



MEDSAFE

NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY

A BUSINESS UNIT OF
THE MINISTRY OF HEALTH

Guideline on the Regulation of Therapeutic Products in New Zealand

Part 6:

Bioequivalence of medicines



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Section 1: Bioequivalence

Section summary

This section:

- *defines bioavailability and bioequivalence*
- *lists international bioequivalence guidelines adopted by Medsafe*
- *lists options for the choice of reference product and relevance to the New Zealand market*
- *lists the products for which comparative bioavailability is/is not required*
- *discusses biowaivers*
- *discusses interchangeability and narrow therapeutic range products*

1.1. Introduction

Bioavailability is a key attribute of medicines used for systemic effects. It is defined as the rate and extent of absorption of the active ingredient in a medicine into systemic circulation. When the bioavailabilities of two different formulations of the same pharmaceutical form and containing the same active ingredient are shown to be comparable after administration of the same dose, the products are said to be bioequivalent.

This comparability is determined by a bioequivalence study (ies) accepted by Medsafe and other international regulators as the substitute to full clinical trials for generic medicines. A bioequivalence study provides bridging of the full clinical dataset held by Medsafe for the innovator medicine to support the efficacy and safety of generic medicines entering the New Zealand market.

The bioequivalence study uses an appropriate statistical assessment to determine whether the relative bioavailabilities of the test and reference formulations fall within internationally accepted limits. These limits ensure closely comparable *in vivo* pharmacokinetic performance, which implies that the test product will have essentially the same efficacy and safety profile as the reference product. There are internationally agreed standards for the bioequivalence study design, conduct, statistical analysis, and acceptance limits which are described in the guidelines listed in section 1.2.

To be approved for distribution in New Zealand, a generic medicine must be bioequivalent to the New Zealand innovator medicine, or other appropriate reference medicine (see section 1.3). Bioequivalence is also required when changes to the formulation or manufacturing process for an approved medicine have the potential to influence its bioavailability, and may be required when registering an additional strength of an approved medicine. For new innovative medicines, bioequivalence is to be used when the formulation to be marketed is different from the formulation used in the pivotal clinical trials.

In some circumstances, a comparison of bioavailabilities is not appropriate and thus a comparison of an appropriate pharmacodynamic effect may be the only available method of determining equivalence (see section 1.4).

1.2. International Bioequivalence Guidelines

Bioequivalence studies should be conducted in accordance with the International Conference on Harmonisation (ICH) *Guidance on Good Clinical Practice (E6)*, and the principles of Good Manufacturing Practice and Good Laboratory Practice should be adhered to where applicable.

For requirements regarding the study design and conduct, validation, and statistical analyses, Medsafe has adopted the following bioequivalence guidelines which are considered current best international practice.

For immediate release orally administered formulations with systemic action:

- ☞ The Committee for Medicinal Products for Human Use (CHMP) *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr).

For modified release orally administered formulations (including sustained/extended release and delayed release):

- ☞ The CHMP *Guideline on the pharmacokinetic and clinical evaluation of modified-release dosage forms* (EMA/CHMP/EWP/280/96 Corr1).

The assay method used to analyse plasma samples for all bioequivalence studies should be validated according to the recommendations in the following guideline.

- ☞ The CHMP *Guideline on bioanalytical method validation* (EMA/CHMP/EWP/192217/2009 Rev. 1 Corr).

Equivalence of inhalation products should be established from physical and clinical comparative studies as outlined in the following guideline.

- ☞ The CHMP *Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of Asthma in children and adolescents* (CPMP/EWP/4151/00 Rev 1).

For topical corticosteroid preparations:

- ☞ The US FDA Guidance for Industry on *Topical Dermatologic Corticosteroids: in vivo bioequivalence*.

For changes to the formulation or manufacturing process of an approved medicine, the recommendations for comparisons with the approved formulation and bioequivalence requirements are outlined in the following guidelines.

- ☞ The US FDA Guidance for Industry on *Immediate Release Solid Oral Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*.
- ☞ The US FDA Guidance for Industry on *Modified Release Solid Oral Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*.
- ☞ The US FDA Guidance for Industry on *Nonsterile Semisolid Dosage Forms, Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Release Testing, and In Vivo Bioequivalence Documentation*.

1.3. Bioequivalence Study Reference Product

To establish bioequivalence for a generic medicine to be registered in New Zealand, the applicant must provide evidence that the generic medicine is bioequivalent to an appropriate reference product. The assumed interchangeability of generic medicines in the New Zealand

market is reliant on selecting an appropriate reference product. To do this, one of the following four options must be fulfilled.

Option one

A bioequivalence study is performed that compares the proposed generic medicine to the innovator medicine obtained from the New Zealand market. This is the preferred option, although Medsafe acknowledges that New Zealand is a small market and thus this option may not always be possible.

Option two

The bioequivalence study can be performed using the innovator product obtained from an overseas market (eg, UK, European countries). For the bioequivalence study to be relevant to the New Zealand market, the overseas sourced innovator product must be shown, using a series of *in vitro* tests, to be the same as the innovator product approved in New Zealand. This evidence is called essential similarity testing (or reference product testing) and includes **all** of the following *in vitro* test comparisons for both the overseas sourced innovator, and the New Zealand sourced innovator.

- ☞ Physical appearance of the products.
- ☞ Mean and individual dimensions data for 20 dosage units each (20 units is appropriate according to pharmacopoeial requirements for uniformity of dosage unit tests).
- ☞ Mean weight and weight uniformity for 20 dosage units each.
- ☞ Comparative dissolution profiles (mean and individual data for 6 dosage units each) at 3 different pHs across the gastro-intestinal range pH 1 to 7.5.
- ☞ Fourier transform infra-red (FTIR) spectra of each product overlaid for comparison.
- ☞ Powder X-ray diffraction (XRD) spectra of each product overlaid for comparison.
- ☞ Results of qualitative and quantitative (where practicable) analyses of the excipients.

Sponsors should note that the above *in vitro* testing cannot be used to compare an overseas innovator (that was used in the bioequivalence study) to the New Zealand market leader product, in place of the New Zealand innovator. This is not sufficient to establish bioequivalence for a new generic medicine.

Option three

When the bioequivalence study is performed using the innovator product obtained from the Australian market, essential similarity may be assumed if sufficient evidence is provided (see list below) demonstrating that the identical innovator product was marketed in both New Zealand and Australia (ie, the innovator was harmonised for the New Zealand/Australian market).

Alternatively, the innovator product used in the bioequivalence study is obtained from an overseas market as per option two, but the New Zealand innovator product has been discontinued or is no longer available from the New Zealand market to conduct essential similarity testing. In this case, essential similarity testing may be conducted against the innovator sourced from the Australian market, **if** evidence can also be provided to confirm that the identical innovator product was marketed in both New Zealand and Australia.

The evidence supporting harmonisation between the New Zealand and Australian innovator product may consist of:

- ☞ copies of the New Zealand and Australian harmonised innovator labelling
- ☞ copies of the New Zealand and Australian harmonised package inserts
- ☞ evidence that the same manufacturing site(s) are registered for the innovator products available in both New Zealand and Australia
- ☞ qualitative comparison of the excipients present in the New Zealand and Australian innovator formulations
- ☞ a comparison of the physical appearance of the New Zealand and Australian innovator products.

Option four

If none of the above three options are possible, a bioequivalence study could be performed comparing the proposed generic product to an alternative reference product sourced from the New Zealand market under some circumstances. Sponsors considering this option are encouraged to consult with Medsafe, prior to conducting the bioequivalence study, for advice on whether there are any appropriate alternative products that can be used as the reference product.

1.4. Product types that require bioequivalence

Bioequivalence is required, unless otherwise justified (see section 1.6), for the following types of new generic **prescription medicines**.

- ☞ Orally administered immediate release tablets and capsules.
- ☞ Orally administered modified release tablets and capsules. In some circumstances, clinical efficacy data may also be required to support modified release formulations.
- ☞ Transdermal patches with systemic action.
- ☞ Orally administered suspensions and solutions (including oral powders for reconstitution). Under some circumstances, bioequivalence may be waived for orally administered aqueous solutions (refer to the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr)).
- ☞ Complex parenteral solutions (eg, emulsions, liposomal and micelle forming formulations). Under some circumstances, bioequivalence may be waived for complex parenteral solutions (refer to the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr)).
- ☞ Non-oral immediate release dosage forms with systemic action (eg, rectal formulations).
- ☞ New fixed combination products (bioequivalence should be demonstrated with the ingredients administered in separate registered formulations). In some circumstances, clinical safety and efficacy data may also be required to support new fixed combination products.
- ☞ New salt, ester, ether, isomer, complex, or other derivative of an active substance if they differ significantly in properties with regard to bioavailability.

Bioequivalence may be required for the following **OTC medicines**.

- ☞ Modified release OTC products.

- ☞ Products containing an active ingredient with an associated level of risk that necessitates bioequivalence to support efficacy and safety.
- ☞ OTC products where the sponsor claims their product is bioequivalent to another brand.

Bioequivalence studies should be performed for the above products according to the requirements described in the guidelines listed in section 1.2. Where there is any doubt about the appropriateness of a bioequivalence study, the applicant is strongly advised to seek Medsafe's advice before submitting the data in support of an NMA or CMN.

1.5. Generic medicines for which a bioequivalence study is not appropriate

The following types of generic medicines require comparative physical and therapeutic equivalence studies with a pharmacodynamic endpoint, when a bioequivalence study is not appropriate.

- ☞ Topical medicines, unless the formulation is identical to the innovator, or unless the medicine has no systemic action.
- ☞ Inhalational products.

Therapeutic equivalence studies should be performed for the above products according to the requirements described in the guidelines listed in section 1.2.

1.6. Product types not requiring bioequivalence

The following products do not require evidence of bioequivalence.

- ☞ Simple aqueous intravenous solutions or powders for reconstitution.
- ☞ Products containing therapeutic substances which are not systemically or locally absorbed (eg, antacids, anthelmintics, barium sulphate enemas or oral suspensions, non-biodegradable ion exchange resins or other non-biodegradable long chain polymers, powders in which no ingredient is absorbed). If there is doubt as to whether absorption occurs, a study or justification may be required.
- ☞ Vaccines (clinical trial data are always required for vaccines).
- ☞ Biosimilars (Requirements for the comparison of biosimilars to the reference biological medicine are found in separate guidelines).
- ☞ Nebuliser solutions.
- ☞ Nasal sprays intended for local action.
- ☞ Medicinal gases.

1.7. Biowaivers

A biowaiver (omission of a bioequivalence study) for any product type listed in section 1.4 must be justified. Sponsors are required to include in Module 1 or Module 5 of the dossier, a

detailed justification of how their proposed generic medicine meets the biowaiver criteria under either circumstance below.

- Additional strengths of the same product range where a bioequivalence study has been performed with one or more strengths (usually the highest). The acceptability of a biowaiver for additional strengths depends on the criteria listed in the guideline, CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr).
- Biopharmaceutics Classification System (BCS) based biowaiver. The requirements for a BCS based biowaiver are listed in the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr – Appendix III).

1.8. Narrow therapeutic index products

A medicine with a narrow therapeutic index (NTI) has a very small margin between therapeutic and toxic plasma levels. As such, small differences in bioavailability of a NTI medicine can have clinically significant consequences. For this reason, tighter acceptance criteria are applied when determining bioequivalence of medicines with a NTI. The specific criteria required for NTI medicines are outlined in the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr).

Medsafe does not have a defined list of NTI medicines; rather, a case-by-case approach is required. Sponsors' decisions regarding whether a medicine may be considered to have a NTI should be based on clinical considerations of the dose- or concentration-response relationships for both efficacy and safety.

Although tighter acceptance criteria are required for bioequivalence, the permitted differences in bioavailability between the innovator and generic NTI product may give rise to significant clinical consequences. Therefore, products with an NTI, (eg, tacrolimus, cyclosporin, warfarin, levothyroxine) are not considered to be interchangeable. Additional information is required in the New Zealand datasheet for non-interchangeable medicines as discussed in section 1.9.

1.9. Interchangeability of generic medicines

If two pharmaceutically equivalent medicines (same active ingredient, dose form, indication, and dosage) have been shown to be bioequivalent, then they are usually interchangeable (substitutable). However, some medicines, although they may be bioequivalent, are not interchangeable due to the inherent nature of the medicine or the pharmacokinetic properties of the active ingredient (eg, levothyroxine, narrow therapeutic index products (see section 1.8)). Bioequivalence is based on population pharmacokinetics so generally two products can be expected to behave the same way, but for some medicines, individual patients may experience differences resulting in serious clinical consequences.

Therefore, if a generic medicine is not interchangeable, or has the potential for individual differences in bioavailability, information and warnings regarding this are required in the New Zealand datasheet. Non-interchangeable medicines usually require individual patient monitoring during switching between formulations. As such, information about switching between formulations is also required in the New Zealand datasheet.