Australian Government
Department of Health
Therapeutic Goods Administration

Guidance 15: Biopharmaceutic studies

Previously ARGPM 15: Biopharmaceutic

Version 1.1, April 2015

TGA Health Safety Regulation

Check the TGA website for up-to-date guidance

The most up-to-date information about prescription medicine registration in Australia is on the TGA website <http://www.tga.gov.au>. Now that guidance is presented in a series of web pages, updates are likely to be more common than in the past. If you subscribe to the TGA guidelines email alert service, you will be emailed every time the TGA web guidance is updated.

TGA web pages are dated, and can be printed.

A PDF format is being provided during the transition between the former version of the ARGPM (Australian Regulatory Guidelines for Prescription Medicines) and the new web format. Please note that information in the PDF should not be relied upon to be up-to-date.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Medicines Authorisation	1/07/2014
V1.1	Minor text update	Scientific Evaluation and Special Product Access Branch	1/04/2015

Contents

Introduction

This guidance is to assist sponsors of prescription medicines to prepare applications to:

- register new prescription medicines on the ARTG
- vary the registration of a prescription medicine on the ARTG.

This guidance covers:

- all matters relating to bioavailability and/or bioequivalence aspects of prescription medicines containing active substances that are synthetic chemical entities
- active substances that are:
  - antibiotics
  - short-chain synthetic polypeptides
- some hormones (steroid hormones and synthetic peptides of usually less than 32 amino acids-some exceptions may apply).

This guidance does not cover:

- Matters relating to other pharmacokinetic studies.

15.1 Adopted European guidelines for biopharmaceutic studies

The guidance is to be applied **in addition to** the following European Union guidelines that have been adopted by the TGA, some with annotations:

- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), adopted with annotation.
- Note for guidance on quality of modified release products - Section 1 (quality): A: Oral dosage forms. B: Transdermal dosage forms (CPMP/QWP/604/96).
- Note for guidance on modified release oral and transdermal dosage forms: Section II (pharmacokinetic and clinical evaluation) (CPMP/EWP/280/96 Corr), adopted with annotation.
- Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004).
- Questions and answers: positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604/2008 Rev 9).

15.2 Comparative dissolution profiles for biopharmaceutic studies

When dissolution profiles or a similar term is used in this guidance, data should be generated in a comparative manner as follows:

- At least 12 dosage units (e.g. tablets, capsules) of each batch must be tested individually, and mean and individual results reported.
- The percentage of nominal content released are measured at a minimum of three (3) suitably spaced time points (excluding zero time point) to provide a profile for each batch (e.g. at 5, 15, 30 and 45 minutes, or as appropriate to achieve virtually complete dissolution).
- The batches are tested using the same apparatus and, if possible, on the same day.
- The stirrer used is normally a paddle at 50 rpm for tablets and a basket at 100 rpm for capsules. However, other systems or speeds may be used if adequately justified and validated.
- Test conditions are those used in routine quality control or, if dissolution is not part of routine quality control, any reasonable, validated method.
- The similarity factor, f2, is calculated using the equation and conditions stated in Appendix I of the European Medicines Agency (EMA) Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) to demonstrate the similarity of two dissolution profiles. The f2 value must be between 50 and 100.
- If more than 85 per cent of the active substance is dissolved within 15 minutes in all tested batches, dissolution profiles are considered to be similar without the need to calculate the similarity factor.
- If there are insufficient quantities of recently manufactured batches available to meet this requirement, then both:
  - test retention batches
  - explain in the test report why this was done, stating the age and storage history of the samples.

15.3 Medicines that do not require biopharmaceutic data

We do not require biopharmaceutic data or a justification for not providing this data for:

- Medicinal gases.
- Peritoneal dialysis solutions.
- Simple aqueous solutions for intravenous injection or infusion. Simple solutions do not include complex solutions such as emulsions, micellar or liposomal solutions.
- Other parenteral routes, e.g. intramuscular or subcutaneous, provided that the test product is of the same type of solution (aqueous or oily) and contains the same concentration of the same active substance and the same excipients in similar amounts as the reference product.
- Simple solutions that do not contain a pharmacologically active drug substance e.g., sodium chloride injection.
- Oral solutions that both:
  - contain the same drug substance(s) in the same concentration as a currently registered oral solution

  - do not contain excipients that may significantly affect: gastric passage or absorption of the drug substance(s) *in vivo* solubility or *in vivo* stability of the drug substance.

- Medicines containing drug substances that are not systemically or locally absorbed. Examples include:
  - barium sulfate enemas
  - oral suspensions
  - nonbiodegradable ion exchange resins
  - other nonbiodegradable long-chain polymers
  - powders from which no ingredient is absorbed.

Note

A study or justification may be required if there is doubt as to whether absorption occurs.

- Medicines applied locally (e.g. inhalation and nasal medicines, ocular, dermal, rectal, or vaginal administration) except where the drug substance is acting systemically.

Note

Inhaled steroid products should be supported by data on systemic exposure as part of the evidence of their safety, even in cases where they are intended to act locally.

Biopharmaceutic data may be relevant in some circumstances as described in the Guideline on the requirements for clinical documentation for orally inhaled products (CPMP/EWP/4151/00 Rev. 1).

- Medicines with an acceptable correlation between the rate and extent of *in vivo* absorption and the *in vitro* dissolution rate, and where the *in vitro* dissolution rate of the new medicine is equivalent (under the same test conditions used to establish the correlation) to a registered medicine.
- Minor formulation changes to colouring agent, inked imprint, flavour or fragrance, provided the changes are Self-Assessable Requests as outlined in Minor variations to registered prescription medicines: Chemical entities.

Note

We require a justification for not providing biopharmaceutic data for all formulation changes to medicines other than those listed in this section (15.3).

Related information and guidance

- Section 5.3A, Minor variations to registered prescription medicines: chemical entities

15.4 Medicines that require biopharmaceutic data

We require biopharmaceutic data (unless otherwise justified) for new medicines that are:

- oral tablets
- oral capsules
- oral suspensions
- complex intravenous solutions for injection
- applied locally (e.g., inhalation and nasal medicines, ocular, dermal, rectal or vaginal administration) where the drug substance is acting systemically
- transdermal medicines.

For a new chemical entity

Absolute bioavailability study (compared with an intravenous injection or infusion). In the absence of an absolute bioavailability study, a relative bioavailability (compared with an oral solution or suspension of defined particle size).

Bioavailability studies to determine the relative bioavailabilities of the individual enantiomers in racemic drug substances.

Bioequivalence of the to-be- marketed formulation(s) compared with the formulation(s) used in pivotal dose-defining and efficacy studies.

Bioequivalence among the different strengths of the medicine proposed for registration.

Bioavailability studies to show the effect of food.

For a new salt

Biopharmaceutic data for the active moiety in the new salt compared with the currently registered salt.

For a new fixed combination medicine

Bioequivalence of the drug substance in the fixed combination medicine to each of the registered medicines containing the single entity.

Additional studies as required by the Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1).

For a new dosage form

Bioequivalence of the new dosage form to the currently registered dosage form(s).

For a new strength

Bioequivalence of the new strength(s) to the currently registered strength(s) of the innovator medicine if the biowaiver criteria are not met according to either:

- ***For immediate release dosage forms*** - Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)
- ***For modified release dosage forms*** - Guideline on the pharmacokinetic and clinical evaluation of modified release oral and transdermal dosage forms (CPMP/EWP/280/96 Corr).

For a new generic medicine

Bioequivalence of the new generic medicine to the corresponding innovator medicine marketed in Australia.

Note

If the innovator medicine is no longer marketed in Australia, please email streamlinedsubmission@tga.gov.au for advice regarding the appropriate reference product against which the bioequivalence study should be conducted.

For a new formulation that may affect bioavailability

For innovator medicines, bioequivalence of the new formulation to the original formulation, unless justified in line with Minor variations to registered prescription medicines: Chemical entities.

For other medicines, bioequivalence of the new formulation to the corresponding innovator medicine, unless justified in line with Minor variations to registered prescription medicines: Chemical entities.

For a new modified-release formulation

The appropriate study(ies) in line with the following TGA adopted EMA guidelines:

- Note for Guidance on Quality of Modified Release Products - Section 1 (quality): A: Oral dosage forms. B: Transdermal dosage forms (CPMP/QWP/604/96).
- Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/96) Corr as amended.

15.5 Validation and quality control of assay procedures used in biopharmaceutic studies

Fully describe analytical procedures and conditions of sampling, in the form of a standard operating procedure.

The analytical methods should be specific and adequately sensitive, and preference should be given to chromatographic techniques such as high-performance liquid chromatography (HPLC) or gas chromatography (GC).

Clearly state the criteria for accepting or rejecting assay data in the protocol or study report.

Provide a few examples of chromatographic printouts to demonstrate sensitivity and selectivity of the analytical test methods.

Retain all of the original printouts in case we require them, but do not include every printout in the application.

Related information and guidance

Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**) briefly outlines the general requirements for validation and quality control of assay procedures used in biopharmaceutic studies, and refers to other EU guidelines on validation of assay procedures.

Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009)

United States Food and Drug Administration's (FDA's) Guidance for industry: bioanalytical method validation.

15.6 Choice of the reference product for bioequivalence of generic medicines

The generic medicine must be bioequivalent to the Australian reference product.

Reference products

Use the Australian reference product wherever possible as the comparator in a bioequivalence study for a generic medicine.

However, in certain circumstances, we may accept bioequivalence studies using an overseas reference product, provided the conditions below are met. Also use this approach for a locally acting medicine where clinical equivalence has been demonstrated against the overseas reference product.

The conditions for bioequivalence studies using an overseas reference product

The reference product must be:

- A conventional, immediate-release, oral dosage form (tablet, capsule or suspension) or an enteric-coated tablet or capsule formulation that releases the medicine promptly once the enteric coating has dissolved.

Note

Sustained release tablets and capsules may be considered on a case-by-case basis.

Due to the complex nature of sustained release dosage forms, a high level of evidence is needed to demonstrate the products are identical.

Changes in manufacturing process may result in changes to drug disposition of a sustained release dosage form e.g, a change from wet granulation to direct

compression of dry powder.

As the information relating to the manufacturing method of a reference product is usually not known to sponsors of generic medicines, the burden of proof to unequivocally demonstrate that the products are identical may be practically unfeasible.

- Registered in, and obtained from, a country with a regulatory system comparable to Australia.
- Marketed in the country of origin by the same innovator company/corporate entity that currently markets the same medicine in the same dosage form and strength in Australia.
- Marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity that currently markets the medicine in Australia.

When using an overseas reference product

Include evidence in the application to demonstrate that the overseas and Australian reference products are identical.

Do not simply state that the overseas and Australian reference products are identical because they are marketed under the same name by the same sponsor. Multinational companies sometimes market different formulations of a medicine in different countries under the same (or different) brand name.

Demonstrating the overseas and Australian reference products are identical

To establish the overseas and the Australian reference products are identical, provide either:

- a declaration from the innovator company that the overseas and Australian reference products are identical in all respects including formulation and method of manufacture. In this case, the reference product could be a sustained release oral dosage form
- the evidence to justify the overseas and Australian innovator products are identical.

Evidence to justify the overseas and Australian reference products are identical

Copies of the labels and product information (or equivalent document) for both the overseas reference product used in the study and the Australian reference product.

Certificates of analysis for both the overseas and Australian reference product analysed using the specifications proposed in the application for the generic medicine.

Evidence that the drug substance has a well-described dose-response curve and does not exhibit:

- a narrow therapeutic range or safety margin (i.e. does not require careful dosage titration or patient monitoring)
- a steep dose-response relationship
- a risk of serious undesired effects

- complicated or variable pharmacokinetics, such as:
  - nonlinear pharmacokinetics
  - variable or incomplete absorption
- an absorption window (i.e. site-specific absorption) or substantial (> 40 per cent) first-pass metabolism.

Comparative dissolution profiles of the overseas and the Australian reference product. The reference product used in the study must exhibit individual and mean dissolution profiles that are comparable to the reference product marketed in Australia, that is:

- Mean dissolution profiles may be compared statistically using the procedure described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**).
- Individual profiles cover similar ranges.
- The dissolution profiles should be determined in at least three media within the physiological range (pH 1-7.5), including 0.1 N HCl, a pH 4.5 buffer and a pH 6.8 buffer. One dissolution medium should be that described in a monograph of a default standard, if one exists. If no monograph exists, the medium recommended in the FDA Office of Generic Drugs Dissolution Methods Database should be used.

Evidence that the overseas product:

- Contains the same nominal quantity of drug substance as the reference product marketed in Australia.
- Is the same as the reference product in Australia with respect to size, weight and type of coating (for example, uncoated, film-coated, sugar-coated, or enteric-coated).
- Physicochemical evidence generated by an accredited laboratory demonstrating the overseas and Australian reference products are quantitatively identical.
  - This may include Fourier transform infrared spectra, X-ray diffraction spectra, and full or partial quantitative chemical analyses (carried out in duplicate) of the excipients in those products.
  - If a tablet is coated, provide spectroscopic and chemical analytical data for both the core and the coating, wherever possible.
  - Provide data for at least two batches of each of the Australian and overseas reference products.
- The precision and accuracy of the analytical methods and the inter-batch variability are critical to deciding if the formulations are identical. The analytical methods and analytical method validation reports used to generate the physicochemical data are typically provided to satisfy this requirement.

Note

As part of the validation of the test methods used, three batches of the proposed product should be tested with the test methods to demonstrate that the results obtained are both accurate and precise.

15.7 Managing dropouts in bioequivalence studies

In a crossover bioequivalence study, some subjects will drop out of the study after (or even before) administration of the first treatment.

The most acceptable way of managing dropouts is to dose several more than the required number of subjects in the first phase and to specify in the protocol how the requisite number of subjects is to be chosen, from those remaining in the study, for dosing in the second phase.

Related information and guidance

The FDA Guidance for industry: statistical approaches to establishing bioequivalence.

15.8 Where to include biopharmaceutic data

Include:

- Biopharmaceutic studies in Module 5.3.1 of the CTD.
- When submitting biopharmaceutic data:
- Complete the Summary of a Bioavailability or Bioequivalence Study form for each study.
- Include these forms in Module 1.11 of the CTD.
- Provide electronic and paper copies of the individual subject concentration versus time results, and the individual subject pharmacokinetic parameters from the pivotal biopharmaceutic studies.
- Include the study report and confirmation that all biopharmaceutic studies submitted to the TGA have been:
  - carried out in accordance with the Declaration of Helsinki, and the principles of good clinical practice
  - approved by an appropriate independent ethics committee or institutional review board.
- Identify and provide reasons, in Clinical Overview in Module 2 and Module 5.3.1 of the CTD, for any studies that have not been conducted in accordance with these requirements.

15.9 Justification for not submitting biopharmaceutic data

If biopharmaceutic data would normally be required but was not generated:

- Include a justification for not submitting the data included in Module 1.11.2 of the CTD.

In preparing a justification:

Address at least the following issues, as applicable:

- the nature of the dosage form
- the solubility of the drug substance(s)
- the similarities of, or differences between, the formulations being considered
- the comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered
- the pharmacokinetic characteristics of the drug substance(s), such as permeability (or absolute bioavailability), linearity, first-pass effect (if any) and its significance
- the clinical consequences of any potential differences in bioavailabilities of the products under consideration (e.g. increased dose leading to toxicity or decreased dose leading to lack of efficacy)
- the margin between the minimum effective and minimum toxic plasma concentration.

Provide copies of any cited literature.

Use, where relevant, the Biopharmaceutic Classification System (BCS) to justify not undertaking *in vivo* bioequivalence studies.

We do not have a list of drug substances that are considered to fall within particular BCS classes.

Therapeutic Goods Administration

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