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Bioequivalence and Generic Prescribing: a Pharmacy View*

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Patients have faith in the quality of the medicines they receive from their pharmacist whether at home or in hospital. Pharmacists have traditionally given patients confidence in the quality of their medicines and the medicine itself is rarely blamed for treatment failure. This trust is based on the track record of medicines supplied by manufacturers to pharmacists, the effectiveness of our licensing and inspection system for medicines, and the professional approach of the pharmacist.

Confidence in the quality of licensed pharmaceuticals has enabled hospital pharmacists to contract for one brand only of medicines that are available from multiple sources and hence purchase medicines at a cost effective price. This policy is coupled with training of prescribers to prescribe medicines by the approved name; that is, to prescribe the medicine the patient needs but to leave the choice of source medicine to the pharmacist. There are many benefits of approved name prescribing some of which are given in Table 1.

The system of approved name prescribing/pharmacist product selection has been practised successfully in hospitals for over 30 years. The cost effectiveness of the policy has been recognized and the policy promoted in general practice (Audit Commission Report 1994). The application of approved name prescribing/pharmacist product selection in general practice does still arouse some controversy; the major issues are highlighted in Table 2.

A cornerstone of this policy is the quality of the medicines supplied by manufacturers to pharmacists. The actual content of active ingredient of a product is taken as read; the debate around quality has concerned the bioequivalence of different licensed sources of a particular medicine. Concern was raised in the mid sixties in this area with the realization that not all digoxin products gave the same patient outcome (Lindenbaum et al 1971). Evaluation of a range of generic products did find that some of the products were found not equivalent with the brand leader. However, there was a surprisingly small number of problem products considering the number of multiple source products investigated (Koch-Weser 1974). Since then, the licensing authorities have developed requirements to ensure that medicines licensed as generic products are bioequivalent to the brand leader (CPMP 1991). There is still concern amongst prescribers, pharmacists and patients about bioequivalence and generic prescribing (Nightingale & Morrison 1987), despite there being few examples of approved name prescribing/pharmacist selection of medicines affecting patient care, or evidence for any UK licensed product failing to meet bioequivalence standards. A recent review (Gleiter & Gundert-Remy 1994) identified eight reports of bioavailability problems (Table 3).

It is in the interest of the pharmaceutical industry to promote brand name loyalty and to put forward counter arguments to those supporting approved name prescribing (Snell 1983). These arguments (Table 4) are cited frequently in the professional and lay press, ensuring that professionals and the public question the quality of generic products. After all we are a nation used to brand loyalty. There is a role for the pharmacist to educate both the public and fellow professionals about the issues involved in approved name prescribing and bioequivalence. There is little understanding of the range of amounts of active ingredient allowed in a tablet; that is, a nominal 100-mg tablet may contain between 90 and 110 mg, or the variability of content uniformity that is allowed in the manufacturing process. Manufacturing is an uncertain science, as is posology. Fortunately for most medicines there is a large safety margin between effective and toxic dose. This variability in delivered dose is compounded by the variance in clearance, both between individuals for a given medicine and between medicines, and the variable dose–response relationship found between patients (Rowland & Tozer 1989).

It is clear that there are many sources of variability associated with medicines and we need to minimize them wherever possible; hence the need to ensure that products containing the same active constituent are bioequivalent. Here again we are faced with interpatient variability. Current guidelines allow the 90% confidence intervals for the ratio of area under the curve to be between 0.8 and 1.25 in order for claims of bioequivalence to be substantiated (CPMP 1991). This may not be appropriate for some medicines which have low therapeutic indices or where very small dose changes can affect outcome. For these medicines we need to apply tighter criteria or the pharmacist and prescriber need to ensure that the patient is first stabilized and then maintained on one brand of the medicine.

Patient pharmacy registration would make a major contribution to patient safety in this area.

Pharmacists have been successful in maintaining patient support for pharmacy selection of product. This policy has saved public money (Audit Commission Report 1994) and reduced inventories. The pharmaceutical industry has

Table 1. Benefits of approved name prescribing.

Name often relates to a drug class
Use of one name reduces confusion
Cost effective for the NHS
Reduces range of products stocked

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Table 2. Issues involved with approved name prescribing.

Pharmacist role in value for money
Pharmacist need to maximise return on investment
Commercial support for brand names
Consumer awareness
Role of MCA in monitoring quality

Table 3. Examples of bioinequivalence (Gleiter & Gundert-Remy 1994).

Drug	Clinical outcome	Year
Amitriptyline	Lack of effect	1978
Carbamazepine	Lack of effect	1987
	Intoxication	1989
Diazepam	Not applicable	1977
Digoxin	Intoxication	1977
	Not applicable	1974
Diltiazem	Not applicable	1990
Glibenclamide	Lack of effect	1983
Oxytetracycline	Lack of effect	1969
Phenytoin	Intoxication	1971

Table 4. Disadvantages of approved name prescribing.

Clinical equivalence not always proven
Confusion to patients
Economic effect on pharmaceutical industry
Medicines bought on price alone
Difficulties with product liability

responded by lobbying for an extension of the life of the product license, to ensure a fair return on the cost of innovation, and by developing modified release products. Modified release products are not subject to generic substitution since each product is deemed unique. There has been a proliferation of such products in recent years, particularly as products near the end of their patent life. The Medicines Evaluation Resource Centre reviewed this area (MERC Bulletin 1995). The extent of duplication can be seen with the number of modified-release nifedipine products which are currently available, listed in Table 5.

The regulatory authorities have been reluctant to tackle this area. It is technically feasible to compare bioavailablity of modified release products and draw up criteria for bioequivalence for products claiming specific concentration/time profiles. This has not been undertaken and as a result we are seeing multiple brands of the same compound, each with claims for the perfect concentration/time profile for that active ingredient. Given the range of variability referred to previously these claims seem over-elaborate. The lack of leadership by the licensing authority in this area is causing confusion to pharmacists and to patients. The problem is compounded by the use of approved name

Table 5. Available nifedipine modified-release preparations March 1995.

Product	Strength and form
Adalat Retard	10 mg tablets
	20 mg tablets
Angiopine	20 mg tablets
Cardilate MR	20 mg tablets
Adalat-LA 30	30 mg tablets
Adalat-la 60	60 mg tablets
Nifelease	20 mg tablets
Nifensor-XL	20 mg tablets

prescribing by general practitioner information systems and on hospital-supplied medicines where the brand name is not always specified on the prescription or label. Few patients know which brand they received previously, a problem which could be resolved by patients being registered with one pharmacy. If no action is taken to apply scientific principles and commonsense in this area then the costs of medicines will increase in the vacuum created by the absence of competition and we will have less money for other aspects of health care.

Product selection by pharmacists when dispensing prescriptions written using the approved name has a good track record of success and support from patients. Current trends need to be monitored to ensure that the benefits of this policy continue to be enjoyed by patients.

There are valid concerns about the bioequivalence of multiple source products. To date, the approach taken by the regulatory authorities has enabled this practice to be undertaken without any risk to patient care so far as the majority of medicines are concerned. There are a small number of medicines where change of product is inappropriate. Pharmacists need to be aware of these products to understand why it is inappropriate in such cases, and to educate the patients about their medicines.

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