MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Guidelines on the Regulation of Therapeutic Products in New Zealand

Bioequivalence of medicines

Edition 3.0

Draft for consultation, including summary of major changes and rationale – June 2025

Contents

Abbreviations and definitions

Abbreviation or term	Definition
BCS	Biopharmaceutics Classification System
ICH	International Conference on Harmonisation
EMA	European Medicines Agency
NTI	Narrow therapeutic index
PHARMAC	Pharmaceutical Management Agency (NZ)
TGA	Therapeutic Goods Administration (Australia)
US FDA	United States Food and Drug Administration

1. Introduction

Bioavailability is a key attribute of medicines used for systemic effects. It is 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 under similar conditions, the products are said to be bioequivalent. Bioavailabilities are considered comparable when they fall within a set of acceptable pre-defined limits. Products that are bioequivalent are expected to exhibit the same efficacy and safety profile.

This comparability is determined by a bioequivalence study (or studies). These studies are accepted by Medsafe and other international regulators as a substitute for full clinical trials for generic medicines. A generic medicine is developed to be the same as a medicine that has already been approved, called the reference medicine (which may be the innovator medicine). Entirely new medicinal products containing new active substances are innovator medicines. A bioequivalence study bridges the full clinical dataset held by Medsafe for the innovator/reference medicine to support the efficacy and safety of the generic medicine. An acceptable generic medicine must be bioequivalent to the New Zealand innovator medicine, or another appropriate reference medicine (see section 3 of this document).

Evidence of 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 or dosage form of an approved parent product. For new innovative medicines, evidence of bioequivalence is necessary when the formulation proposed to be marketed is different from the formulation used in the pivotal clinical trials.

The bioequivalence study uses an appropriate statistical assessment to determine whether the relative bioavailabilities of the test product (generic, post-change product) and reference products 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 under the same conditions. 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 2 of this document.

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 5 of this document).

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.

Medsafe requirements regarding study design and conduct, validation, and statistical analyses are based on the following bioequivalence guidelines.

Web pages for accessing product-specific guidance issued by the European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) are provided below. Note that new product-specific guidance issued by the EMA and US FDA is regularly published and made available through the agency websites:

- The EMA product-specific bioequivalence guidance
- The US FDA product-specific guidances for generic drug development

For general guidance on immediate release orally administered formulations with systemic action:

- The EMA *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr).
- The ICH guideline *ICH M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms*.

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

- The EMA *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CHMP/EWP/280/96 Rev1).

For biopharmaceutics classification system (BCS)-based biowaivers:

- The ICH guideline *ICH M9: Biopharmaceutics Classification System-Based Biowaivers*

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

- The ICH guideline *ICH M10: Bioanalytical Method Validation and Study Sample Analysis*.

Statistical methods for the analysis of bioequivalence trial data are described in the following guidance document:

- The US FDA guideline on *Statistical Approaches to Establishing Bioequivalence, Guidance for Industry*.

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

- The EMA *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 guideline on *Topical Dermatologic Corticosteroids: in vivo bioequivalence, Guidance for Industry*.

For changes to the formulation or manufacturing process of an approved medicine, the recommendations for comparisons with the approved formulation, bioequivalence requirements and *in vitro*/*in vivo* correlation are outlined in the following US FDA and EMA guidelines:

- The US FDA guidance on *Immediate Release Solid Oral Dosage Forms, Scale- up and Post-approval Changes (SUPAC): Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, Guidance for Industry*, US FDA, CDER.
- The US FDA guideline on *Modified Release Solid Oral Dosage Forms, Scale-up and Post-approval Changes (SUPAC): Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, Guidance for Industry*, US FDA, CDER.
- The EMA *Guideline on quality of oral modified release products* (EMA/CHMP/QWP/428693/2013).
- The US FDA guideline on *Nonsterile Semisolid Dosage Forms, Scale-up and Post-approval Changes (SUPAC): Chemistry, Manufacturing, and Controls, In Vitro Release Testing, and In Vivo Bioequivalence Documentation, Guidance for Industry*, US FDA, CDER.

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. In general, the reference product used in a bioequivalence study should either be sourced from the New Zealand market or obtained from outside New Zealand. In the latter case, evidence should be provided demonstrating that it is fundamentally the same as the New Zealand innovator product. Evidence may be provided in the form of a paper comparison or by submission of comparative *in vitro* data. Where a comparative *in vitro* study is employed, this is referred to as a study of essential similarity.

There may be more than one reference product, especially where two products containing the same active ingredient have received approval on the basis of independent clinical trial and pharmacology data. The strategy to choose an appropriate reference product should follow one of the *options* laid out in section 3.1 of this document.

3.1 Choice of reference product

Option 1 – New Zealand innovator

A bioequivalence study should ideally compare the proposed generic medicine to the respective innovator medicine obtained from the New Zealand market. This is the preferred option.

Option 2 – overseas reference product (paper comparison)

Where the reference product is sourced from outside New Zealand, evidence is required to demonstrate that the reference product and New Zealand-sourced innovator product are manufactured at the same site(s) with identical manufacturing processes and formulations.

Option 3 – overseas reference product (*in vitro* comparison)

Where the reference product is sourced from outside New Zealand, but 'Option 2' requirements cannot be met, essential similarity testing is required. This testing must demonstrate that the reference and New Zealand innovator products are the same. Evidence of essential similarity should include the following *in vitro* comparative tests.

Solid oral dosage forms:

- Physical appearance.
- Qualitative and quantitative (where practicable) formulation analyses.
- Dimensions and uniformity of weight (mass) analysed as per pharmacopeial (BP/Ph Eur or USP) requirements.
- Certificates of analysis for both the overseas and New Zealand reference products tested according to the specifications and analytical methods proposed in the application for the test product.
- Comparative dissolution profiles between the overseas and the New Zealand reference products. The profiles should be determined across the physiological pH range (pH 1.2-6.8) using the quality control method proposed in the

application for the test product (mean and individual data for at least 6 dosage units each should be provided).
- Copies of the labels and summary of product characteristics (or equivalent document) for both the overseas and New Zealand reference products.

Non-solid oral dosage forms:

- Physical appearance.
- Qualitative and quantitative (where practicable) formulation analyses.
- Particle size distribution of suspended drug substance between the overseas and New Zealand reference products.
- Comparable re-suspension times between the overseas and New Zealand reference products.
- Certificates of analysis for both the overseas and New Zealand reference products tested according to the specifications and analytical methods proposed in the application for the generic medicine.
- Comparative dissolution profiles between the overseas and the New Zealand reference products. The profiles should be determined across the physiological pH range (pH 1.2-6.8) using the proposed quality control method.
- Copies of the labels and summary of product characteristics (or equivalent document) for both the overseas and New Zealand reference products.

The pharmaceutical dosage forms listed in section 4 of this document (product types that require bioequivalence), other than oral dosage forms:

- Physical appearance.
- Qualitative and quantitative (where practicable) analyses of the formulation.
- Certificates of analysis for both the overseas and New Zealand reference products tested according to the specifications and analytical methods proposed in the application for the generic medicine.
- Copies of the labels and summary of product characteristics (or equivalent document) for both the overseas and New Zealand reference products.

Option 4 – Australian reference product (trans-Tasman harmonisation)

Where the reference product is sourced from the Australian market, evidence may be provided to confirm that the identical innovator product was marketed in both New Zealand and Australia (ie, the innovator was harmonised for the New Zealand/Australian markets). The evidence supporting trans-Tasman harmonisation should include comparisons of the approved details of the reference product in Australia and New Zealand, for example:

- Manufacturing sites.
- Formulation (qualitative and quantitative).
- New Zealand approved labelling (showing the AUST R number).
- Comparisons of the New Zealand and Australian data sheets and consumer medicine information.

Option 5 – overseas reference product (*in vitro* comparison with Australian innovator)

Where the reference product is sourced from outside New Zealand, essential similarity testing as per Option 3 may be conducted against the innovator sourced

from the Australian market, so long as trans-Tasman harmonisation can be demonstrated as per Option 4. If the generic medicine application is submitted via the abbreviated pathway based on Therapeutic Goods Administration (TGA) approval, only evidence of harmonisation as per Option 5 is required.

3.2 Reference product not available

Where the innovator product has been discontinued (ie, is no longer approved or available in the New Zealand market) or has never been approved in New Zealand, alternative evidence must be provided to support the clinical safety and efficacy of the proposed generic medicine. In these cases, it is recommended that the sponsor seeks early advice from Medsafe before submitting an application to determine the best options. Below are some possible scenarios.

New Zealand innovator not available*

- Bioequivalence data comparing the proposed test product to the current New Zealand market leader (eg, the product with a PHARMAC[1] sole or primary supply contract).
- A biowaiver with appropriate supporting information may be used to support bioequivalence of the proposed test product versus the overseas innovator (eg, BCS-based biowaiver) (see section 7 of this document).

*Note that where the innovator has a valid approval but is not available in the New Zealand market, evidence that all practicable efforts have been made to secure supply of the innovator for essential similarity testing (as per Option 3 above) and/or that Option 5 is not applicable should be provided before any reduced data requirements are considered. Alternatively, the unavailable New Zealand innovator product can be demonstrated to be identical to an overseas reference product via a paper comparison (ie, evidence to show the reference and New Zealand innovator products were manufactured at the same site(s) with identical manufacturing processes and formulations).

Overseas innovator never approved in New Zealand

- Safety and efficacy data from clinical studies using the proposed product.
- Evidence to support the safety and efficacy of the overseas innovator or active ingredient in general (ie, clinical trial results and/or data in published literature), and bioequivalence data comparing the proposed test product to that overseas innovator.**

**Note that Medsafe does not currently have a specific guideline regarding the use and content of literature-based or hybrid submissions such as these. In its absence, sponsors are recommended to refer to relevant guidance adopted by other regulatory authorities (eg, TGA Literature-Based Submission guidance).

[1] The Pharmaceutical Management Agency (PHARMAC) decides which medicines to fund and manages a fixed budget for funding those medicines.

4. Product types that require bioequivalence

Bioequivalence studies are required, unless otherwise justified (see section 6 of this document), to support applications for approval of 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.
- Oral solutions with quantitative differences in critical excipients (case-by-case basis).
- Oral oily solutions with different oil vehicles.
- Oral suspensions for systemically acting products.
- Intravenous solutions with different surfactants and different excipients.
- Intramuscular and subcutaneous solutions for injection with different oily vehicles and different surfactants.
- Intramuscular and subcutaneous suspensions for injection.
- Emulsions for injection with qualitatively different antioxidants and preservatives.
- Micellar solutions for injection with different surfactants.
- Non-oral immediate release dosage forms with systemic action (eg, rectal formulations).
- New fixed-dose 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-dose 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 **over the counter (OTC) medicines**.

- Modified release formulations.
- Products containing an active ingredient with an associated level of risk that necessitates bioequivalence to support safety and efficacy.
- Products where the sponsor claims their medicine 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 2 of this document. 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 a New Medicine Application (NMA) or Changed Medicine Notification (CMN).

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, and therefore a bioequivalence study is not appropriate.

- Topical medicines, unless the formulation is identical to the innovator, or unless the medicine has no systemic action (for locally applied, locally acting cutaneious products refer to EMA/CHMP/QWP/708282/2018 Corr.1*).
- Inhalational products that have demonstrated comparability *in vitro* (eg, complete droplet size distribution and the delivered dose) with the reference product (EMEA/CHMP/QWP/49313/2005 Corr).

6. Product types not requiring bioequivalence

The following product types do not require evidence of bioequivalence to support approval.

- Oral aqueous solutions (case-by-case basis).
- Oral oily solutions with the same oily vehicles as the reference product.
- Oral oily solutions including qualitative changes in excipients.
- Oral suspensions for locally acting products (case-by-case basis).
- Soft gelatin capsules where identical quantitative formulations and the physicochemical equivalence of justified parameters.
- Intravenous solutions for injections with the same excipients, including changes in preservatives, buffer agents, antioxidants, and isotonic agents.
- Intramuscular and subcutaneous solutions for injection with aqueous solutions, with the same oily vehicles, and/or with the same excipients, including changes in preservatives, buffer agents, antioxidants, and isotonic agents.
- Emulsions for injection with qualitatively identical antioxidants and preservatives.
- Micellar solutions for injection with identical surfactants (only if the micelle dissembles on dilution), including qualitatively different buffer agents, antioxidant, preservatives, and co-solvents.
- Vaccines (clinical trial data is always required for vaccines).
- Biosimilars (requirements for the comparison of biosimilars to a reference biological medicine are found in separate guidelines).
- Nebuliser solutions (in-vitro characterisation and clinical documentation should be presented) (refer to CPMP/EWP/4151/00 Rev. 1).
- Nasal sprays intended for local action.
- Medicinal gases.
- Peritoneal dialysis solutions.

7. Biowaivers

A biowaiver (omission of a bioequivalence study) for any product type listed in section 4 of this document must be justified in accordance with relevant guidelines. Sponsors are required to include in Module 1 and/or Module 5 of the dossier a detailed justification, including supporting evidence, for how their proposed generic medicine meets the biowaiver criteria under each 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 *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) and *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CHMP/EWP/280/96 Rev1).
- Biopharmaceutics Classification System (BCS) based biowaiver. The BCS-based biowaiver approach is intended to reduce the need for *in vivo* bioequivalence studies to provide a substitute for *in vivo* bioequivalence. *In vivo* bioequivalence studies could be exempted if *in vitro* data justify satisfactorily the *in vivo* performance according to BCS-based biowaiver requirements. The requirements for a BCS-based biowaiver are listed in the *ICH M9: Biopharmaceutics Classification System-Based Biowaivers* and CPMP/EWP/QWP/1401/98 Rev. 1/Corr – Appendix III. It is important to note that the requirements of section 3 apply to BCS-based biowaivers that use an overseas reference product.
- A biowaiver may be accepted on the basis of the dosage form of the proposed product. For example, for an aqueous oral solution that contains the same concentration of active ingredient as the innovator oral solution product that also has a similar qualitative/quantitative composition, bioequivalence studies could be waived. For further details on such a waiver, see CPMP/EWP/QWP/1401/98 Rev. 1/ Corr – Appendix II.

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 an NTI medicine can have clinically significant consequences. For this reason, tighter acceptance criteria are applied when determining bioequivalence of medicines with an NTI. The specific criteria required for NTI medicines are outlined in *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' justifications regarding whether a medicine may be considered to have an NTI should be based on clinical considerations of the dose- or concentration-response relationships for both efficacy and safety and should be supported by scientific literature.

Although tighter acceptance criteria are required for bioequivalence, the permitted differences in bioavailability between the innovator and generic NTI products may still result in significant clinical consequences. Therefore, products with an NTI (eg, tacrolimus, cyclosporin, warfarin, levothyroxine) are not considered to be readily substitutable. In addition, some other specific medicine classes, such as antiepileptic medicines (eg, acetazolamide, carbamazepine, clonazepam, diazepam) can be associated with difficulties when switching between different innovator/generic medicines, which may lead to loss of efficacy and/or worsening of side effects.

Therefore, if a proposed generic medicine contains an NTI, or is not considered readily substitutable, or has the potential for individual differences in bioavailability, information and warnings regarding these factors are required in the New Zealand data sheet. Non-substitutable medicines usually require individual patient monitoring during switching between formulations. As such, information about switching between such formulations is required in the New Zealand data sheet.

Summary of major changes and rationale

Proposed changes	Rationale
Section 1 (Introduction): Amendments and/or additions of the definitions for 'bioavailability', 'bioequivalence', 'generic', and 'innovator'.	To align Medsafe guidance with internationally recognised definitions.
Section 2 (International bioequivalence guidelines): Updates to the references for international guidelines.	To update Medsafe guidance with the latest internationally recognised guidance for the study design, conduct, validation, and statistical analyses of bioequivalence studies.
Section 3 (Bioequivalence study reference product): • Now includes an introduction, and subsections 3.1 (Choice of reference product) and 3.2. (No reference product available). • Clarification on the definition of 'essential similarity' and information on the test requirements for non-oral dosage forms. • Added option for a paper comparison of an overseas reference product with the New Zealand innovator to demonstrate acceptability of a bioequivalence study reference product. • Added guidance on options available when an NZ reference product is not available.	To update Medsafe guidance with current Medsafe practices and recommendations with clarification of the options available to sponsors in choosing an acceptable bioequivalence study reference product.
Section 4 (Product types that require bioequivalence): Expanded list of products that require bioequivalence data.	To align Medsafe guidance with current internationally recognised approaches to establish *in vivo* comparability of specific dosage forms.
Section 5 (Product types for which a bioequivalence study is not appropriate): General rewording.	To offer greater clarity for sponsors.
Section 6 (Product types not requiring bioequivalence): Expanded list of products that do not require bioequivalence data.	To align Medsafe guidance with current internationally recognised approaches to establish *in vivo* comparability of specific dosage forms.

Section 7 (Biowaivers): • Updated international guideline references. • Clarification on the purpose and function of Biopharmaceutical Classification System (BCS)-based biowaivers. • Added information on a dosage-form based biowaiver.	To align Medsafe guidance with the latest internationally recognised guidance and to offer more information for sponsors on the function and purpose of BCS-based and dosage-form based biowaivers.
Section 8 (Narrow therapeutic index products): • Removed reference to 'interchangeability', replacing the term with 'readily substitutable'. • Added more information on the substitutability of specific medicine classes, including antiepileptic medicines. • Relevant information included in Section 1.9 of the current guideline (Interchangeability of medicines) is now incorporated into section 8. • Section 1.9 of the current guideline is removed.	To align with current Medsafe practice and international guidance relating to narrow therapeutic index medicines and medicine types that may be susceptible to issues related to product substation, and how bioequivalence and other requirements may differ for these products.