

## Notice

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Health Canada is pleased to announce the release of two guidance documents, entitled *Conduct and Analysis of Comparative Bioavailability Studies* and *Comparative Bioavailability Standards: Formulations used for Systemic Effects*.

The purpose of these documents is to update and consolidate eleven existing Health Canada documents related to the conduct and analysis of comparative bioavailability studies and the standards to be met in those studies in order to comply with Sections C.08.002(2)(h), C.08.002.1(2)(c)(ii) and C.08.003(3) of the *Food and Drug Regulations*.

Draft versions of these guidance documents were released for consultation in January 2010. Comments from stakeholders have been considered in the development of these final versions.

Comments received during the most recent consultation process, together with responses from the TPD have been collated in a separate document, which is available *upon request*. Requests for this document should be directed to the e-mail address below.

The documents which will be superseded by these guidances when they come into effect, are as follows:

1. *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects* (1992).
2. Report C (of the Expert Advisory Committee on Bioavailability and Bioequivalence): Report on Bioavailability of Oral Dosage Formulations, Not in Modified Release Form, of Drugs Used for Systemic Effects, Having Complicated or Variable Pharmacokinetics (1992).
3. *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations* (1996).
4. *Draft Policy: Bioequivalence Requirements: Drugs Exhibiting Non-Linear Pharmacokinetics* (2003).
5. Notice to industry: Removal of Requirement for 15% Random Replicate Samples (2003).
6. *Draft Guidance for Industry: Use of Metabolite Data in Comparative Bioavailability Studies* (2004).

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7. Notice to industry: Bioequivalence requirements for combination drug products (2004).
8. *Guidance for Industry: Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State* (2005).
9. Notice to Industry: Bioequivalence Requirements for Drugs for Which an Early Time of Onset or Rapid Rate of Absorption Is Important (rapid onset drugs) (2005).
10. Notice to Industry: Bioequivalence Requirements for Long Half-life Drugs (2005).
11. *Guidance for Industry: Bioequivalence Requirements: Critical Dose Drugs* (2006).

These guidance documents will come into effect for submissions filed on or after July 1, 2012, with the following exceptions. Where the requirements in these guidance documents are reduced relative to existing guidance, the reduced requirements will be effective immediately. Where the requirements in these guidance documents are increased relative to existing guidance, the increased requirements will only be applied to studies initiated on or after July 1, 2012.

With respect to bioanalytical method validation and analysis of study samples, these guidance documents now make reference to the principles and procedures described in the European Medicines Agency Guideline on bioanalytical method validation. Questions or concerns in this regard or related to the *Guidance Documents: Conduct and Analysis of Comparative Bioavailability Studies* and *Comparative Bioavailability Standards: Formulations used for Systemic Effects* should be directed to:

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# GUIDANCE DOCUMENT

## Comparative Bioavailability Standards: Formulations Used for Systemic Effects

Published by authority of the  
Minister of Health

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**Health Products and Food Branch**

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by:</p> <ul style="list-style-type: none"><li>• minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,</li><li>• promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.</li></ul> <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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*Également disponible en français sous le titre : Ligne directrice : Normes en matière d'études de biodisponibilité comparatives : Formes pharmaceutiques de médicaments à effets systémiques*

## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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## **1 INTRODUCTION**

### **1.1 Policy Objectives**

To ensure that sponsors of new drug submissions have the information necessary to comply with Sections C.08.002(2)(h), C.08.002.1(2)(c)(ii) and C.08.003(3) of the *Food and Drug Regulations* with respect to comparative bioavailability and comparative pharmacodynamic studies used in support of the safety and efficacy of a drug.

### **1.2 Policy Statement**

When comparative bioavailability studies versus a reference product, are submitted in support of the safety and efficacy of a drug, the relevant pharmacokinetics parameters should meet the standards described in this guidance.

When pharmacodynamic studies are submitted in support of the equivalence of a drug to a reference product, the parameters for assessment and the methodology detailed in this guidance should be taken into consideration.

### **1.3 Scope and Application**

The data requirements and bioequivalence criteria outlined in this guidance are intended to be applied to all comparative bioavailability studies which provide pivotal evidence of the safety and efficacy of a product, regardless of whether it is a first-entry or subsequent-entry product. Examples of cases where this guidance applies are:

- a) comparative bioavailability studies in support of the bioequivalence of subsequent-entry products to the Canadian Reference Product.
- b) bridging studies where the formulation to be marketed is different from the formulation used in the pivotal clinical trials.
- c) studies in support of significant post-approval changes and line extensions.
- d) safety studies for non-systemic drugs, where systemic drug concentrations may be measured for safety assessment of products with drugs that are intended to act locally, for example, drugs administered by metered-dose inhaler.
- e) comparative bioavailability studies in support of Drug Identification Number (DIN) Applications.

While this guidance is oriented toward solid oral dosage formulations, the principles and standards described may also be applied, as appropriate, to other oral dosage forms and non-injectable formulations such as transdermal patches, suppositories, inhalers, etc., that are

intended to deliver medication to the systemic circulation. This guidance document should be read in conjunction with the associated Health Canada Guidance Document entitled: *Conduct and Analysis of Comparative Bioavailability Studies*.

## 2 GUIDANCE FOR IMPLEMENTATION

### 2.1 Bioequivalence Standards

Please see the Health Canada Guidance on *Conduct and Analysis of Comparative Bioavailability Studies* for advice on study design and statistical analysis etc.

**Note:** These standards are not intended to be used for the determination of bio-inequivalence.

For the majority of drugs, with the exception of subsequent-entry biologic products, the following standards obtained in single dose cross-over comparative bioavailability studies determine bioequivalence:

- a) The 90% confidence interval of the relative mean area under the concentration versus time curve to the time of the last quantifiable concentration ( $AUC_T$ ) of the test to reference product should be within 80.0% to 125.0% inclusive.
- b) The relative mean maximum concentration ( $C_{max}$ ) of the test to reference product should be between 80.0% and 125.0% inclusive.

These standards should be met on log transformed parameters calculated from the measured data. The measured drug content of the lots of the test and reference products, used in the study (expressed as percent of the label claim) should be within 5% of each other. Certificates of analysis documenting potency should be generated within 6 months prior to the start of the study.

In exceptional cases where a reference batch with a measured drug content differing less than 5% from the test product cannot be found, potency correction may be accepted. If potency correction is to be used, this intention should be pre-specified in the protocol and justified. The results from the potency assay of the test and reference products should be submitted. In such cases, the applicable bioequivalence standards should be met on both potency-corrected and uncorrected data.

These studies should generally be carried out in the fasted state. If, however, there is a documented serious safety risk to subjects from single-dose administration of the drug or drug product in the absence of food or if drug concentrations after administration in the fasted state



are too low to be reliably measured, then an appropriately designed study conducted in the fed state may be acceptable for purposes of bioequivalence assessment. This approach should be scientifically justified *a priori* by the sponsor.

### 2.1.1 Exceptions That Require Modifications to the Standards

The methodology and standards given in this document may require modification for certain medicinal ingredients or drug products, for example, those with one or more of the following characteristics:

For products with more than one of the characteristics listed below, the most rigorous combination of criteria will be applied.

#### 2.1.1.1 Modified-release dosage forms

Requirements for modified-release dosage forms differ from those for immediate-release formulations because a greater likelihood exists that increased inter-subject variability in bioavailability will occur, including the possibility of dose-dumping. There may also be an increased risk of adverse effects such as gastrointestinal irritation, depending on the site of drug release, or absorption, or both. Hence, for all modified-release dosage forms (including delayed-release formulations), bioequivalence should be demonstrated under both fasted and fed conditions.

Steady-state studies are not generally required. However, if a steady-state study is conducted, the following standards should be met:

- a) The 90% confidence interval of the relative mean area under the concentration versus time curve at steady state over the dosing interval ( $AUC_{tau}$ ) of the test to reference formulation should be within 80.0% to 125.0% inclusive.
- b) The relative mean  $C_{max}$  at steady state of the test to reference formulation should be within 80.0% to 125.0% inclusive.
- c) The relative mean minimum concentration ( $C_{min}$ ) at steady state of the test to reference formulation should not be less than 80.0% inclusive.

#### 2.1.1.2 Drugs with serious toxicity within the normal dosage range

Some drugs may be expected to have serious toxicity within the normal dosage range and it may therefore be necessary to conduct studies in patients who are already receiving the drug as part of treatment, rather than in healthy subjects. Where a drug is being administered chronically, it may be possible to study bioavailability only during a dose

interval at steady-state. The test drug product would be required to replace the reference drug product over a period of at least five half-lives, where feasible, before sampling. Standardization of the study conditions is essential, particularly with respect to the time of day of drug administration and posture of the subject. Ethical considerations may also dictate that these studies be conducted in parallel groups rather than by a cross-over design.

The standards to be applied in such multiple-dose studies are as listed for modified-release dosage forms above.

#### 2.1.1.3 Drugs exhibiting non-linear pharmacokinetics

A drug will be considered to exhibit non-linear pharmacokinetics based on an assessment of the peer-reviewed scientific literature and the approved Canadian labelling for the drug.

For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths resulting in greater than proportional increases in AUC with increasing dose, the comparative bioavailability study should be conducted on at least the highest strength.

For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths due to saturable absorption and resulting in less than proportional increases in AUC with increasing dose, the comparative bioavailability study should be conducted on at least the lowest strength (single dose unit).

For drugs with non-linear pharmacokinetics in the single unit dose range of approved strengths due to limited solubility of the medicinal ingredient and resulting in less than proportional increases in AUC with increasing dose, the comparative bioavailability studies should be conducted on at least the lowest strength (single dose unit) in the fasted state and the highest strength in both the fasted and fed states.

#### 2.1.1.4 Drugs with a terminal elimination half-life of more than 24 hours

For drugs which exhibit a terminal elimination half-life greater than 24 hours, bioequivalence standards in comparative bioavailability studies will be applied to the AUC to 72 hours post-dose ( $AUC_{0-72h}$ ) rather than  $AUC_T$ . For the purpose of bioequivalence assessment, it will not be necessary to sample for more than 72 hours post-dose, regardless of the half-life, since it is assumed that absorption will be completed in most subjects within 72 hours. Effects of the dosage form itself are

expected to be completed within this period since normally any unabsorbed remnant of the dosage form or the drug would be eliminated from the body. Alternate designs such as parallel studies could be considered.

Other requirements are as described in Section 2.1.

#### 2.1.1.5 Drugs with an important time of onset of effect or rate of absorption

For drugs for which an early time of onset or rapid rate of absorption is important for therapeutic effects, for example, an analgesic for rapid relief of pain, the following standard should be met, in addition to the requirements listed in Section 2.1 above:

The relative mean area under the curve to the time of the maximum concentration of the reference product ( $AUC_{Ref_{t_{max}}}$ ) of the test to reference formulation should be within 80.0% to 125.0% inclusive.

The  $AUC_{Ref_{t_{max}}}$  ratio for each subject should be calculated using values for test and reference products obtained with that subject, and not using a central value (mean or median) for the reference product.

This applies to comparative bioavailability (bioequivalence) studies only. Submissions that make a claim of a more rapid onset of effect, compared to that of the reference product, may require additional pharmacokinetic, pharmacodynamic or clinical data.

#### 2.1.1.6 Critical dose drugs

Critical dose drugs are defined as those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious.

The full definition of a serious adverse drug reaction may be found in C.01.001 of the *Food and Drug Regulations*.

For these drugs:

- a) The 90% confidence interval of the relative mean AUC\* of the test to reference formulation should be within 90.0% to 112.0% inclusive.

[\* This refers to the relevant AUC for the type of study and drug involved, for example (e.g.), it could refer to  $AUC_T$ , or  $AUC_{\tau}$  for multiple dose-studies, or  $AUC_{0-72h}$  for drugs with a half-life greater than 24 hours.]

- b) The 90% confidence interval of the relative mean  $C_{\max}$  of the test to reference formulation should be between 80.0% and 125.0% inclusive.

These requirements are to be met in both the fasted and fed states.

Steady-state studies are not required for critical dose drugs unless warranted by exceptional circumstances. If a steady-state study is required, the 90% confidence interval of the relative mean  $C_{\min}$  of the test to reference formulation should also be between 80.0% and 125.0% inclusive.

Due to the nature of these drugs, for example the possibility of serious adverse effects, it may be necessary to conduct studies in patients who are already receiving the drug as part of treatment, rather than in healthy subjects. The variability of the disease states in patients in whom the studies are performed will be an important consideration in deciding the size of cohort which will have to be investigated in order to meet the standards. It is highly recommended that the study group be as homogeneous as possible with respect to predictable sources of variation in drug disposition.

Where a drug is being administered chronically, it may be possible to study bioavailability only during a dose interval at steady-state. The test drug product would be required to replace the reference drug product over a period of at least five half-lives, where feasible, before sampling. Standardization of the study conditions is essential, particularly with respect to the time of day of drug administration and posture of the subject. Ethical considerations may also dictate that these studies be conducted in parallel groups rather than by a cross-over design.

Currently, these standards apply to formulations including, but not limited to, those containing the following:

- cyclosporine;
- digoxin;
- flecainide;
- lithium;
- phenytoin;
- sirolimus;
- tacrolimus;
- theophylline; and
- warfarin.

Additions or deletions to the above list of drugs may be made in one of two ways. Amendments may be initiated by the Therapeutic Products Directorate (TPD) where required. Amendments may also be initiated as a result of stakeholder proposals. Stakeholders may propose changes to the list by providing relevant concentration/effect data and supporting justification to the TPD for consideration.

#### 2.1.1.7 Combination products

For all combination products, the pharmacokinetic parameters to be reported and assessed are those which would normally be required of each drug if it were in the formulation as a single entity.

#### 2.1.1.8 Drugs with highly variable pharmacokinetics

For the purpose of bioequivalence testing, there is no compelling need for a distinct category of "highly variable" drugs, given that there is sufficient permitted flexibility in study design to address exceptional cases. For example, it may be possible to justify, *a priori*, conducting the study in a pre-screened sub-population such as slow metabolizers, in which the variability may be lower for the particular drug being studied. This type of flexibility in study design does not require the application of special bioequivalence standards.

Notwithstanding the potential need for relatively large numbers of subjects in some bioequivalence studies, the current requirements do not present an unreasonable barrier to product approval.

Furthermore, the ethical concern surrounding the exposure of a relatively large number of healthy subjects to study drugs does not outweigh the potential risk of exposing the patient population to a bio-inequivalent drug.

#### 2.1.1.9 Drugs with measurable endogenous levels

In cross-over studies, test and reference products should be administered at the same time of day, to reduce the potential contribution of diurnal variation to observed differences between products.

Drug doses should be high enough to differentiate exogenous levels from endogenous levels.

Correction for individual endogenous levels should be done by subtracting the estimated endogenous baseline concentration from each post-dose concentration in the profile. It is recommended that individual baseline levels be calculated in each period as the mean of

three concentrations during an interval prior to dosing that is appropriate given the known fluctuations in endogenous concentrations. Negative concentrations should be set to zero. Baseline-corrected plasma concentrations should be used in statistical analysis.

Alternate approaches to dealing with endogenous levels may be acceptable but must be clearly justified and stated *a priori* in the study protocol. Prior consultation with Health Canada is recommended.

#### 2.1.1.10 Drugs for which pharmacodynamic studies are appropriate alternatives to comparative bioavailability studies of oral dosage formulations

A pharmacodynamic study can be used to establish bioequivalence when it is shown to provide a legitimate and robust test of product performance. The following information should be considered:

##### Parameters for Assessment and Methodology:

If only pharmacodynamic data are provided, the sponsor should give an outline of other methods which have been tried and the reasons why they were unsuitable, or why other methods could not be used. Several issues should be recognized in the design of such studies including:

The response which is measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy.

The methodology should be validated for precision, accuracy, reproducibility and specificity.

Neither the test nor the reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses which give maximum or near-maximum effects.

Investigation of dose-response relationships may be a necessary part of the design.

The response should be measured quantitatively under double blind conditions, and be recordable in an instrument-produced or instrument-recorded fashion on a repetitive basis to provide a record of the pharmacodynamic events which are substitutes for plasma concentrations. In those instances where such measurements are not possible, recording on visual analog scales may be used. In other instances where the data are limited to qualitative (categorized) measurements special statistical analysis will be required.

Non-responders should be excluded from the study by prior screening. The criteria by which responders versus non-responders are identified should be stated in the protocol.

In instances where an important placebo effect can occur, comparison between drug products can only be made by *a priori* consideration of the placebo effect in the study design. This may be achieved with a placebo cross-over phase in the pharmacodynamic study.

The underlying pathology and natural history of the condition should be considered in the study design. There should be knowledge of the reproducibility of base-line conditions.

A cross-over design should be used. Where this is not appropriate, a parallel group study design may be used.

The requirements of a pharmacodynamic study should be comparable to those of standard bioavailability or bioequivalence studies, including measures of the magnitude, onset and duration of response. Criteria similar to those defined for bioavailability and bioequivalence studies that use drug concentration measurements should be derived; for example, AUC of measured pharmacodynamic response and maximum response. In addition, similar standards should be met in these criteria to establish bioavailability and bioequivalence.

#### 2.1.1.11 Drugs for which urine drug concentration data is used

In exceptional cases only, bioequivalence may be determined based on drug concentrations (parent drug only) in urine. The standards to be met are:

- a) The 90% confidence interval of the relative mean cumulative amount excreted to the last sampling time ( $A_{eT}$ ) of the test to reference product should be within 80.0% to 125.0% inclusive.
- b) The relative mean maximum rate of excretion ( $R_{max}$ ) of the test to reference product should be between 80.0% and 125.0% inclusive.

## Appendix 1 Glossary of Terms

**Accuracy** - The extent to which an experimentally determined value agrees with the true or absolute value.

**AUC (area under the curve)** - The area under the concentration versus time curve. The AUC symbol may be qualified by a specific time (e.g., 72 hours, or  $AUC_{0-72h}$ ), time of last quantifiable concentration ( $AUC_T$ ), or infinity ( $AUC_I$ ).

**$A_{eT}$**  - The cumulative amount of drug excreted in the urine, measured to the last sampling time.

**$AUC_I$  (AUC to infinity)** - The area obtained by extrapolating to infinity the  $AUC_T$ . This can be calculated by adding  $C_T/\lambda$  to  $AUC_T$  where  $C_T$  is the estimated last quantifiable concentration and  $\lambda$  is the terminal disposition rate constant.

**$AUC_{Ref_{max}}$**  - The area under the curve, for a test product, to the time of the maximum concentration of the reference product, calculated for each study subject.

**$AUC_T$  (AUC to the last quantifiable concentration)** - The AUC to the time of the last quantifiable concentration.  $AUC_T$  is calculated from observed data at specific time points.

**$AUC_{\tau}$  (AUC over a dosing interval)** - The area under the concentration versus time curve at steady state, over the dosing interval in a multiple-dose study.

**Bioavailability** - The rate and extent of absorption of a drug into the systemic circulation.

**Bioequivalence** - A high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects, or both.

**Bioequivalent** - Test and reference products are bioequivalent when they contain an identical drug or drugs and, after comparison in an appropriate bioavailability study, are found to meet the standards for rate and extent of absorption specified in this guidance.

**$C_{max}$  (maximum observed concentration)** - The observed maximum or peak concentration.

**$C_{min}$  (minimum observed concentration)** - The observed minimum concentration.

**Formulation** - An ingredient or mixture of specific ingredients; that is, drug substances and excipients in specific amounts, defining a given product.



**Modified-release dosage form** - A dosage form for which the drug-release characteristics of time-course or drug-release location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

Modified-release dosage forms are drug formulations that differ from conventional formulations in the rate at which the drug is released. For the purpose of these guidances, modified-release forms include formulations designed to meet one or more of the following objectives:

- To delay disintegration, de-aggregation, or dissolution so that the drug's rate of degradation is altered.
- To delay or decrease the rate of absorption so that the likelihood of gastrointestinal or other adverse effects is diminished (e.g., enteric-coated forms).
- To provide effective drug concentrations for a longer period of time after a single dose.
- To deliver the drug initially at a rate similar to that obtained with the conventional form, and to provide effective drug concentrations for a longer period of time.
- To minimize fluctuations in drug concentrations during the dosing interval.
- To provide, after single administration, multiple peaks and troughs in the serum concentration-time curves similar to those achieved after repeated dosing with the conventional formulation.

**90% Confidence interval** - An interval about the estimated value that provides 90% assurance that it contains the true value.

**Non-linear pharmacokinetics** - A general term referring to dose or time dependency in pharmacokinetic parameters arising from factors associated with absorption, first-pass metabolism, binding, and excretion.

**Precision** - The closeness of agreement of values obtained in the analysis of replicate samples of the same specimen, usually indicated by the coefficient of variation (relative standard deviation).

**R<sub>max</sub>** - Maximum rate of urinary drug excretion.