

**PAN AMERICAN NETWORK ON DRUG REGULATORY HARMONIZATION
Bioavailability and Bioequivalence Working Group**



**Proposed criteria for bioequivalence testing (*in vitro* and *in vivo*) and for
waivers of *in vivo* testing of generic drug products.**

EDITED VERSION # 4

Recommendations from the WG/BE:

The Working Group (WG/BE) developed the following recommendations to be presented for adoption by the IV Pan American Conference on Drug Regulatory Harmonization:

- A) The Conference approves this document: *Proposed criteria for bioequivalence testing (in-vivo and in-vitro) and for waivers of in-vivo testing of generic products*, as presented, for use in the American Region as a reference document in the performance of BE studies;
- B) Regulatory authorities should adopt the criteria for BE studies developed by PANDRH's WG/BE in their national or regional regulations or agreements.
- C) National regulatory authorities should promote the harmonization of the list of active ingredients and require that BE studies use as reference the present comparative List of BE Products as required by countries and to take into account the Model Developer (Health Risk and Observed reality);
- D) National officials and educational institutions as well as the pharmaceutical industry should include the BE criteria developed by PANDRH in their educational programs on Bioequivalence;
- E) The PANDRH's WG/BE should develop a specific chapter on BE for Antiretrovirals;
- F) In analyzing national situations, drug regulatory authorities should consider PANDRH's WG/BE as a source in the implementation of BE requirements.

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I. CRITERIA FOR BIOEQUIVALENCE TESTING (*in-vivo* and *in-vitro*) AND FOR WAIVERS OF *in-vivo* TESTING OF GENERIC PRODUCTS¹

1. Background

A meeting on Bioavailability-Bioequivalence was held in January 1997 in Caracas, Venezuela² to analyze the implementation of BE studies and requirements in the American Region. Expert participants developed several recommendations; among them, the need for countries to gradually implement BE studies to assure interchangeability of pharmaceutical products.

In November 1997 the I Pan American Conference on Drug Regulatory Harmonization took place in Washington D.C. Regulatory authorities from all PAHO Member States, representatives from the industry, academia, consumer groups and economic integration sub-regional groups in the Americas, recommended holding periodic fora to discuss related to the drug regulatory harmonization processes. Participants also identified Bioequivalence as a second priority to address the issue of BE implementation and established a working group (WG/BE). Among the main responsibilities of the WG/BE were the development of a set of criteria for bioequivalence-bioavailability testing of generic drug products, implementation of technical educational seminars on BE; and, identification of ways to follow up BE implementation in the Region.

The II Pan American Conference (November 1999) established the Pan American Network for Drug Regulatory Harmonization (PANDRH) and rules and regulations for the Network and its working groups. According to those regulations, harmonized proposals developed by the WGs are to be presented at the Conferences for their adoption or approval.

Accordingly, the PANDRH WG/BE prepared its Mission Statement which is to contribute to the development of harmonized bioequivalence criteria for the interchangeability of pharmaceutical products in the Americas through the promotion of technical bases to assure interchangeability of multisource products, within an international and a national context, by proposing the establishment of reference materials as comparators for bioequivalence testing.

Within this context, Dr. Salomon Savtchanski and Dr. Ricardo Bolaños, both members of the WG/BE, were assigned the task of developing a draft proposal on *Criteria for Bioequivalence Testing (in-vivo and in-vitro) and for Waivers of in-vivo Testing of Generic Products*; and, a proposed *Strategy for Countries to Promote the Harmonization Process through the Requirement of BE Studies*, respectively.

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² Consultation of Experts on Bioequivalence of Pharmaceutical Products. Caracas, Venezuela. January 13-15, 1997. Program on Essential Drugs and Technology (HSE). Division of Health Systems and Services Development (HSP). June 1999.

2. Introduction

2.1 Objectives

This document discusses the marketing of pharmaceutical products that are therapeutically equivalent and thus interchangeable but are produced by different manufacturers.

2.2 Statement of Purpose

Drug regulatory authorities must ensure that all pharmaceutical products, including generic drug products, conform to the same standards of quality, efficacy and safety required of innovator drug products. Therefore, regulatory frameworks must be established to prove that generic drug products are therapeutically equivalent and interchangeable with their associated innovator's product. Such regulatory frameworks would necessitate proof of bioequivalence.

In the absence of such a regulatory framework, this document prepared by the PANDRH's Bioavailability-Bioequivalence Working Group, seeks to provide recommendations to countries in the Americas that are in the process of establishing regulatory frameworks to provide these assurances.

Since bioequivalence is the main mechanism used to link the generic product to the innovator's original documentation on its safety and efficacy, the following framework is proposed to assist drug regulatory authorities in establishing requirements for proof of interchangeability by describing when bioequivalence testing is required for generic/multisource products. Further, it also defines the type of testing, *in vivo* and/or *in vivo*, which should be submitted for marketing approval.

In vivo and/or *in-vitro* bioequivalence testing is required for most generic drug products submitted for marketing approval. A proposed generic drug product must be compared *in vivo* and/or *in vitro* to the officially designated reference drug product.

The recommendations made in this report are based on the following guidelines:

1. Guidelines Published by the Food and Drug Administration
2. Health Canada's Guideline on Preparation of DIN Submissions
3. WHO document (1999) entitled "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: a Manual for Drug Regulatory Authorities, Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability."
4. ICH documents
5. Note for Guidance on the Investigation of Bioavailability and Bioequivalence, Committee for Proprietary Medicinal Products (CPMP), 26 July 2001 (CPMP/EWP/QWP/98)

3. Equivalence Documentation for Marketing Authorization

Pharmaceutically equivalent multisource pharmaceutical products must be verified to be therapeutically equivalent to one another in order to be considered interchangeable. Several test methods are available to assess equivalence, including:

1. Comparative bioavailability (bioequivalence) studies, in which the active drug substance or one or more metabolites is measured in an accessible biologic fluid such as plasma, blood or urine.
2. Comparative pharmacodynamic studies in humans.
3. Comparative clinical trials.
4. *In vitro* dissolution tests in combination with the Biopharmaceutics Classification System (Section 6)

Acceptance of any test procedure in the equivalence documentation between two pharmaceutical products by a drug regulatory authority depends on many factors, including characteristics of the active drug substance and the drug product and the availability of resources to carry out a specific type of study. Wherever a drug produces meaningful concentrations in an accessible biologic fluid, such as plasma, bioequivalence studies are preferred. Wherever a drug does not produce measurable concentrations in an accessible biologic fluid, comparative clinical trials or pharmacodynamic studies may be necessary to document equivalence. *In vitro* testing, preferably based on a documented *in vitro/in vivo* correlation or on consideration based on the Biopharmaceutics Classification system, may sometimes provide an indication of equivalence between two pharmaceutical products

Additional criteria indicating when equivalence studies are necessary are discussed in the following sections.

4. Oral Drugs/Drug Products for which *in vivo* Equivalence Documentation is Important

This guideline recommends that registration authorities required equivalence documentation for multisource pharmaceutical products in which the product is compared to the reference pharmaceutical product. Studies must be carried out using the formulation proposed for marketing.

For certain drugs and dosage forms, *in vivo* equivalence documentation, through either a bioequivalence study, a comparative clinical pharmacodynamic study, or a comparative clinical trial, is considered especially important. The following are the factors and the oral drugs/drug products that should be considered when requiring *in vivo* equivalence documentation.

- (a) Immediate-release oral pharmaceutical products with systemic action when one or more of the following criteria apply:
 - (i) Indicated for serious conditions requiring definite therapeutic response;
 - (ii) Narrow therapeutic window/safety margin, steep dose-response curve;

- (iii) Pharmacokinetics complicated by variable or incomplete absorption or absorption window, non-linear pharmacokinetics, pre-systemic elimination/high first-pass metabolism >70%;
 - (iv) Unfavorable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability, etc.;
 - (v) Documented evidence of bioavailability problems related to the drug or drugs of similar chemical structure or formulations;
 - (vi) Where there is a high ratio of excipients to active ingredients.
- (b) Non-oral and non-parenteral pharmaceutical products designed to act through systemic absorption (such as transdermal patches, suppositories, etc.).
 - (c) Sustained or otherwise modified release pharmaceutical products designed to act through systemic absorption.
 - (d) Fixed combination products (see WHO Technical Report Series No. 825, 1992) with systemic action.
 - (e) Non-solution pharmaceutical products for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc. application) and intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence. This does not, however, exclude the potential need for drug concentration measurements in order to assess unintended partial absorption.

In cases (a) to (d) plasma concentration measurements over time (bioequivalence) are normally sufficient proof for efficacy and safety. In case (e) the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence.

The following are factors and oral drugs/drug products that should be considered when requesting a waiver of evidence of *in vivo* bioavailability or bioequivalence documentation.

5. Recommended Criteria to Waive evidence of *in vivo* Bioavailability or Bioequivalence

Generally, both *in-vivo* and *in-vitro* testing are necessary for orally administered drug products. *In-vivo* testing is required for all generic drug products with certain exceptions. Based on scientific information regulatory authorities may waive the requirement for bioavailability or bioequivalence.

In vivo comparative bioavailability or bioequivalence of a drug product may be waived if the product meets one of the following criteria:

The drug product: For certain formulations and under certain circumstances, equivalence between two pharmaceutical products may be considered self-evident and no further documentation is required. For example:

- (a) When multisource pharmaceutical or generic products are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations.

- (b) When multisource pharmaceutical or generic products are solutions for oral use, contain the active substance in the same concentration, and do not contain an excipient that is known or suspected to affect gastro-intestinal transit or absorption of the active substance.
- (c) Gas-based multisource pharmaceutical or generic products.
- (d) When the multisource pharmaceutical or generic products are powders for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above.
- (e) When multisource pharmaceutical or generic products are otic or ophthalmic products prepared as aqueous solutions, containing the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;
- (f) When multisource pharmaceutical or generic products are topical products prepared as aqueous solutions, containing the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;
- (g) When multisource pharmaceutical or generic products are inhalation or nasal spray products, tested to be administered with or without essentially the same device, prepared as aqueous solutions, and containing the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations. Special *in vitro* testing should be required to document comparable device performance of the multisource inhalation product.

For elements (e), (f) and (g) above, it is incumbent upon the applicant to demonstrate that the excipients in the multisource product are essentially the same and in comparable concentrations as those in the reference product.

In the event the applicant cannot provide this information about the reference product and the drug regulatory authority does not have access to these data or the data is protected under data exclusivity rights according to local regulations, *in vivo* studies should be performed.

6. For certain drug products, Bioavailability or Bioequivalence may be demonstrated by evidence obtained *in vitro* in lieu of *in vivo* Data

Regulatory authorities should waive the requirement for the submission of evidence obtained *in vivo* demonstrating the bioavailability of the drug product if the drug product meets one of the following criteria:

- a) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product manufactured at the same site for which the same manufacturer has obtained approval and the following conditions are met:
 - 1. The bioavailability of this other drug product has been demonstrated;

2. Both drug products meet an appropriate *in vitro* test approved by a drug regulatory authority and/or accepted reference pharmacopeias, or has demonstrated *in vivo*-*in vitro* correlation (e.g., correlation level A, etc.).
3. The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients. That is, the ratio of active ingredients and excipients between strengths is essentially the same.
4. The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met:
 - a) The bioavailability of the other product has been demonstrated;
 - b) Both drug products meet an appropriate *in vitro* test approved by the regulatory authority.
5. Regulatory authorities, for good cause, may require evidence of *in vivo* bioavailability or bioequivalence for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product. The Bioavailability and Bioequivalence Working Group strongly recommends that in the case of anti-retroviral drug products proof of pharmaceutical equivalence and bioequivalence be required to infer therapeutic equivalence.

7. In-Vitro Testing – New Paradigm

7.1 Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS)³ is a scientific framework for classifying drug substances (active ingredient) based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from Immediate Release (IR) solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

- Class 1: High Solubility - High Permeability
- Class 2: Low Solubility - High Permeability
- Class 3: High Solubility - Low Permeability
- Class 4: Low Solubility - Low Permeability

In addition, immediate-release solid oral dosage forms are classified as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a tool for drug development or post approval manufacturing changes to assist sponsors justify requests for bio waivers.

³ (FDA Guidance Waiver of *in vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System; <http://www.fda.gov/cder/guidance/3618fnl.htm>)

Observed *in vivo* differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution *in vivo*. However, when the *in vivo* dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of *in vivo* Bioavailability or Bioequivalence may not be necessary for drug products containing Class 1 drug substances, as long as the inactive ingredients (excipients) used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach can be used to justify bio waivers for highly soluble and highly permeable drug substances (i.e., Class 1) in immediate-release solid oral dosage forms that exhibit rapid *in vitro* dissolution using USP recommended test methods. The recommended methods for determining solubility, permeability, and *in vitro* dissolution are discussed below.

7.2 Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a bio waiver request. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

7.3 Permeability

The permeability class boundary is indirectly based on the extent of absorption (fraction of dose absorbed, non-systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfers across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., *in vitro* epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

7.3.1 Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract:

- (1) *in vivo* intestinal perfusion studies in humans;
- (2) *in vivo* or *in situ* intestinal perfusion studies using suitable animal models;
- (3) *in vitro* permeation studies using excised human or animal intestinal tissues; or
- (4) *in vitro* permeation studies across a monolayer of cultured epithelial cells.

In vivo or *in situ* animal models and *in vitro* methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by the efflux of drugs via membrane transporters such as P-glycoprotein (P-gp). When the efflux transporters are absent in these models, or their degree of expression is low compared to that in humans, there may be a greater likelihood of

misclassification of permeability class for a drug subject to efflux compared to a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques such as bi-directional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., Cyclosporine A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed *in vitro* efflux of a drug. For example, there may be fewer concerns associated with the use of *in vitro* methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) of a drug is demonstrated in humans.
- Lack of dependence of the measured *in vivo* or *in situ* permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) in the perfusion fluid.
- Lack of dependence of the measured *in vitro* permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 ml) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable *in vitro* cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For *in vivo* intestinal perfusion studies in humans, six model drugs are recommended. For *in vivo* or *in situ* intestinal perfusion studies in animals and for *in vitro* cell culture methods, twenty model drugs are recommended. Depending on the study's variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation between drug substances of low and high intestinal permeability attributes.

To demonstrate the suitability of a method, model drugs should represent a range of low (e.g., < 50%), moderate (e.g., 50 - 89%), and high (\geq 90%) absorption. Sponsors may select compounds from the list of drugs and/or chemicals provided in Attachment A or they may choose to select other drugs for which there is information available on the absorption mechanism and reliable estimates of the extent of drug absorption in humans.

After demonstrating suitability of a method and maintaining the same study protocol, it is not necessary to retest all selected model drugs for subsequent studies intended to classify a drug substance. Instead, a low and a high permeability model drug should be used as internal standards (i.e., included in the perfusion fluid or donor fluid along with the test drug substance). These two internal standards are in addition to the fluid volume marker (or a zero permeability compound such as PEG 4000) that is included in certain types of perfusion techniques (e.g., closed loop techniques). The choice of internal standards should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions). Whenever it is not feasible to follow this protocol, the permeability of internal standards should be determined in the same subjects, animals, tissues, or monolayers, following evaluation of the test drug substance. The permeability values of the two internal standards should not differ significantly between different tests, including those conducted to demonstrate suitability of the method. At the end of an *in situ* or *in vitro* test, the amount of drug in the membrane should be determined.

For a given test method with set conditions, selection of a high permeability internal standard with permeability in close proximity to the low/high permeability class boundary may facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

7.4 Dissolution

An immediate-release drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using U.S. Pharmacopeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

Under certain circumstances, product quality (manufacture under GMP's), Bioavailability and Bioequivalence can be documented using *in vitro* approaches (e.g., *in vitro* dissolution profiles). For highly soluble, highly permeable, rapidly dissolving, immediate release orally-administered drug products, documentation of Bioequivalence using an *in vitro* approach (dissolution studies) is appropriate based on the Biopharmaceutics Classification system.

This approach may also be suitable under certain circumstances in assessing Bioequivalence during the initial registration period, and in the presence of certain post-approval changes (SUPAC guidelines) to approved applications. Dissolution testing is also used to assess batch-to-batch quality, where the dissolution tests, with defined procedures and acceptance criteria, are used to allow batch release.

Dissolution testing is also used to:

1. Provide process control and quality assurance.
2. Assess whether further BE studies related to minor post-approval changes be conducted, where dissolution can function as a signal of bio-nonequivalence.

3. Assess batch-to-batch quality, where the dissolution tests, with defined procedures and acceptance criteria, are used to allow batch release.

In vitro dissolution characterization is encouraged for all product formulations investigated (including prototype formulations), particularly if *in vivo* absorption characteristics are being defined for the different product formulations. Such efforts may enable the establishment of an *in vitro-in vivo* correlation. When an *in vitro-in vivo* correlation or association is available the *in vitro* test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform *in vivo*.

It is recommended that in general the following information be included in the dissolution method development report for solid oral dosage forms.

For new drug products applications, and “Similar Products” already approved in the market before implementation of the bioequivalence and bioavailability requirements of the new health law.

4. The pH solubility profile of the drug substance.
5. Dissolution profiles (multiple data points, 0, 10, 15, 20, and 30 minutes) generated at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm) for U.S. Pharmacopoeia (USP) Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle)). A minimum of 12 dosage units should be evaluated.
6. Dissolution profiles generated on all strengths in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). using *U.S. Pharmacopoeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants are recommended.

It is also recommended that the sponsor select the agitation speed and medium that provides adequate discriminating ability, taking into account all the available *in vitro* and *in vivo* data.

For Generic Products:

For Immediate-Release Drug Products

It is recommended that dissolution profiles at multiple points using the appropriate USP method be submitted. If there is no USP method available, the regulatory authority's method for the reference drug product may be used if not under the period of data exclusivity protection. If the USP and/or regulatory authority methods are not available, a dissolution method development report can be submitted with proper validation of all methods used.

For Modified-Release Products

1. Dissolution profiles using the appropriate USP method (if available) may be submitted. If there is no USP method available, the regulatory authority's method for the reference drug product may be used if not under the period of exclusivity protection.
2. Profiles using at least three other dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) and water would be provided.

Three batches for both new drug applications and generic drug applications are used to set dissolution specifications for modified-release dosage forms, including extended-release dosage forms. In addition, bioavailability and bioequivalence studies in human volunteers are to be conducted in all modified release products.

8. Illustrative List of Products for which *in-vivo* BE Studies are not Necessary

- A. Injectable, ophthalmic and otic solutions – provided that the active and inactive ingredients are qualitatively and quantitatively the same as the reference listed drug (REFERENCE LISTED DRUG).
- B. Oral and topical solutions – provided that differences in inactive ingredients are characterized and do not affect the absorption of the active ingredient of the product.
- C. Immediate-release drug products with a determination of efficacy, which are not known to have bioproblems (see Section 3a). The regulatory authority may request *in vitro* dissolution testing for oral solid dosage forms. Examples include: Acetaminophen and codeine tablets, folic acid tablets, Hydrocortisone cream and ointment, Triamcinolone ointment, Cytarabine injectable, and dacarbazine injectable.
- D. Biopharmaceutics Classification System (BCS) class 1: Example: Metoprolol.

9. Food Effects

Food can change the bioavailability of a drug and can influence the Bioequivalence between test and reference products.

Food effects on bioavailability can have clinically significant consequences. Food can alter Bioavailability through various means, including:

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Food effects on Bioavailability are generally greater when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the

meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. The use of high-calorie and high-fat meals during food-effect bioavailability and fed bioequivalence studies is recommended.

Administration of a drug product with food may change the BA by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies.

Important food effects on BA are least likely to occur with many rapidly dissolving, immediate release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution.

However, for some drugs in this class, food can influence BA when there is a high first-pass effect, extensive adsorption, complexation, or instability of the drug substance in the GI tract. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of BE. For rapidly dissolving formulations of BCS Class I drug substances, food can affect C_{max} and the time at which this occurs (T_{max}) by delaying gastric emptying and prolonging intestinal transit time. However, it can be expected that the food effect on these measures to be similar for test and reference products in fed BE studies.

For other immediate-release drug products (BCS Class II, III, and IV) and for all modified released drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on formulation BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a fed BE study.

9.1 Immediate-Release Drug Products

1. For uncomplicated drugs in immediate-release dosage forms, bioequivalence must be demonstrated under fasted conditions. In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions:
 - When both test product and Reference Listed Drug are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I) (see footnote 3), or
 - When the Dosage and Administration section of the Reference Listed Drug label states that the product should be taken only on an empty stomach, or
 - When the Reference Listed Drug label does not make any statements about the effect of food on absorption or administration.

- When the Reference Listed Product label does not make any statements about the effect of food on absorption or administration.
- 2. For complicated drugs in immediate-release dosage forms, e.g., narrow therapeutic range drugs (drugs with a steep dose – response curve, critical drugs), highly toxic drugs and drugs known to have non-linear pharmacokinetics. Bioequivalence must be demonstrated under both fasted and fed conditions.
- 3. Non-linear drugs. Bioequivalence must be demonstrated under both fasted and fed conditions unless the non-linearity occurs after the drug enters the systemic circulation and there is no evidence that the product exhibits a food effect.
- 4. Drugs in modified-release dosage forms. BE must be demonstrated under both fasted and fed conditions.

9.2 Modified Release Products

In addition to a bioequivalence study under fasting conditions, a bioequivalence study under fed conditions should be conducted for all orally administered modified-release drug products.

9.3 Test Meal

It is recommended that food-effect bioavailability and fed bioequivalence studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report.

9.4 Administration

9.4.1 Fasted Treatments

Following an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 ml (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water may be allowed as desired, except one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

9.4.2 Fed Treatments

Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to the administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 ml

(8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water may be allowed as desired, except one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

10. Pharmacodynamic Studies

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products. These studies may become necessary if quantitative analysis of the drug and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurements of drug concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product, e.g., for topical products without an intended absorption of the drug into the systemic circulation.

If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies, and the principles of GCP (see WHO Guideline for GCP for Trials on Pharmaceutical Products) must be followed.

The following requirements must be recognized when planning, conducting, and assessing the results of a study intended to demonstrate equivalence by means of measuring pharmacodynamic drug responses.

- i. The response that is being measured should be a pharmacological or therapeutic effect that is relevant to the claims of efficacy and/or safety.
- ii. The methodology must be validated for precision, accuracy, reproducibility, specificity, and ruggedness.
- iii. 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 that give maximum or near-maximum effects. Investigation of dose-response relationships may be a necessary part of the design.
- iv. The response should be measured quantitatively under double blind conditions and be recorded in an instrument-produced or instrument-recorded fashion on a repetitive basis to provide a record of the pharmacodynamic events that are substitutes for plasma concentrations. In those instances where such measurements are not possible, recordings on visual analogue scales may be used. In other instances where the data are limited to qualitative (categorized) measurements, appropriate special statistical analysis will be required.
- v. Non-responders should be excluded from the study through prior screening. The criteria by which responders *versus* non-responders are identified must be stated in the protocol.
- vi. In instances where an important placebo effect can occur, comparison between pharmaceutical products can only be made by *a priori* consideration of the placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment in the design of the study.
- vii. The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of base-line conditions.

- viii. A crossover design may be used. Where this is not appropriate, a parallel group study design should be chosen.

In studies in which continuous variables could be recorded, the time course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations were measured, and parameters can be derived which describe the area under the effect-time curve, the maximum response and the time when maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are, in principle, the same as outlined for the bioequivalence studies. However, a correction for the potential non-linearity of the relationship between the dose and the area under the effect-time curve should be performed on the basis of the outcome of the dose-ranging study as mentioned above. However, it should be noted that the conventional acceptance range as applied for bioequivalence assessment is not appropriate (too large) in most of the cases but should be defined on a case-by-case basis and described in the protocol.

11. Model Drugs Suggested for Use in Establishing Suitability of a Permeability Method

The permeability of these compounds was determined based on data available to the FDA. Potential *internal standards* (IS) and *efflux pump substrates* (ES) are also identified.

Drug	Permeability Class
Antipyrine	High (Potential IS candidate)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (Potential IS candidate)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High (Potential ES candidate)
Amoxicillin	Low
Atenolol	Low
Furosemide	Low
Hydrochlorthiazide	Low
Mannitol	Low (Potential IS candidate)
Methyldopa	Low
Polyethylene glycol (400)	Low
Polyethylene glycol (1000)	Low
Polyethylene glycol (4000)	Low (Zero permeability marker)
Ranitidine	Low

12. References for Bioequivalence Testing Requirements

- A. United States Code of Federal Regulations, Title 21 (21 CFR 314 and 320):

21 CFR 314. 94(a) (7) Content and format of an abbreviated drug application – establishes the requirement for BE in ANDAs.

http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfrv5_02.html

(Click on 314, then on 314.94) Click on 320 for regulations on BA/BE)

21 CFR 320.1 provides definitions of BA/BE, drug product, pharmaceutical equivalents, pharmaceutical alternatives and BE requirement.

320.21 Requirements for submission of *in vivo* BA and BE data.

320.23 Basis for demonstrating *in vivo* BA or BE

320.24 Types of evidence to establish BA or BE

SOURCES

<http://www.fda.gov/cder/guidance/index.htm> :

Under Biopharmaceutics:

Guidance for Industry "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"

Food-Effect Bioavailability and Fed Bioequivalence Studies

[Waiver of *In vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System](#)

Under Chemistry:

[SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, *In vitro* Dissolution Testing, and *In vivo* Bioequivalence Documentation](#)

[SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum](#)

[SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls; *In vitro* Dissolution Testing and *In vivo* Bioequivalence Documentation](#)

3. Health Canada's Guideline on Preparation of DIN Submissions (February 22, 1995)
<http://www.hc-s.gc.ca/hpb-dgps/therapeut/htmleng/guidemain.html#PrepDIN>

4. The WHO document (1999) entitled "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: a Manual for Drug Regulatory Authorities."

II. REGIONAL CONSIDERATIONS⁴

1. IMPLEMENTATION STRATEGIC FRAMEWORK

The current requirements for BE studies were compared among the USA, Canada and 8 Latin American countries with information available as of March 2004: Argentina (Arg), Brazil (Bra), Chile (Ch), Colombia (Col), Costa Rica (Cor), Cuba (Cu), Mexico (Mex) and Venezuela (Ven). The API list published in the WHO Report Series No. 863 (1996) was used as the Reference List for this comparison. It was used only for orally administered API, due to the higher probability for bioavailability problems.

The list for each country needs to be exhaustive because the list takes into account only products with expired patents, and countries have different legislations. Countries may require BE studies for drugs that are not in the reference list. The results are presented in Table I.

Table I. Active Pharmaceutical Ingredient subject to BE study requirement in different countries in the American Region.

Active Pharmaceutical Ingredient	Argentina	Brazil	Canada	Chile ⁶	Costa Rica	Cuba	Colombia	USA	Mexico	Venezuela	Total Countries
Acetazolamide		X	X			X		X			4
Folic Acid + Ferrous Sulfate			X								1
Nalidixic Acid			X			X		X			3
Valproic Acid	X	X	X	X	X	X	X	X	X	X	10
Albendazole			0					0	X		1
Allopurinol		X	X			X		X			4
Amiloride			X					X			2
Aminophylline (See Theophylline)											
Amitriptyline		X	?					X	X		3
Amoxicillin			X					X	X		3
Atenolol		X	X					X	X		4
Azathioprine			X	X		X		X	X		5
Biperiden			X			X		X	X		4
Captopril			X					X	X		3
Carbamazepine	X	X	X	X	X	X	X	X	X	X	10
Carbidopa (See Levodopa)											
Cyclosporine	X	X	X	X	X	X	X	X	X	X	10
Cimetidine			X					X			2
Ciprofloxacin			X			X		X			3
Clofazimine			0					X			1
Clomiphene			X			X		X	X		4
Clomipramine			X					X			2

⁴ Prepared by Dr. Ricardo Bolaños, Physician-Pharmacist, MD, PhD (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Argentina); Dr. Regina Pezoa, PhD, Pharmaceutical Chemist (Instituto de Salud de Chile); Dr. Irene Gonçalves, Pharmaceutical Chemist (Instituto de Salud de Venezuela).

⁶ Compendium Suisse de Medicaments. Document. Basilea, 1996.

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Active Pharmaceutical Ingredient	Argentina	Brazil	Canada	Chile *	Costa Rica	Cuba	Colombia	USA	Mexico	Venezuela	Total Countries
Chloramphenicol			?					X			1
Chlorpromazine			?					X			1
Cloxacillin			?					X			1
Co-Trimoxazole			X			X		X	X		4
Dapsone			?					X			1
Dexamethasone		X	?					X	X		3
Diazepam			X					X			2
Diethylcarbamazine			0					X			1
Digoxine	X	X	?	X	X				X	X	6
Doxycycline		X	X			X		X	X		5
Erythromycine			?					X			1
Spirolactone		X	X	X		X		X			5
Ethambutol			X			X		X			3
Ethinylestradiol (Associated)			X	X		X		X		X	5
Etoposide		X	X			X		X		X	5
Ethosuximide	X	X	?					X			3
Phenytoin	X	X	X	X	X	X	X	X	X	X	10
Phenoxymethylpenicillin			0					X			1
Phytomenadione			X					X			2
Fludrocortisone			X			X		X			3
Calcium folinate			X					X			2
Furosemide			X	X		X		X	X		5
Griseofulvin		X	?	X				X			3
Haloperidol			X					X	X		3
Hydrochlorothiazide		X	?	X				X			3
Dextran Iron								X			1
Ibuprofen			X					X			2
Indometacin		X	X					X	X		4
Isoniazid + Rifampicin			0					X			1
Dinitrate Isosorbide		X	X	X		X		X	X	X	7
Ketoconazole			X	X		X		X	X		5
Levamisole			X			X		X			3
Levodopa + IDD	X	X	X					X	X		5
Levonorgestrel			X					X		X	3
Levothyroxine			?		X					X	2
Lithium Carbonate	X	X	X	X		X		X		X	7
Mebendazole			X			X		X	X		4
Medroxyprogesterone (Depot)			?					X			1
Mefloquine			X			X		X			3
Mercaptopurine		X	X			X		X		X	5
Methyldopa			?					X			1
Metoclopramide			X					X	X		3
Methotrexate		X	X	X		X		X	X	X	7
Metronidazole (Tablet)			X	X		X		X	X		5
Niclosamide								X			1
Nifedipine			X	X		X		X	X	X	6

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Active Pharmaceutical Ingredient	Argentina	Brazil	Canada	Chile *	Costa Rica	Cuba	Colombia	USA	Mexico	Venezuela	Total Countries
Nystatin								X			1
Nitrofurantoin			?					X			1
Norethisterone			X					0		X	2
Oxamniquine			0					X			1
Oxcarbazepine (not listed)	X	X					X			X	4
Paracetamol			X					0	X		2
Penicillamine			X					X			2
Piperazine			(-)					X			1
Pyrantel (Suspension)			0					X			1
Pyrazinamide			X			X		X			3
Pyridostigmine	X		X					X			3
Pyrimethamine (+Sulfadoxine)			X			X		X	X		4
Praziquantel			0					X	X		2
Prednisolone (Tablet)		X	?					X			2
Procainamide		X	X			X		X		X	5
Procarbazine			X			X		X	X		4
Promethazine			?					X			1
Propylthiouracil			?					X			1
Propranolol		X	X	X		X		X	X		6
Quinidine	X	X	?					X	X	X	5
Quinine			?					(-)	X		1
Rifampicin			X			X		X			3
Salbutamol (Tablet)		X	X			X		X	X		5
Sulfadoxine (See Piracetam.)											
Sulfasalazine			X	X		X		X			4
Tamoxifen			X	X		X		X	X	X	6
Theophylline	X	X	?	X				X		X	5
Tetracycline			?					X	X		2
Tolbutamide	X	X	X	X		X		X	X	X	8
Verapamil	X	X	X		X	X		X	X	X	8
Warfarine	X	X	?					X		X	4
TOTAL	15	32	60 23*	22*	7	40	5	88	39	23	

References:

*: In process

X: Bioequivalence Studies

+f: Pharmacodynamic Studies

+c: Clinical Studies.

-: *In-vivo* studies are not required.

¿: Decision pending on *in-vivo* studies.

O: No information is available.

No data: The API is not cited in country list.

Comments:

- Out of the 96 active ingredients, only 4 active ingredients commonly require BE studies in all 10 countries: Valproic Acid, Carbamazepine, Cyclosporine and Phenytoin. All of them are considered high health risks.
- Twenty-two active ingredients require BE studies: 20 in USA and two in Mexico.
- The country with less number of active ingredient with BE study requirements is Colombia (only 5) followed by Costa Rica (only 7).
- Chile is in the process of establishing that requirement for all active ingredients that require BE studies.
- Most countries require BE studies on drugs used for high health risk.
- The wide divergence observed among countries in their requirement for BE studies, with the exception of the USA and Canada, which are quite similar in their requirements, indicates the need to continue working toward harmonization.

III. PHARMACEUTICAL PRODUCTS CRITERIA USED IN HEALTH RISK SITUATION

Health Risk Categories

From the report of a meeting of experts on bioequivalence was held in Caracas, Venezuela, in January 1999. In the last paragraph of the Conclusions, specifically point 3), establishes that whenever countries cannot totally apply the (bioequivalence) standard, it is recommended that the same be gradually applied.

Due to different operational and administrative reasons, the countries of the Region cannot fully apply the standard requirement of BE studies for all the products that require it.

This situation brings up a matter of significant importance because the inability to fully apply the standard demands a *rational* selection of active ingredients on which bioequivalence studies should be required.

The selection of active ingredients for which BE studies should be required is a public health decision and as such should take into account the Benefit/Risk ratio of the same.

This situation leads to the Health Risk concept, that is, which active ingredients require rigorous handling to prevent public health problems. One way of doing this is to take into account which active ingredients, because of their pharmacological characteristics, should be controlled through blood determinations.

Definition

As operational definition, the Health Risk concept should be established in the context of the problems of bioequivalence. For this purpose it would be reasonable to establish what are the health consequences when a drug is outside (under or above) the therapeutic window (the margin determined by the non-toxic maximum concentration and the effective minimum concentration).

Thus, in relating the therapeutic window (the margin whose limits are the non-toxic maximum and effective minimum concentrations) and adverse effects of the drugs, three risk levels can be established, as described below.

HIGH HEALTH RISK: This is the probability of the appearance of threatening complications of the disease for the life or the psychophysical integrity of the person and/or serious adverse reactions (death, patient hospitalization, extension of the hospitalization, significant or persistent disability, disability or threat of death), when the blood concentration of the active ingredient is not within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 3 (three).

INTERMEDIATE HEALTH RISK: This is the probability of the appearance of non-threatening complications of the disease for the life or the psychophysical integrity of the person and/or adverse reactions, not necessarily serious, when the blood concentration of the active ingredient is not found within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 2 (two).

LOW HEALTH RISK: This is the probability of the appearance of a minor complication of the disease and/or mild adverse reactions, when the blood concentration of the active ingredient is not within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 1 (one).

Methodology Proposal to Harmonize the Selection of Active Ingredients for which Bioequivalence Studies should be Required

While there are other factors to be considered such as the physicochemical and pharmacokinetic parameters, from the standpoint of Public Health the most important element to take into account is the Health Risk. Table II lists the active ingredients classified in accordance with their Health Risk and the established scores.

Table II. – Classification of Active Ingredients According to their Health Risk.

Active Ingredient	Health Risk
Valproic Acid	3
Carbamazepine	3
Cyclosporine	3
Phenytoin	3
Tolbutamide	3
Verapamil	3
Lithium Carbonate	3
Digoxin	3
Procainamide	3
Quinidine	3
Theophylline	3
Oxcarbazepine*	3
Warfarine	3
Ethambutol	3
Ethosuximide	3
Griseofulvin	3
Methotrexate	2
Propranolol	2
Tamoxifen	2
6-mercaptopurine	2
Azathioprine	2
Doxycycline	2
Spironolactone	2
Ethinylestradiol	2
Etoposide	2
Furosemide	2
Ketoconazole	2
Levodopa + Inhib. DDC	2
Metronidazole	2
Salbutamol, sulfate	2
Atenolol	2

Biperiden	2
Cyclophosphamide	2
Co-Trimoxazole	2
Indometacin	2
Pyrimethamine	2
Procarbazine	2
Amitriptyline	2
Amoxicillin	2
Ciprofloxacin	2
Flucytosine	2
Fludrocortisone	2
Haloperidol	2
Hydrochlorothiazide	2
Levonorgestrel	2
Metoclopramide	2
Piridostigmina	2
Rifampicin	2
Amiloride	2
Cimetidine	2
Clomipramine	2
Levotiroxina	2
Norestisterona	2
Paracetamol	2
Penicillamine	2
Tetracycline	2
Clofazimine	2
Chloramphenicol	2
Clorpromazine	2
Dapsone	2
Diethylcarbamazine	2
Erythromycin	2
Isoniazid	2
Methyldopa	2
Nitrofurantoin	2
Oxamniquine	2
Piperazine	2
Promethazine	2
Propylthiouracil	2
Quinine	2
Isosorbide Dinitrate	1
Nifedipine	1
Acetazolamide	1
Allopurinol	1
Clomifene	1
Mebendazole	1
Sulfasalazine	1
Nalidixic Acid	1

Captopril	1
Dexamethasone	1
Levamisole	1
Mefloquine	1
Pyrazinamide	1
Diazepam	1
Phytomenadione	1
Calcium Folate	1
Ibuprofen	1
Praziquantel	1
Cloxacillin	1
Phenoxymethylpenicillin	1
Folic Acid + Ferrous Sulfate	1
Niclosamide	1
Nystatin	1
Pirantelo	1
Aminophylline (see Theophylline)	
Sulfadoxine (See Pirimetam.)	

Having considered the *situation observed* in the countries of the Region, it was decided to select a Weighted Model in which both aspects were taken into account: Health Risk and Observed Reality, but giving a different weight to each. Thus, the following Model emerges:

$$\text{Total Score} = (\text{Health Risk} \times 3) + (\text{No. of countries that require studies} \times 1).$$

Health Risk: Three points were assigned to High Health Risk, 2 points to Intermediate Health Risk and 1 point to Low Health Risk.

Taking Phenytoin as an example, the following is obtained:

Health Risk: High (3 points)

No. of countries in which bioequivalence studies are required: 10

Total Score = (3 x 3) + (10 x 1) = 19 points.

Table III shows the order of the corresponding scores for each analyzed active ingredient applying the proposed weighted model.⁶ The Table is based on the list of active ingredients used as reference and the situation observed in various countries of the Region (see Table I).

Table III – Active Ingredients Ranked by Score

DRUG	HEALTH RISK	WEIGHT	WEIGHTED RISK	COUNTRY REQUIREMENT	WEIGHST	WEIGHTED REQUIREMENT	TOTAL SCORE
Valproic Acid	3	3	9	10	1	10	19
Carbamazepine	3	3	9	10	1	10	19
Cyclosporine	3	3	9	10	1	10	19
Phenytoin	3	3	9	10	1	10	19
Tolbutamide	3	3	9	8	1	8	17
Verapamil	3	3	9	8	1	8	17
Lithium carbonate	3	3	9	7	1	7	16
Digoxin	3	3	9	6	1	6	15
Procainamide	3	3	9	5	1	5	14
Quinidine	3	3	9	5	1	5	14
Theophylline	3	3	9	5	1	5	14
Oxcarbazepine*	3	3	9	4	1	4	13
Warfarine	3	3	9	4	1	4	13
Methotrexate	2	3	6	7	1	7	13
Ethambutol	3	3	9	3	1	3	12
Ethosuximide	3	3	9	3	1	3	12
Griseofulvin	3	3	9	3	1	3	12
Propranolol	2	3	6	6	1	6	12
Tamoxifen	2	3	6	6	1	6	12
6-mercaptopurine	2	3	6	5	1	5	11
Azathioprine	2	3	6	5	1	5	11
Doxycycline	2	3	6	5	1	5	11
Spirolactone	2	3	6	5	1	5	11
Ethinylestradiol	2	3	6	5	1	5	11
Etoposide	2	3	6	5	1	5	11
Furosemide	2	3	6	5	1	5	11
Ketoconazole	2	3	6	5	1	5	11
Levodopa + Inhib. DDC	2	3	6	5	1	5	11
Metronidazole	2	3	6	5	1	5	11
Salbutamol, sulfate	2	3	6	5	1	5	11
Atenolol	2	3	6	4	1	4	10
Biperiden	2	3	6	4	1	4	10
Cyclophosphamide	2	3	6	4	1	4	10
Co-Trimoxazole	2	3	6	4	1	4	10
Dinitrate of isosorbide	1	3	3	7	1	7	10
Indometacin	2	3	6	4	1	4	10
Pyrimethamine	2	3	6	4	1	4	10
Procabazine	2	3	6	4	1	4	10
Amitriptyline	2	3	6	3	1	3	9
Amoxicillin	2	3	6	3	1	3	9
Ciprofloxacin	2	3	6	3	1	3	9
Flucytosine	2	3	6	3	1	3	9
Fludrocortisone	2	3	6	3	1	3	9
Haloperidol	2	3	6	3	1	3	9
Hydrochlorothiazide	2	3	6	3	1	3	9
Levonorgestrel	2	3	6	3	1	3	9

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Metoclopramide	2	3	6	3	1	3	9
Nifedipine	1	3	3	6	1	6	9
Piridostigmina	2	3	6	3	1	3	9
Rifampicin	2	3	6	3	1	3	9
Amiloride	2	3	6	2	1	2	8
Cimetidine	2	3	6	2	1	2	8
Clomipramine	2	3	6	2	1	2	8
Levotiroxina	2	3	6	2	1	2	8
Norestisterona	2	3	6	2	1	2	8
Paracetamol	2	3	6	2	1	2	8
Penicillamine	2	3	6	2	1	2	8
Tetracycline	2	3	6	2	1	2	8
Acetazolamide	1	3	3	4	1	4	7
Allopurinol	1	3	3	4	1	4	7
Clofazimine	2	3	6	1	1	1	7
Clomifene	1	3	3	4	1	4	7
Chloramphenicol	2	3	6	1	1	1	7
Clorpromazine	2	3	6	1	1	1	7
Dapsone	2	3	6	1	1	1	7
Diethylcarbamazine	2	3	6	1	1	1	7
Erythromycin	2	3	6	1	1	1	7
Isoniazid	2	3	6	1	1	1	7
Mebendazole	1	3	3	4	1	4	7
Methyldopa	2	3	6	1	1	1	7
Nitrofurantoin	2	3	6	1	1	1	7
Oxamniquine	2	3	6	1	1	1	7
Piperazine	2	3	6	1	1	1	7
Promethazine	2	3	6	1	1	1	7
Propylthiouracil	2	3	6	1	1	1	7
Quinine	2	3	6	1	1	1	7
Sulfasalazine	1	3	3	4	1	4	7
Nalidixic Acid	1	3	3	3	1	3	6
Captopril	1	3	3	3	1	3	6
Dexamethasone	1	3	3	3	1	3	6
Levamisole	1	3	3	3	1	3	6
Mefloquine	1	3	3	3	1	3	6
Pyrazinamide	1	3	3	3	1	3	6
Diazepam	1	3	3	2	1	2	5
Phytomenadione	1	3	3	2	1	2	5
Calcium Folate	1	3	3	2	1	2	5
Ibuprofen	1	3	3	2	1	2	5
Praziquantel	1	3	3	2	1	2	5
Cloxacillin	1	3	3	1	1	1	4
Phenoxymethylpenicillin	1	3	3	1	1	1	4
Folic Acid + Ferrous Sulfate	1	3	3	1	1	1	4
Nicosamide	1	3	3	1	1	1	4
Nystatin	1	3	3	1	1	1	4
Pirantelo	1	3	3	1	1	1	4
Aminophylline (see Theophylline)							
Sulfadoxine (See Piracetam.)							

* Not in the Reference List

From the analysis of Table III, it is apparent that there is a clear coincidence regarding the ranking of active ingredients by risk only and with the weighted model, taking note that the requirement aggregate in countries of the Region acts as validation factor.

For purposes of proceeding with the progressive selection and using statistical criteria, the use of the percentile⁷ is recommended (prior ranking of the active ingredients per total score, from higher to lower), in accordance with the following formula:

$$\text{Percentile } X = X (n + 1) / 100$$

The Percentile is a “measure of position” of a series of data ranked in ascending order or from higher to lower and consists of dividing the series of data in 100 equal parts. Thus, the number of percentile is equivalent to the percentage.

For example, Percentile 10 indicates that 10% of the value of the data series under analysis is below the value obtained in the position resulting from the formula, for data ranked in ascending order.

In short, the result of the formula indicates the “position” (for example, line 20) of the ranked data. the value of the variable is found in that position, that is, the result of the formula does not correspond to the value of the variable, but to the position in which such value is found in the ranked series of data.

Example:

Position	Value of the variable
1	19
2	18
3	17
4	16
5	15
6	14
7	13
8	12
9	11
10	10

Percentile 20 will be, in accordance with the previously expressed formula:

$$N = 10 \text{ (total number of observations).}$$

$$\text{Percentile } 20 = 20 (10 + 1) / 100 = 220 / 100 = 2.2 = 2 \text{ (rounded).}$$

Going to Position 2 (left column), it is observed that the value of the variable (right column) is 18. It is concluded that 20% of the values, are 18 or more (from higher to lower ranking).

⁷ Each country can adopt the methodology it considers most adequate.

IV. ANNEXES: Glossary of Terms.

(NEEDS TO BE COMPARED WITH WHO DEFINITIONS)

Bioavailability

This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the action site. For drug products not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the action site.

Bioequivalence

Means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional rate difference (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the achievement of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

Bioequivalence Requirement

Means a requirement imposed by the Regulatory Authority for *in vitro* and/or *in vivo* testing of specified drug products that must be satisfied as a condition of marketing.

Bioequivalent Drug Products

This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. The Regulatory Authorities describes one set of conditions under which a test and reference listed drug shall be considered bioequivalent: the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the achievement of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be appropriate.

Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo*

bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

Bulk Drug Substance

Any substance represented for use in a drug and when in the manufacturing, processing, or packaging of a drug becomes an active ingredient of a finished dosage form. This does not include intermediates used in the synthesis of such substances.

Critical 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 adverse drug reactions that may be persistent, irreversible, slowly reversible, or life threatening events.

Distributor

Means the distributor of a product under a custom or own label. The product is manufactured and labeled by a registered establishment.

Drug Product

Means a finished dosage form, e.g., tablet, capsule, or solution that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.

Dosage Form

The form of the completed pharmaceutical product, e.g. tablet, capsule, injection, elixir, suppository.

Drug

Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Drug Master File

A drug master file (DMF) is a master file that provides a full set of data on an API. In some countries, the term may also comprise data on an excipient or a component of a product such as a container.

Drug Regulatory Authority

A national body that administers the full spectrum of drug regulatory activities, including at least all of the following functions:

- Marketing authorization of new products and variation of existing products;
- Quality control laboratory testing;
- Adverse drug reaction monitoring;
- Provision of drug information and promotion of rational drug use;
- Good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers, and distribution channels;
- Enforcement operations;
- Monitoring of drug utilization.

Essential drugs

Essential drugs are those that satisfy the health care needs of the majority of the population. As indicated by the Expert Committee on the Use of Essential Drugs (5), each country may generate its own list of essential drugs.

Excipient

Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

Finished Product

A product that has undergone all stages of production, including packaging in its final container and labeling.

Formulation

The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

Generic Products

Generic products may be marketed either under the approved non-proprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the innovator products. Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for active pharmaceutical ingredients (APIs). The term *generic product* has somewhat different meanings in different jurisdictions. Use of this term is therefore avoided as much as possible, and the term *multisource pharmaceutical product* (see below) is used instead.

Importer/Broker

Firm that arranges for the importation of foreign articles and who usually guarantees proper custody and handling of the shipment in addition to maintaining the records of importation. Importers who are also the initial distributors of medical devices are required to register with the Center for Devices and Radiological Health.

Immediate Release Dosage Form

A dosage form that is intended to release the entire active ingredient on administration with no enhanced, delayed or extended release effect.

Innovator Pharmaceutical Product

Means a pharmaceutical product that was first authorized for marketing (normally as a patented drug) based on documentation of its safety, efficacy and pharmaceutical quality (according to contemporary regulatory requirements). When drugs have been available in the marketplace for many years, it may not be possible to identify an innovator pharmaceutical product. In these cases an innovator product may be defined as a medicinal authorized and marketed on the basis of a full dossier i.e., including chemical, biological, pharmacological-toxicological and clinical data.

Innovator Pharmaceutical Product

The innovator pharmaceutical product is generally one that was first authorized for marketing (normally as a patented product) based on documentation of its efficacy, safety and quality (according to requirements at the time of the authorization). When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.

Interchangeability

An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

Multisource and Single-Source Drug Products

In most instances it refers to those pharmaceutical equivalents available from more than one manufacturer that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

Narrow Therapeutic Index

It means that there is less than a 2-fold difference in median lethal dose (LD 50) and median effective doses (ED 50) values, or have less than 2-fold difference in the minimum toxic concentration and minimum effective concentration in the blood; steep dose response.

Pharmaceutical Product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Note: In many countries in Latin America multisource drug products are referred to as "productos similares" and are marketed under an approved new brand proprietary. However, when they are marketed under the non-proprietary name (unbranded), are usually known as "generic products." These products cannot be considered interchangeable until appropriate evidence has been submitted to show interchangeability.

Pharmaceutical Equivalents

Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutical Alternatives

Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Data are generally not available for FDA to make the determination of tablet to capsule bioequivalence. Different dosage forms

and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.

Reference Product

Means the pharmaceutical product with which the “new” product is intended to be interchangeable in clinical practice. The reference product is usually the innovator’s product for which safety, efficacy and quality has been documented.

Note: When the innovator product is not available, the product that is the market leader may be used as a reference product provided it passes the regulatory requirements for bioavailability, *in vitro* dissolution, and other appropriate tests and that safety, efficacy and quality has been properly documented. A reference product must be an innovator product.

Therapeutic Equivalents

Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

The FDA classifies as therapeutically equivalent those products that meet the following general criteria:

- (1) they are approved as safe and effective;
- (2) they are pharmaceutical equivalents in that they
 - (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration,
 - (b) meet compendial or other applicable standards of strength, quality, purity, and identity;
- (3) they are bioequivalent in that
 - (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or
 - (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard;
- (4) they are adequately labeled;
- (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.

The concept of therapeutic equivalence, as used in developing the List, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., propoxyphene hydrochloride vs. pentazocine hydrochloride for pain treatment).

Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder’s drug product even if the application holder’s drug product is single source or

coded as non-equivalent (e.g., BN). Also, distributors or re-packagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for non-approved, off-label indications.

The FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.