Health Canada Santé Canada

DRAFT GUIDANCE DOCUMENT

Comparative Bioavailability Standards: Formulations Used for Systemic Effects

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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 equivalence 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: comparative bioavailability studies in support of the bioequivalence of subsequent-entry products to the Canadian reference product, bridging studies where the formulation to be marketed is different from the formulation used in the pivotal clinical trials, studies in support of significant post-approval changes and line extensions. While this guidance is oriented toward oral dosage formulations, the principles and criteria described may also be applied, as appropriate, to other non-parenteral 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 Draft 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, the following standards obtained in single dose cross-over comparative bioavailability studies determine bioequivalence:

a) The 90 percent confidence interval of the relative mean area under the concentration versus time curve (AUC_T) of the test to reference product should be within 80.0 percent to 125.0 percent.

b) The relative mean measured maximum concentration (C_{max}) of the test to reference product should be between 80.0 percent and 125.0 percent.

These standards should be met on log transformed parameters calculated from the measured data. Measured drug content of the test and reference formulations, used in the study, should be within 5 percent of each other. Certificates of analysis documenting potency should be generated immediately prior to the study.

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

Where bioequivalence is to be determined based on drug concentrations (parent drug only) in urine, the standards to be met are:

a) The 90 percent 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 percent to 125.0 percent.

b) The relative mean maximum rate of excretion (R_{max}) of the test to reference product should be between 80.0 percent and 125.0 percent.

These standards should be met on log transformed parameters calculated from the measured data. Measured drug content of the test and reference formulations, used in the study, should be within 5 percent of each other.

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:

1. Modified-release dosage forms:

   Bioequivalence to the reference formulation 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:

   The 90 percent confidence interval of the relative mean area over a steady-state dosing interval (AUC_{τ}) of the test to reference formulation should be within 80.0 percent to 125.0 percent.

   The relative mean measured C_{max} at steady state of the test to reference formulation should be within 80.0 percent to 125.0 percent.

   The relative mean measured C_{min} at steady state of the test to reference formulation should not be less than 80.0 percent.

2. 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.

   Bioequivalence to the reference formulation should be demonstrated under both fasted and fed conditions. In certain situations, as defined below, a waiver from the requirement to demonstrate bioequivalence under fed conditions may be justified.

   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 studies should be conducted

on at least the **highest** strength. For high solubility medicinal ingredients, it may be possible to justify a waiver from the requirement to demonstrate bioequivalence under fed conditions.

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 studies should be conducted on at least the **lowest** strength (single dose unit). For high solubility medicinal ingredients, it may be possible to justify a waiver from the requirement to demonstrate bioequivalence under fed conditions.

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) and the **highest** strength. If bioequivalence to the reference product is demonstrated under fasted and fed conditions with the lowest strength (single unit dose) and under fasted conditions with the highest strength, it may be possible to justify a waiver from the requirement to demonstrate bioequivalence under fed conditions with the highest strength.

For the purpose of this section, a drug substance will be considered highly soluble when the highest dose strength is soluble in 250 millilitres or less of aqueous media over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5˚C).

A waiver from the requirement to demonstrate bioequivalence under fed conditions may be granted for drugs which exhibit non-linear pharmacokinetics due to processes that are not related to the absorption phase, including first-pass metabolism, of the drug's disposition.

Drugs which exhibit time-dependent non-linear pharmacokinetics will be considered on a case-by-case basis.

3. 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 $AUC_{0\text{-}72h}$. 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. Alternate designs such as parallel studies could be considered.

Other requirements are as described in Section 2.1.

4. An important time of onset of effect or rate of absorption:

The relative mean $AUC_{Reftmax}$ of the test to reference formulation should be within 80.0 to 125.0 percent, where $AUC_{Reftmax}$ for a test product is defined as the area under the curve to the time of the maximum concentration of the reference product, calculated for each study subject. Other requirements for drugs for which an early time of onset or rapid rate of absorption is important because of therapeutic or toxic effects (for example, an analgesic for rapid relief of pain) are as in Section 2.1 .

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.

5. 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.

Note: 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:

The **90 percent** confidence interval of the relative mean AUC of the test to reference formulation should be within **90.0 to 112.0 percent.**

The **90 percent** confidence interval of the relative mean measured C_{max} of the test to reference formulation should be between **80.0 and 125.0 percent.**

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

These standards should be met on log transformed parameters calculated from the measured data. Measured drug content of the test and reference formulations, used in the study, should be within 5 percent of each other.

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

Note: Due to the nature of these drugs, it may be necessary to conduct studies in patients 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 crossover design.

Currently, these standards apply to formulations 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.

6. 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.

7. 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.

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.

8. Drugs with measurable endogenous levels:

Where feasible, drug doses should be high enough to differentiate exogenous levels from endogenous levels.

Baseline-corrected plasma concentrations should be used in statistical analysis.

Endogenous baseline levels should be estimated by averaging at least three pre-dose concentrations prior to period 1 dosing for each subject in the study.

Correction for endogenous levels should be done by subtracting the pre-dose concentration from each post-dose concentration in the profile. Negative concentrations should be set to zero and positive concentrations following a negative concentration after Cmax should also be set to zero. An analysis of the magnitude and frequency of the negative and positive concentrations removed should be done by the sponsor, as differences in either could be related to formulation differences.

Alternate approaches to dealing with endogenous drug levels may be acceptable but must be clearly justified and stated *a priori* in the study protocol.

9. Drugs for which pharmacodynamic studies are appropriate alternatives to comparative bioavailability studies of oral dosage formulations:

When pharmacodynamic studies are the only option for establishing bioequivalence the following information should be considered:

Parameters for Assessment and Methodology:
If pharmacodynamic data only 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.