



**Australian Government**

**Department of Health and Ageing**

Therapeutic Goods Administration

# Australian regulatory guidelines for prescription medicines

## Appendix 15: Biopharmaceutic studies

June 2004

**TGA** Health Safety  
Regulation



## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- 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.

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# 1. Introduction

Biopharmaceutics is the study of the ways that the physical and chemical properties of drug substances, drug products and routes of administration affect bioavailability (the rate and extent of drug absorption). Biopharmaceutic studies of new medicines typically include the investigation of bioavailability, relative bioavailability and bioequivalence of different dosage forms or formulations, and the effect of food or antacids on their bioavailability.

The Therapeutic Goods Administration (TGA) has adopted the Committee for Medicinal Products for Human Use (CHMP) *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*<sup>1</sup> with the following notation:

While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the CPMP *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations.

The procedure for abridged applications claiming essential similarity to a reference product (that is, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia.

<sup>1</sup> <http://www.tga.gov.au/industry/pm-euguidelines-quality.htm>

The TGA has also adopted the CHMP *Note for Guidance on Quality of Modified Release Products: A: Oral Dosage Form. B: Transdermal Dosage Forms; Section 1 (Quality)* (CPMP/QWP/604/96)<sup>2</sup> which provides additional guidance on dissolution and bioavailability aspects of modified release products.

A copy of the CHMP guidelines can be found on the TGA web site. The introductions to the CHMP guidelines lists a number of other CHMP and International Conference on Harmonisation (ICH) guidelines relevant to biopharmaceutic data and those that have been adopted by the TGA are also available from the TGA web site.

The CHMP guidelines outline the types of biopharmaceutic data that normally need, or do not need, to be submitted in support of applications for the various types of new and changed medicines. This Appendix provides guidance supplementary to the CHMP guidelines and outlines TGA policy on particular aspects of biopharmaceutic studies to assist applicants.

This Appendix addresses the biopharmaceutic studies to be submitted in support of applications to register new medicines or change currently registered medicines. More extensive studies are expected to characterise the pharmacokinetics of new drug substances, even if otherwise excluded below (for example, absolute bioavailability studies are normally required for all new chemical entities except those intended for intravenous administration).

Note that when *dissolution profiles* or a similar term is used in this document, data should be generated in a comparative manner as follows: At least six (and preferably 12) dosage units (for example, tablets, capsules) of each batch are tested individually and mean and individual results reported. 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. The percentage of nominal content released is measured at a number of suitably spaced time points providing a profile for each batch, for example, at 10, 20 and 30 minutes, or as appropriate to achieve virtually complete dissolution. The batches are tested using the same apparatus and if possible on the same day. Test conditions are normally those used in routine quality control or, if dissolution is not part of routine quality control, any reasonable, validated method.

Under some circumstances, insufficient recently manufactured batches may be available. It would then be acceptable to test retention samples, and to explain in the test report why this was done, stating the age and storage history of the samples. If in a particular case the sponsor believes that single point dissolution results would suffice, for example if >85% of the drug is released under acceptable test conditions in 15 minutes, an argument to this effect may be provided.

## 2. Products for which biopharmaceutic data are not normally required

Applications to register or make changes to the types of products listed below need not normally be accompanied by biopharmaceutic data or a justification for not providing such data:

- solutions, complex or simple, which do not contain any ingredient which can be regarded as a pharmacologically active substance;

<sup>2</sup> <http://www.tga.gov.au/industry/pm-euguidelines-quality.htm>

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- haemodialysis solutions and peritoneal dialysis solutions;
  - simple aqueous solutions intended for intravenous injection or infusion. *Simple* solutions do not include complex solutions such as micellar or liposomal solutions;
  - solutions for injection that contain the same active ingredients and excipients in the same concentrations as currently registered products and which are administered by the same route(s);
  - oral solutions containing the same active ingredient(s) in the same concentration as a currently registered oral solution and not containing excipients that may significantly affect gastric passage or absorption of the active ingredient(s);
  - products containing therapeutic substances which are not systemically or locally absorbed, for example, barium sulphate enemas 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;
  - preparations for inhalation, except where the active ingredient is to be delivered to the systemic circulation via inhalation. However, inhaled steroid products should normally be supported by data on systemic exposure to allow for an assessment of the products safety;
  - medicinal gases;
  - monoclonal antibodies;
  - products for which an acceptable correlation has been shown between the rate and extent of *in vivo* absorbance and the *in vitro* dissolution rate, and the dissolution rate *in vitro* of the new product is equivalent to that of an already registered leading brand under the same test conditions as were used to establish the correlation;
  - new strengths of an already registered product, provided all of the following conditions hold:
    - the pharmacokinetics of the drug are linear within the therapeutic dose range;
    - the products are direct scales (or, in the case of small strengths where the active ingredient forms only a few percent of the total formulation, the ratio between the excipients is the same);
    - both products are produced by the same manufacturer at the same site;
    - a biopharmaceutic study has been performed with the original product;
    - under the same test conditions, the dissolution rate *in vitro* is essentially the same (allowing for any differences due to differences in surface area).
  - minor changes in formulation to certain dosage forms. Applications to make the following changes to registered products need not normally be accompanied by biopharmaceutic data or a justification for not providing biopharmaceutic data:
    - immediate release tablets and capsules, and immediate release compressed implants, suppositories and pessaries;
    - minor adjustments to the quantities of currently used hydrophilic excipients, including hydrophilic; lubricants/glidants, where dissolution of the new and **old formulations have been shown to be in the same range as previously;**

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- minor changes to the content of talc where dissolution profiles (see note above at the end Section 1) of the new and old formulations have been shown to be in the same range as previously;
  - minor changes to the quantity and/or type of colorant in the formulation;
  - minor changes to the film coating formulation or the capsule shell formulation.
  - *moulded suppositories and pessaries*. Minor quantitative changes in the currently used excipients where the dissolution profile is in the same range as previously, and microscopic imaging of particles has shown no visible change in size distribution and morphology (particle sizing may also be conducted by other suitable means). The requirement to determine particle size distribution does not apply where the drug substance is in solution at any stage during manufacture of the finished product, or if it is in solution in the finished product, or it is present as liquid globules;
  - *simple aqueous solutions for oral ingestion*. Minor changes to the nature or quantity of excipients, if such changes are unlikely to affect bioavailability;
  - *aqueous oral suspensions*. Minor quantitative changes to currently used excipients where evidence is provided (as above for moulded suppositories and pessaries) that the particle size and morphology of the active ingredient are unaltered or dissolution profiles are unchanged;
  - *ointments, cream and lotions*. Minor changes in the quantitative content of currently used excipients where evidence is provided (as above for moulded suppositories and pessaries) that the particle size and morphology of the active ingredient are unaltered;
  - liquids for intravenous injection;
  - liquids for intramuscular or subcutaneous injection. Addition or deletion of an excipient except where the change could alter the absorption characteristics of the product;
  - other minor reformulations and minor changes to manufacturing procedure where it can be argued convincingly that the change will not affect bioavailability and, where relevant, the dissolution profiles in vitro under the same test conditions are equivalent;
  - changes to site of manufacture, method of manufacture, manufacturing equipment or source of active ingredients. With the following riders, applications to make these changes to registered products need not normally be accompanied by bioavailability data or a justification for not providing such data. The following should normally be provided:
    - evidence that the dissolution profile is in the same range as previously for all solid dosage forms including for example tablets, capsules, suppositories, pessaries, implants etc., and all modified release dosage forms administered by whatever route, for example, oral, transdermal and vaginal modified release products. However, the TGA reserves the right to ask for additional information in certain cases, such as a major change in method of manufacture for a modified release product;
    - for semisolid and liquid products (for example, ointments, creams, lotions, moulded suppositories and pessaries etc.), evidence (as above for changes in formulations of moulded suppositories and pessaries) that the particle size and morphology of the active ingredient are unaltered.

# 3. Products for which biopharmaceutic studies need to be submitted

Biopharmaceutic data as indicated below should be submitted, unless otherwise justified, for any new medicinal product which is an oral tablet, capsule or suspension, intramuscular or subcutaneous injection, topical medicine, product for inhalation or transdermal dosage form where the product has a systemic action.

Unless otherwise justified, studies should be carried out for each strength of a product.

## 3.1 New innovator medicine containing a new chemical entity

- Absolute bioavailability (compared with that of an intravenous injection or infusion);
- relative bioavailability (with that of an oral solution or suspension of defined particle size) where the absolute bioavailability of the new finished product has not been determined but that of a solution or suspension has been determined;
- bioavailability studies to determine the relative bioavailabilities of the individual enantiomers in racemic drug substances;
- effect of food study(ies);
- bioequivalence of the market formulation(s) compared with the (different) formulation(s) used in pivotal dose-defining and efficacy studies.

## 3.2 New salt

- Relevant biopharmaceutic data for the active moiety in the new salt as compared with the same moiety in the currently registered salt.

## 3.3 New fixed combination product

- Biopharmaceutic studies as for a new chemical entity (if relevant);
- bioequivalence of the active ingredients in the fixed combination product to the ingredients administered separately in registered formulations.

## 3.4 New dose form

- Bioequivalence of the new dose form to the currently approved dose form(s);
- for racemic drug substances, relative bioavailabilities of the individual enantiomers in the new dose form.

### **3.5 New strength**

- Bioequivalence of the new strength to the previously registered strength(s) if the formulation is not a direct scale of the previously registered strength(s) and the differences between the formulations of the new and registered strength(s) are such that bioequivalence cannot reasonably be assumed.

### **3.6 New generic medicine**

- Bioequivalence of a new generic medicine to the corresponding innovator product as marketed in Australia.

### **3.7 New formulation of a registered product where the change(s) may affect bioavailability**

- Bioequivalence of the changed formulation to the original formulation or to the corresponding innovator product, as applicable. For further information see Appendix 12.

### **3.8 New modified release formulation**

- In vitro and in vivo studies to establish the release and absorption characteristics of the new product. For further details see CHMP Note for Guidance on Quality of Modified Release Products: A: Oral Dosage Form. B: Transdermal Dosage Forms; Section 1 (Quality) (CPMP/QWP/604/96)<sup>2</sup>.

## **4. Justification for not submitting biopharmaceutic data**

In some situations where biopharmaceutic data would normally be required in support of an application, there may be reasons why certain data need not be generated for the particular product concerned. In this case the sponsor should submit for consideration a justification for not submitting the data. In preparing a justification, the sponsor should address at least the following issues, as applicable:

- the nature of the dosage form;
- the solubility of the active ingredient(s);
- the comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered;
- the pharmacokinetic characteristics of the active ingredient(s), such as permeability (or absolute bioavailability), linearity or otherwise, first pass effect (if any) and its significance;

- the clinical consequences of any potential differences in bioavailabilities of the products under consideration (for example, increased dose leading to toxicity or decreased dose leading to lack of efficacy);
- the width of the margin between the minimum effective and minimum toxic plasma concentration;
- the similarities of, or differences between, the formulations being considered.

Copies of any cited literature should be provided.

If the justification is not considered adequate by the TGA, the sponsor will be required to provide relevant biopharmaceutical data.

## 5. Administration and summary forms

Sponsors should refer to Module 1.11 of the Common Technical Document (CTD) for guidance on Australian administrative requirements for biopharmaceutical studies<sup>3</sup>.

Biopharmaceutical studies (which are to be located in Module 5.3.1 of the CTD) are normally evaluated along with the quality (Module 3) data as part of the assessment of the quality of the medicinal product concerned. Clinical pharmacokinetic studies (which are to be located in Module 5.3.3 of the CTD) are evaluated by the TGA as part of the assessment of the clinical data for new medicines.

Because some of the data relating to biopharmaceutical studies may be located in different parts of the dossier, and to assist the evaluator(s) in identifying the studies to be assessed and locating the relevant information, sponsors submitting biopharmaceutical data are strongly encouraged to complete, for each study, the optional *Summary of a Bioavailability or Bioequivalence Study* form<sup>4</sup>.

Completed Summary Forms should be included as part of Module 1.11.

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<sup>3</sup> <http://www.tga.gov.au/industry/pm-ctd.htm>

<sup>4</sup> <http://www.tga.gov.au/industry/pm-forms-bioavailability.htm>

## 6. Validation and quality control of assay procedures used in biopharmaceutical studies

The CHMP *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*<sup>1</sup> briefly outlines the general requirements for validation and quality control of assay procedures used in biopharmaceutical studies, and refers to other CHMP/ICH guidelines on validation of assay procedures.

The following papers provide helpful additional background information on bioanalytical method validation:

V. P. Shah, *et al*, Bioanalytical Method Validation – A Revisit with a Decade of Progress, *Pharmaceutical Research*, 2000, Vol. 17, No. 12, pp. 1551-7.

K. J. Miller, *et al*, Workshop on Bioanalytical Methods Validation for Macromolecules: Summary Report, *Pharmaceutical Research*, 2001, Vol. 15, No. 9, pp. 1373-83.

The information in this Section is provided to inform sponsors of the TGA's specific expectations for the validation and quality control of assay procedures used in biopharmaceutical studies.

Analytical procedures and conditions of sampling should be fully described, preferably in the form of a standard operating procedure. The chosen analytical methods should be specific and adequately sensitive. Preference should be given to chromatographic techniques such as high pressure liquid chromatography (HPLC) or gas chromatography (GC). Assay validation should be conducted in the laboratory that generated the study data, using the same analytical procedures. Quality control of assays while conducting the study is vital. The investigators criteria for accepting or rejecting assay data should be stated clearly in the protocol or study report.

If an assay procedure is to be used at different sites, it should be validated at each site and cross-site comparability of results and variability should be established.

Copies of all of the original chromatographic printouts need not be included in the study report, but a few examples to demonstrate sensitivity and selectivity should be provided. However, all of the original printouts should be retained by the investigators and be available for copies to be produced and supplied promptly to the TGA if requested.

### 6.1 Chromatographic assay validation

Detailed validation data on the specificity, accuracy, reproducibility and sensitivity of the analytical procedure and stability of the analytes in plasma/serum or other applicable body fluids should be included in the study report or in a separate analytical report. The validation data must be generated at the laboratory where the actual study samples are analysed. If two or more laboratories are involved in the analysis of study samples, the assay procedure must be validated at each laboratory and inter-laboratory validation must be carried out to confirm that each laboratory can obtain the same assay results (within appropriate limits) for the same samples.

Any subsequent changes to assay procedures before or during the actual study must be validated and, if appropriate, correlated with the previously validated procedure.

### **6.1.1 Specificity**

Evidence should be provided that the assay does not suffer from interference by endogenous compounds, degradation products, other medicines likely to be present in study samples, and metabolites of the medicine(s) under study. Where the assay procedure is required to be stereoselective, its stereospecificity must also be established.

### **6.1.2 Stability of measured medicine/metabolites**

Data should be accumulated which establish the stability of the measured entities (normally parent medicine and/or active metabolites) in stock solutions and in the relevant biological environment from time of sampling to assay, under the conditions and duration of storage that apply. The absence of any sorption by the sampling containers and stoppers should also be established.

### **6.1.3 Limit of quantification (LOQ)**

Terms such as *limit of detection* and *minimum detectable concentration* may be misleading in this context since it is typically possible to detect quantities of an analyte substantially below those which can be assigned a meaningful quantitative value. The parameter *three times baseline noise* is often encountered in this context, but reflects what concentration can be detected rather than what can be quantified. A better approach is to define the limit of quantification (LOQ) as the lowest concentration that has a coefficient of variation of 20% for multiple repetitions of the isolation, extraction and injection procedure.

### **6.1.4 Response function (shape of calibration curve)**

Linearity is preferred. The shape of the calibration curve should be defined in mathematical terms on more than one occasion (preferably three) over a concentration range from the LOQ to a value greater than the highest  $C_{\max}$  expected in the study. The coefficient of determination ( $r^2$ ) should normally exceed 0.99 ( $r > 0.995$ ). Alternative approaches may be used provided justification is supplied.

### **6.1.5 Assay precision and accuracy**

Precision (the degree of reproducibility of individual assays) is established by replicate assays on standards, preferably at several concentrations. Accuracy is the degree to which the *true* value is estimated by the assay. Precision and accuracy should normally be documented for at least 5 determinations per concentration and at least three concentrations (low, medium, high) where *low* is in the vicinity of the lowest concentration to be measured, *high* is a value in the vicinity of  $C_{\max}$  and *medium* is a suitable intermediate value near the middle of the anticipated concentration range.

Intra-assay precision (within days) in terms of coefficient of variation should be not more than 10-15% for medium to high concentrations and not more than 20% at concentrations near the LOQ. Inter-assay precision (between days) may be higher than 10-15% but should not be more than 20%.

Accuracy can be assessed in conjunction with precision and is a measure of the extent to which measured concentrations deviate from true or nominal concentrations of analytical standards. In general, an accuracy of not more than  $\pm 15\%$  should be attained for medium to high concentrations and not more than  $\pm 20\%$  for concentrations near the LOQ.

### **6.1.6 Recovery**

Documentation of extraction recovery at high, medium and low concentrations is essential since methods with low recovery are, in general, more prone to inconsistency. If recovery is low, alternative methods should be investigated. Recovery of any internal standard used should also be assessed.

## 6.2 Other Assay Methods

Similar principles apply to chromatographic assays, chemiluminescence and fluorescence assays, ligand-binding assays (incl. immunoassays, enzymatic methods - ELISA, assays to measure anti-drug antibodies, bioassays and biomarkers assays), and pharmacological procedures, but the details may vary.

In addition to the principles outlined above for chromatographic methods, the following points relate to immunoassays:

### 6.2.1 Antibody

The characteristics of the immunoassay depend on the antibody. Therefore, the following validation details should be repeated for each new batch of antibody: specificity, calibration curve, LOQ, precision, and accuracy. It is preferable to use the same batch of antibody for the whole study.

### 6.2.2 Specificity (cross-reactivity)

Data should be provided that the degree of binding of closely related substances such as metabolites and breakdown products at the antibody titre employed. Specific antibodies should be employed.

### 6.2.3 Calibration curve

For immunoassays, calibration curves should be fitted to a computer model or transformed by a logit analysis to give a linear relationship between percent bound and concentration of analyte.

### 6.2.4 Controls

Controls for immunoassay should include blanks comprising pre-dose samples (for example, plasma) from each subject in the study. These should demonstrate that the assay does not indicate the presence of antigen when it is absent. A set of standards from 0 to 90% displacement of label is necessary.

## 6.3 Chromatographic assay of study samples

The following guidelines describe an acceptable approach to assaying samples.

### 6.3.1 Daily calibration standards

Calibration standards and a sample blank (for example, plasma) are analysed with each batch of study samples on a daily basis. The most acceptable approach is to use at least five concentrations of standards from the LOQ to the highest concentration encountered in the study. Calibration standards should be blank samples (for example, plasma) spiked with known concentrations of drug substance, and prepared freshly each day from pure reference substance. Quality control samples (see below) should be spaced throughout the batch.

For chromatographic assays, at least 75% of the daily calibration standards, when back-calculated should fall within  $\pm 15\%$  of their nominal concentrations, except for the LOQ standard which should fall within  $\pm 20\%$  of its nominal concentration. For immunoassays (which are inherently less precise and accurate than chromatographic methods), at least 75% of the daily calibration standards, when back-calculated should fall within  $\pm 25\%$  of their nominal concentrations

Failure to obtain acceptable reproducibility and linearity for the daily standards necessitates re-assay of the batch.

### 6.3.2 Quality control samples

Quality control samples (sometimes called *spikes* or *seeded controls*) are an essential component of in-study quality assurance. Control samples at three or more concentrations covering the expected concentration range (for example, one within 3x of the LOQ, one in the mid-range, and one at the high end of the range) are prepared in plasma in bulk at the time of pre-study assay validation, or at the time of study sample collection, and are aliquoted into storage vessels and stored deep frozen.

A quality control sample for each concentration is assayed in duplicate on each occasion that study samples are assayed, and the concentration determined by reference to that day's calibration standards. For chromatographic assay methods, at least 67% (4 out of 6) of the concentration values determined for the controls should be within  $\pm 15\%$  of their nominal concentrations; 33% of the controls (but not all replicates at the same concentration) may deviate from nominal by more than  $\pm 15\%$ . For immunoassays, at least 67% (4 out of 6) of the concentration values determined for the controls should be within  $\pm 25\%$  of their nominal concentrations; 33% of the controls (but not all replicates at the same concentration) may deviate from nominal by more than  $\pm 25\%$ .

If the results deviate from nominal by more than these limits the batch should be re-analysed unless there is very good reason not to do so.

Quality control samples provide a constant reference point between batches of assays as well as confirming that the medicine is stable under the storage conditions used.

### 6.3.3 Re-analysis of samples

In most studies some samples will require re-analysis because of aberrant results due to processing errors, equipment failure or poor chromatography. The reasons for re-analysis of such samples should be stated.

When the results of repeat assay differ from the original by more than  $\pm 15\%$  for a chromatographic assay or  $\pm 25\%$  for an immunoassay, a third analysis should be carried out. When the three analyses indicate that one is spurious, then the average of the other two should be used.

### 6.3.4 Range of reported values

Concentration values less than the LOQ should be reported as zero and should not normally be used in data analysis. Concentration values marginally (up to 20%) above the highest daily calibration standards may be reported if pre-study linearity data extended beyond such values.

## 7. Choice of the reference product for bioequivalence of generic medicines

Where bioequivalence is a requirement, a generic medicine must be shown to be bioequivalent to the corresponding strength of a leading brand (normally the innovator product) as marketed in Australia.

The actual batch of reference product (comparator) used in a bioequivalence study for a generic medicine should normally be obtained in Australia. This is the TGA's strong preference. However, in certain circumstances, the TGA may accept bioequivalence studies carried out using a batch of

reference product obtained from outside Australia, provided the sponsor can support this with compelling evidence that the formulation of the product used is the same as the formulation marketed in Australia.

The sponsor might argue that the overseas-sourced innovator product is identical to that available in Australia because they are marketed under the same brand name, by the same sponsor, in both countries. However, this argument is not accepted because the TGA is aware that multinational companies sometimes market different formulations of a medicinal product in different countries under the same (or different) brand name.

In the European Union, it is acceptable for an application for registration of a generic product to be based upon a bioequivalence study where the reference product was obtained in another member state. However, member states of the EU are able to share information regarding the formulation and other characteristics of the innovator brands registered in their respective countries, in order to establish unequivocally the identity of reference products from different member states. This is not possible in Australia.

In order to establish that the overseas reference product is identical to the leading Australian brand, a generic sponsor may be able to provide a declaration from the innovator company that it markets the same product (that is, identical in all respects, including formulation and method of manufacture) in both countries. The TGA would refer such a declaration to the local subsidiary if the declaration was not provided by the local subsidiary company or licensee.

Where such a declaration cannot be provided the following requirements must be met, unless otherwise justified. Otherwise, the sponsor should demonstrate equivalence of the generic product to the Australian-sourced reference product by conducting an appropriate bioequivalence study or studies.

- The reference product is a conventional, immediate-release, oral dosage form (tablet, capsule or suspension) or an enteric coated tablet or capsule formulation that releases the drug substance promptly once the enteric coating has dissolved. Sustained release tablets and capsules may be considered on a case-by-case basis.
- The reference product is registered in and obtained from a country with a regulatory system comparable to that in Australia.
- It is documented that the reference product is marketed in the country of origin by the same innovator company or corporate entity that currently markets the same drug substance in the same dosage form and strength in Australia, or that it is marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity that currently markets the product in Australia.
- The sponsor provides copies of the labels and Product Information (PI) (or equivalent document) for both the overseas reference product used in the study and the innovator product marketed in Australia, together with Certificates of Analysis for both the overseas and Australian products, analysed using the specifications proposed in the submission for the generic product.
- Except for minor excipients unlikely to affect bioavailability (for example, colourants and inks) the ingredients of the reference product used in the bioequivalence study are qualitatively identical to those in the corresponding innovator product registered in Australia.
- The drug substance(s) and the finished product satisfy the following criteria:
  - the drug substance(s) has a well described dose response curve and **does not** exhibit:

- § a narrow therapeutic range or safety margin (thus it does not require careful dosage titration or patient monitoring);
  - § a steep dose/response relationship;
  - § a risk of serious undesired effects;
  - § complicated or variable pharmacokinetics (for example, non-linear pharmacokinetics; variable or incomplete absorption; an absorption window, that is, site-specific absorption; substantial [ $>40\%$ ] first-pass metabolism.).
- the reference product used in the study:
- § contains the same nominal quantity of drug substance as the innovator product marketed in Australia;
  - § is the same as the drug product marketed in Australia with respect to size, weight and type of coating (for example, uncoated, film-coated, sugar-coated, or enteric-coated);
  - § exhibits individual and mean dissolution profiles comparable to the product marketed in Australia. Mean dissolution profiles may be compared statistically using the procedure described in the CHMP *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*<sup>1</sup>. Individual profiles should cover similar ranges;
  - § the dissolution profiles should be determined in at least three media within the physiological range (pH 1-7.5 ), including 0.1N HCl, a pH 4.5 buffer and a pH 6.8 buffer. One dissolution medium should be that described in the BP or USP monograph, if one exists.
- The sponsor provides physicochemical and chemical evidence that the overseas and Australian reference products are identical, for example, FTIR spectra, X-ray diffraction spectra, full or partial quantitative chemical analyses (carried out in duplicate) of the excipients in those products. Where a tablet is coated, spectroscopic and chemical analytical data should be provided for both the core and the coating, wherever possible. Spectroscopic and chemical analytical data, generated by an accredited laboratory, should be provided for at least 2 (and preferably 3) batches each of the Australian and overseas formulations to allow an assessment of the inter-analysis and inter-batch variability. The precision and accuracy of the analytical methods and the inter-batch variability will be critical to the decision-making about the acceptability of the data as evidence of identity of the formulations concerned.

In any case, where a sponsor wishes to submit bioequivalence data for a product compared with a reference product obtained from outside Australia, the sponsor should first discuss with the TGA the situation and the available data supporting the claim of identity of the overseas and Australian formulations to ensure that the data are likely to be acceptable and adequate.

A higher level of proof of identity of the overseas and Australian innovator product may be required for drugs that are poorly soluble and poorly absorbed, whereas some of the requirements may be waived on a case-by-case basis for some highly soluble and highly permeable drugs.

Where the available data are unlikely to be sufficient to convince the TGA and its advisory committees that the reference product used in the study is the same as the formulation marketed in Australia, the sponsor may be required to provide additional supporting data or, instead, be required to carry out a new bioequivalence study using a reference product obtained from the Australian market.

## 8. Replacement of dropouts in bioequivalence studies

It is often unavoidable that, in a crossover bioequivalence study, some subjects will drop out of the study after (or even before) administration of the first treatment. The question arises whether it is acceptable for additional subjects to be recruited to replace the subjects who have dropped out.

The CHMP guidelines on the investigation of bioavailability and bioequivalence do not specifically exclude the use of replacement subjects, but state that the protocol should specify methods for handling dropouts.

The FDA Guidance for Industry *Statistical Approaches to Establishing Bioequivalence*<sup>5</sup> states:

Sponsors should enter a sufficient number of subjects in the study to allow for dropouts. Because replacement of subjects during the study could complicate the statistical model and analysis, dropouts generally should not be replaced. Sponsors who wish to replace dropouts during the study should indicate this intention in the protocol. The protocol should also state whether samples from replacement subjects, if not used, will be assayed. If the dropout rate is high and sponsors wish to add more subjects, a modification of the statistical analysis may be recommended. Additional subjects should not be included after data analysis unless the trial was designed from the beginning as a sequential or group sequential design.

The TGA, like the FDA, considers that the most acceptable way of dealing with 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 for dosing in the second phase, from those remaining in the study.

## 9. Sequential (add-on) designs

The CHMP guidelines on the investigation of bioavailability and bioequivalence do not address the issue of sequential designs. A review of the scientific literature and overseas regulatory guidelines on this subject has revealed that several statistical methods have been proposed for handling such studies. However, at the time of publication, there appeared to be no international consensus on the most appropriate method of analysis.

The present TGA policy is:

- until there is consensus on the most appropriate method of statistical analysis of sequential designs, sequential (add-on) studies are discouraged;
- if a sequential study is used it must be foreshadowed in the study protocol. It is not acceptable to analyse the results of a study and then to decide to enrol more subjects because the study was underpowered and bioequivalence criteria were not met;

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<sup>5</sup> <http://www.fda.gov/cder/guidance/3616fnl.htm>

- if a sequential study is planned in the protocol then the initial statistical analysis must be modified to meet more rigorous requirements (even if, ultimately, a second group of subjects is not used). In the absence of consensus on the most appropriate method of statistical analysis, the most conservative of the approaches proposed in the literature, the Bonferroni correction, should be applied. This corresponds to the calculation of 95%, rather than 90%, confidence intervals.

## 10. Data requirements for biopharmaceutical studies

All biopharmaceutical studies submitted to the TGA must have been carried out in accordance with the Declaration of Helsinki and the principles of good clinical practice (GCP), and have been approved by an appropriate independent ethics committee or institutional review board. Confirmation of this should be included with the study report or elsewhere in the application dossier. Any studies not conducted in accordance with the above should be identified and the reasons given (Clinical Overview in Module 2 of CTD).

To enable any biopharmaceutical study to be evaluated by the TGA, the study report should include (as a minimum) the information listed below. Where information is not in the actual study report, it may be located elsewhere in the application dossier, but its location must be clearly identified. For example, the assay procedure and its pre-study validation may be detailed in a separate report, particularly if the same procedure was used for several studies:

- table of contents;
- title of study and any relevant identification code (for example, a protocol number);
- the full protocol for the study including the criteria for inclusion, exclusion or removal of subjects;
- names and affiliations of the responsible investigators;
- signatures of at least the principal investigator authenticating the completeness and accuracy of the whole report and, if available, the signatures of other responsible investigators authenticating their respective sections of the report;
- name(s) and address(es) for the site(s) where the clinical and analytical aspects of the study were carried out;
- the period (dates) over which the study was conducted;
- names and batch numbers of the reference and test products compared;
- the source of the reference product
- if applicable, justification for use of a reference product obtained from outside Australia and evidence that it is the same as the corresponding product available on the Australian market (see section 7 above);
- the formulation(s) of the test product(s) or a signed declaration that this was identical to a particular formulation described elsewhere in the dossier or that intended for marketing;

- if relevant, information on the polymorphic form of the active ingredient used in manufacture of the test product (and/or the reference product, if applicable) and its particle size distribution;
- results of assays and other pharmaceutical tests (for example, physical description, dimensions, mean weight, weight or content uniformity, comparative dissolution) carried out on the batches of reference and test products compared;
- age, height, weight, sex, ethnicity and smoking habit data for the subjects;
- randomisation schedule;
- details of and a justification for any deviations from the protocol;
- details of any adverse reactions observed (for new strengths, new dose forms, or new generics where no clinical data are submitted);
- details of any drop-outs or withdrawals from the study and replacement thereof;
- details of analytical methods used, full pre-study validation data, quality control sample data, and the criteria for accepting or rejecting assay results (see Section 6 above)
- representative chromatograms demonstrating the specificity and sensitivity of the assay procedure (Copies of all of the chromatograms need not be included with the study report, but should be available and able to be supplied, if requested by the TGA);
- actual sampling times;
- all individual and averaged concentration vs. time assay results presented in tables;
- all individual concentration vs. time profiles presented as both linear-linear and log-linear graphs;
- average concentration vs. time profiles for the reference and test products presented as linear-linear graphs (preferably all on the same page to allow comparison);
- details of how pharmacokinetic parameters (for example,  $k_{el}$ ,  $t_{1/2}$ , AUC) were determined;
- individual and summarised average pharmacokinetic parameters;
- details and results of statistical analyses;
- justification for any departures from conventional statistical methodology';
- summary and conclusions;
- copies of any literature referred to in the report.

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Reference/Publication #