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The availability of generic medicines gives consumers greater choice in the brand and price of their medicines. However, misconceptions remain about the interchangeability of different brands and the proliferation of brands has potential for confusion. This issue of *NPS News* considers some principles about generic prescription medicines and brand substitution.

Substituting brands safely

Consumers' ability to pay for medicines is likely to influence whether they take their medication as directed.¹ Using generic medicines is one way for consumers to minimise the cost of their medicines. While price differences between generic and brand prescription products are, on average, less than \$3.00 per item (see page 2), a generic medicine can result in important savings for many people.

Change can be confusing

Clear communication is needed between the health professional and patient to avoid confusion if brands are changed. Consumers report becoming confused when their health professionals do not ensure that they have understood that there has been a change in the brand of their medicine. Many consumers do not realise that medicines have both a *generic name* and a *brand name* — they may not distinguish between switching to a different brand and switching to a different drug. People taking multiple medicines may also rely on the colour and shape of their tablets to help them to remember what to take and when to take it.²

Consumers who do not realise that the brand of their medicine has changed may take both the new and the old brand, thus taking a double dose^{3,4}, or avoid taking the new and unfamiliar tablet and miss out on a medicine.

Talking to consumers about brand substitution

Consumers are entitled to make choices about the brand and price of their medicines but substituting brands should not place them at risk.⁵

Consumers should be made aware of the availability of cheaper brands and have an opportunity to discuss their medicines choices with their doctor and/or pharmacist.

Brand substitution should only occur after consultation with, and the informed agreement of, the consumer or carer (Box 1). The decision to switch brands should take into account:

- the consumer's ability to understand and manage the change
- whether the presence of particular inactive ingredients (e.g. lactose) limits their choice of brands
- whether packaging differences might present problems.

Minimise confusion for people on long-term therapy by keeping them on their usual brand. This requires consistency in brand selection by pharmacists and providing access to usual brands for people in hospital or respite care, where possible.⁵

Box 1: Discussing brand substitution with consumers

- Advise that alternative brands contain the same amount of the same active ingredient and are as effective and safe.
- Reassure that all medicines registered in Australia are required to meet the same strict quality standards.
- Explain which medicine the new brand will replace and that the consumer should not take both medicines at once.
- Identify and discuss any differences in appearance between the old brand and the new one.
- Provide the active ingredient name and point it out on the packaging and/or consumer medicine information (CMI).
- Provide the CMI for the new brand.

What are generic medicines?

The company that first develops a medicine takes out a patent to ensure its exclusive right to produce and market it. Once the patent expires, typically 10 years after the medicine is first marketed, others can copy and market the same active ingredient. These alternative brands are called **generic medicines**.

To register a new medicine for use in Australia, a company must demonstrate its safety and efficacy in clinical trials. To register a generic medicine,

a company need not conduct extensive clinical trials if they show that their product achieves such similar blood concentrations of the drug that its efficacy and safety will be no different from the original product (i.e. it is **bioequivalent** — see opposite).

The number of alternative brands for an off-patent medicine usually relates to the size and profitability of the market for that medicine. The patent expiry of simvastatin saw 10 generic versions listed on the PBS.

Box 2: Similarities and differences

Efficacy and safety

A generic medicine must be shown to be bioequivalent to another registered brand to be interchangeable with that brand. **Bioequivalence** is based on the principle that a medicine's effects are related to its plasma concentration. The criteria for bioequivalence aim to exclude the possibility of clinically important differences between brands.

Quality

All medicines approved in Australia, including generic medicines, are required to meet the same quality criteria. Manufacturers of medicines registered in Australia must comply with an Australian code of manufacturing to ensure that all medicines are safe, reliable and of consistent high quality.⁶

Name

Generic medicines may be marketed under their own brand name or their generic name. For example, Simvar, Simvastatin-DP and Terry White Chemists Simvastatin are all brands of simvastatin.

Manufacturer

Some companies specialise in producing generic medicines. However, originator companies may manufacture and market alternative brands of

their own products. In some cases, the same product manufactured on the same production line will be marketed under two brand names and at two prices.

Ingredients

Inactive ingredients (or **excipients**, such as binders and fillers) may differ between bioequivalent products. Adverse reactions to excipients are extremely rare, so these differences will not usually be clinically significant. However, the presence of some excipients (such as gluten or animal-derived gelatin and stearic acid) may be important for people with allergies or who observe particular religious or cultural practices. Ingredients are listed at the end of the consumer medicine information (CMI) for each brand.

Appearance

Bioequivalent products may differ in colour, size, shape, taste and markings.

Packaging

Alternative brands may be packaged in different ways: for example, blister packs or bottles.

Price

A company may include a premium on the price of its brand, making it more expensive for consumers (see below).

How much do they cost?

Under the Pharmaceutical Benefits Scheme, the Australian Government pays the same amount for medicines that provide the same health outcomes. However, a company can set a higher price for their brand than the subsidy provided by the Government. In such cases, the difference between the subsidy and the price set by the company is passed on to the consumer as a brand premium.

A company can only impose a premium on their product when there is at least one equivalent brand of the drug available without a premium. Brand premiums range from \$0.06 to \$79.48, with an average of \$2.94.⁷

In the example (right column), 8 brands of enalapril 10 mg tablets are available without a premium and 2 have brand premiums (denoted by a superscript B). For people with a concession card, brands of enalapril

without premiums will cost \$4.70 for one month's supply; the brands with premiums will cost \$7.05 or \$7.75.⁸

CARDIOVASCULAR SYSTEM —cont.							
Code	Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Premium	Dispensed Price for Max Qty \$	Maximum Recordable Value for Safety Net \$	Proprietary Name and Manufacturer
1368B	ENALAPRIL MALEATE—cont. Tablet 10 mg	30	5	...	21.35	22.32	* Alphapril AF * Auspril SI * Chem mart CH * Enalapril * Enalhexal HX * Enalabell BF * Enalapril-DP DP 10mg * GenRx; Enalapril GX * Terry White Chemists TW Enalapril * Amprace 10 AD * Renitec MK
					^B 2.45	23.80	
					^B 3.15	24.50	
					^B 2.45	22.32	
					^B 3.15	22.32	

From *Schedule of Pharmaceutical Benefits*, 1 December 2005.⁸
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What is bioequivalence?

Two products are considered bioequivalent when they produce such similar plasma concentrations of the same active ingredient that their effects should be identical.

The two products may either contain the same amount of the same active substance in the same dosage form or contain the same active moiety but in a different chemical form (for example, omeprazole magnesium and omeprazole) or dosage form.

How is bioequivalence assessed?

Bioequivalence is usually assessed in healthy volunteers. On two separate occasions, single oral doses of each of the two products being compared are given (Figure 1).

The peak plasma concentration (C_{max}) and the extent of absorption (area under the concentration–time curve, AUC) of the new brand and the old brand are compared. To be bioequivalent, the 90% confidence intervals for the ratio of each pharmacokinetic parameter must lie between 0.8 and 1.25. That is, there is 90% certainty that the true difference in the rate and extent of absorption between the two brands is no greater than –20% to +25% (Figure 1).

This is sometimes interpreted as meaning that the rate and extent of absorption may differ between brands by up to 20–25%. However, for the 90% confidence intervals to lie between 0.8 and 1.25, the mean ratio must usually be very close to 1. For example, in 127 generic drugs applications to the US Food and Drug Administration in 1997 the mean difference was 3.3% for AUC and 4.3% for C_{max} .⁹

How do I know which products are bioequivalent?

One source of this information is the *Schedule of Pharmaceutical Benefits*, in which products that are equivalent are marked with a 'bioequivalence indicator' (a superscript a or b).⁸ These bioequivalence indicators show that a company has demonstrated that their product is equivalent to another listed product or provided justification for equivalence data not being required. From 1 April 2006, all new generic medicines listed in the *Schedule* must be marked as bioequivalent.¹⁰

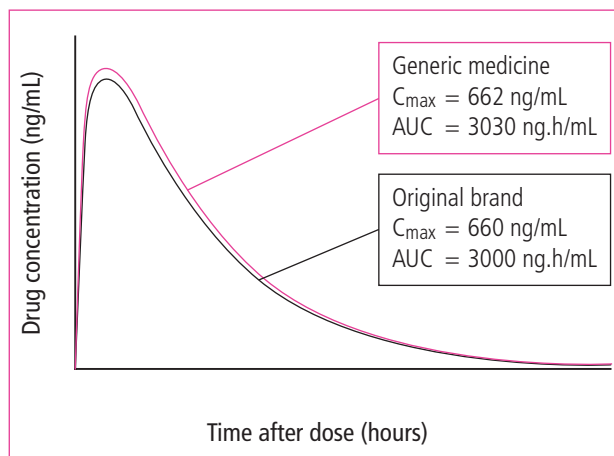
In the example below, 4 brands of paracetamol 500 mg are marked as bioequivalent. The others are not marked with the bioequivalence indicator so cannot be assumed to be bioequivalent.

NERVOUS SYSTEM —cont.									
Code	Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Premium	Dispensed Price for Max. Qty	Maximum Recordable Value for Safety Net	Proprietary Name and Manufacturer		
• Anilides									
1746X	PARACETAMOL Tablet 500 mg	100			7.39	8.36	Dymadon P Febridol Panamax Paralaxal Paralgin Pamol Terry White Chemists Paracetamol Tylenol	PC DG SW HX FM AW TW	
1747Y	Oral liquid 120 mg per 5 mL, 100 mL	†1	2	..	7.68	8.65	Panamax	SW	
1770E	Oral liquid 240 mg per 5 mL, 200 mL	†1	2	..	8.95	9.92	Panamax 240 Elixir	SW	
PARACETAMOL Restricted benefit. Chronic arthropathies.									
8784H	Tablet 500 mg	300	4	..	*12.67	13.64	Dymadon P Febridol	PC DG	

From *Schedule of Pharmaceutical Benefits*, 1 December 2005.⁸
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Figure 1: Bioequivalence analysis — a hypothetical bioequivalence study

Mean concentration–time curves for single oral doses of two brands



C_{max} = peak plasma concentration AUC = area under the concentration–time curve

The original brand:generic medicine ratio for AUC is 0.99 (90% CI 0.91 to 1.04) and for C_{max} is 0.99 (90% CI 0.92 to 1.07).

The 90% confidence interval of the mean AUC for the two drugs lies entirely between 0.8 and 1.25, indicating that the two products are bioequivalent (below).

Ratio and 90% confidence interval for area under the concentration–time curve



What about critical dose medicines?

Concerns are sometimes raised that the regulatory criteria for bioequivalence do not exclude the possibility of clinically significant differences in the efficacy and safety of critical dose medicines. These are medicines for which relatively small variations in plasma concentrations may cause significant adverse effects or loss of efficacy. Examples include cyclosporin, digoxin and warfarin.

When a patient is stabilised on a particular brand of a critical dose medicine, avoid switching brands if possible because the effects of potential medication errors after brand switching are likely to be more serious than with other medicines. Consider the comparative cost of, and patient preference for, particular brands at the outset of treatment. The decision to use a generic medicine should ideally be made when treatment begins.

There is debate about whether switching between brands of critical dose medicines considered to be bioequivalent by regulatory authorities could cause clinically significant changes in plasma concentrations. Evidence of adverse effects or loss of efficacy associated with switching brands is often of poor quality. For example, while some surveys of health professionals and consumers have reported high rates of problems thought to be associated with switching brands of anti-arrhythmic or anti-epileptic drugs¹¹⁻¹³, such evidence is extremely susceptible to bias. Very few well-designed studies have assessed the effect of switching brands on clinical outcomes such as seizure frequency or toxicity.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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