Health Canada Santé Canada

Guidance Document

Comparative Bioavailability Standards: Formulations Used for System Effects

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Canada

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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.

Document change log

Date: 2018/06/08

Change: Addition of a sentence

"In cases where the products are not considered to be pharmaceutically equivalent, the data requirements and criteria outlined in this guidance apply for a determination of comparative bioavailability."

Location (section, paragraph): Section 1.3

Nature of and/or reason for change: This clarification covers cases where, for example, different pharmaceutical forms or chemical forms with the same active moiety are being compared, i.e., cases where comparative bioavailability is being assessed, as opposed to bioequivalence.

Change: change the wording of the standards as follows:

From:

(a) The relative mean maximum concentration (C_{max}) of the test to reference product should be between 80.0% - 125.0% inclusive.

To:

(a) The relative mean maximum concentration (C_{max}) of the test to reference product should be within 80.0% - 125.0% inclusive.

Location (section, paragraph): Section 2.1

Nature of and/or reason for change: Clarification of the standard.

Change: Addition of the following sentence:

"Health Canada invites sponsors to request written feedback from the Division of Biopharmaceutics Evaluation (DBE) or a pre-submission consultation meeting for more details or product specific guidance."

Location (section, paragraph): Section 2.1

Nature of and/or reason for change: The document provides general guidance. Some submissions may require more specific clarification of requirements. Sponsors are invited to consult with Health Canada.

Change: Abbreviation of section 2.1.1.10

Location (section, paragraph): Section 2.1.1.10

Nature of and/or reason for change: Portions of this section were transferred to the guidance on the Conduct and Analysis of Comparative Bioavailability Studies since the information was more relevant to study design than to standards.

Change: Deletion of section 2.1.1.11

Location (section, paragraph): Table of contents and in the document

Nature of and/or reason for change: Section was removed since urine data is no longer used for assessment of comparative bioavailability and the information is therefore no longer relevant.

Change: change the wording of the standards as follows:

From:

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.

To:

b) 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 product should be within 80.0% to 125.0% inclusive.

From:

b) The relative mean C_{max} at steady state of the test to reference formulation should be within 80.0% to 125.0% inclusive.

To:

b) The relative mean C_{max} at steady state of the test to reference product should be within 80.0% to 125.0% inclusive.

From:

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.

To:

c) The relative mean minimum concentration (C_{min}) at steady state of the test to reference product should not be less than 80.0% inclusive.

Location (section, paragraph): Section 2.1.1.1

Nature of and/or reason for change: Clarification of the standard

Change: Addition of a paragraph

Modified-release products with multiphasic plasma concentration profiles demonstrated to be integral to their therapeutic effect will be subject to standards on the partial area under the concentration versus time curve (pAUC), defined over a restricted time interval(s) after drug administration. These standards will be applied in addition to those normally applied in the assessment of bioequivalence (i.e. AUC and Cmax).

The requirement for pAUC assessment metrics for multiphasic modified-release formulations will be based on data available from various sources, including but not limited to peer-reviewed scientific literature and the approved Canadian labelling, as applicable. The time course of changes in the rate of drug delivery throughout the day should be reconciled with generally accepted and clinically relevant response data generated from a well-designed randomized clinical trial program. Specifically, standards based on the 90% confidence interval of pAUC metrics should be met. The specific pAUC time intervals to be considered will be based on clinical data showing the therapeutic relevance of the particular time interval (e.g. early onset, maintenance, dose clearance, fasted versus fed state). Selected time intervals should be justified, specified a priori and applied to all study subjects for both the test and reference products.

Location (section, paragraph): Section 2.1.1.1

Nature of and/or reason for change: Addition of guidance for multiphasic modified-release products as per advice from the Scientific Advisory Panel on Modified Release Dosage Forms.

Change: Change the wording of the following:

From:

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

To:

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

Location (section, paragraph): Section 2.1.1.5

Nature of and/or reason for change: Clarification of the standard.

Change: Change the wording of the standards and following paragraph:

From:

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.

To:

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

From:

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.

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 product should also be within 80.0% and 125.0% inclusive.

To:

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.

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 product should also be within 80.0% and 125.0% inclusive.

Location (section, paragraph): Section 2.1.1.6

Nature of and/or reason for change: Clarification of the standard.

Change: Replacement of the entire text

Location (section, paragraph): Section 2.1.1.8

Nature of and/or reason for change: To incorporate published policy on Bioequivalence Standards for Highly Variable Drug Products (2015) which superceded the 2012 guidance with respect to these products.

Change: Minor revision to the definition of “Modified-release dosage form” to include multiphasic drug product formulations.

From:

- 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 (i.e., multiphasic modified-release dosage forms).

To:

- To provide, after single administration, multiple peaks and troughs in the concentration-time curves (i.e., multiphasic modified-release dosage forms).

Location (section, paragraph): Appendix 1

Nature of and/or reason for change: Revised for purpose of clarification.

Change: Addition of the definition pAUC

Location (section, paragraph): Appendix 1

Nature of and/or reason for change: Definition needed for new criterion (partial AUC) introduced for multiphasic modified-release products.

Change: Deletion of the following:

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

R_{max} - Maximum rate of urinary drug excretion.

Location (section, paragraph): Appendix 1

Nature of and/or reason for change: Urine data is no longer used for assessment of comparative bioavailability and this information is therefore no longer relevant.

Table of Contents

1. Introduction

1.1 Policy objective

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 pharmacokinetic 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. In cases where the products are not considered to be pharmaceutically equivalent, the data requirements and criteria outlined in this guidance apply for a determination of comparative bioavailability. 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% - 125.0% inclusive.

b) The relative mean maximum concentration (C_{max}) of the test to reference product should be within 80.0% - 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.

Health Canada invites sponsors to request written feedback from the Division of Biopharmaceutics Evaluation (DBE) or a pre-submission consultation meeting for more details or product specific guidance.

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 below listed characteristics.

For products with more than one of the following characteristics, 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 steadystate over the dosing interval (AUC_{tau}) of the test to reference product should be within 80.0% - 125.0% inclusive.

b) The relative mean C_{max} at steadystate of the test to reference product should be within 80.0% - 125.0% inclusive.

c) The relative mean minimum concentration (C_{min}) at steady state of the test to reference product should not be less than 80.0% inclusive.

Modified-release products with multiphasic plasma concentration profiles demonstrated to be integral to their therapeutic effect will be subject to standards on the partial area under the concentration versus time

curve (pAUC), defined over a restricted time interval(s) after drug administration. These standards will be applied in addition to those normally applied in the assessment of bioequivalence (i.e. AUC and Cmax).

The requirement for pAUC assessment metrics for multiphasic modified-release formulations will be based on data available from various sources, including but not limited to peer-reviewed scientific literature and the approved Canadian labelling, as applicable. The time course of changes in the rate of drug delivery throughout the day should be reconciled with generally accepted and clinically relevant response data generated from a well-designed randomized clinical trial program. Specifically, standards based on the 90% confidence interval of pAUC metrics should be met. The specific pAUC time intervals to be considered will be based on clinical data showing the therapeutic relevance of the particular time interval (e.g. early onset, maintenance, dose clearance, fasted versus fed state). Selected time intervals should be justified, specified a priori and applied to all study subjects for both the test and reference products.

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 their 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 ($AUC_{0\text{-}72h}$) 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:

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

The $AUC_{Reftmax}$ 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 product should be within 90.0% - 112.0% inclusive.

   [* This refers to the relevant AUC for the type of study and drug involved, for example, it could refer to AUC_T, or AUC_{tau} for multiple dose-studies, or $AUC_{0\text{-}72h}$ 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 product should be within 80.0% - 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 product should also be within 80.0% - 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 their 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. 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 product

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 Highly variable drug products

A drug product may be considered to exhibit highly variable pharmacokinetics if the within-subject coefficient of variation (CV) of the applicable AUC for the reference product is greater than 30.0%. The AUC to which the HVDP criteria and expanded confidence limits will apply is the AUC subject to bioequivalence standards. The following approach, using average bioequivalence with expanding limits based on the within-subject variability of the reference product (reference scaling), may be used. Critical dose drugs are not eligible for the application of this approach of expanding the bioequivalence intervals.

Evidence from the literature, or the results of well conducted studies, should be provided to indicate that the AUC is highly variable. The proposal for expanding the bioequivalence interval should be defined a priori in the study protocol. A scientific rationale should be provided to support the position that the high variability in exposure is not clinically significant. Submissions for HVDPs should also be supported by a justification to demonstrate that the CV estimates are reliable and not subject to the influence of outliers.

For HVDPs, replicate design comparative bioavailability studies must be conducted with the reference product (R) administered at least twice to determine the within-subject variability for the reference product. The test product (T) should be administered either once in a 3-period design (RTR, TRR, RRT) or twice in a 4-period design (TRTR, RTRT). The lower and upper limits of the expanded bioequivalence interval should be calculated using the within-subject standard deviation of the log-transformed values of AUC of the reference product (s_{WR}). Expansion of the bioequivalence interval may be permitted up to a maximum width of 66.7% - 150.0% (equivalent to a scaled criterion for CV = 57.4%).

The following comparative bioavailability standards should be met:

a) The 90% confidence interval of the relative mean AUC of the test to reference product should be within the following limits, inclusive:

   i) 80.0%-125.0%, if $s_{WR} \leq 0.294$ (i.e., CV ≤30.0%)

   ii) $[\exp(-0.76 s_{WR}) \times 100.0\%]$-$[\exp(0.76 s_{WR}) \times 100.0\%]$ if $0.294 < s_{WR} \leq 0.534$ (i.e., 30.0% <CV ≤57.40%) or,

   iii) 66.7%-150.0%, if $s_{WR} > 0.534$ (i.e., CV >57.4%)

b) The relative mean AUC of the test to reference product should be within 80.0% - 125.0% inclusive.

c) The relative mean maximum concentration (C_{max}) of the test to reference product should be within 80.0% - 125.0% inclusive.

References:

Endrenyi L. and Tothfalusi L. (2009). Regulatory conditions for the determination of bioequivalence of highly variable drugs. J. Pharm. Pharmaceut. Sci. 12: 138-149.

Tothfalusi L. and Endrenyi L. (2012). Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs. J. Pharm. Pharmaceut. Sci. 15(1) 73-84.

As an alternative to the use of expanded bioequivalence limits for HVDPs, the variability in the drug's pharmacokinetics may be addressed through the study design. 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.

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 in vivo comparability when it is shown to provide a legitimate and robust test of product performance. 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.

The study endpoints and schedule of response assessments should be chosen to yield quantitative results that permit equivalence analyses comparable to those of standard comparative bioavailability or bioequivalence studies. These should include measures of the magnitude, onset, and duration of response. For example, the cumulative pharmacodynamic response may be assessed similarly to an AUC, and the peak response may be assessed similarly to a C_{max}. To establish comparability, these results should be evaluated against acceptance criteria similar to those defined for comparative bioavailability studies. These criteria should be predefined in the study protocol.

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.

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

$AUC_{Reftmax}$
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 area under the concentration versus time curve to the time of the last quantifiable concentration.

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.

$AUC_{0\text{-}72h}$ (AUC to 72 hours)
The area under the concentration versus time curve from time 0 to 72 hours.

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.

HVDP - Highly variable drug product
A drug product may be considered to exhibit highly variable pharmacokinetics if the within-subject coefficient of variation (CV) of the area under the concentration versus time curve (AUC) for the reference product is greater than 30.0%.

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 concentration-time curves (i.e., multiphasic modified-release dosage forms).

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.

pAUC
Partial area under the concentration versus time curve defined over a restricted time interval after drug administration.

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).