

Guidelines on the Regulation of Therapeutic Products in New Zealand

Bioequivalence of medicines

Edition 3.0

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Contents

Abbreviations and definitions.....	3
1. Introduction.....	4
2. International bioequivalence guidelines.....	5
3. Bioequivalence study reference product.....	7
4. Product types that require bioequivalence	11
5. Generic medicines for which a bioequivalence study is not appropriate	12
6. Product types not requiring bioequivalence.....	13
7. Biowaivers.....	14
8. Narrow therapeutic index products and substitution of generic medicines	15
Document History	16

Abbreviations and definitions

Abbreviation or term	Definition
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
CDER	Center for Drug Evaluation and Research (United States)
CMN	Changed Medicine Notification
COPD	Chronic obstructive pulmonary disease
EMA	European Medicines Agency
FTIR	Fourier transform infrared spectroscopy
ICH	International Conference on Harmonisation
NMA	New Medicine Application
NTI	Narrow therapeutic index
OIP	Orally inhaled products
OTC	Over the counter
Ph. Eur.	European Pharmacopoeia
Pharmac	Pharmaceutical Management Agency (NZ)
SUPAC	Scale-Up and Post-Approval Changes
TGA	Therapeutic Goods Administration (Australia)
US FDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
XRD	X-ray diffraction

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 is usually 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 guideline).

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 (a proposed generic medicine, or approved medicine with formulation and/or manufacturing process changes) and reference product 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 guideline.

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 guideline).

Note that guidance on biosimilars is out of the scope of this guideline.

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](#).

For guidance on synthetic peptide-based medicines where the reference innovative product contains an active ingredient that is manufactured by biological/recombinant processes:

- The US FDA guideline [ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry](#).
- The EMA Guideline on the Development and Manufacture of Synthetic Peptides (draft) ([EMA/CHMP/CVMP/QWP/387541/2023](#)).

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 reference product used in a bioequivalence study may 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 guideline.

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, although Medsafe acknowledges that New Zealand is a small market and thus this option may not always be possible.

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. Medsafe acknowledges that this information is likely to be unobtainable in most instances, in which case the below options are available.

Option 3 – overseas reference product (*in vitro* comparison/essential similarity testing)

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 (including immediate and modified release):

- Physical appearance.
- Qualitative and quantitative* 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[§], OR Fourier transform infra-red (FTIR) spectra and powder X-ray diffraction (XRD) spectra of each product overlaid for comparison.
- 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) including 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).

Non-solid oral dosage forms:

- Physical appearance.
- Qualitative and quantitative[†] formulation analyses.
- Particle size distribution of suspended drug substance between the overseas and New Zealand reference products (where applicable).
- Comparable re-suspension times between the overseas and New Zealand reference products (where applicable).
- 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[§], OR FTIR spectra and XRD spectra of each product overlaid for comparison.
- 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) including the proposed quality control method (mean and individual data for at least 6 dosage units each should be provided).

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

- Physical appearance.
- Qualitative and quantitative[†] 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 test product[§], OR FTIR spectra and XRD spectra of each product overlaid for comparison.
- 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) (where relevant), including the proposed quality control method (mean and individual data for at least 6 dosage units each should be provided).[#]

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. Acceptable evidence includes, but is not limited to:

- Manufacturing sites.
- Formulation (qualitative and quantitative*).
- New Zealand approved labelling (showing the AUST R number).
- New Zealand and Australian data sheets/prescriber information 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 also 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 4 is required (ie, *in vitro* essential similarity data in accordance with Option 3 is not required).

* Medsafe acknowledges that quantitative analysis may not be practicable in many instances. In these cases, quantitative analysis is not strictly required. However, such data should be provided if readily available.

§Abridged certificates of analysis with justified parameter omissions may be accepted.

#Comparative dissolution analyses are only required for dosage forms for which dissolution is included as a parameter in the proposed product's specifications and/or pharmacopoeial dosage form monograph.

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 and where the best options are not clear from the guidance below, it is recommended that the sponsor seeks early advice from Medsafe before submitting an application. The following is a non-exhaustive list of possible scenarios and acceptable alternative evidence.

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 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 guideline).

†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 (eg, 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](#)).

4. Product types that require bioequivalence

Bioequivalence studies are required, unless otherwise justified (see [section 6](#) of this guideline), 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 with systemic action
- 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 excipients.
- Micellar solutions for injection with different surfactants.
- Non-oral immediate release dosage forms with systemic action (eg, rectal formulations).
- New fixed-dose combination products for which there is no reference product with the proposed combination of active ingredients (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 guideline. 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/or 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 cutaneous 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 ([EMA/CHMP/QWP/49313/2005 Corr](#)). There may be instances where a pharmacodynamic endpoint study is not necessary, but the lack of such studies in applications should be justified in accordance with the above EMA guideline and will be assessed on a case-by-case basis.

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 with identical quantitative formulations and equivalence of justified physicochemical 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 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 disassembles on dilution), including qualitatively different buffer agents, antioxidant, preservatives, and co-solvents.
- Vaccines (clinical trial data is always required for vaccines).
- Biosimilars (a guideline describing requirements for the comparison of biosimilars to a reference biological medicine is under development).^{||}
- 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.

^{||}There are certain scenarios where medicines containing synthetically manufactured peptide-based active ingredients are developed as generic versions of innovative medicines containing active ingredients produced by biological means (eg, recombinant processes). Where certain requirements are met (refer to [section 2](#) for relevant guideline), such products may be considered generic medicines (as opposed to biosimilars), in which case the normal bioequivalence requirements described in this guideline would apply.

7. Biowaivers

A biowaiver (omission of a bioequivalence study) for any product type listed in [section 4](#) of this guideline 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 and substitution of generic medicines

A medicine with a narrow therapeutic index (NTI) has a very small margin between therapeutic dose range 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 has 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.

Document History

Revision Date	Edition number	Summary of Changes
November 2025	3.0	New GRTPNZ template Major amendments