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RED PANDRH

PAN AMERICAN NETWORK ON DRUG REGULATORY HARMONIZATION

WORKING GROUP ON BE

FRAMEWORK FOR IMPLEMENTATION OF EQUIVALENCE REQUIREMENTS FOR PHARMACEUTICAL PRODUCTS

Proposal to be submitted to the V Conference for Drug Regulatory Harmonization

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Contents

PRESENTATION

This document has been prepared by the Working Group on BE (WG/BE) of the Pan American Network on Drug Regulatory Harmonization (PANDRH) with the objectives of contributing to Drug Regulatory Authorities (DRAs) of the Region of the Americas and recommending harmonized criteria concerning the equivalence of drugs. The document consists of two parts.

The first part refers to **scientific criteria for implementing therapeutic equivalence**. In developing this part of the document, the WG/BE analyzed in detail the WHO document "Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability,"[2] prepared by the WHO Expert Committee for Pharmaceutical Preparations. The WG/BE decided unanimously to endorse the document and to promote its implementation in the Americas. This document recommends that the 192 WHO Member States tend to the demonstration of therapeutic equivalence and declaration of interchangeability of all multisource products. Also, basic criteria should be established for performing in vivo and in vitro studies to ensure the interchangeability of multisource products without compromising the safety, quality, and efficacy of the pharmaceutical products. The WG/BE also endorsed the criteria of the Biopharmaceutical Classification System (BCS) for waivers of in vivo studies.[3]

The second part of the document refers to the **strategic framework for the implementation of studies of drug equivalence.** This part describes the reality of the Region of the Americas, serving the special features of Latin America and considering that most of the multisource products (products of different origin and/or manufacturers) marketed in the region were approved in accordance with the drug registration requirements of each country at the time of their registration. The gradual implementation of equivalence demonstration requirements (BE) through in vivo studies based on the health risk of the products is recommended, and this document describes the methodology, which complements the biowaivers outlined in the BCS of the WHO guidelines. Furthermore, cases are presented for which there are no valid or unified products of reference. Finally, a flow chart is presented that integrates the requirements of meeting good manufacturing practices (GMP), the validity and reliability of the products of reference, and the concept of gradualism in prioritization according to health risk and biowaivers.

I. BACKGROUND OF PANDRH AND WG/BE

The Pan American Network on Drug regulatory Harmonization (PANDRH) was established in 1999 during the Second Pan American Conference on Drug Regulatory Harmonization. Participants at these Pan American Conferences include national regulatory authorities (NRAs) of all PAHO Member States, representatives from the five subregional economic integration blocs in the Region, the industry, academia, and non-governmental organizations (NGOs). PANDRH is a regional strategic effort to improve the quality, safety, and efficacy of the pharmaceutical market in the Region. Its work is based on the Pan Americanism spirit that is carried out in PAHO/WHO continental activities and is supported by Resolution CDR 11 of the 42nd PAHO/WHO Directive Council.

[2]WHO Technical Report Series 937. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 7, Pp. 347–390. 2006.
[3]Idem. Annex 8, p. 391. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines, immediate-release, solid oral dosage forms. Page 391-437

PANDRH has four components: the Pan American Conference (highest decision-making level), the Steering Committee, the working groups, and the Secretariat. Operational guidelines, norms, and regulations are developed by the working groups, which are made up primarily of experts from NRAs. At present, PANDRH has 12 working groups in different areas of drug harmonization: Good Manufacturing Practices, Bioequivalence and Bioavailability, Registration Requirements, Good Clinical Practices (GCPs), Drug Counterfeiting, Drug Classification, Drug Promotion/Advertisement, Good Laboratory Practices (including the External Quality Control Program), Vaccines, Medicinal Plants, Pharmacopoeia, and Pharmacovigilance.

Although the WG on Bioequivalence/Bioavailability was formally established in November 1999, the First Pan American Conference (1997) recommended to start working on BE/BD as an urgent second priority-subject for regulatory harmonization, being the first priority, GMPs and followed by CGP and combating Drug Counterfeiting. Following that recommendation, in January 1999, PAHO sponsored a meeting of experts on bioavailability-bioequivalence in Caracas, Venezuela,[4] to analyze the implementation of BE studies and requirements in the Region of the Americas. Expert participants developed several recommendations, among them the need for countries to implement BE studies gradually to ensure interchangeability of pharmaceutical products.

A report of the expert meeting was presented at the Second Pan American Conference. Conference participants also identified bioequivalence as a second priority and established a Bioequivalence Working Group (WG/BE) with the following responsibilities:

1) Development of a set of scientific criteria for bioequivalence-bioavailability testing of generic drug products;
2) Implementation of technical educational seminars on BE; and
3) Follow-up on the implementation of BE testing in the Region.

The recommendations of PANDRH with regard to the implementation strategy in the Region were outlined in 1999, with the following basic concepts:

- Ensure the efficacy, safety, and quality of all products on the market;
- Employ in vivo and in vitro methods for demonstrating therapeutic equivalence;
- Apply health high-risk criteria to set priorities; and
- Apply the criteria of gradual implementation of BE studies according to the availability of human resources, installations, and infrastructure to conduct the studies and to evaluate the registration applications.

Within this context, Dr. Salomon Stavchansky (from the University of Texas) and Dr. Ricardo Bolaños, (from Argentina's National Administration of Medications, Food and Medical Technology (ANMAT)), both members of the WG/BE, assumed the tasks of developing draft proposals. Dr. Stavchansky developed scientific criteria for bioequivalence testing (in vivo and in vitro) and for waivers of in vivo testing of generic products. Dr. Bolaños developed a strategy proposal for countries to promote the harmonization process through the requirements of BE studies. The document would describe when BE in vivo studies are necessary and not necessary and would describe when pharmaceutical products are considered to be equivalent without the need for further documentation. As planned, the draft of the document

[4]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.

was presented at the Fourth Pan American Conference on Drug Regulatory Harmonization in March 2005, where it was recognized that the document is an advancement in the application of studies of BE in the Region. The Conference also recommended that the document be submitted for discussion during the coming year to allow a review of aspects such as biowaivers and biopharmaceutical classifications, among others. It was also recommended that the WG/BE complete the document and present the final version at the next Conference for endorsement by countries in the Region.[5]

At the same Conference, the PANDRH WG/BE presented its mission statement, which was modified by the WG as follows: "The working group should contribute to harmonized bioequivalence criteria to *promote* the interchangeability of pharmaceutical products in the Americas"[6]

The Conference also approved the following objectives for the WG/BE:

1. To develop scientifically based criteria for products requiring and not requiring in vitro and/or in vivo BE studies;
2. To develop prioritized lists of pharmaceutical products for which in vivo BE studies are necessary;
3. To develop a list of pharmaceutical products for which in vivo BE studies are not necessary;
4. To develop a list of comparators for BE studies to be used in the Region of Americas;
5. To formulate recommendations and guidelines for the interpretation, evaluation, and application of the scientific principles of BE;
6. To promote and develop educational training activities in the countries of the Americas on the application of BE principles;
7. To promote implementation of BE of pharmaceutical products in the Americas;
8. To modify the training programs to incorporate and exchange the regulatory experiences gained during the execution of studies in the Americas; and
9. To develop a set of indicators to evaluate the implementation of BE studies in the Americas.[7]

While implementing national seminars to discuss the issue of BE, the WG/BE reviewed in detail the documents of the WHO Expert Committee in Pharmaceutical Preparations. After reviewing several national and international documents, the WG/BE decided to propose adoption for the Americas of the WHO document "Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability" and to center the regional proposal of the PANDRH in the strategies of implementation of BE studies conducted in the Region.

[5]http://www.paho.org/english/ad/ths/ev/pandrh_conclusions_recommendations-ivconference.pdf.

[6]Minutes of the VI WG/BE Meeting, August 2005, Panama. See http://www.paho.org/english/ad/ths/ev/been-6thmeeting.pdf.

[7]http://www.paho.org/english/ad/ths/ev/be-obj-engl.pdf.

II. SCIENCE-BASED BE CRITERIA

1. Introduction

As indicated above, the PANDRH WG/BE decided to endorse the document prepared by WHO since that document responds to the principles that the WG/BE was studying for the Region. It should be pointed out that principles for the implementation of studies of equivalence are also found in other WHO documents that were reviewed by the WG/BE, among them:

- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 7. pag 347-390. WHO. 2006. WHO Technical Report Series 937

- Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 8. Pag 391-437. WHO Technical Report Series 937

- Additional Guidance for organization performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 9 Pag 439-461

- Revision/update of the Guidance on the selection of Comparator pharmaceutical products for equivalence assessment of interchangeable Multisource (Generic) products

The WHO document recommends that the 192 Member States seek demonstration of therapeutic equivalence and declaration of interchangeability of all multisource products. At the same time, they should establish basic criteria for performing in vivo and in vitro studies in order to ensure the interchangeability of multisource products without compromising the safety, quality, and efficacy of pharmaceutical products, considering the criteria for waivers of in vivo studies based on the BCS.[8] It is important to note that waivers based on BCS are not waivers from establishing bioequivalence, but a waiver of conducting in-vivo studies.

The WHO document also states that the science-based criteria for bioequivalence are intended to provide recommendations to sponsors on the requirements for approval of multisource (generic) pharmaceutical products in their respective countries. Appropriate in vivo and in vitro requirements are provided to ensure interchangeability of multisource pharmaceutical products without compromising the safety, quality, and efficacy of the products.

The WHO guidelines also state that national health and drug regulatory authorities should ensure that all pharmaceutical products subject to their control conform to acceptable standards of safety, efficacy, and quality and that all premises and practices employed in the manufacture, storage, and distribution of these products comply with GMP standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end user.

In a given country, all pharmaceutical products, including multisource products, should be used only after approval has been granted by local authorities. Regulatory

[8]Idem. Annex 8, p. 391. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms.

authorities should require documentation of multisource pharmaceutical products to meet the following: GMP, quality control specifications, and pharmaceutical product interchangeability.[9]

2. Suitable Methods to Assess Equivalence

The WHO document states that *multisource pharmaceutical products must be shown, either directly or indirectly, to be therapeutically equivalent to the comparator product in order to be considered interchangeable. Suitable test methods to assess equivalence are:*

> *(a) comparative pharmacokinetic studies in humans, in which the active pharmaceutical ingredient and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures, such as AUC and C_{max} that are reflective of the systemic exposure;*
> *(b) comparative pharmacodynamic studies in humans;*
> *(c) comparative clinical trials; and*
> *(d) comparative in vitro tests.*[10]

The applicability of each of these four modalities is discussed in different sections of the WHO guidelines. Detailed information is provided to conduct an assessment of equivalence studies using pharmacokinetic measurements and in vitro methods, which are currently the most often used methods to document equivalence for most orally administered pharmaceutical products for systemic exposure. NRAs should consider the applicability of the four modalities when developing or adapting national legislation related to equivalence requirements. In addition, implementations using a strategy based on the health risk criteria (see next section of this document) of each product would facilitate the harmonization of equivalence requirements in the Region.

3. Reporting of Results

Reporting of results is an important tool for harmonization. After reviewing several cases, the WG/BE decided to present the Health Canada model of reporting for other NRAs to use as a reference tool in developing their own methods and formats or to adopt as is. It is recommended that NRAs in the Region harmonize reporting mechanisms and formats to the extent to which this is feasible. Annex 2 presents the Canadian model for reporting BE studies.

4. Special Considerations Involving Clinical Trials

Clinical trials are an important component of implementing equivalence studies. The PANDRH Working Group on GCPs developed a guideline that was approved by the Conference: "Good Clinical Practices: Document for the Americas."[11] This document, along with other important international guidelines, should be considered by NRAs in regulating, inspecting, and monitoring GCP implementation.

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[9]WHO Technical Report Series 937. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 7, p. 348. 2006.
[10]WHO Technical Report Series 937. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 7, p. 352. 2006.
[11]Good Clinical Practices: Document of the Americas. PANDRH, WG/GCP, 2004. See http://www.paho.org/english/ad/ths/ev/GCP-Eng-doct.pdf.

III. STRATEGIC FRAMEWORK FOR IMPLEMENTATION

1. Introduction

Registration (marketing authorization) of medicinal pharmaceutical products on the American continent is heterogeneous. The processes associated with registration of different innovator products are not identical, nor are those associated with registration of different non-innovator products. Moreover, non-innovator products involve both *generic* forms and so-called *similar* products. In the majority of the countries of the Region, mainly in Latin America, declaration of interchangeability is not indissolubly linked to demonstration of therapeutic equivalence. More than 10 countries require demonstration of therapeutic equivalence for either registration or marketing of multisource products; however, these products are not always declared interchangeable once this requirement is fulfilled. Only four countries (Canada, the United States, Brazil, and Mexico) have regulated the registration of generic products and will declare them interchangeable once they have proven to be therapeutically equivalent to the reference product.

In Latin America, three different approaches are used in the registration of non-innovator products: the one used in the United States in and Canada, the one used in Brazil and Mexico, and the one used in the rest of the Spanish-speaking countries.

The United States and Canada always require proof of therapeutic equivalence in order to allow health authorities to declare interchangeability between the non-innovator product (the generic product) and the reference product (generally the innovator product).

Mexico and Brazil have had regulations for registration of generic products in place since 1999 and require proof of therapeutic equivalence in order to allow health authorities to declare interchangeability between the non-innovator product (the generic product) and the reference product. In Brazil, also there are similar products, which have a special regulation since 2003. This regulation establishes a timetable for requirement of tests of bioequivalence that started in December 2004 and ends in 2014.

Finally, the rest of the Spanish-speaking countries do not have regulations for registration of generic products as such. They register non-innovator products without requiring a declaration of interchangeability, and usually these products are called *similar* products. However, in some countries, an inference of therapeutic equivalence (through either in vitro or in vivo methodology) is also required as a condition, either for registration or commercialization, in the case of some non-innovator products selected according to the aforementioned criteria of gradual implementation and high health risk (Annex 1 presents details of some experiences). In some countries, expert meetings are being held to discuss ways to include therapeutic equivalence study requirements in regulations. In this regard, there is a recognition of the importance of the BCS (and its extension to Class 1 and portions of Classes 2 and 3) as a complementary tool that will allow estimation of the therapeutic equivalence of many multisource products by in vitro methods. The flow chart (decision tree) presented later reflects the application of these criteria.

It is of fundamental importance to sustain the criterion of using valid and reliable products of reference. Studies of safety and efficacy should be conducted, or, in the case of local manufacturers or imports from third countries, therapeutic equivalence with the original product should be demonstrated. This concept, also included in the

flow chart, does not allow the conduct of a comparative study (either in vivo or in vitro) until the validity and reliability of the reference product are confirmed.

After considering the situation in the Region, the WG recommends that:

1. A strategic framework be developed for the implementation and evaluation of therapeutic equivalence requirements (in vivo or in vitro), taking into consideration prioritization of products, when appropriate, and considering a health risk-based analysis and the countries' realities and capabilities.

2. The definition of a valid and reliable reference product include the requirement of a link of the proposed reference product registration documentation to documentation of the quality, safety, and efficacy of the innovator primary pharmaceutical product. (Reference products are those for which clinical trials were carried out in order to establish efficacy and safety in Phases I to III.)

3. The implementation plan should include short- and long-term goals. Because of differences in realities, capabilities, and priorities in the countries of the Americas, implementation plans will vary from country to country.

4. Factors considered in implementation plans cover general needs such as personnel, training, equipment, guidelines, and legislation, as well as specific concerns such as:
    - Reference products (comparator);
    - Study sites;
    - GCP, GLP, and BE standards;
    - Communication of strategies to key stakeholders: NRAs, pharmaceutical industry (both research and development and national), investigators, research sites, medical community, etc; and
    - Interactions between technical experts and policy decision makers.

5. As a tool to facilitate the development of a strategic implementation plan, the PANDRH WG/BE develop a methodology for health risk-based prioritization selection criteria and a flow chart diagram for application of these criteria.

2. Risk-Based Selection Criteria for Prioritizing APIs Requiring In Vivo Equivalence Studies

The methodology for health risk-based prioritization selection criteria is consistent with the conclusions of the meeting on bioequivalence held in Caracas, Venezuela, in January 1999, which specifically recommended that whenever countries cannot completely apply (bioequivalence) standards, standards be gradually applied.

Due to different operational and administrative reasons, the countries of the Region cannot fully apply the standard requirements of BE studies for all products that require them. This situation brings up a matter of significant importance because the inability to fully apply standards demands *rational* selection of active ingredients for which bioequivalence studies should be required. 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.

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

To this end, health risk categories are defined using as an example the API list of WHO Technical Report 863 (1996), with scores from 1 to 3 assigned according to the following:

As an operational definition, the health risk concept should be established in the context of problems associated with bioequivalence. For this purpose, it would be reasonable to establish the health consequences when the drug is outside (under or above) the therapeutic window (the margin determined by the nontoxic maximum concentration and the effective minimum concentration). Thus, in relating the therapeutic window and adverse effects, three risk levels can be established, as described below.

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

Intermediate Health Risk: This is the probability of the appearance of nonthreatening complications 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 within the therapeutic window. This risk level was assigned a score of 2.

Low Health Risk: This is the probability of the appearance of a minor complication and/or mild adverse reactions when the blood concentration of the active ingredient is not within the therapeutic window. This risk level was assigned a score of 1.

While there are other factors to be considered, such as physicochemical and pharmacokinetic parameters, from the standpoint of public health the most important element to take into account is health risk. Table I lists active ingredients classified in accordance with their health risk and established scores. However, the WG/BE considers it vital to clarify that the list is just a proposal. The list should be continuously updated, and each country should consider its own national pharmaceutical market when developing its adaptation of the methodology.

Table I
Classification of Active Ingredients According to Health Risk

Active Ingredient	**Health Risk**
Carbamazepine	3
Cyclosporine	3
Digoxin	3
Ethambutol	3
Ethosuximide	3
Griseofulvin	3
Lithium Carbonate	3
Oxcarbazepine*	3
Phenytoin	3
Procainamide	3

Quinidine	3
Theophylline	3
Tolbutamide	3
Valproic Acid	3
Verapamil	3
Warfarin	3
6-mercaptopurine	2
Amiloride	2
Amitriptyline	2
Amoxicillin	2
Atenolol	2
Azathioprine	2
Biperiden	2
Chloramphenicol	2
Cimetidine	2
Ciprofloxacin	2
Clofazimine	2
Clomipramine	2
Clorpromazine	2
Co-Trimoxazole	2
Cyclophosphamide	2
Dapsone	2
Diethylcarbamazine	2
Doxycycline	2
Erythromycin	2
Ethinylestradiol	2
Etoposide	2
Flucytosine	2
Fludrocortisone	2
Furosemide	2
Haloperidol	2
Hydrochlorothiazide	2
Indometacin	2
Isoniazid	2
Ketoconazole	2
Levodopa + Inhib. DDC	2
Levonorgestrel	2
Levotiroxina	2
Methotrexate	2
Methyldopa	2
Metoclopramide	2
Metronidazole	2
Nitrofurantoin	2
Norestisterona	2
Oxamniquine	2
Paracetamol	2
Penicillamine	2
Piperazine	2
Piridostigmina	2
Procarbazine	2
Promethazine	2
Propranolol	2

Propylthiouracil	2
Pyrimethamine	2
Quinine	2
Rifampicin	2
Salbutamol Sulphate	2
Spironolactone	2
Tamoxifen	2
Tetracycline	2
Acetazolamide	1
Allopurinol	1
Calcium Folinate	1
Captopril	1
Clomifene	1
Cloxacillin	1
Dexamethasone	1
Diazepam	1
Folic Acid + Ferrous Sulfate	1
Ibuprofen	1
Isosorbide Dinitrate	1
Levamisole	1
Mebendazole	1
Mefloquine	1
Nalidixic Acid	1
Niclosamide	1
Nifedipine	1
Nystatin	1
Phenoxymethylpenicillin	1
Phytomenadione	1
Pirantelo	1
Praziquantel	1
Pyrazinamide	1
Sulfasalazine	1
Aminophylline (see Theophylline)	
Sulfadoxine (see Pirimetam)	

*Not in the reference.

3. Requirements of Bioequivalence Studies in Selected Countries

Requirements for bioequivalence studies (in vivo pharmacokinetic studies in humans) involving different pharmaceutical products differ between countries. Historically, requirements for BE studies have been basically as follows: (a) case-by-case study, (b) application of criteria established by a National Advisory Committee, and (c) application of national regulations in appropriate instances.[12]

A comparative investigation was conducted of the requirements of bioequivalence studies (pharmacokinetic in vivo studies in humans) in the U.S., Canada, and seven Latin American countries with available information as of July 2006, to include Argentina, Brazil, Chile, Costa Rica, Cuba, Mexico, and Venezuela.

[12]Appendix 1, pages 163–174. 34° Report. WHO, Series of Technical Reports N° 863. Geneva, 1996.

The WHO list of active ingredients that require bioequivalence studies (pharmacokinetic in vivo studies in human beings) was used as a reference in the United States, Canada and Germany. This list was published in the WHO expert document on specifications for pharmaceutical preparations.[13] The list is based on WHO's Model List of Essential Drugs and is not exclusive. Countries may require BE studies for other active ingredients. The list takes into account the active ingredients of the list of essential drugs taken as reference drugs (1995) and identifies what countries require BE studies (pharmacokinetic in vivo studies in humans) of those drugs.

It should also be taken into account that not all of the active ingredients in the list are marketed in all of the countries analyzed. For each active ingredient, it was identified how many countries require BE studies for the purpose of establishing which active ingredients are more frequently subjected to bioequivalence study requirements. The results of this analysis are presented in Table II.

Table II

Active Pharmaceutical Ingredients Subject to BE In Vivo studies in Different Countries of the Americas

Active Pharmaceutical Ing	Argentina	Brazil	Canada	Chile*	Costa Rica	Cuba	EUA	Mexico	Venezuela	Total Countries
Acetazolamide		X	X				X			3
Albendazole		X	**				X			2
Allopurinol		X	X				X	X		4
Amiloride		X	X				X			3
Aminophylline (See Theophyll										
Amitriptyline		X	X				X	X		4
Amoxicillin		X	X				X	X		4
Atenolol		X	X				X	X		4
Azathioprine		X	X				X	X		4
Biperiden		X	X					X		3
Calcium folinate		X	X							2
Captopril		X	X				X	X		4
Carbamazepine	X	X	X	X	X	X	X	X	X	9
Carbidopa (see Levodopa)		X					X			
Chloramphenicol		X	X				X	X		4
Chlorpromazine		X	X				X	X		4
Cimetidine		X	X				X			3
Ciprofloxacin		X	X				X	X		4
Clofazimine		X	**				X			2
Clomiphene		X	X				X	X		4
Clomipramine		X	X				X			3
Cloxacillin		X	X				X			3
Co-Trimoxazole		X	X				X	X		4
Cyclosporine	X	X	X	X	X	X	X	X	X	9

[13] Idem.

Active Pharmaceutical Ing	Argentina	Brazil	Canada	Chile*	Costa Rica	Cuba	EUA	Mexico	Venezuela	Total Countries
Dapsone		X	X				X	X		4
Dexamethasone		X	X				X	X		4
Dextran Iron		X	X				X			3
Diazepam		X	X				X	X		4
Digoxine	X	X	X	X	X	X	X	X		8
Dinitrate Isosorbide		X	X	X			X	X	X	6
Doxycycline		X	X				X	X		4
Erythromycine		X	X				X	X		4
Ethambutol		X	X			X	X	X		5
Ethosuximide	X	X	X				X			4
Ethynylestradiol (Associated)		X	X	X			X	X	X	7
Etoposide		X	X				X		X	4
Fludrocortisone		X	X				X			3
Folic Acid + Ferrous Sulfate			X*					X		2
Furosemide		X	X				X	X		4
Griseofulvin		X	X				X			3
Haloperidol		X	X				X	X		4
Hydrochlorothiazide		X	X				X	X		4
Ibuprofen			X				X			2
Indometacin		X	X				X	X		4
Isoniazid + Rifampicin		X	X				X	X		4
Ketoconazole		X	X				X	X		4
Levamisole			X				X			2
Levodopa + IDD	X	X	X		X		X	X		5
Levonorgestrel		X	X				X		X	4
Levothyroxine		X	X		X		X	X	X	6
Lithium Carbonate	X	X	X	X		X	X	X	X	8
Mebendazole			X				X			2
Medroxyprogesterone (Depot)		X	X				X	X		4
Mefloquine		X	X				X			3
Mercaptopurine		X	X				X	X	X	5
Methotrexate		X	X	X		X	X	X	X	7
Methyldopa		X	X				X	X		3
Metoclopramide		X	X				X	X		4
Metronidazole (Tablet)		X	X				X	X		4
Nalidixic Acid		X	X				X			3
Niclosamide			X				X			2
Nifedipine		X	X	X			X	X	X	6
Nitrofurantoin		X	X				X	X		4
Norethisterone		X	X				*			2
Nystatin			X							1
Oxamniquine		X	**				*			1
Oxcarbazepine (not listed)	X	X	X				X		X	5
Paracetamol			X					X		2
Penicillamine		X	X				X			3
Phenoxymethylpenicillin (Peni		X	X				X			2
Phenytoin	X	X	X	X	X	X	X	X	X	9

Active Pharmaceutical Ing	Argentina	Brazil	Canada	Chile*	Costa Rica	Cuba	EUA	Mexico	Venezuela	Total Countries
Phytomenadione			X				X			2
Piperazine			X				X			2
Praziquantel		X	X				X	X		3
Prednisolone (Tablet)		X	X				X			3
Procainamide		X	X				X		X	4
Procarbazine		X	X				X	X		4
Promethazine		X	X				X			3
Propranolol		X	X				X	X		4
Propylthiouracil		X	X				X			3
Pyrantel (Suspension)			X				**			1
Pyrazinamide		X	X				X	X		4
Pyridostigmine	X	X	X				X	X		5
Pyrimethamine (+ Sulfadoxin		X	X				X	X		4
Quinidine	X	X	X				X	X	X	6
Quinine		X	X				X	X		4
Rifampicin		X	X				X	X		4
Salbutamol (Tablet)		X	X				**			2
Spironolactone		X	X	X			X			4
Sulfadoxine		X					X			2
Sulfasalazine		X	X				X			3
Tamoxifen		X	X	X		X	X	X	X	7
Tetracycline		X	X				X	X		4
Theophylline	X	X	X	X		X	X	X	X	8
Tolbutamide	X	X	X	X			X	X	X	7
Valproic Acid	X	X	X	X	X	X	X	X	X	9
Verapamil	X	X	X	X	X	X	X	X	X	9
Warfarin	X	X	X			X	X	X	X	7
TOTAL	15	87	92	15	8	12	88	59	21	

(1) Only when the amount of Folic Acid in the presentation is one that the daily dose is equal or larger than 1 mg.

** Not marketed

Comments

- Out of 98 APIs analyzed, only 5 have BE study requirements in all 9 countries (valproic acid, verapamil, carbamazepine, cyclosporine, and phenytoin).
- The countries with the highest numbers of APIs requiring BE studies are Canada (92) and the United States (87).
- In Latin America, results were as follows (number of APIs from the WHO list): Brazil, 89; Mexico, 59; Venezuela, 21; Chile, 15; Argentina, 15; Cuba, 12; and Costa Rica, 8.
- Similarity was observed among countries in requirements for studies of bioequivalence with regard to high-risk active ingredients. This indicates a solid basis for using this criterion (of health risk) in the decision-making process.
- Finally, this comparative analysis demonstrates that the regulatory situations in the analyzed countries are diverse.

4. Model to determine weighted score for the decision-making

Having considered the situation observed in the countries of the Region, it was decided to select a Weighted Model in which the following aspects were taken into account: The health risks and the Reality Observed, but giving a different weight to each one. As a result, the following Model arises:

Total Score = (Health Risk x 3) + (No. of countries that require studies x 1).

Health risk: Three points were assigned to High Risk, two to Intermediate Risk and 1 to Low Risk.
Taking as an example phenytoin, the results are:
High Risk: High (3 points)
No. Of countries that require BE: 9
Total score: = (3 x 3) + (9 x 1) = 18 points.

Table III shows the order of the scores corresponding to each active ingredient analyzed applying the proposed weighted model [14,15,16] The table is based on the list of active ingredients used as references and the situation observed in various countries of the Region (see Table II).

The WG/BE recognizes that DRAs can face the situation of identifying APIs that require BE studies and that are not in this base list or were recently incorporated into the WHO list. In these cases, even if the API is high in terms of health risk, it may not be identified as a priority for BE studies. This will be without a doubt a subject addressed by the WG/BE.

The proposed model is for orientation purposes. If a new active ingredient were to be incorporated, health risk should be prioritized after taking into account the stated categories of risk. In establishing high risk, it is also useful to take into account one or more of the following characteristics:

(a) high toxicity,
(b) nonlinear pharmacokinetics, and
(c) half-life greater than 12 hours.

It is recommended as well that, before implementation, the DRAs consult with other DRAs of the Region.

[14] Compendium Suiss de Medicaments. Documed. Basilea, 1996.
[15] PDR Generics, Medical Economics, New Jersey, 1998.
[16] Martindale. The Extra Pharmacopoeia. 30th Ed. The Pharmaceutical Press. London, 1993.

TABLE III. ACTIVE PHARMACEUTICAL INGREDIENTS ORDERED BY POINTS

Active Ingredient	Health Risk	weighted	Risk Adjusted by weight	Require_ment in countries	weight	Requeri-ment adjusted by weight	Total Points
Valproic Acid	3	3	9	9	1	9	18
Carbamazepine	3	3	9	9	1	9	18
Ciclosporine	3	3	9	9	1	9	18
Fenitoína	3	3	9	9	1	9	18
Vearapamilo	3	3	9	9	1	9	18
Litio carbonato	3	3	9	8	1	8	17
Teofilina	3	3	9	8	1	8	17
Digoxina	3	3	9	8	1	8	17
Tolbutamida	3	3	9	7	1	7	16
Warfarina	3	3	9	7	1	7	16
Quinidina	3	3	9	6	1	6	15
Oxcarbazepina	3	3	9	5	1	5	14
Ethambutol	3	3	9	5	1	5	14
Procainamida	3	3	9	4	1	4	13
Metotrexato	2	3	6	7	1	7	13
Tamoxifeno	2	3	6	7	1	7	13
Etosuximida	3	3	9	4	1	4	13
Etinilestradiol	2	3	6	6	1	6	12
Levotiroxina	2	3	6	6	1	6	12
Griseofulvina	3	3	9	3	1	3	12
6-Mercaptopurina	2	3	6	5	1	5	11
Levodopa+ IDD	2	3	6	5	1	5	11
Piridostigmina	2	3	6	5	1	5	11
Propranolol	2	3	6	4	1	4	10
Azatioprina	2	3	6	4	1	4	10
Doxiciclina	2	3	6	4	1	4	10
Espironolactona	2	3	6	4	1	4	10
Etopósido	2	3	6	4	1	4	10
Furosemida	2	3	6	4	1	4	10
Ketoconazol	2	3	6	4	1	4	10
Metronidazol	2	3	6	4	1	4	10
Atenolol	2	3	6	4	1	4	10
Biperideno	2	3	6	4	1	4	10
Co-Trimoxazol	2	3	6	4	1	4	10
Indometacina	2	3	6	4	1	4	10
Pirimetamina	2	3	6	4	1	4	10
Amitriptilina	2	3	6	4	1	4	10
Amoxicilina	2	3	6	4	1	4	10
Ciprofloxacina	2	3	6	4	1	4	10
Haloperidol	2	3	6	4	1	4	10
Levonorgestrel	2	3	6	4	1	4	10
Metoclopramida	2	3	6	4	1	4	10
Rifampicina	2	3	6	4	1	4	10
Cloramfenicol	2	3	6	4	1	4	10
Isoniazida	2	3	6	4	1	4	10

Hidroclorotiazida	2	3	6	4	1	4	10
Clorpromazina	2	3	6	4	1	4	10
Tetraciclina	2	3	6	4	1	4	10
Dapsona	2	3	6	4	1	4	10
Eritromicina	2	3	6	4	1	4	10
Nitrofurantoína	2	3	6	4	1	4	10
Quinina	2	3	6	4	1	4	10
Procarbazina	2	3	6	4	1	4	10
Dinitrato de Isosorbide	1	3	3	6	1	6	9
Nifedipina	1	3	3	6	1	6	9
Amilorida	2	3	6	3	1	3	9
Cimetidina	2	3	6	3	1	3	9
Clomipramina	2	3	6	3	1	3	9
Penicilamina	2	3	6	3	1	3	9
Metildopa	2	3	6	3	1	3	9
Prometazina	2	3	6	3	1	3	9
Propiltiouracilo	2	3	6	3	1	3	9
Fludrocortisona	2	3	6	3	1	3	9
Salbutamol sulfato	2	3	6	2	1	2	8
Norestisterona	2	3	6	2	1	2	8
Paracetamol	2	3	6	2	1	2	8
Clofazimina	2	3	6	2	1	2	8
Alopurinol	1	3	3	4	1	4	7
Clomifeno	1	3	3	4	1	4	7
Oxamniquina	2	3	6	1	1	1	7
Captopril	1	3	3	4	1	4	7
Pirazinamida	1	3	3	4	1	4	7
Diazepam	1	3	3	4	1	4	7
Dexametasona	1	3	3	4	1	4	7
Acetazolamida	1	3	3	3	1	3	6
Sulfasalazina	1	3	3	3	1	3	6
Ácido Nalidíxico	1	3	3	3	1	3	6
Mefloquina	1	3	3	3	1	3	6
Cloxacilina	1	3	3	3	1	3	6
Hierro Dextrano	1	3	3	3	1	3	6
Praziquantel	1	3	3	3	1	3	6
Mebendazol	1	3	3	2	1	2	5
Levamisol	1	3	3	2	1	2	5
Fitomenadiona	1	3	3	2	1	2	5
Ibuprofeno	1	3	3	2	1	2	5
Ácido Fólico+Sulfato terroso	1	3	3	2	1	2	5
Fenoximetilpenicilina	1	3	3	2	1	2	5
Niclosamida	1	3	3	2	1	2	5
Folinato de calcio	1	3	3	2	1	2	5
Sulfadoxina	1	3	3	2	1	1	5

It is evident, when analyzing Table III, that there is a clear pattern with respect to the rankings of the active ingredients with the weighted model, with the aggregate requirements in the countries of the Region acting as a validation factor.

To continue the progressive selection and using the statistical criteria, use of the percentile (previous ranking of the active ingredients by total score) is recommended in keeping with the following formula:
Percentile X = X (n + 1)/100

The percentile is a "measure of position", which indicates the percentage of values in a distribution with values below it. It is part of a series of data organized in descendent order which is obtained by dividing the series of data into 100 equal parts. As a result, the number of percentiles is equivalent to the percentage.

In short, the results of the formula indicates the "position" in the table (for example, line 2) of the classified data. In other words, the results of the formula do not correspond to the variable value, but to the position in which the value is found in the classified series of data.

For example, Percentile 10 indicates that 10% of the values in the series of data under analysis are under the value 10 for the variable.

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 (total number of observations).
Percentile 20 = 20 (10 + 1)/100 = 220/100 = 2.2 = 2 (rounded).
Moving to Position 2 (left column), it can be seen 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).

5. Decision Tree for Implementing Equivalence Studies in the Region

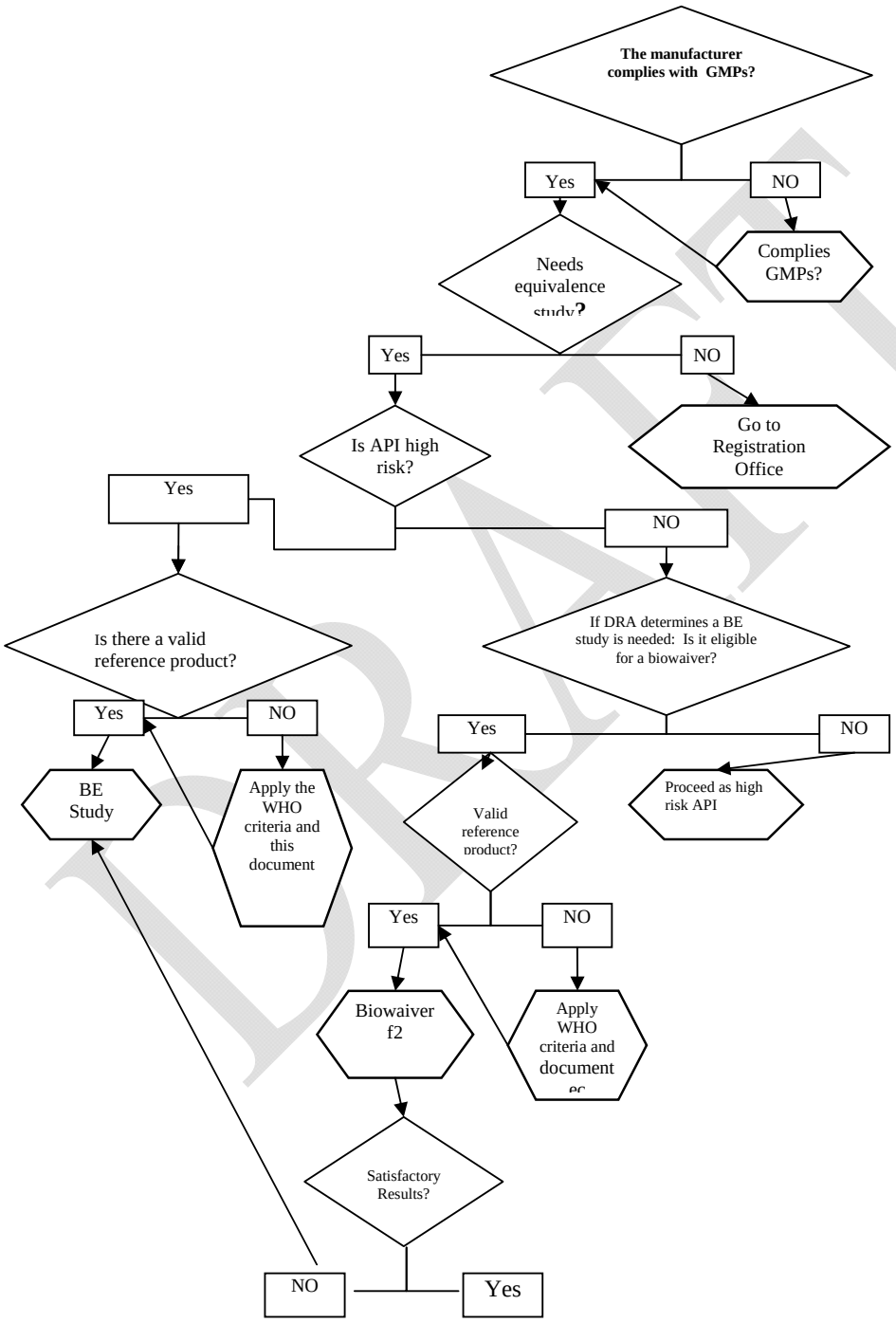
The following flow chart integrates both the GMP requirements and of establishing the validity and reliability of the Reference Product, as well as the concepts of gradual implementation, prioritization according to health risk, and biowaivers.

The main characteristics of the flow chart are as follows:

- The criterion of health risk is critical.
- It follows the tool of the SCB and Biowavers (in vitro equivalence: f2) for demonstrating therapeutic equivalence.
- It establishes the fundamental importance of GMP.
- Implementation of BE of studies is contingent upon the previous demonstration of the validity and reliability of the Reference Product.

- Provide advise to DRAs in defining the priorities to require BE studies.
- DRAs should keep in mind the recommendations of the WHO document (Tech. Rep. 937 – Series 40 2007 – Anex 8) and its updates y can use additional risk criteria to establish priorities to require BE studies.

Decision Tree to guide in the Implementing Equivalence Studies in the Region



API: *Active Pharmaceutical Ingredient* **BE**: *Bioequivalence*
GMP:*Good Manufacturing Practices* **RP**: *Reference Product*
DRA: *Drug Regulatory Agency* **WHO**: *World Health Organization*

6. How to Select Comparator Products

The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety, and efficacy should have been well assessed and documented in pre-marketing and post-marketing monitoring schemes.

Nonetheless, in Latin America the above situation is not always easy to define due to a number of factors such as the following:

- Countries may not have required data linking (correlated[17]) the innovator product intended to be marketed locally to the original innovator formulation for which clinical S&E data have been demonstrated.
- The science of bioequivalence has evolved over time.
- Global sourcing strategies are complex due to the nature of the innovator industry.

WHO guidance[18] has provided suitable options listed in order of preference to help guide DRA decisions. But given the unique situation in Latin America described above, it is critically important to understand the different scenarios that the DRA confronts when selecting these options as comparator products at the national level.

In Latin America there are three scenarios involving innovator products to be considered when selecting comparator products:

- Scenario A: Innovator Product
    1. Imported from an ICH or ICH observer country where it has been approved on the bases of S&E and currently registered and marketed in that country.
    2. Imported from an ICH or ICH observer country where it has not been approved and is currently not registered or marketed in that country.
    3. Imported from a non-ICH/ICH observer country and may or may not be currently registered and marketed in the exporting country.

- Scenario B: Locally Manufactured Innovator Product
    1. Currently registered, marketed, and manufactured in local market in Latin America without having demonstrated linkage to the S&E data for the original product.

- Scenario C: Innovator Product Not Available Locally
    1. Innovator company product unknown or cannot be identified.
    2. Innovator not locally registered or marketed.

Given these scenarios, each DRA would need to carefully assess on a case-by-case basis the specific reference product, as detailed below:

Is the innovator product that is marketed in the country reliably linked to clinical safety and efficacy data (see Choice 1 in Section 6.5.2 of WHO document)?

[17]The product of reference selected in a country has proven to be bioequivalent with the product of reference with which the efficacy and safety in Phases I–III were demonstrated (through a study in vivo (BE), through a biowaiver with determination of f2, or through SUPAC).

[18] Ibid, página 5.

If yes (Scenario A.1), the imported product comes from an ICH or ICH observer country, use it as reference.

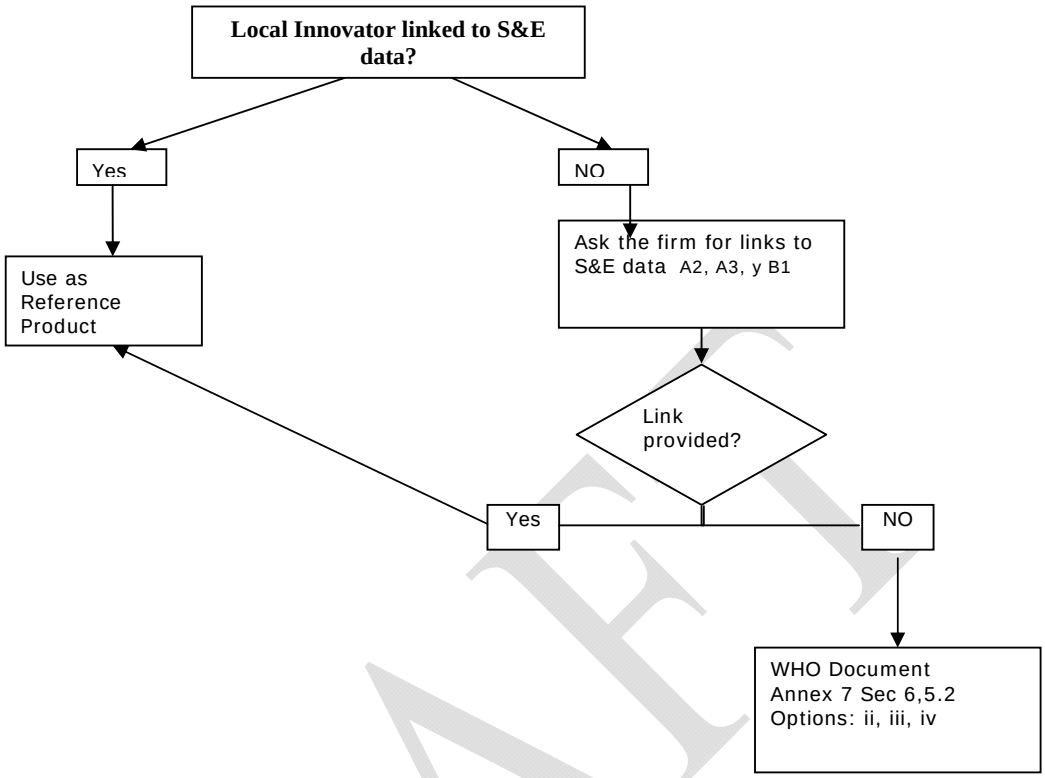
If not (Scenarios A2, A3, and B1):

1. Ask the innovator if data (SUPAC or BE studies) are available to link the locally marketed product to clinical S&E information of the product registered and marketed in the original country. If yes, use it as reference.

2. If not (includes Scenario C1/C2), find a comparator product that is reliably linked to the original clinical data (see Choices ii, iii, and iv in Section 6.5.2 of WHO document).

   When the reliable comparator product finally chosen is not the locally commercialized innovator product, all products (multisource and innovator) locally commercialized must go through the appropriate equivalence studies employing the reliable comparator product finally chosen as reference.

7. Decision Tree for Selecting Comparator Products



S&E: Safety and efficacy

To the extent that the stated criteria are applied, they will facilitate the selection of the same comparator products among countries, which will benefit subregional and regional markets. In this regard, it is recommended that DRAs exchange information on processes and outcomes in the selection of comparators. The definition of regional comparators continues to be a challenge for the DRAs of the Region and will continue to be addressed by the PANDRH WG/BE.

IV. CONCLUSION

This document provides an example of a methodology based on health risk that countries can use to determine prioritization in implementing in vivo equivalence studies when these studies are pertinent.

The list of API used in this document should be used as a reference. Use of this methodology requires that DRAs update their own national lists, which should be dynamic and based on health risk categories.

The document also includes experiences of countries in the utilization of this and other methodologies that can be useful for the development of plans of implementation on the part of DRAs.

As evidenced in Annex 1 (which include examples of countries' experiences to date), it is not feasible to develop a universal plan that will fit all countries' needs. Countries should not be discouraged in facing the tasks ahead and should assess their own situations and realities and define their own path toward implementation.

V. REFERENCES

1. 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

2. 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-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/din/pre_din_ind_e.html

Conduct and analysis of bioavailability and bioequivalence studies Part A: Oral Dosage Formulations Used for Systemic Effects (http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bio-a_e.html)

Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bio-b_e.html

4. WHO Technical Report Series 937. WHO Expert Committee on Specification for Pharmaceutical Preparation. Geneva. 2006

5. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: The use of essential drugs. Sixth report of the WHO Expert Committee. Geneva, World Health Organization, 1995:97-137 (WHO Technical Report Series, No. 850).

6. WHO Technical report series No. 902, 2002: 161-180.

ANNEX 1: COUNTRY CASES ON REGULATING EQUIVALENCE

Chile

Important changes in health have taken place in Chile in the last years. Three among the most highlighted : a) the New Medicine Policy (Res Ex 515 published on April 02, 2004); b) the "AUGE" law (Nº 19966), also called Explicit Guarantees in Health (*Garantías Explícitas en Salud*; "GES" law), published in the *National Newspaper* on September 03 2004; and c) changes to the Regulation of the National System of Pharmaceutical Product Control (DS 1876), being the latter one, related to bioequivalence and therapeutic equivalence, among other matters – on 17 February 2005.

The *Instituto de Salud Pública de Chile (ISP)* is responsible for the Pharmaceutical Products Regulation to assure quality and efficacy of the products marketed in the country. The Biopharmacy Unit of the Sub-department of Safety of the National Control Department is in charge of the operative application of the EQT norm, to test bioequivalence of similars in the country. At the beginning, it was established that the bioequivalence norm should be preceded by training of pharmacists and physicians on bioequivalence. Therefore, since its creation, that Unit has been developing educational activities other than its work on regulatory affairs in order to better implement new regulatory requirements in that area. The educational activities that have been developed with the industry and the academia include among others: "Bioavailability (BA) and Bioequivalencia (BE) International Workshop," the "International Biopharmacy Program," "Course on Pharmaceutical dosage form," and the "International Dissolution Workshop." These workshops were developed in collaboration with the International Pharmaceutical Federation, the American Association of Pharmaceutical Scientists (AAPS), and the Drug Delivery Foundation. Additionally, the following documents that regulate implementation of bioequivalence studies in Chile, has been prepared.

- "*Norma que define criterios para establecer Equivalencia Terapéutica (EQT) a productos farmacéuticos en Chile" (Res. Ex. 727, published in the* National Newspaper o*n November 29, 2005)*

- "*Listas de Principios activos contenidos en productos farmacéuticos que deben establecer Equivalencia Terapéutica mediante estudios in vivo o in vitro" (Res. Ex. 726, published in the* National Newspaper on *November 29, 2005)*

- *Technical in vivo guideline: G-BIOF 01: " Estudios de biodisponibilidd comparativa con producto de referencia para establecer equivalencia terapéutica" and in vitro guideline G-BIOF 02: " Bioexención de los estudiso de biodisponibilidad/bioequivalencia para establecer equivalencia terapéutica de formas farmacéuticas sólidas orales," both Res. Ex. 4886/08)*

- *Resolution that defines the molecules that are required for BE in vivo methods (carbamazepina) and in vitro (resoin ex 3235/08) for the 2008-2009 period.*

Additionally, it is responsibility of the Biopharmacy Unit to select the reference product that will be used in classic bioequivalence estudies or in vitro studies to opt for biowaiver. The certification of centers for biopharmaceutical studies has started to opt for biowaivers in pharmaceutical industries or external quality control laboratories at the national level. Up until now, the certification process of centers for bioequivalence studies has been slow, thus to allow this type of studies in counties like Brazil or Argentina, in this latter country with the verification of the conditions of the center. Finally, the Ministry of Health together with the Instituto de

Salud Pública of Chile decided to create a commission to study the inclusion of new molecules that should demonstrate therapeutic equivalence, which complete the list of resolution No.727. This new list includes sanitary risk prioritized molecules and economic criteria that affect the public health sector budget and whose bioequivalence condition is fundamental to assure the access to safe and efficient generic medicines.

Costa Rica

In 2000, the new Regulation for Registry, Control, Import and Advertisement of Medicines was published (Decree No. 28466-S, 2000) in which were incorporated the biowaiver criteria of the bioequivalence (BE) requirement for multisource pharmaceutical products. This BE requirement would be effective 6 months after the prioritized active principles and reference products are published in the *National Gazette*.

In 2000, the national regulatory authority created a "Consultant Commission on Quality of Drugs" (industry, academia, regulators), aimed to develop proposals for regulations and to assess training needs. Subcommissions in priority topics (GMP, BE, Stability, Validation, etc.) were created.

The Subcommission on BE reviewed the different regulations and criteria published by agencies with more experience in the topic: USA, Brazil, the EU, and Canada, other Latin American countries, documents on BE from WHO and literature on technical articles. The commission developed a list of active principles (APIs) candidates to require in vivo BE studies, which included the measurement of different risk criteria: pharmacokinetics, physicochemical, NTI and consume. In 2001, the first list of 7 active pharmaceutical ingredients that require BE was published: valproic acid, phenytoin, carbamazepine, cyclosporine, digoxin, levothyroxine, and verapamil.

In 2005, the Regulation for Sanitary Risk for Medicines that require demonstrating Therapeutic Equivalence (Decree No 32470-S) was published. It included logistics for the implementation of the requirement, legal technical documents necessary for registration, criteria for the selection of the reference product and biowavers.

Now, they are focused in the modifications approved to the current GMP regulations, and the publication of new regulations in the next 2 years: the reference products for tests, technical guidelines for the industry, the preparation of tools to request and submit the final report on the results of the studies, as well as the means of information to the public on BE in the NRA's web page.

They are concerned about the need to assure additional technical resources to work on the topics. They need to assure a permanent budget to have trained reviewers and a BE unit within the DRA. They acknowledge that PANDRH and their membership to the WG/BE has allowed the NRA to develop more activities in collaboration with national and international experts, and they to share the experience and the regulatory harmonized aspects with the NRA from Central America and the Caribbean.

Venezuela

BE implementation has been slow. On 14 August 2006, the country officially published a norm on Bioavailability and Bioequivalence for medicines. In its transitory rules, it is denied which active principles require these tests from the date

of the publication and which have been granted a 30-month period to comply with them.

Since the approval of the norm, a laboratory for Bioequivalence and Bioavailability at the IVIC has been create. A course has been carried out and is ongoing to train the staff from the RA as well as the industry. More training information in the analytical areas is pending.

The industry in general has been receptive of in complying with the norm, the majority prefer requirement for in vitro studies and the ones defined in the System for Biopharmaceutical Classification and are waiting for the classification of the medicines according to this last norm. They are also waiting for guidelines for the certification of Center for Bioequivalence Studies.

Argentina—ANMAT

In Argentina, there is no law for generic drugs. “Similars” are registered and can be pharmaceutical equivalents or pharmaceutical alternatives. This includes different salts and esters and different dosage forms but the same routes. The BE study program is prospectively and retrospectively based on health risk. There are approximately 150 products which BE studies have been completed and include the revision of data from original products. BE protocols are submitted to ANMAT together with the request for its application and they are review to verify if they comply with the current legislation. ANMAT inspects clinical centers and those where bioanalytical assays are conducted. The reference product is the innovator marketed in the country, when it is available, or on the contrary, ANMAT follows the 2002 WHO decision tree. ANMAT requires consistency in GMP for 3 batches and analyzes batch records before BE study is carried out.

ANNEX 2: MODEL OF FORMAT FOR REPORTING RESULTS

DRAFT COMPREHENSIVE SUMMARY—BIOEQUIVALENCE (CS-BE) HEALTH CANADA *(version: 2004-05-06)*

FOREWORD

The *Draft Comprehensive Summary—Bioequivalence (CS-BE)* (Module 1.4.2) may be used by sponsors to summarize the conduct and analysis of pivotal comparative bioavailability (including bioequivalence) studies submitted in support of DIN Applications (DINAs), New Drug Submissions (NDSs) and their supplements, and Abbreviated New Drug Submissions (ANDSs) and their supplements that are filed with Health Canada pursuant to Part C, Division 1 or 8 of the *Food and Drug Regulations*. This would exclude submissions for Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs.

If the CS-BE is completed for submissions that rely solely on pivotal comparative bioavailability studies to establish safety and efficacy, Modules 2.4–2.7 of the CTD do not need to be completed.

The Administrative Section, Submission Tracking Identifiers and Status, and the Project Management Section will be completed by the Therapeutic Products Directorate. All remaining sections are to be completed by the sponsor. If a section or field does not apply, this should be indicated as such by reporting "Not applicable" in the appropriate area with an *accompanying explanatory note*. The use of tabular summaries is encouraged where possible. In addition, each section of the template should be cross-referenced to the location of supporting documentation or raw data within the application.

As made available, this document provides for only a single study. However, if a submission includes more than one pivotal comparative bioavailability study, the sponsor should simply duplicate the relevant portions of the template and paste them into the original. A heading should be added to indicate what study the duplicated section(s) refer to.

Sponsors should consult the relevant Health Canada guidance documents for further details (e.g., *Guidance for Industry—Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*).

When completing the CS-BE, this Foreword should be deleted.

Health Canada Santé Canada

Canada

HEALTH PRODUCTS AND FOOD BRANCH
DIRECTION GENERALE DES PRODUITS DE SANTE ET DES ALIMENTS

To/A: Division Manager [Reviewing Division] [BUREAU]	SECURITY CLASSIFICATION-CLASSIFICATION DE SECURITE: HC PROTECTED
From/De: [Name] [Reviewing Division] [BUREAU]	FILE - REFERENCE: [CR FILE NUMBER]
	DATE:

DRAFT COMPREHENSIVE SUMMARY: BIOEQUIVALENCE (CS-BE)

To be completed by the TPD:

ADMINISTRATIVE SECTION	
Brand (Proprietary) Name of Drug Product	
Non-Proprietary or Common Name of Drug Product	
Proper, Common or Non-Proprietary Name of Drug Substance	[medicinal ingredient(s)]
Code Name/No.	
Manufacturer/Sponsor	
Therapeutic Classification	
Dosage Form(s)/Strength(s)	
Route(s) of Administration	

SUBMISSION TRACKING IDENTIFIERS AND STATUS	
Type of Submission	□ NDS □ SNDS □ NC □ ANDS □ SANDS □ DINA If applicable: □ NAS □ Resp. to NON □ Resp. to NOD □ Priority Review □ Resp. to Commitment for NOC/c □ NOC/c-QN
Date Accepted for Review	
TPD Target Date	[as per the DSTS]
CR File Number	
Submission Control No.	[DSTS number]
Data Submitted	[original information and material – number of volumes, CD-ROMs, diskettes]

Review Completion	□ NOC □ Rec. to other Bureau □ NOD □ NOD/W □ NON □ NON/W □ NSN □ NOL □ Rec. DIN [for DINAs only] Date :
Statements to be included in notification	See page no.:
Note to other review units	See page no.:
Product Monograph revisions issued	See page no.:

PROJECT MANAGEMENT SECTION	
Project Manager	
Lead Review Bureau	□ BPS □ SMAB □ BMORS □ BGIVD □ BCANS
Review Target Date	[as per review plan]
Nonclinical Evaluators	
Clinical Evaluators Comparative BA/BE Primary Evaluator Peer Evaluator	
Chemistry & Manufacturing Evaluators	
Consultations	□ Not Applicable □ Office of Science □ TPD Science Advisory Committee □ Other (specify:_____)
Labelling Evaluator(s) (PID)	

To be completed by the manufacturer/sponsor:

Manufacturer/Sponsor	
Brand (Proprietary) Name	
Medicinal Ingredient(s)	
Dosage Form	
Strength(s)	
Contact Person	
Telephone Number	
Facsimile Number	

Tabulation of the Composition of the Proposed Formulation(s)

(State the location of the master formulae in the submission)
(Tabulate the composition of each product strength using the table below. For solid oral dosage forms the table should contain only the ingredients in the product core. A copy of the table should be filled in for the coating ingredients, if any.)

Component and Quality Standard	Function	Strength (label claim)			
		XX mg		XX mg	
		Quantity per unit	%*	Quantity per unit	%*

TOTAL					

**Each ingredient is expressed as a percentage of the total core or coating weight.*

1.0 Regional Information for Canada

1.1 Canadian Reference Product Confirmation

(Volume and page number in the submission where a copy of the purchase receipt(s), or signed confirmation in writing that the reference product was purchased in Canada may be found.)

1.2 Justification for use of a Canadian reference product purchased outside of Canada

1.3 Waiver Requests

(If comparative bioavailability data has not been submitted for all strengths, the sponsor should provide a scientific justification for not submitting such data. Issues such as the proportionality of formulations included in the submissions should be addressed.)

1.4 Certificates of Analysis

(*State location of the certificate of analysis in the submission)*

1.5 Product Labelling

(*State location of product labelling in the submission)*

1.5.1 Product Monograph

1.5.2 Inner and Outer Labels

1.6 Comments from review of Section 1.0—*TPD use only*

2.0 Identification of Drug Characteristics and Dosage Form Properties: Determination of Applicable Standards

2.1 Identify the type(s) of formulation included in the submission

(e.g., immediate release, enteric-coated modified release, etc.)

2.2 Indication(s) for use

2.3 State whether the dosage form is a combination product

(i.e., is there more than one drug substance in the formulation? If so, ensure that the remaining sections are completed with regard to both ingredients)

2.4 Common name or compendial name of the active ingredient(s)

2.5 Is the bioequivalence assessment to be based on the parent compound or metabolite?

(If the assessment is to be based on a metabolite, a justification should be provided as to why the parent compound cannot be used.)

2.6 Physicochemical Characteristics

(i) Aqueous Solubility

2.7 Pharmacokinetic Characteristics

(Please cite the sources for all information in this section)

2.7.1 Absorption

(i) Identify primary site(s) of absorption

(ii) Summarize reported information on the rate and extent of absorption from pertinent dosage forms *(Include reported values for AUC, T_{max}, and C_{max})*

(iii) Identify any reported effect of food on absorption

2.7.2 Distribution

(i) Identify site(s) of distribution

(ii) State the extent of protein binding *(as a percentage of total drug)*

2.7.3 Elimination

(i) Identify the route(s) and the percentage of drug elimination attributable to each route

(ii) State the reported terminal elimination half-life of the drug

2.7.4 Metabolism

(i) Identify the site(s) and pathway(s) of metabolism

(ii) Identify the extent of first-pass metabolism

2.7.5 Other Pharmacokinetic Considerations

(i) State whether genetic polymorphism affects the pharmacokinetics of this drug
(List affected route(s) of metabolism and any toxicologic concerns)

(ii) State whether the substance is chiral. Identify the effects of the chirality on the activity and pharmacokinetics of the substance *(Pay particular attention to stereospecific absorption and metabolism)*

(iii) If the substance is chiral, was a stereospecific assay used? If not, please justify.

(iv) State whether the drug displays non-linear kinetics within the usual dosage range. Particular attention should be paid to absorption and first-pass metabolism
(State concentrations at which non-linearity occurs and any known explanations)

(v) State whether metabolism is capacity limited
(If so, provide information on doses affected by capacity limitations)

2.8 Therapeutic and Toxicity Concerns

(i) Identify site(s) and mechanism(s) of action

(ii) State whether the time to onset of action is important

(iii) State the normal therapeutic range of the drug

(iv) Identify the minimum drug concentrations at which toxic effects are observed

(v) State whether the drug is considered to be highly toxic

(vi) State whether the drug is considered to have a narrow therapeutic range

2.9 Comments from Review of Section 2.0—*TPD use only*

3.0 Biopharmaceutic Studies
Comparative Bioavailability (BA) and Bioequivalence (BE)

3.1 Summary of Bioavailability/Bioequivalence Studies Performed

(Provide a brief description of each comparative bioavailability study included in the submission)

3.2 Has comparative bioavailability data been submitted for all strengths?

(If comparative bioavailability data has not been submitted for all strengths, provide a scientific justification for not submitting such data. Issues such as the proportionality of formulations included in the submission should be addressed in Section 1.3—Waiver Requests.)

Sections 3.3–9.0 below should be copied and completed separately for each pivotal comparative bioavailability study performed. In addition, Sections 1.1–1.4 must also be copied and completed for each pivotal comparative bioavailability study.

3.3 Clinical Study Report

Study #:
Study Title:
Location of Study Protocol:
Start and stop dates for each phase of the clinical study:

3.4 Ethics

(a) Name of review committee, date of approval of protocol and consent form, location of approval letter in the submission

(b) State location of a reference copy of the informed consent form

3.5 Investigators and Study Administrative Structure

(a) Name of principal investigator(s) *(State location of C.V. in the submission)*

(b) Clinical Facility *(Name and full mailing address)*

(c) Clinical Laboratories *(Name and full mailing address)*

(d) Analytical Laboratories *(Name and full mailing address)*

(e) Company performing pharmacokinetic/statistical analysis *(Name and full mailing address)*

3.6 Study Objectives

Briefly state the study objectives.

3.7 Investigational Plan

3.7.1 Overall Study Design and Plan—Description
(*Describe the type of study design employed in 1–2 sentences*)

3.7.2 Selection of Study Population

3.7.2.1 Inclusion Criteria

3.7.2.2 Exclusion Criteria
(List the exclusion criteria applied to subjects)

3.7.2 Removal of Patients from Therapy or Assessment

(a) Number of subjects enrolled in the study
(All subjects including alternates, withdrawals, and dropouts)

(b) Withdrawals
(Identify each withdrawal by subject and provide the reason for withdrawal and at what point in the study the withdrawal occurred)

3.7.2.3 Health Verification
(Individual data should be included in the submission)

(a) List criteria used and all tests performed in order to judge health status

(b) Indicate when tests were performed

(c) Study site normal values
(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)

(d) Report any results that were outside of study site normal values
(State location in submission of the summary of anomalous values)

3.7.3 Treatments Administered

3.7.3.1 Test Product

(a) Strength (label claim) of product(s) used in pivotal comparative bioavailability study.

(b) Batch number and date of manufacture for the test product

(c) Potency (measured content) of test formulation as a percentage of label claim

(This information should be cross-referenced to the location of the certificate of analysis in the submission)

3.7.3.2 Reference Product

(a) Name and manufacturer of the reference product

(b) List of dosage form(s) and strength(s) marketed in Canada by the manufacturer of the reference product

(c) Strength (label claim) of product(s) used in pivotal comparative bioavailability study

(d) Batch number and expiry date for the reference product

(e) Potency (measured content) of the reference formulation as a percentage of label claim *(This information should be cross-referenced to the location of the certificate of analysis in the submission)*

3.7.4 Selection of Doses in the Study

(a) State dose administered
(Indicate the number of dosage units comprising a single dose, e.g., 400 mg as 1 x 400 mg or 2 x 200 mg tablets)

3.7.5 Selection and Timing of Dose for Each Subject

(a) State volume and type of fluid consumed with dose

(b) Interval between doses *(i.e., length of washout)*

(c) Protocol for the administration of food and fluid

(d) Restrictions on posture and physical activity during the study

3.7.6 Blinding

3.7.6.1 Identify which of the following were blinded. If any of the groups were not blinded, provide a justification for not doing so.

(a) Study monitors
(b) Subjects
(c) Analysts

3.7.6.2 Identify who held the study code and when the code was broken

3.7.7 Drug Concentration Measurements

3.7.7.1 Biological fluid(s) sampled

3.7.7.2 Sampling Protocol

(a) Number of samples collected per subject

(b) Volume of fluid collected per sample

(c) Total volume of fluid collected per subject per phase of the study

(d) List the study sampling times

(e) Identify any deviations from the sampling protocol
(State location of summary in the submission)
(Describe and explain reasons for deviations from sampling protocol. Comment on impact on study. Indicate whether the deviations were accounted for in the pharmacokinetic analyses.)

3.7.7.3 Sample Handling

(a) Describe the method of sample collection

(b) Describe sample handling and storage procedures

3.8 Comments from review of Section 3.0—*TPD use only*

4.0 Study Patients

4.1 Demographic and Other Baseline Characteristics

(a) Identify study population *(i.e., normal, healthy adult volunteers or patients)*

(b) Summary of ethnic origin and gender of subjects
(Individual data should be included in the submission)

(c) Identify subjects noted to have special characteristics and state notable characteristics
(e.g., fast acetylators of debrisoquine)

(d) Range and mean age ± SD of subjects
(Individual data should be included in the submission)

(e) Range and mean height and weight ± SD of subjects
(Individual data should be included in the submission)

(f) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table

4.2 Number of smokers included in the study

(a) Indicate how many cigarettes smoked per day per subject

(b) Comment on the impact on study

4.3 Comments from review of Section 4.0—*TPD use only*

5.0 Protocol Deviations

5.1 Protocol deviations during the clinical study
(Describe any such deviations and discuss their implications with respect to bioequivalence)

5.2 Comments from review of Section 5.0—*TPD use only*

6.0 Safety Evaluation

6.1 Identify adverse reactions observed

(List any adverse reactions by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. State location of this summary in the submission.)

(Discuss the implications of the observed adverse reactions with respect to bioequivalence)

6.2 Comments from review of Section 6.0—*TPD use only*

7.0 Efficacy Evaluation:
Efficacy Results and Tabulations of Individual Patient Data

7.1 Presentation of Data

(a) State location in submission of tables of mean and individual subject concentrations

(b) State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots

7.2 Pharmacokinetic (PK) Parameters

(Complete the following tables for uncorrected and potency corrected data, modify the units if required. A set of tables is provided for both a single-dose and a steady-state study. Please delete the unused set of tables.)

(a) The following parameters have been derived:

SUMMARY TABLE OF COMPARATIVE BIOAVAILABILITY DATA
[Table for single dose studies]

Analyte Name
(___ x ___ mg)
From measured data
uncorrected for potency
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval#
AUC_T‡ (units)				

Analyte Name (___ x ___ mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval#
AUC_I (units)				
C_{max} (units)				
T_{max}§ (h)				
$T_{½}$€ (h)				

*Identity of the test product

†Identity of the reference product, including the manufacturer, and origin (country of purchase)

‡For drugs with a half-life greater than 24 hours AUC_T should be replaced with AUC_{0-72}

§Expressed as either the arithmetic mean (CV%) only or the median (range) only

€Expressed as the arithmetic mean (CV%) only

#Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for AUC_T, AUC_I, and C_{max} (if required)

corrected for potency Geometric Mean				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval#
AUC_T (units)				
AUC_I (units)				
C_{max} (units)				

#Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for AUC_T, AUC_I, and C_{max} (if required)

SUMMARY TABLE OF COMPARATIVE BIOAVAILABILITY DATA
[Table for multiple dose studies]

Analyte Name (___ x ___ mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval#
AUC_{tau} (units)				
C_{max} (units)				
C_{min} (units)				
T_{max}§ (h)				
FL¶ (%)				

*Identity of the test product
†Identity of the reference product, including the manufacturer, and origin (country of purchase)
§Expressed as either the arithmetic mean (CV%) only or the median (range) only
¶Expressed as the arithmetic mean (CV%) only
#Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for AUC_{tau} and C_{max} (if required)

corrected for potency Geometric Mean				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval#
AUC_{tau} (units)				
C_{max} (units)				
C_{min} (units)				

#Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for AUC_{tau} and C_{max} (if required)

(b) Ratio of AUC_T to AUC_I
(State mean ratio for both test and reference)

(c) Other parameters calculated
(Identify and provide mean for both test and reference)

7.3 Statistical Analysis

(Provide the following results from the ANOVA on the logarithmically transformed AUC_T and C_{MAX} and other relevant parameters, e.g. in the case of steady-state designs, AUC_τ , C_{MAX} , and C_{MIN})

(a) Mean Square Error, derived CV, and associated degrees of freedom
(Provide location of tabulation in submission)

PK Parameter	MSE	CV	DF
AUC_T			
AUC_I			
C_{max}			

7.4 Comments from review of Section 7.0—*TPD use only*

7.5 Comments on Statistical Assessment of Submitted Subject Data as Detailed in Appendix A—*TPD use only*

8.0 Analytical Study Report

8.1 Analytical Technique

8.1.1 Analytical protocol
(State the location of the analytical protocol)

8.1.2 Identify analyte(s) monitored

8.1.3 Identify analytical technique employed

8.1.4 Identify method of detection

8.1.5 Identify internal standard

8.1.6 If based on a published procedure, state reference citation

8.1.7 Identify any deviations from protocol

8.1.8 Dates of subject sample analysis

8.1.9 Longest period of subject sample storage
(Identify the time elapsed between the first day of sample collection and the last day of subject sample analysis)

8.1.10 State whether all samples for a given subject were analyzed together in a single analysis run

8.2 Standard Curves

(State location in submission of tabulated raw data and back calculated data with descriptive statistics)

(a) List number and concentration of calibration standards used

(b) State number of curves run during the study

(c) Summarize descriptive data including slope, intercept, correlation coefficients

(d) Describe the regression model used including any weighting

(e) State the limit of quantization (LOQ)
(Summarize inter-day and intra-day precision and accuracy at the LOQ)

(f) State the limit of detection (LOD)

8.3 Quality Control Samples

(a) Identify the concentrations of the QC samples, their date of preparation, and the storage conditions employed prior to their analysis

(b) State the number of QC samples in each analytical run per concentration

8.4 Precision and Accuracy

(a) Summarize inter-day and intra-day precision and accuracy of QC samples analyzed during subject sample analysis and inter-day precision of back-calculated standards

8.5 Repeat Analyses

(a) List repeats by sample identification and include the following information for each repeat: initial value: reason for repeat, repeat value(s), accepted value, and reason for acceptance

(b) Report the number of repeats as a percentage of the total number samples assayed

8.6 Chromatograms

(State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, and pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period;

sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas)

8.7 Comments from review of Section 8.0—*TPD use only*

9.0 Analytical Validation Report

9.1 Precision and Accuracy

(a) Summarize inter-day and intra-day accuracy and precision during assay validation

(b) Summarize inter-day and intra-day accuracy and precision during assay re-validation
(If applicable)

9.2 Stability

(For each section provide the location of the raw data, a description of the methodology employed, and a summary of the data)

(a) Summarize data on long-term storage stability

(b) Summarize data on freeze-thaw stability

(c) Summarize data on bench top stability

(d) Summarize data on auto sampler storage stability

(e) Summarize data from any other stability studies conducted
(e.g., stock solution stability)

9.3 Specificity
(Methods to verify specificity against endogenous/exogenous compounds and results)

9.4 Recovery

(Method and results of assessment for analyte and internal standard including mean and CV%)

9.5 Comments from review of Section 9.0—*TPD use only*

10.0 Summary of Correspondence Between the Sponsor/Manufacturer and TPD—*TPD use only*

11.0 Conclusions and Recommendations—*TPD use only*

(Include location of and signatories to the submission certification letter)