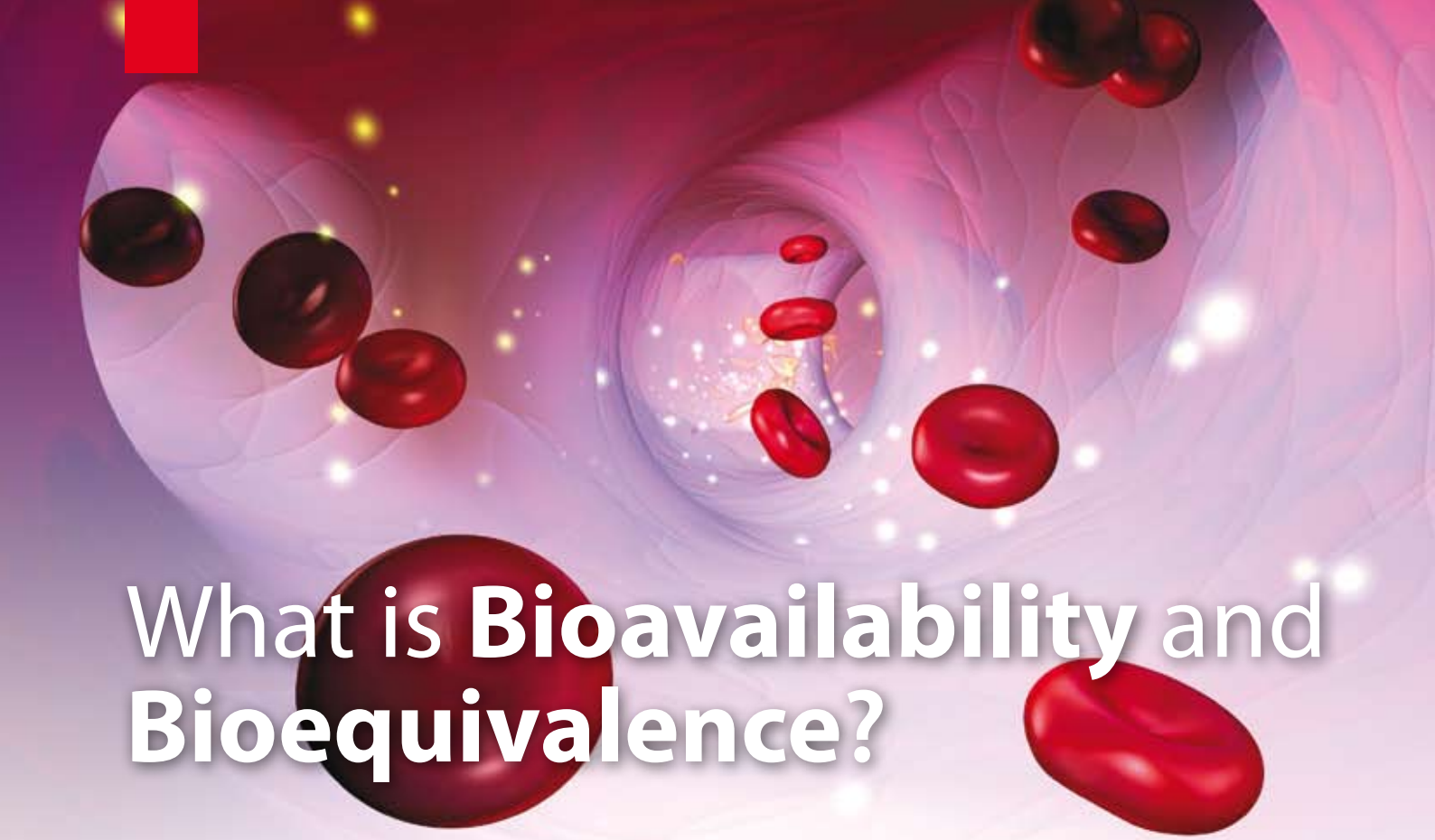


What is **Bioavailability** and **Bioequivalence?**

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.[1] 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

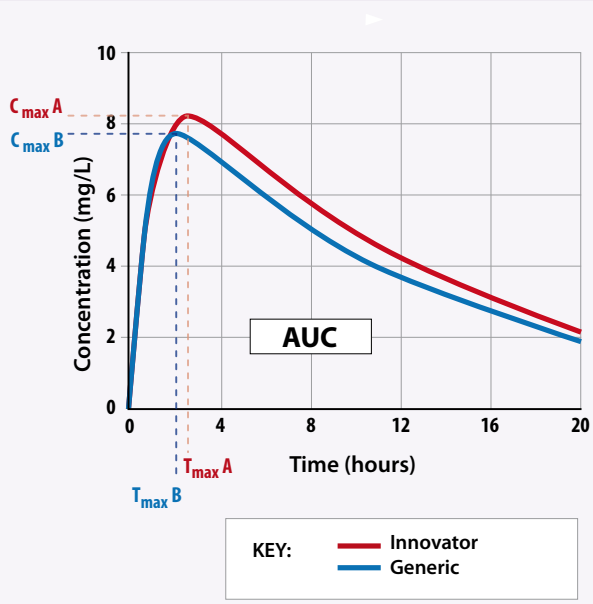
Bioequivalence is determined based on the relative bioavailability of the innovator medicine versus the generic medicine. It is measured by comparing the ratio of the pharmacokinetic variables for the innovator versus the generic medicine where equality is 1.

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)



C_{max} maximum plasma drug concentration

T_{max} time required to achieve a maximal concentration

AUC total area under the plasma drug concentration-time curve

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.

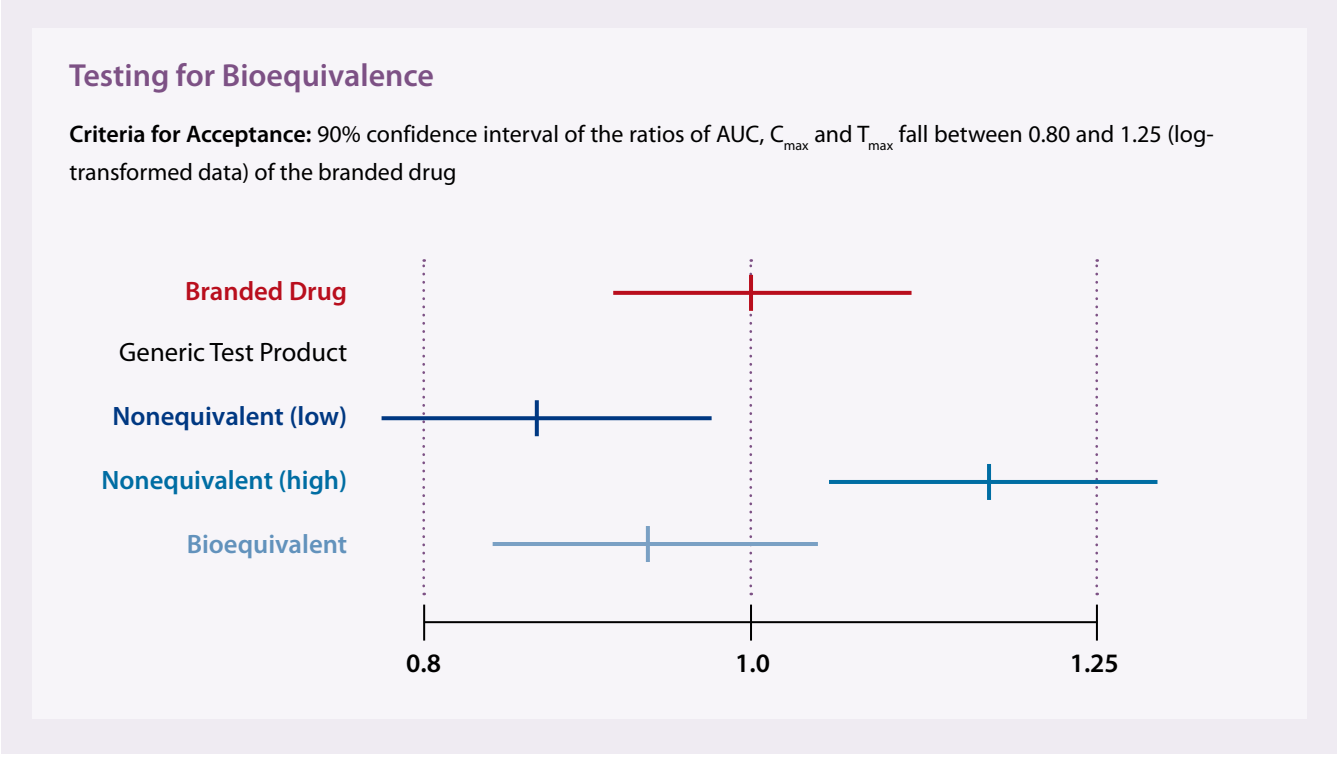


Figure 2: Bioequivalence confidence intervals

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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