it is finding it hard to cope.

The limitations of the testing procedures are known in theory but have not been accurately mapped to enable the MRBs, the industry and other stakeholders to appreciate where the boundaries of precision and accuracy lie. Sustained and extended release preparations are more complex to manufacture and, as the case quoted above suggests, achieving the required consistency of performance from batch to batch is more difficult. Bioavailability studies are usually single dose studies and may not adequately reflect the levels attained with repeated dosing. The studies are not carried out in children or the elderly, nor are different ethnic groups used, and variability in practice may arise because of differences between these groups.

Wholesalers and importers are looking at the ever expanding range of countries producing generics and seeking to use their products. To verify that the manufacturing standards have been appropriately assessed and are being maintained, in some countries, and in certain cases, poses problems for MRBs. Testing product quality before granting authorisation, and again importation, is one way of reducing the complexity of the problem. But rapid, independent testing, especially for an adequate sample of batches, is a cost in itself and the testing laboratory must also be subject to regulation and inspection. The results of testing and the enforcement actions of MRBs are often classed as confidential information, given the regulations that govern the client-MRB relationship, but those outside the regulatory process might have a different perspective.

Parallel authorised products and parallel

imported products add to workload of the MRBs and to the potential for confusion of prescribers, pharmacy staff and patients. Quite often they are viewed as generics by at least one of the three groups, even though they are not.

Health Service Issues

The use of generic products as equivalent medicines with a lower acquisition cost saves money, and hence policies to require or promote generic use have been adopted by many health services.

Autonomy is an important concept in healthcare, and one that most healthcare professionals hold dear. In primary care, where the majority of practitioners are independent contractors, the State can only use incentives and sanctions to promote generic use. The Indicative Drug Budgeting Scheme for GP prescribing of a few years ago, popularly known as the 'fifty-fifty cash-back' scheme, may have promoted use of cheaper treatments in general, but it did not ensure therapeutically equivalent treatments and its effects seem to have been short-lived. Since the State has little access to detailed information about the clinical issues surrounding prescribing, it does not have the data upon which to base its policies or monitor their effectiveness. At the dispensing stage of the drug use process, the HSE has been investigating current practices but, once again, the data to which it has access do not describe the circumstances around which dispensing decisions are being taken.

Nevertheless, in its dispute with the wholesalers, the HSE seems to have considered alternative importing procedures. It is likely that any such contracts could only be awarded on the basis of tenders that were submitted and assessed. While tendering for a health service-wide supply would appear an attractive option, it exposes the service to several risks. First of all, for such a major segment of the market to become the preserve of one supplier would leave the remainder competing for a number of smaller sectors, and in the context of the small market that Ireland represents, this would probably not be a viable business model. The market of generics is global and all of Ireland's European neighbours are bigger markets with potentially greater returns on investment. The withdrawal, even temporarily, of suppliers would create a dependency between State and preferred supplier that would be unhealthy for both. Secondly, primary care usage of generics could not be predicted, since prescribers have autonomy in their prescribing choices, making it difficult to negotiate volume-related discounts and to arrange the supply of large volumes of stock during periods of intensive demand, therefore necessitating the formulation of contingency plans for times of shortage. Thirdly, no one supplier is likely to produce the complete range of generics required, leading to the commitment of substantial management resources to establish, develop and maintain the programme with several, periodically changing, suppliers.

The scale and predictability of generic use in the acute hospital sector, and the potential to control the extent of use through the alignment of hospital prescribing practices supported by formularies/prescribing guides and Drugs and Therapeutics Committees, makes identifying preferred providers a logical and attractive option. In addition, hospital practice could use a wider range of generics than primary care since it is possible for them to monitor their patients more intensively. Prescriber and patient concerns about generic use could be more easily addressed in the hospital environment, providing there is adequate pharmacy staff to provide information, education and counselling. However, it is not only the acquisition cost that must be considered. It would be necessary to monitor the quality of the products at the tendering stage and during subsequent supply of the products. This procedure is used in the UK and provides purchasers with access to independent information about quality, which, linked to cost and availability information, enables them to plan for a consistent supply and to effect changes in a co-ordinated, prudent and assured manner. The companies whose products are assessed have the opportunity to respond to the reports, providing a responsive and transparent process.

Practice Issues

There are two circumstances in which generic drugs are used, either from the first moment the drug is prescribed, or at a later stage in treatment the patient may be switched to a generic. The former, sometimes known as the 'prescribability', is really what bioequivalence testing is most suited for. Switching raises additional concerns.

Within the total patient population the proportion being treated for chronic diseases is increasing and will continue to increase. Most of these patients will be treated in both primary care and in the acute hospital setting. While 'shared care' and seamless care are the ideals, they are not often available and less often achieved. GPs claim that their prescribing for these patients is dictated by the hospital doctor and, conversely, the hospital doctors often claim that GPs change the patients' medicines without consideration for their concerns. Hence, prescribability versus switchability can become issues early on.

Irish prescribers and patients have a history of mistrusting generics and continuity of supply worries both of them. Patients know little about the process of medicines approval in this and most other countries. As a result they are less confident, from their own knowledge, of the quality of generic medicines. Prescribers are a ware of the process and of the structure of the industry, but retain an anxiety that generic companies, particularly if they do not manufacture in Ireland, may not be able to maintain supply over time, and for long-term treatment, this is a potential drawback.

Primary Care Prescribers in this country have

never been in favour of generic substitution and, even if they prescribe using an approved drug name, many of them want their patient to receive the same product each time they present their prescription. However, since their patients visit different pharmacies it is unlikely that they all receive the same generic. The slight doubt that switching from one generic to another has no clinical consequences contributes to primary care prescribers' reluctance to prescribe generically. Similarly, a small proportion of patients do not use the same pharmacy all of the time, and some of the messages from the DoHC and HSE and others over the years have implied that 'shopping around' is a good idea. Changes in reimbursement and remuneration procedures often provoke pharmacists to monitor their suppliers and to try to manage their acquisition costs efficiently.

Having all of the generic products marketed in Ireland available for immediate dispensing to patients is an idea to which some subscribe. Pharmacists in both community and hospital know the reality of this; the physical impossibility of stocking and the managerial inefficiency of ordering and tracking such a volume of stock are not understood by public officials or health service personnel outside pharmacy.

Generics in the UK are typically known by the International Non-Proprietary Name (INN) or approved name and the strength of the preparation, whereas in Ireland, branded generics are much more common. In Ireland today, brand appears to be everything, and in response, almost all of the luxury brands have opened bespoke outlets or arranged marketing deals with exclusive retailers. The love affair with brands seems to apply also to generics because in Ireland branded generics are prescribed more often than unbranded generics and prescribers sometimes tell their private patients that they have prescribed the 'brand leader'.

The profusion of branded generics means that there are several brand names for one drug, with potential for confusion. Undergraduate students in this country have to learn that branded generics are rarely listed in the BNF, but can be found in the IMF and in MIMS. The branding of generics creates work for the Irish Medicines Board, since it must minimise the possibility of look-alike and sound-alike names. The confusion over names extends to healthcare professionals, particularly now that Ireland has many nurses, pharmacists and doctors from a wide variety of different countries. The WHO has been steadily working towards a system of agreeing INNs to remove names from the list of sources of error that compromise patient safety.

Although generic medicines contain the same active, they are formulated with different excipients and may have a different appearance and taste to the original brand. As one patient visiting Dublin once put it, "They're not that colour in Mayo." Appearance is one aspect that branded generic manufacturers try to address, because they know it influences patient acceptability.

As a consequence their products are often relatively easily identified.

Non-branded products are more likely to be 'little white tablets' without obvious identifying marks and that is a source of anxiety to prescribers and occasionally to patients or their carers, especially when unintentional non-compliance is a problem. The issue of following up an ADR and identifying the product can be resolved once the dispensing pharmacy has been identified, since it should be possible to verify the source of the dispensed product, but the health service does not always realise that this is a possibility nor appreciate its value.

Patient's intolerance of generics is a frequent problem. Although the excipients used in generics are approved materials of appropriate quality, they are not inert and a very small number of patients will react to them. The majority however, are likely to exhibit a reaction that is akin to the 'nocebo' effect, in which patients given a placebo of a drug or drug type to which they have previously experienced a side effect, report the same side effect on taking the placebo. Gastro-intestinal symptoms are often reported by patients and only if the patient is reassured of its quality and is prepared to persist with the preparation will they resolve.

Reports of adverse events associated with generic drug use have been published. It may not be feasible to obtain sufficient clinical information to re-classify the event as a reaction. Most reports concern drugs with a narrow therapeutic index, such as anti-epileptics, and/or vulnerable patient groups. Although the evidence is not clear cut, it is generally accepted that for anti-epileptic drugs both product-related factors and patient-related factors can lead to clinical problems.

Clinical and drug-specific issues have been the main impediments to increased generic use. In fact, it is the combination of a drug with a narrow therapeutic index in a patient with a condition in which serious clinical sequelae follow a change in plasma levels. Drugs with a narrow therapeutic index, such as warfarin and theophylline, seem at first to be unsuitable candidates for generic products. And yet they have been, and remain in use, especially in North America. From time to time, reports from the USA indicate that generic warfarin products from one supplier or another are giving rise to concern. There have been small studies of generic substitution that reported no problems, a need for increased dosages or more frequent monitoring of INRs (International Normalised Ratio). However, in Ontario in Canada, a policy of generic substitution of warfarin has been evaluated for over 30,000 patients, using the first nine months for which the substitution policy was in place, and 40 months prior to the policy as a comparison. There was no change in the rate of INR testing, nor any alteration in the admission rates for major haemorrhage or cerebral thromboembolism, but substantial cost savings were made. Reports of both benefits and adverse effects of the use of generic anti-epileptics have also been

published, particularly for carbamazepine, phenytoin and valproate. Where generic substitution policies have been implemented, anti-epileptic drugs have usually been excluded, thus limiting the amount of published experience. Transplant patients are vulnerable because their condition alters their handling of drugs, because non-compliance is a significant contributing factor to graft rejection, and because they are treated with a combination of drugs, each of which has its own potential for plasma concentration-related adverse effects. Several small studies have been carried out and, although the results reported were mixed, the American Society of Transplantation accepts that generic substitution may not be suitable for some patients.

Complicating each of these examples is the issue of continuity of supply. For patients with chronic conditions, with potentially serious outcomes from altered drug use, remaining consistently on a suitable product, generic or branded is important. The range of bioequivalence values allowed (80-125%) may be statistically appropriate, but for some drugs in some patients, if the previously used product was near the lower limit and the new product is near the upper limit, the difference in plasma levels could be as much as 40%. In Ontario, only three warfarin preparations were allowed - the brand original and two specified generics - and patients were maintained on one of these once stabilised. This almost certainly has contributed to the consistency in control shown by the INR testing rates.

For extended and modified release preparations, it is more difficult to establish the equivalence of their release characteristics. Added to this is the possibility that patient variability alters the performance of these preparations and that this variability may not be seen or quantified in a standard bioequivalence study.

Patients, prescribers and pharmacists all hold beliefs that affect their attitude to generics and often these are subconscious influences on their behaviour. Patients also respond to their prescriber's and their pharmacist's attitudes to generics. One of the more acknowledged factors is the country of origin of the product. A 'Guaranteed Irish' product has an advantage over an imported product. From their professional viewpoint, prescribers and pharmacists may be concerned that expenditure on generics decreases the income of the patent-led companies and may, in the longer term, reduce investment in research and development for new products. But more subtly the cost price may itself be an influence. Everyone knows that the placebo effect can produce a significant improvement in symptoms in the short-term but could price feature in the same way? A study from the heart of Irish America, Boston, Massachusetts, has shown that patients given a tablet that was purportedly a new codeine-like analgesic but was in fact a placebo, reported more pain relief if they were told beforehand that it was available at its 'regular' price \$2.50, than if they told it had been discounted to a low price of \$0.10. From this it seems that patients also

apply the maxim 'You get what you pay for' to the price that they pay for their medicine. Whether prescribers and/or pharmacists think the same has not been studied.

Practical Issues

Prescriptions must be written for, and dispensed, as products that hold an appropriate market authorisation, unless the product is exempt. Prescriptions written as a branded product should be dispensed as that product. However, if the specified brand is unavailable and the patient does not want to bring the prescription elsewhere, another brand may be dispensed. This raises the issue of consent. Informed consent is the appropriate term, and in clinical trials, and before the performance of an investigative or medical procedure, written, informed consent is obtained. If a patient is given a generic drug without their consent and they experience an adverse event associated with the preparation, the provider may be liable.

Pharmacists should be aware that in jurisdictions where generic substitution is mandatory, the following categories of patients are usually exempt from this requirement:

- very young, very old, those with multiple conditions for which they are receiving multiple drugs, patients who live alone and do not receive regular care visits
- patients whose conditions have potentially serious, acute clinical outcomes should their drug therapy become sub-optimal, e.g. epilepsy, chronic disease patients with intercurrent illness when drug-disease interactions could have serious consequences

In primary care, switching to a generic preparation is not advisable unless there are adequate facilities for patient evaluation and monitoring with these types of preparations: warfarin; lithium; ciclosporin; antiepileptics (especially phenytoin, carbamazepine and valproate, and possibly lamotrigine); antiarrhythmics; combination preparations; modified release preparations, especially those containing theophylline.

Conclusions

For most generic drugs and for most patients, there are no clinically significant problems associated with their use. Despite this, and despite attempts to increase their use in the health service, prescribers, patients and pharmacists remain anxious enough to keep generic use in this country at a low level. Prescribing a generic at the outset is easier than switching a patient at a later stage. There is some evidence to suggest that, in those countries in which pharmacists can substitute, generic drug use is higher. Limited evidence suggests that the use of generics as part of a carefully designed programme of care can realise substantial benefits, even for drugs with a narrow therapeutic index. However, more evidence is needed about other drugs and other groups of patients. Studies are

needed to demonstrate how generics can be incorporated into patient care programmes – and these programmes must address the needs and concerns of patients and practitioners in an equitable way, and facilitate care across the primary-acute hospital interface. Programmes that focus solely on cost-reduction will not promote appropriate use and usually create perverse incentives.

Many concerns relate to quality issues. Over 10 years ago, the Consumers' Association in the UK suggested that information about the bioequivalence of generics should be made more widely available, once they were approved, to allay those concerns. Not only would this improve confidence in generics, it could also do more. The types of generics and sources of generics will change rapidly as China, India and other countries expand their production. Most of the special generic anti-HIV drugs approved for use in low income countries are produced in India. Generic versions of biotechnology products, biosimilars (or follow-on biologics) as they are known, will be approved in Europe by an adapted version of the existing procedures, designed to demonstrate the 'comparability' of the similar to the original. There is increasing awareness and anxiety about counterfeit pharmaceutical products. Although most of these are marketed through internet sites, some have found their way into the supply chain through intermediary companies. An efficient system for the rapid, regular testing of products would identify counterfeits and their producers at the earliest possible stage and at the same time exclude genuine products and producers from suspicion.

Increased generic drug use could save significant sums but there are considerable barriers to their appropriate use that remain unaddressed in Ireland. However, the potential benefits of generics will never be fully realised in this country until the DoHC and the HSE recognise that their policies and programmes must act on each step of the drug use process to provide, not only access to generics at reasonable cost, but also incentives for their appropriate use, and support for their use with the public, prescribers and pharmacists. In doing this, reasonable expectations about generic drug therapy, and its cost, and rational decision-making about when and how to use generic drugs would be promoted.

References ~

- European Generic Medicines Association 2007.
- Martinez B and Goldstein J Big Pharma Faces Grim Prognosis. Wall Street Journal, December 6, 2007.
- Stenson J Report questions generic antidepressant MSNBC, October 12, 2007; available from www.MSBN.com.
- Anon. Generic Medicines – can quality be assured? Drugs and Therapeutics Bulletin 1997; 35: 9-11.
- Waber, R.L., Shiv, B., Carmon, Z., Ariely, D. Commercial features of placebo and therapeutic efficacy. JAMA 2008; 299: 1016-1017.
- Gross, D. Generic Drugs. AARP Public Policy Institute, Washington, 2003.
- Patterson, J.M., Naglie, G., Laupacis, A. Clinical consequences of generic warfarin substitution: an ecological study. JAMA 2006; 296: 1969-1972.
- Berwin, S.J. Policy relating to generic medicines in the OECD. London: National Economic Research Associates YRCR Ltd., 1999.
- Alloway, R.R., Issacs, R., Lake, K. et al. Report of the American Society of Transplantation Conference on Immunosuppressive drugs and the use of generic immunosuppressants. Am J Transpl 2003; 3: 1211-1215.
- National Medicines Information Centre. Generic Prescribing. 2000; 3:
- Barry, M., Heerey, A., Feely, J. Drug reimbursement in Ireland. Ir Med J. 2000; 93(3): 71-2, 74.
- Tilson, L., McGowan, B., Ryan, M., Barry, M. Generic drug utilisation on the General Medical Services (GMS) scheme in 2001. Ir Med J. 2003; 96(6): 176-9.
- Tilson, L., Bennett, K., Barry, M. The potential impact of implementing a system of generic substitution on the community drug schemes in Ireland. Eur J Health Econ. 2005; 6(3): 267-73.