

BEST PRACTICE

SPECIAL EDITION

Generics



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This magazine is printed on an environmentally responsible paper managed under the environmental management system ISO 14001, produced using Certified ECF pulp sourced from Certified Sustainable & Legally Harvested Forests.

We would like to thank to following for their assistance in producing this publication:

Clive Cannons
Professor Stephen Duffull
Dr Stewart Jessamine
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Best Practice Journal (BPJ)

ISSN 1177-5645

BPJ, Special Edition: Generics

July, 2009

BPJ is published and owned by bpac^{nz} Ltd

Level 8, 10 George Street, Dunedin, New Zealand.

Bpac^{nz} Ltd is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

We develop and distribute evidence based resources which describe, facilitate and help overcome the barriers to best practice.

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This Special Edition of Best Practice is funded through contracts with PHARMAC.

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Key Points

- The quality, safety and effectiveness of generic medicines in New Zealand is evaluated by Medsafe following processes that are at least as stringent as those in Australia, Europe and the USA.
- Medicines that are evaluated as being bioequivalent are very unlikely to have altered clinical effects or adverse effect profiles.
- Generic medicines have been used effectively and safely for many years in many countries, including New Zealand.
- Negative perceptions about generic medicines can influence patient acceptability. Explanation and counseling by prescribers and pharmacists can help to allay concerns.
- Simple strategies such as the doctor prescribing generically and the pharmacist labeling the container with the name of the active ingredient (generic name) can help to avoid patient confusion when brand changes occur.
- Healthcare professionals have an important role in helping patients understand that generic medicines are safe and effective.
- Generic prescribing and dispensing would enable patients to be educated about the names of the active ingredient of their medicine to avoid confusion between different brands of the same medicine.
- Reporting mechanisms are in place (e.g. CARM) to monitor the safety and effectiveness of generic medicines.



Introduction

Generic drugs are reproductions of the original innovator medicine which are made widely available when a drug's patent expires. They have been widely used in many countries for over 40 years, including New Zealand. The use of generic medicines is an important part of health care, providing economical alternatives to more expensive branded products and allowing considerable savings for the overall health care budget. With this potential for savings the use of quality generic medicines is becoming increasingly part of national medicines management strategies. For example, the UK will introduce generic substitution from 2010 and there are similar initiatives in Australia.

We can expect the use of generic medicines to increase in New Zealand. This publication is intended to inform health professionals about the processes by which generic

medicines are tested, approved and monitored, to provide reassurance of their quality, safety and effectiveness. As our patients are often misinformed or have concerns about the use of generic medicines we also provide advice on how to increase acceptance of generics amongst patients. Finally, we discuss the monitoring processes in place in New Zealand to ensure that if problems do occur they are identified and resolved in a timely manner.

A few words about the terminology used in this publication. When we mention brand switching it will usually mean a switch from an innovator brand such as the Aropax brand of paroxetine to Loxamine, which is the generic brand. Occasionally, the generic medicine does not have a brand name and may be simply known by the approved chemical name. When bioequivalence studies are described, we refer to the generic compared to the innovator medicine.



What is Bioavailability and Bioequivalence?

All generic medicines in New Zealand are approved by Medsafe and have been shown to be bioequivalent to innovator medicines, according to internationally accepted criteria and standards.⁴ This means that any differences in bioavailability between generic and innovator medicines are not clinically significant.

Bioavailability

Bioavailability is a measurement of the extent of a therapeutically active medicine that reaches the systemic circulation and is therefore available at the site of action.

For most medicines that are taken orally, the active ingredients are released in the gastrointestinal (GI) tract and arrive at their site of action via the systemic circulation. Blood concentrations of the active ingredients and/or their active metabolites thereby provide a marker for the concentration at the site of action and a valid measure of bioavailability.

A blood concentration – time curve (achieved by serial measurements over time) reflects not just the release of the active ingredient from the medicine and its absorption

from the GI tract, but also other factors including pre-systemic metabolism, distribution and elimination.

Bioavailability is assessed using three main pharmacokinetic variables (see Figure 1);

- the area under the blood drug concentration versus time curve (AUC)
- the maximum blood concentration (C_{max})
- the time to reach maximum concentration (T_{max})

Bioavailability example

A hypothetical drug given orally has a bioavailability of 50% (or 0.5), this is due to:

1. incomplete absorption in the GI tract so that only 70% of the initial dose is absorbed.
2. subsequent metabolism of a further 20% before it reaches the systemic circulation (e.g. first pass through the liver).

Therefore only 50% of the original oral dose reaches the systemic circulation.

Bioequivalence

If two medicines are bioequivalent there is no clinically significant difference in their bioavailability.

Although bioequivalence is most commonly discussed in relation to generic medicines, it is important to note that bioequivalence studies are also performed for innovator medicines in some situations such as:

- between early and late clinical trial formulations or between the formulations used in clinical trials and the product to be marketed for new medicines
- when changes in formulation have occurred after an innovator product has been approved, for example a change in one or more excipients (inactive ingredients)

Bioequivalence studies are a surrogate marker for clinical effectiveness and safety data as it would not normally be practical to repeat clinical studies for generic products. It is accepted that if plasma concentrations of the active ingredient of the generic and innovator medicines are the same, then their concentration at the site of action and therefore their safety and effectiveness will be the same. In addition to being bioequivalent, a generic medicine must conform to high quality standards in terms of the method of manufacture and the purity of the final pharmaceutical form.

There are internationally agreed standards for measuring and assessing bioequivalence (see Appendix One).

Acceptance Criteria for Bioequivalence

Bioequivalence is determined based on the relative bioavailability of the innovator medicine versus the generic medicine. It is measured by comparing the ratio of the pharmacokinetic variables for the innovator versus the generic medicine where equality is 1.

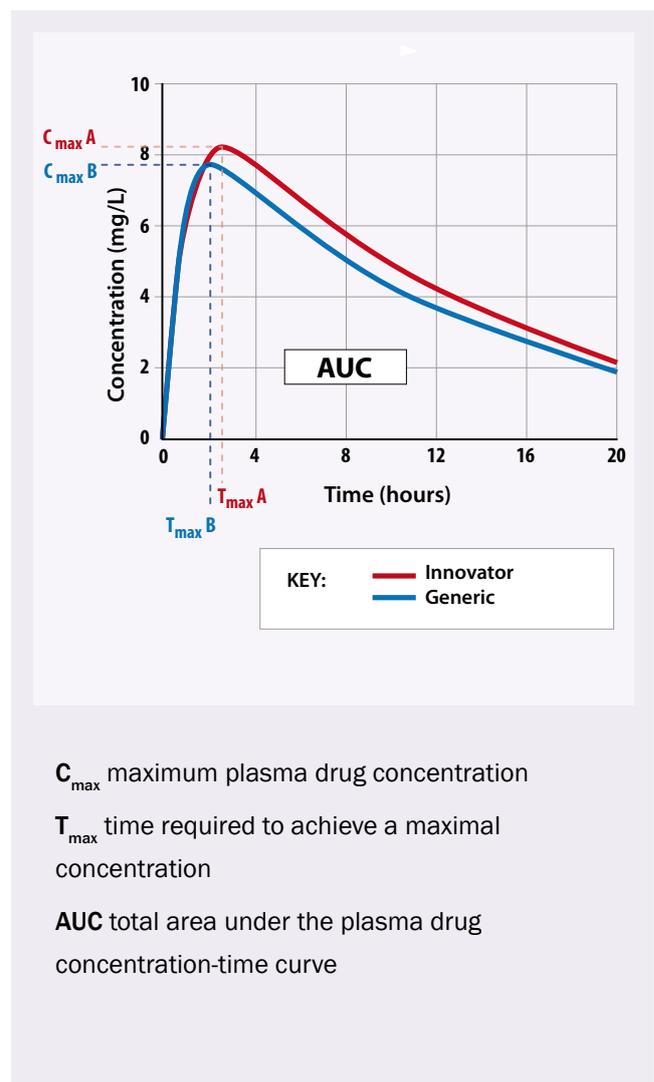
The acceptance criteria are such that to be classified as bioequivalent, plasma concentrations of the generic medicine will not differ significantly compared with the

innovator medicine. **Studies have demonstrated that actual differences between observed mean plasma concentrations of generic and innovator medicines were no greater than 5%.**

In order to determine that two medicines are bioequivalent there must be no more than a 20% difference between the AUC and C_{max} . This is based on international consensus that differences less than this are not clinically significant. In order to establish this, the AUC and C_{max} for the generic medicine are compared to that for the innovator medicine (Figure 1).

Figure 1: Simulation of a drug concentration versus time curve for two drug products

(Adapted from Reference 2)



Bioequivalence is based on a comparison of ratios where the ratio of generic to innovator for each pharmacokinetic variable does not differ by more than 8:10, this is how the range for the confidence intervals is defined:

- $8/10 = 0.80$ gives the lower limit
- $10/8 = 1.25$ gives the upper limit

The 90% confidence intervals for the ratios of both C_{max} and AUC should be contained within the limits 0.80–1.25 (see Figure 2). Thus bioequivalence is based on ratios where the nominal equality is 1. It is not based on differences in absolute values.

In practice, the generic product should have a ratio of mean values (AUC and C_{max} generic: innovator) close to 1, indicating equality. If the observed ratio is closer to 0.8 or 1.25, then the data would have to contain little or no variation from the mean for the 90% confidence intervals of the ratio to lie in the 0.8 to 1.25 range that is necessary to demonstrate bioequivalence.²

Testing bioequivalence in a “normal and healthy” population

When an innovator medicine is developed, evidence is required of its pharmacokinetic properties, efficacy and safety in healthy volunteers as well as the target patient population. However, bioequivalence studies are normally only performed in healthy volunteers in order to reduce the variability not related to differences between products.

This raises the question as to whether the generic medicine would perform differently in a target patient population, taking into consideration factors such as co-morbidities, concurrent prescriptions and physiological factors including differences in first pass metabolism, gastric pH and bacterial flora.⁴

Scientifically, there is no reason to suppose that differences in metabolism, that may effect the plasma disposition of an active substance from an innovator medicine, will not equally effect the plasma disposition of an active substance from a generic medicine.

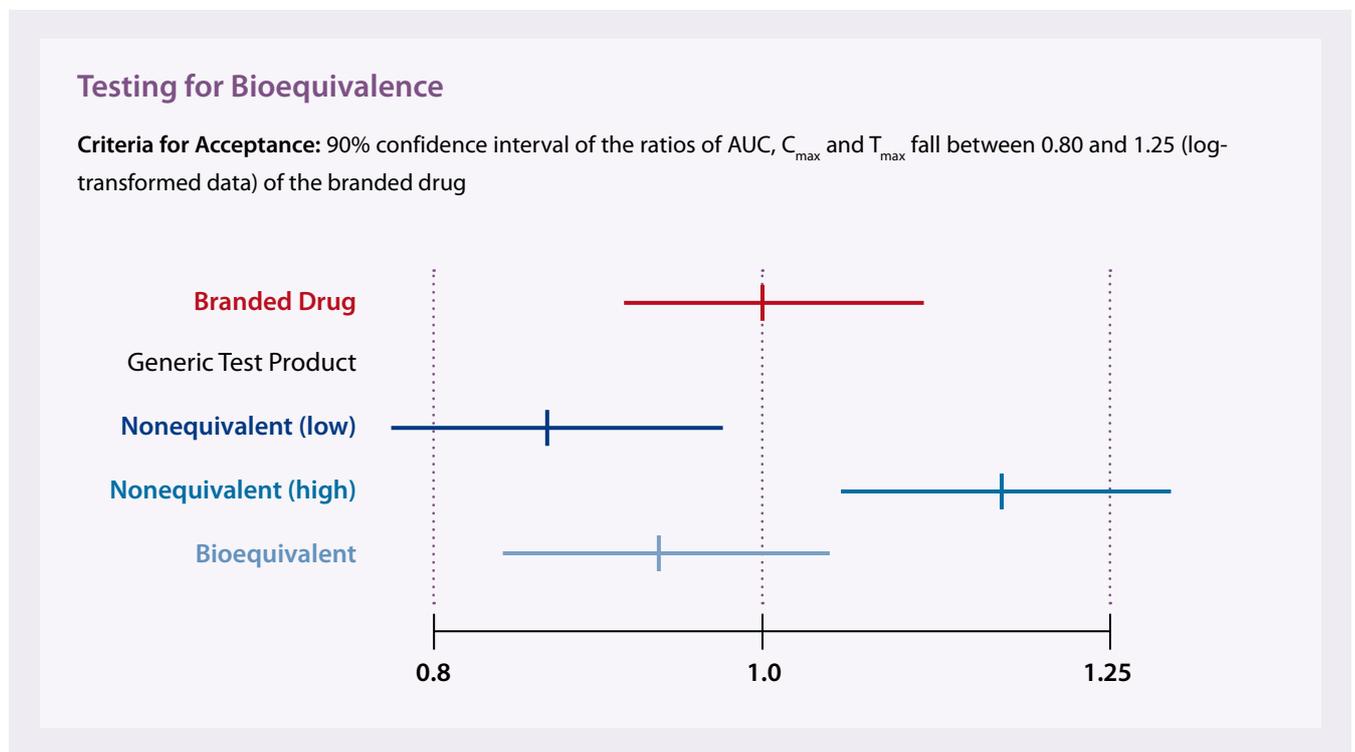


Figure 2: Bioequivalence confidence intervals

Bioequivalence studies are cross-over studies in which each subject acts as their own control. This model, (*in vivo* healthy volunteers) is regarded as adequate to detect formulation differences. The results obtained allow extrapolation to populations in which the reference product is approved (e.g. the elderly, children, patients with renal or liver impairment).

The potential effect of excipients on bioequivalence studies

Bioequivalence studies usually involve single doses of a medicine.¹ It is theoretically possible that excipients used in the generic formulation (preservatives, pH adjusters, thickening agents etc) could affect the absorption and metabolism at steady state without producing these differences from a single dose.⁵ However this is extremely unlikely and would normally be apparent from differences observed in the bioequivalence study.

Any difference that may exist is negligible compared to the variability of the conditions in the gastrointestinal tract and its effect on absorption.

Non-interchangeable medicines

If approved by Medsafe it can be assumed that a generic medicine is therapeutically equivalent to the innovator unless the medicine is considered to be non-interchangeable. For a limited number of medicines with a narrow therapeutic range such as carbamazepine, phenytoin and digoxin, a relatively small change in systemic concentration of these medicines can lead to altered therapeutic response or toxicity.

Warfarin also has a narrow therapeutic range and bioequivalence has not been established between the two main brands of this medicine. Therefore clinical guidelines state that there should be no switching between different brands of these medicines.

Can the bioavailability of bioequivalent products differ by up to 45%?

For two drugs to be bioequivalent, the 90% confidence intervals (90% CI) for the ratio of the means of C_{max} and AUC must lie within the range 0.8 – 1.25. There is a commonly held perception that this means that the plasma concentration of the active ingredient could vary by up to 45 % (ie -20 to +25%) between innovator and generic and still be classed as bioequivalent. This is incorrect.

The 90% CI of 0.8–1.25 reflects the limits for a comparison of ratios where equality equals 1. It is not a direct measure of the difference in systemic concentrations of the active ingredient resulting from administration of the two medicines. The confidence interval provides a range of values in which we can say with a degree of certainty the true value lies. For example, in a study the observed ratio for C_{max} is 0.95 (representing a 5% difference between products). If the 90% confidence interval was 0.85 to 1.01, this means that we can be confident that if the same study was conducted 100 times, then 90 of those times the observed result for the ratio of C_{max} would lie somewhere in the range 0.85 to 1.01.

The acceptance limits mean that the C_{max} and AUC ratios (generic:innovator) estimated for each formulation can vary by +/- 20%. In reality, for a medicine to demonstrate bioequivalence, the ratio of the mean values must be close to 1 in order for the upper and lower limits to be contained within the accepted range, and any difference in bioavailability is likely to be less than 10%.

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} .³

Adverse effects of excipients contained in different products

Excipients include diluents, binders, fillers, surfactants, lubricants, coatings and dyes. Lists of the excipients contained in a medicine are included in the Medicines Data Sheet, available on the Medsafe web site: www.medsafe.govt.nz

All manufacturers must supply Medsafe with the details of all excipients in their products to ensure that they are internationally approved, non-toxic and have a low potential to cause adverse effects such as hypersensitivity.

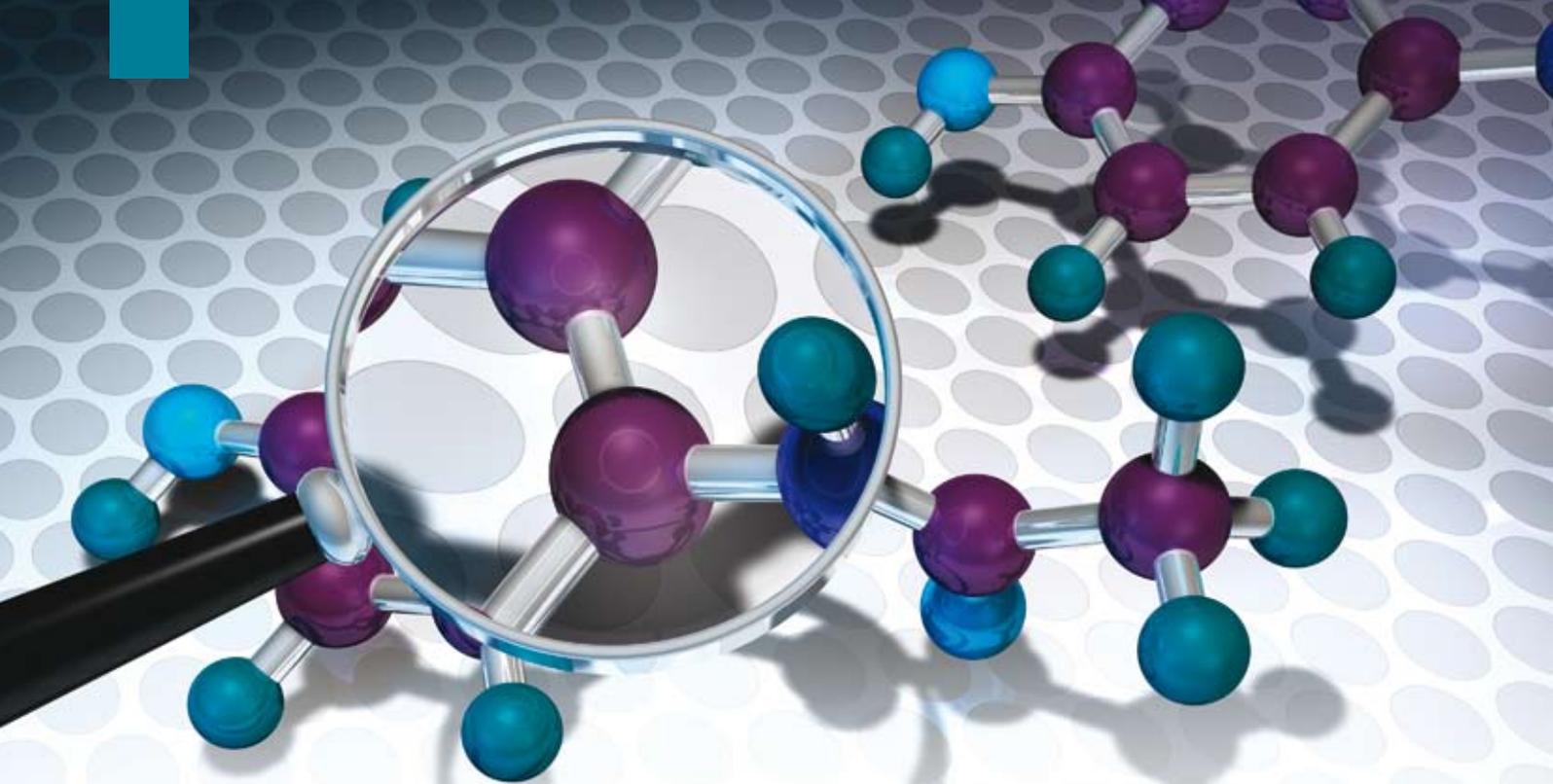
It is possible that a person may have a reaction to an excipient when switching between innovator and generic (or vice-versa), or from one generic to another, but such events are rare. The main potential problem is allergy or intolerance to a specific ingredient such as lactose or parabens.

If a person has a known allergy or intolerance, the data sheet can be checked to see if the causative agent is contained in the medicine.

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The regulation and oversight of **Generic Medicines** in New Zealand

In New Zealand, Medsafe is responsible for the regulation of generic medicines. This involves evaluating the manufacturing processes, assessing product quality and evaluation of bioequivalence study reports.

Medsafe regulations are based on current international best practice. New Zealand regulation is consistent with most (if not all) overseas regulators.

In the wake of recent high profile medicine brand changes, pharmacists, general practitioners and patients have raised a number of questions about the regulation and oversight of generic medicines. We put these questions to **Dr Stewart Jessamine** and **Dr Enver Yousof** from Medsafe.

Q Do our methods and standards in NZ comply with international standards such as those used in the USA and Europe?

A The quality, safety and efficacy evaluations for generic medicines used by Medsafe follow processes that are at least as stringent as those in the USA, Europe and Australia.

The basic requirements for approval of generic and innovator medicines are the same. The generic medicine manufacturer is not required to repeat the safety and efficacy studies conducted by the developer of the original product. In approving a generic medicine, Medsafe relies on previous findings that the innovator product is safe and effective, both in terms of the excipients and active ingredients.

The generic version must have the same dosage form, strength, route of administration, and conditions of use as the innovator product. The applicant must show that a generic product delivers the same amount of its active ingredient in the same amount of time as the trade-name counterpart. This bioequivalence is critical for drawing the conclusion that both the original and generic medicines will produce similar therapeutic results.

With respect to bioequivalence testing, Medsafe may in fact go further than some countries in that the pharmacokinetic data provided by the applicant is taken and recalculated to ensure that it fulfils the criteria for bioequivalence.

In addition to bioequivalence testing, Medsafe, in common with other agencies, also require that comparative dissolution testing is performed on a generic medicine. This test is designed to determine that the generic tablet or capsule will perform in the same way as the innovator formulation under a variety of conditions e.g. pH. Demonstrating that dissolution is the same for two medicines gives an indication that the active substance is made available for gastrointestinal absorption in the same way.

Q For how long has compliance with these standards been in place, i.e. have there been any significant changes in standards or approval processes in the last few years?

A Medsafe work to the same standards as other international regulatory authorities. These standards have been in place for the last 30 years but are reviewed on a regular basis.

Q Who conducts the bioequivalence studies? Are they done in New Zealand?

A Very few bioequivalence studies are undertaken in New Zealand. Because the studies are cross-over studies and subjects are their own controls the results

may be extrapolated to any population regardless of where the original study was conducted.

Q Do manufacturers usually supply the results of their own bioequivalence studies or do they sub-contract to other agencies?

A Manufacturers supply their own data; more often than not the manufacturers have contracted a clinical research centre to undertake a bioequivalence study on their behalf.

Q What safeguards are in place to assure quality and validity of the bioequivalence data provided ?

A Regardless of where they are undertaken, bioequivalence studies must have been undertaken according to 'Principles of Good Clinical Practice' and the samples analysed according to 'Principles of Good Laboratory Practice'. The manufacturers self-certify that this was the case and this is open to audit at any point. This system of self-certification is used by regulatory authorities overseas including the FDA, and the TGA as well as by Medsafe.

Q If two medicines are confirmed to be bioequivalent is it possible for differences in therapeutic effect or adverse effects to occur?

A Bioequivalence is a statistical test and is derived from population pharmacokinetics. It is feasible that at an individual patient level, for a very small proportion of patients, changes in formulation may lead to differences in bioavailability. For the majority of these patients any differences should be clinically insignificant.

Q Are the medicines data sheets for generics always the same as the innovator product? What process is in place to assure this?

A The datasheets for generic medicines do not have to be identical to the innovator, but they should be

consistent with that for the innovator product. The datasheet for the generic medicine cannot contain more indications or any less safety information than those for the innovator product. Datasheets are checked as part of the evaluation process and changes to them requested as appropriate.

Q If there are reports of adverse events (including reduced therapeutic effects) to the Centre for Adverse Reactions Monitoring (CARM), what is done with this information, and at what stage would the registration of the generic be reviewed?

A CARM receives spontaneous adverse event reports including those associated with brand switches. These reports are analysed and held on a database. Medsafe meet weekly with CARM who raise any signals that may have been identified as a result of their monitoring. Where necessary, reports are reviewed by the Medicines Adverse Reaction Committee (MARC) who provides advice to Medsafe regarding steps that should be undertaken to minimise the risk to the public.

Advice provided by MARC could range from ongoing monitoring with changes to the datasheet through to the recommendation that the medicine is removed from the New Zealand market.

Q Are there any safety issues with generic medicines?

A As part of the dossier submitted by the generic medicine manufacturer, safety data from bioequivalence studies are provided. Any difference between the safety profile of the innovator and generic medicine is reviewed and questions raised as necessary. Details of all excipients and non-active compounds are provided and these may differ from the innovator product. However, the toxicological profile of all excipients is checked in order to ensure their approved use for this purpose.



For further information about Medsafe see the Medsafe website:

www.medsafe.govt.nz



Medicine Brand Changes

Patient acceptance of a medicine brand change can be influenced by many factors including their own beliefs, the attitudes of health professionals, misunderstandings and lack of information about the change.

The introduction to the market of a generic medicine, especially when replacing the innovator counterpart, is often met with suspicion and concern by health care providers and patients. Concerns mainly involve issues of effectiveness and safety. Generic medicines may be perceived as inferior due to their lower cost and country of origin.

When an innovator product is replaced with a generic alternative, there are many issues that must be taken into consideration.

Prescribers attitudes towards generic substitution are most often related to their general prescribing behaviour, perception of therapeutic efficacy, beliefs about generic medicines and previous experience with using generic alternatives, including any negative effects.¹

Pharmacists may consider the overall quality of the medicine as well as the potential for patient confusion and their comfort with a brand change.

Patients undergoing a brand change to a generic are generally most concerned about potential changes in therapeutic effects, adverse effects and practical issues relating to use (e.g. size, shape, appearance). Increasing age is associated with less favourable attitude towards generic medicines and patients are often less accepting of using a generic medicine to treat a serious disease.²

Differences in appearance, and brand loyalty

Generic medicines often differ in appearance and packaging from the innovator product which may cause anxiety and confusion in patients. Those receiving pharmacological treatments for psychological disorders may be especially vulnerable to this.³ Changing the colour, taste or form of a medicine can result in non-adherence. Although there is no evidence that generic medicines are inferior to innovator products, patients may often resist changing from a brand they know well to a generic equivalent which may look different.⁴ Patients prefer to stick to a brand name medicine if they have already been familiarised with it.¹ The longer a generic brand has been available, the more likely it is used by pharmacists and prescribers. Prescriber and pharmacist habits and preferences may be influenced by informational constraints, loyalties to pharmaceutical companies and desire to satisfy patients.²

Colour and form and public acceptance of brand change- Losec to Losec MUPS

The importance of colour and form for the acceptance of a product was clearly demonstrated in the Netherlands when Losec was switched to Losec MUPS. Both branded products originated from the same company and bioequivalence and pharmacodynamic studies had established that they were therapeutically equivalent. However, shortly after the introduction of Losec MUPS a large number of adverse reactions – about 25% were of reduced therapeutic effect- were reported to the Netherlands centre for pharmacovigilance.

Although subtle changes in pharmacokinetics and patient response cannot be completely excluded, this example does provide good evidence that form and shape are important in the perception of a difference between two brands of an equivalent medicine.⁵

Generic Medicines & Brand Change

Resources

For more information and articles and interviews on brand change and generic medicines visit us at:

www.bpac.org.nz

keyword: generics





Counseling patients through a brand change

Health care professionals have an important role in helping patients understand that generic medicines are as safe and effective as the innovator medicine.

Patients should be educated about the names of the active ingredient of their medicine to avoid confusion between different brands of the same medicine.

Accentuate the positive

The pharmacist is in an ideal position to counsel patients about a change to a generic medicine. A good understanding of the likely reasons behind any objections, and a positive reinforcement of the facts during the first interaction with the patient will ensure greater acceptance of change.

It is important to realise that in both clinical trials and in practice there is a significant placebo effect. This applies to most medical conditions. This means that the actual taking of a 'medicine' whether it contains an active ingredient or not can elicit a measured clinical response. It can therefore be logically argued that even if a generic medicine was identical with respect to active ingredient and the rate of release, a person's actual perception or acceptance of receiving something different may influence therapeutic effect, especially if there is a degree of subjectivity involved.

Experiences with the paroxetine brand change

In March 2007, bpac^{nz} initiated an education programme for pharmacists to coincide with the change of funding to paroxetine brands. The programme was evaluated and the results showed:

- Almost all pharmacists accessed programme resources and rated them useful or extremely useful
- An average of four minutes was spent explaining the brand change to each patient
- Just over half of the pharmacists had a concern with Loxamine, mainly in regards to bioequivalence and ability to split the tablet
- Pharmacists with a previous negative experience with brand change, and those who participated in the education programme were more likely to provide private counseling at the time of change
- Pharmacists who did not actively participate in the programme were more likely to have concerns about bioequivalence
- Almost all pharmacists would like to see similar programmes for future brand changes

Counseling - three common questions and answers

Q **Why the change?**

A The rationale for change is outlined in both the medicine specific patient information pamphlet produced by PHARMAC, as well as the “My Medicine Looks Different” pamphlet.

Giving this pamphlet to the patient and working through the key points with them should provide the patient with sufficient understanding of the reasons for the change. Although the current leaflet ‘My Medicine Looks Different’ mentions brand changes, it can be explained that this is the same as changing to a generic.

Q **Is it the same medicine, and will it do the same job?**

A A confident response can be supported with a professional knowledge of the regulatory process and bioequivalence (see page 4) and other information in this journal.

You can explain that the medicine itself is not changing but it is being supplied by a different manufacturer.

“Medsafe, the agency that approves medication for use in New Zealand, approved the generic medicine after carefully considering clinical study data. To gain this approval, the new supplier had to show that the generic delivers the same amount of the same medicine at the same rate as your previous brand. This means you should have the same clinical effect from taking the generic medicine as you did from your previous brand. If you notice any change you should discuss this with your pharmacist or doctor.”

Q **Will there be any adverse effects from changing to a generic?**

A Understanding the potential for ‘new’ adverse effects is the key to an effective response to this question

and will require a considered approach from the pharmacist. Some adverse effects are related to the dose of medicine and may be more apparent if the amount of medicine received is increased, others can occur when the dose of medicine received is suddenly reduced.

At the extremes of compliance with international standards of bioequivalence testing, it is possible that there may be small differences in the amount of the active ingredient compared with the reference product. This may lead to subtle changes if the effect is related to plasma concentrations. However, such effects are unlikely and, in theory, similar differences can also occur between different batches of the same brand.

It is also worth pointing out that generic medicines are not new. They have been available and in use in New Zealand and other countries for many years.

Practice Tips for health professionals

All health professionals have a role in successfully guiding patients through brand changes and acceptance of generic medicines

- **GPs** - Prescribe by generic name
- **Pharmacists** - provide appropriate counseling

Avoiding confusion over names

The best way to avoid confusion over names is to prescribe generically. This allows the medicine to be dispensed with the generic name on the label.

Many generics have a brand name (e.g. Loxamine) and this can lead to confusion. In addition, patients may perceive the generic name as a different medicine to the brand they were formerly taking.

It is useful to encourage patients to know the name of the active ingredient in the medicine they are taking rather than the product brand name.

Pharmacists can assist with this by counseling and appropriate labelling. This will help the patient to understand that the same medicine may be available with different names.

Hospitals may have a different range of innovators and generics to those available in community. This emphasises the need for patients to have a list of their medicines by generic name as they move in and out of hospital.

A further challenge is product appearance and taste and it is not uncommon for patients to associate the tablet or capsule colour with the active ingredient. In order to maintain adherence, it is important for GPs and pharmacists to explain that these changes do not compromise clinical effectiveness.



Patient Information Programmes make brand changes easier

Health professionals, especially GPs can have a significant influence on patient acceptance of generic medicines. In a consumer survey, 50% indicated they would not use a generic medicine without checking with their GP, despite agreeing that the generic medicine contained the same active ingredients as the branded medicine.⁶

A study based in Spain⁴ assessed the acceptance of substitution of innovator medicines for generic medicines for chronic conditions in primary care. Of the patients who received verbal and written information on generic medicines, almost all agreed to receive a generic medicine. The reasons for refusal in the remaining patients included the influence of prescribers other than the general practitioner, patients' satisfaction with the innovator product and concern about adverse effects.

There was no statistically significant difference between patients that agreed and those that didn't agree with substitution based on age, gender or educational level. There were however, significant differences in acceptability rates according to individual primary care centres, suggesting differences in quality of information provided.

It was concluded that an individual educational intervention (that lasted less than five minutes in most cases) in patients with repeat prescriptions resulted in a high rate of generic acceptability. The intervention also helped to stimulate health practitioner's knowledge of generic medicines.⁴

In a study that assessed the impact of introducing generic substitutes to patients in a general practice clinic in Scotland, 70% accepted the generics and were satisfied with the change. Of the remaining patients, 19% were still taking the branded medicine, 4% were on other prescribed treatment, 4% had stopped treatment and 3% were purchasing their own alternative. Patients were either sent an explanatory letter detailing the change or were informed when first collecting their repeat prescription.

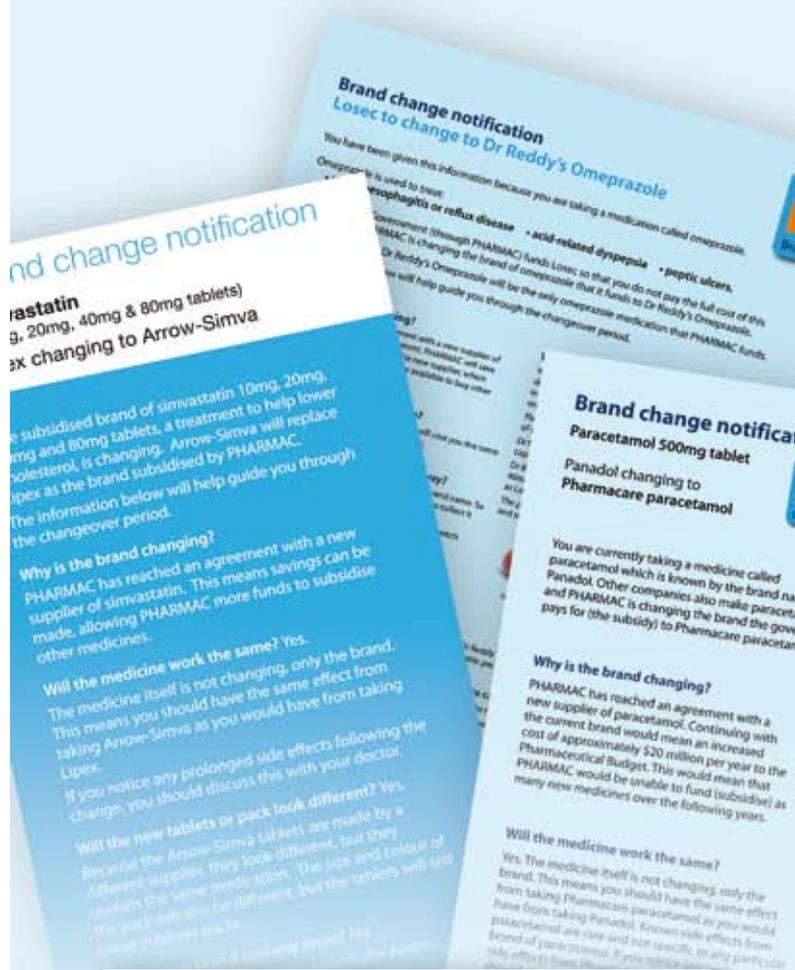
Reasons for dissatisfaction were largely due to the quality of information provided to the patient rather than problems with the generic medicine itself. Almost three quarters of patients (73%) could recall being informed of the change in at least one way. Satisfaction with the communication received was closely correlated with satisfaction about the change to the generic medicine itself. After four months, generic prescribing increased from 37% to 58%.⁷

The results of these studies suggest that appropriate care must be taken to inform patients properly. Interviews with patients showed the most common cause for dissatisfaction was a failure of communication. Patients were much more likely to be willing to accept the change if they understood the rationale and could be reassured about safety and effectiveness.

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Brand Change Patient Leaflets



Free from PHARMAC online:
www.pharmaonline.co.nz



Monitoring of generic medicines and brand changes

Contributed by Dr Michael Tatley, CARM

Reports to CARM following brand change

Unlike other national monitoring centres internationally, CARM receives reports of patients' adverse experiences on changing brands of medicines that contain the same active ingredient. Almost exclusively, these reports follow a change in brand subsidy by PHARMAC, but also occur when the availability of a medicine changes for other reasons.

The initial reports of adverse experiences are usually received by CARM within the first few weeks following the brand change. Typically, these reports describe a loss of therapeutic effect when compared to the original product. Other events are also described, the most frequent of which are gastrointestinal (nausea vomiting diarrhoea), skin (rash and/or pruritus) and neurological events (headache and or dizziness). Occasional reports are suggestive of increased therapeutic effect such as hypotension with enalapril.

CARM has received reports following brand change for a range of medicines since 1998. However, CARM began to focus on this phenomenon in 2001 when the frequency

of reporting increased following the change to a generic version of fluoxetine.

Following a brand change, reports generally follow a predictable pattern that peaks typically in the range of 15-40 reports and then declines over a three month period (Figure 1).

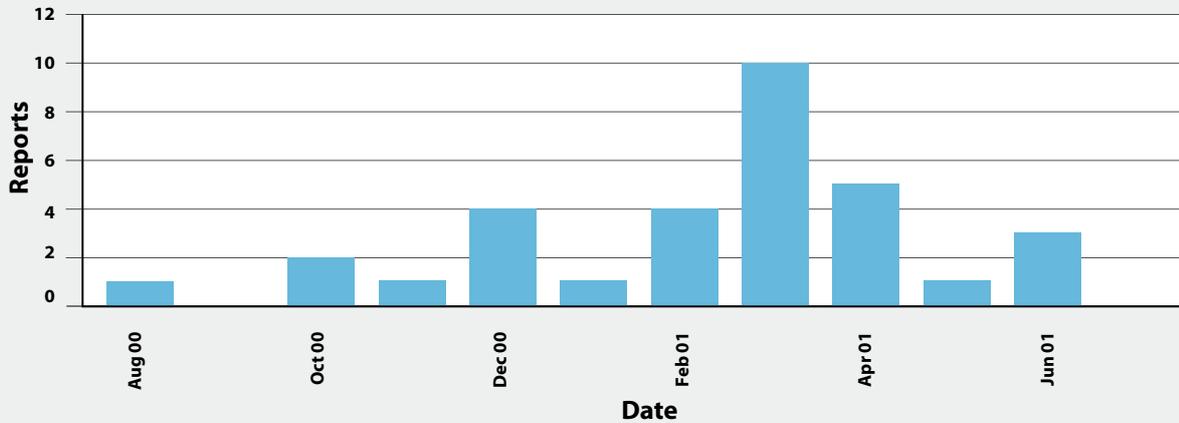
In the fluoxetine graph in Figure 1, the first series represents the change from Prozac to Plinzine (innovator to generic), and the second period the change from Plinzine to Fluox (generic to generic).

This pattern with an initial peak then decline, despite the new medicine continuing to be available, suggests that the adverse reaction reports are a phenomenon of the change process rather than medicine *per se*.

Reports associated with brand change are assessed and evaluated at CARM in the same manner as all other reports of adverse events. This includes assigning the reaction terms and causal association and then addition to the to the CARM database. The receipt of each additional report contributes to the emerging pattern. The nature of the

FLUOXETINE Brand change Reporting Patterns

Innovator to Generic



Generic to Generic

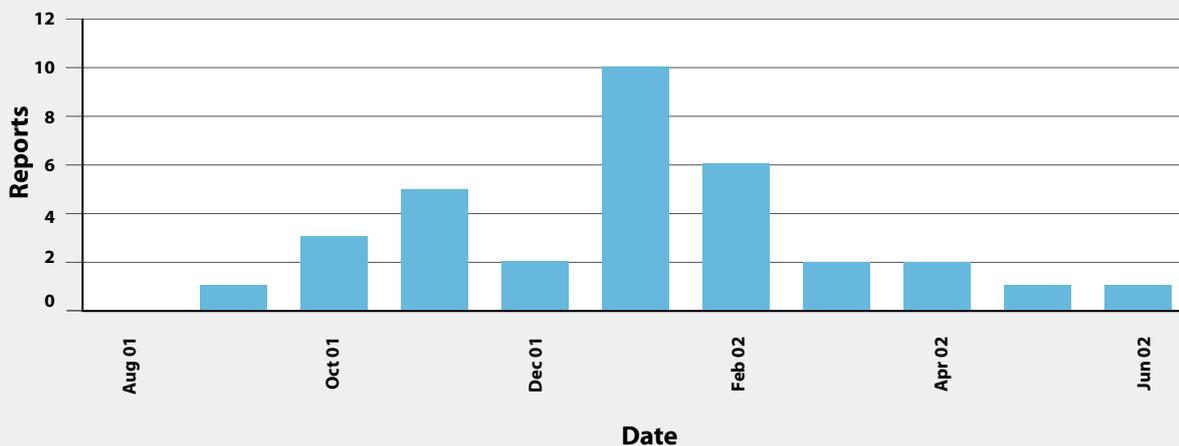


Figure 1: An example of early brand change reporting patterns for fluoxetine

events, their frequency and duration are monitored over time.

If the few isolated reports begin to increase to more frequent or regular reporting, Medsafe is notified of the existence of a potentially new brand change phenomenon and a brief overview of the spectrum of the reported events is provided with regular updates. Each quarter, the Medicine Adverse Reactions Committee (MARC) receives a summary report of new and ongoing brand change reports.

Although most brand change issues follow a predictable and transient pattern, deviations from this pattern

provide a basis for identifying signals of a potentially more significant problem.

The existence of a potential issue is formally brought to the attention of Medsafe and MARC for further consideration when:

- there are more than 40 reports for any brand change
- the issue persists for more than three months without indication of decline
- the events themselves, irrespective of number of reports or duration, are of a serious nature

It has become apparent from the content of the reports that media attention, internet blog sites and anti-PHARMAC sentiment are important factors for some brand changes that result in high numbers or sustained reporting.

Some recent examples of deviations from the expected pattern observed by CARM that have resulted in further attention include the following:

Ritalin SR to Rubifen SR

The change from Ritalin SR to Rubifen SR in 2006-7 resulted in CARM receiving over 200 reports of reduced therapeutic effect as well as a more concerning presentation of aggressive and other psychiatric reactions largely in children, but also adults. There were suggestions that these behaviours could be part of the spectrum of ADHD manifestation, or that they reflected social resistance to the new product.

Action taken by Medsafe and MARC resulted in extensive re-evaluation of Rubifen SR which confirmed that the product met all bioequivalence specifications. Further product testing was unable to demonstrate any composition factor that could account for the observed events. However, given the number and nature of the events, PHARMAC introduced special authority access to Ritalin for those who had reported psychiatric events of concern.

Eltroxin formulation change

The reports with Eltroxin were associated with a formulation change instituted by the manufacturer and not due to a switch to a generic medicine due to a funding change. However, the example serves well to demonstrate the pharmacovigilance process.

Eltroxin underwent a formulation change, introduced by the innovator manufacturer in late 2007. The formulation change was supported by bioequivalence data and approved in 25 other countries. At the time no alternative products were registered in New Zealand.

At the time of this change around 40 reports were received, however the fact that they persisted over a

6-8 month period (culminating in a total of about 1400) resulted in a review and report to Medsafe and MARC. The reports described reduced therapeutic effect, headaches, eye pain, allergic events and symptoms affecting the central nervous system such as memory and cognition disturbances. More extensive reviews were performed during the sustained reporting and Medsafe initiated an independent investigation of the product.

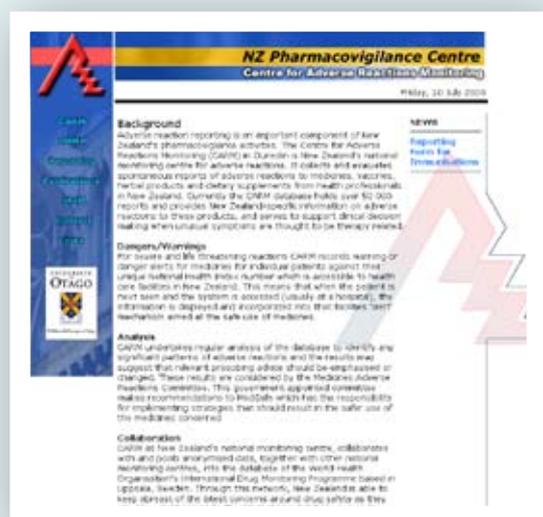
No adequate explanation for the reports was established. In addition, these reports appeared unique to New Zealand, despite the identical product having been marketed in other countries. Due to the scale of problem and reports of improvement on changing to an alternative unregistered product, Medsafe facilitated the registration of alternatives which were also subsidised by PHARMAC.

Making a report to CARM

Reports can include adverse effects or changed therapeutic response and are made on the standard CARM reporting card, online or through the *bestpractice* Adverse Drug Reaction module on the toolbar of your practice management system.

Telephone: **03 479 7247**

Website: **www.otago.ac.nz/carm**



How does PHARMAC assess if a brand change is appropriate?

Contributed by Dr Dilky Rasiah, PHARMAC

PHARMAC carefully considers whether brand changes for specific medicines are appropriate, taking into account clinical risks. Clinical risks are particularly important where there are limited treatment options within the therapeutic group, where the medicine has a narrow therapeutic index, or where patient adherence is considered critical and could be compromised by the brand change. PHARMAC does not usually consider these types of medicines for sole supply.

Over the years PHARMAC have learnt a considerable amount about what the trigger factors are for negative reactions to brand changes. This may lead to a medicine not being tendered or, if tendered, an increased focus on implementing the change. Trigger factors include:

- Does the medicine have a large patient population (over 50,000 patients)?
- Is the current brand well-known with high brand loyalty (e.g. Ventolin, Panadol, Losec)?

- Is the medicine heavily marketed to patients and doctors?
- Does the new brand have a different colour, shape or taste?
- Is the medicine primarily used by children, or elderly people?
- Has there been negative feedback to consultation, or political lobbying around the change?

In addition to careful internal deliberation, PHARMAC takes advice on brand change options from clinicians and pharmacists. This includes seeking advice from PHARMAC's standing clinical committees and consulting with healthcare professionals more widely.

PHARMAC only seeks to implement brand changes if the new brand is approved by Medsafe. Although not the norm, PHARMAC sometimes awards tenders subject to Medsafe-approval being achieved due to the uncertainty of the product gaining approval.

Advice from clinicians

PHARMAC drafts an annual “invitation to tender” containing numerous medicines and then seeks feedback on a draft tender list from medical groups, clinicians, pharmaceutical companies, DHBs and other interested parties. Comments from consulted parties, typically relating to potential clinical concerns for sole supply for any of the medicines on the tender list, are taken to PHARMAC’s Tender Medical Evaluation Subcommittee for comment. This committee of doctors and pharmacists provides advice on all issues related to tendering medicines, including switching brands.

The Tender Medical Evaluation Subcommittee may also seek further advice from other PTAC subcommittees specialising in therapeutic areas.

Other purchasing methods

Should a medicine not be included in the tender, other methods can be used, including (a) Dual supply – this is used for the influenza vaccine; (b) Listing multiple brands with reference pricing – this is used for the asthma inhaler salbutamol; (c) Ongoing contracting with incumbent supplier – sometimes necessary to maintain patient health and compliance, but has risks if suppliers wish to increase prices; and (d) Special Access by authorisation – this is currently being used for the ADHD treatment Ritalin; however PHARMAC has identified adherence issues that make this scheme difficult to manage.

No matter how much advice is sought, brand changes often come down to a judgement call about the level of potential benefits versus the potential costs and risks. Should a change in pill colour, or a bigger pill, be avoided and forego significant savings? This is the typical dilemma PHARMAC faces, and savings can be in the millions of dollars for each medicine. Even if a brand change is considered to pose issues with acceptance, effective education and implementation strategies may still allow the brand to be changed.

Bioequivalence is established by undertaking a single or in certain circumstances a number of bioequivalence studies.

Most bioequivalence studies employ a randomised crossover design in healthy volunteers, in which each individual acts as his/her own control. Clearance, volume of distribution, and physiological variables that might affect absorption (e.g. gastric emptying, motility, pH), distribution and elimination will normally have lower within-patient than between-patient variability. Therefore, a crossover design will usually have more statistical power for a given number of subjects than a parallel-group design.

The test (generic) and reference (innovator) products should be administered with a standard quantity of water under fasting conditions or following a standard meal.

So that each subject returns to a 'baseline' state prior to each treatment period, a 'washout' period of no treatment should be employed between each treatment period. The washout period should be at least 5 half lives of the substances to be measured and the absence of carryover of plasma concentrations into the second period should be confirmed by pre-dose plasma assay. If significant carryover is present in the data, the trial results will be considered void.

Sampling times should be appropriate to describe the absorption, distribution, and elimination phases of the drug. Sampling frequency around T_{max} should be sufficient to provide an accurate estimation of C_{max} . Sampling duration should be sufficient to provide an accurate estimation of AUC extrapolated to infinity (measured AUC_{0-t} should be at least 80% of extrapolated $AUC_{0-\infty}$). At least three to

four samples can be obtained during the terminal log-linear phase of the elimination period in order to calculate terminal elimination rate constant accurately.

Usually drug or metabolites are measured in serum or plasma. Where plasma measurement is not possible total urine collection may be more appropriate for analysis.

The number of subjects required for a bioequivalence study is determined statistically and is typically about 20, although smaller numbers can be used if sufficient statistical power has been determined.

Plasma concentration curves for the test and the reference product are derived from the data obtained in the study (see Figure 1, page 5). As it is very difficult to test whether two curves are sufficiently similar to each other the internationally accepted indices of area under the curve (AUC), peak and timing of the peak drug concentration (C_{max}) are used to characterise the curves. If differences are apparent between either the values for the C_{max} of the two products or those for the AUC then the two curves will have different shapes.

The data from each individual patient is used to calculate the mean, standard deviation and confidence intervals of the pharmacokinetic variables (C_{max} and AUC).

Statistically the assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means (test/reference) for the variables under consideration. This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level.



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