PANDRH Technical Report Nº 8

Pan American Network on Drug Regulatory Harmonization

Working Group on Bioequivalence (BE)

Framework for Implementation of Equivalence Requirements for Pharmaceutical Products

Pan American Health Organization
Regional Office of the World Health Organization

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Washington, DC
June 2011

Pan American Health Organization
Regional Office of the World Health Organization
RED PARF PANDRH

PAHO HQ Library Cataloguing-in-Publication

Pan American Health Organization. *"Framework for Implementation of Equivalence Requirements for Pharmaceutical Products".* PANDRH Technical Report Series Nº 8. Washington, D.C.: PAHO, © 2011.

ISBN 978-92-75-13222-7

I. Title

1. BIOEQUIVALENT DRUGS

2. PHARMACEUTICAL PREPARATIONS

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LM WA 730

Document approved in the V Conference
for Drug Regulatory Harmonization, November 2008

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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.

2. WHO. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Geneva: WHO; 2006: pp. 347–390. 2006. Technical Report Series Nº 937. Disponible en: *http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.pdf*.

3. *Ibídem*. Annex 8: Proposal to waive *in vivo* bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms. Geneva: WHO; 2006: pp. 391–437. Technical Report Series Nº 937. Disponible en: *http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex8_eng.pdf*.

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.

PANDRH has four components: the Pan American Conference (highest decisionmaking 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.

4. PAHO. Consultation of Experts on Bioequivalence of Pharmaceutical Products. Caracas, Venezuela, January 13-15, 1997. Final Report. Essential Drugs and Technology Series No. 9 HSP/HSE. Washington, DC, 1999.

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 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. IV Pan American Conference on Drug Regulatory Harmonization. Available at: http://www.paho.org/english/ad/ths/ev/pandrh_conclusions_recommendations-ivconference.pdf.
6. Minutes of the VI WG/BE Meeting, August 2005, Panama. Available at: http://www.paho.org/english/ad/ths/ev/been-6thmeeting.pdf.
7. PANDRH Bioequivalence Working Group. Available at: http://new.paho.org/hq/index.php?option=com_content&task=view&id=1052&Itemid=513.

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. Fortieth Report; Annex 7. Geneva: WHO; 2006: pp. 347-390. 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. Fortieth Report; Annex 8. Geneva: WHO; 2006: pp. 391-437. WHO Technical Report Series 937.
- Additional guidance for organization performing *in vivo* bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report; Annex 9. Geneva: WHO; 2006: pp. 439-461. WHO Technical Report Series 937.
- Revision/update of the guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. Working document QAS/05.143/Rev.1 RESTRICTED, 2005.
- Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth Report; Annex 11. Geneva: WHO; 2002: pp. 161-180. WHO Technical Report Series 902.

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.

8. WHO. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Annex 8: Proposal to waive *in vivo* bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms. Geneva: WHO; 2006: p. 391. Technical Report Series 937.

In a given country, all pharmaceutical products, including multisource products, should be used only after approval has been granted by local authorities. Regulatory 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. The Canadian model for reporting BE studies could be found at: *http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guideld/din/pre_din_ind_e.html*.

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. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Geneva: WHO; 2006: p. 348. 2006. Technical Report Series 937.

10. *Ibídem*, p. 352.

11. Good Clinical Practices: Document of the Americas. PANDRH, WG/GCP, 2004. Available at: 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 noninnovator 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 noninnovator 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 noninnovator products selected according to the aforementioned criteria of gradual implementation and high health risk (the Annex 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
	...

ACTIVE INGREDIENT	HEALTH RISK
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
	...

ACTIVE INGREDIENT	HEALTH RISK
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
	...

ACTIVE INGREDIENT	HEALTH RISK
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

Note: *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.

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.

12. WHO. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth Report. Annex 9: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Appendix 1: Examples of national requirements for in vivo equivalence studies for drugs included in the WHO Model List of Essential Drugs (Canada, Germany and the USA, December 1994). Geneva: WHO; 1996: pp. 141-152. Technical Report Series 863.

13. *Ibídem*.

Table II. **Active Pharmaceutical Ingredients Subject to BE *In Vivo* studies in Different Countries of the Americas**

ACTIVE PHARMACEUTICAL INGREDIENT	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 Theophylline)										
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			2
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
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	6
Etoposide		X	X				X		X	4
Fludrocortisone		X	X				X			3
Folic Acid + Ferrous Sulfate			X*					X		2

...

ACTIVE PHARMACEUTICAL INGREDIENT	ARGENTINA	BRAZIL	CANADA	CHILE	COSTA RICA	CUBA	EUA	MEXICO	VENEZUELA	TOTAL COUNTRIES
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		6
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		4
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 (Penicillin)		X	X				X			3
Phenytoin	X	X	X	X	X	X	X	X	X	9
Phytomenadione			X				X			2
Piperazine			X				X			2
Praziquantel		X	X				X	X		4
Prednisolone (Tablet)		X	X				X			3
Procainamide		X	X				X		X	4
Procarbazine		X	X				X	X		4
Promethazine		X	X				X			3
										...

ACTIVE PHARMACEUTICAL INGREDIENT	ARGENTINA	BRAZIL	CANADA	CHILE	COSTA RICA	CUBA	EUA	MEXICO	VENEZUELA	TOTAL COUNTRIES
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 (+ Sulfadoxine)		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	397

Notes:

* 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.

Table III. **Active Pharmaceutical Ingredients Ordered by Points**

ACTIVE INGREDIENT	HEALTH RISK	WEIGHTED	RISK ADJUSTED BY WEIGHT	REQUIREMENT IN COUNTRIES	WEIGHT	REQUERIMENT 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
							...

14. Compendium Suisse des médicaments, Documed. Basel, 1996.
15. PDR Generics, Medical Economics, New Jersey, 1998.
16. Martindale. The Extra Pharmacopoeia. Thirtieth Ed. The Pharmaceutical Press. London, 1993.

ACTIVE INGREDIENT	HEALTH RISK	WEIGHTED	RISK ADJUSTED BY WEIGHT	REQUIREMENT IN COUNTRIES	WEIGHT	REQUERIMENT ADJUSTED BY WEIGHT	TOTAL POINTS
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
							...

ACTIVE INGREDIENT	HEALTH RISK	WEIGHTED	RISK ADJUSTED BY WEIGHT	REQUIREMENT IN COUNTRIES	WEIGHT	REQUERIMENT ADJUSTED BY WEIGHT	TOTAL POINTS
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

...

ACTIVE INGREDIENT	HEALTH RISK	WEIGHTED	RISK ADJUSTED BY WEIGHT	REQUIREMENT IN COUNTRIES	WEIGHT	REQUERIMENT ADJUSTED BY WEIGHT	TOTAL POINTS
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 (Annex 8: Proposal to waive *in vivo* bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms. Geneva: WHO; 2006: pp. 391–437. Technical Report Series 937) and its updates y can use additional risk criteria to establish priorities to require BE studies.

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 postmarketing 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.

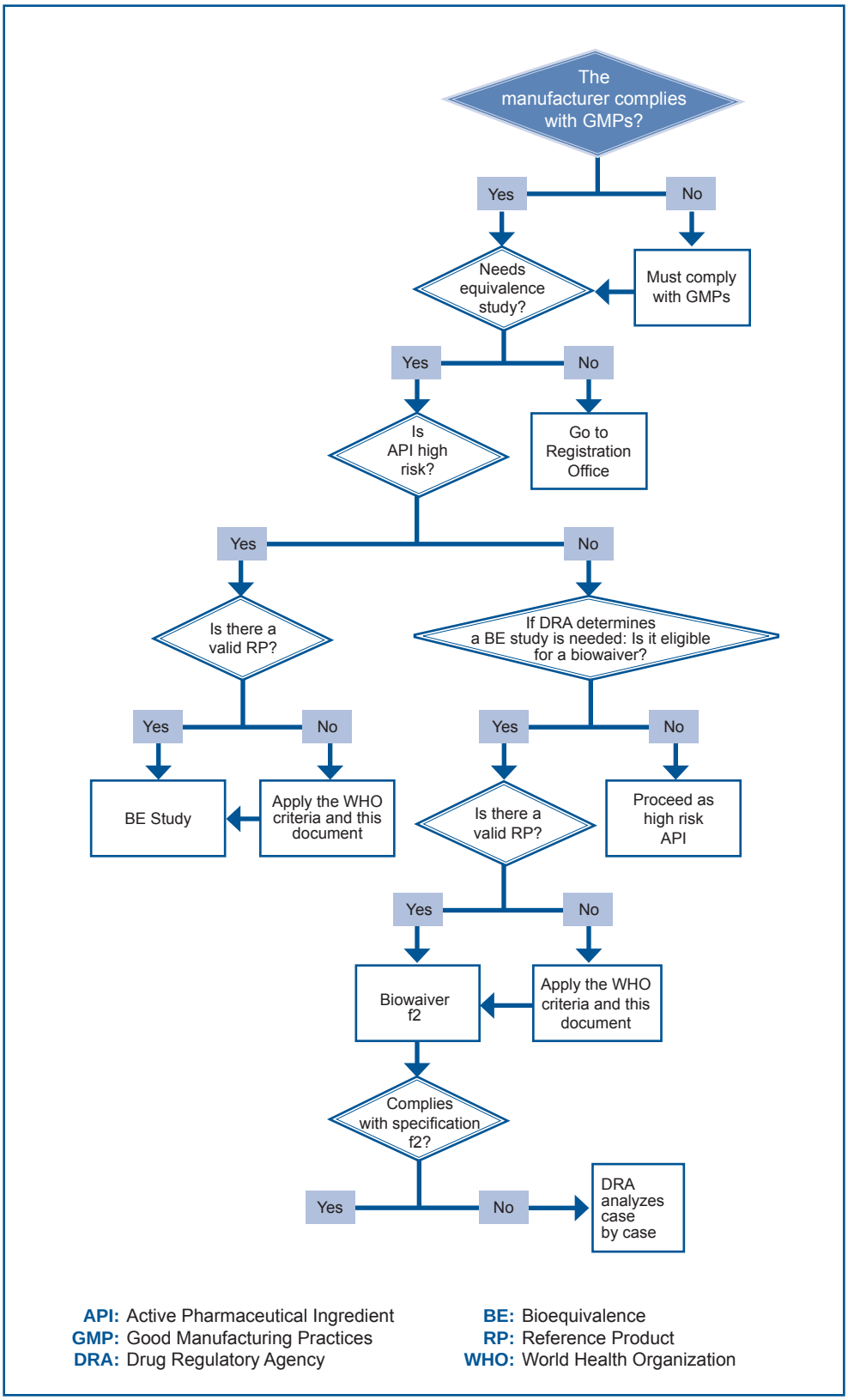
In Latin America there are three scenarios involving innovator products to be considered when selecting comparator products:

- 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.

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. PAHO. Consultation of Experts on Bioequivalence of Pharmaceutical Products. Caracas, Venezuela, January 13-15, 1997. Final Report. Essential Drugs and Technology Series No. 9 HSP/HSE. Washington, DC, 1999.

Figure I. **Decision Tree to Guide in the Implementing Equivalence Studies in the Region**



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 WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth Report, Annex 11, WHO 2002; or, Fortieth Report, Annex 7, WHO 2006).

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):

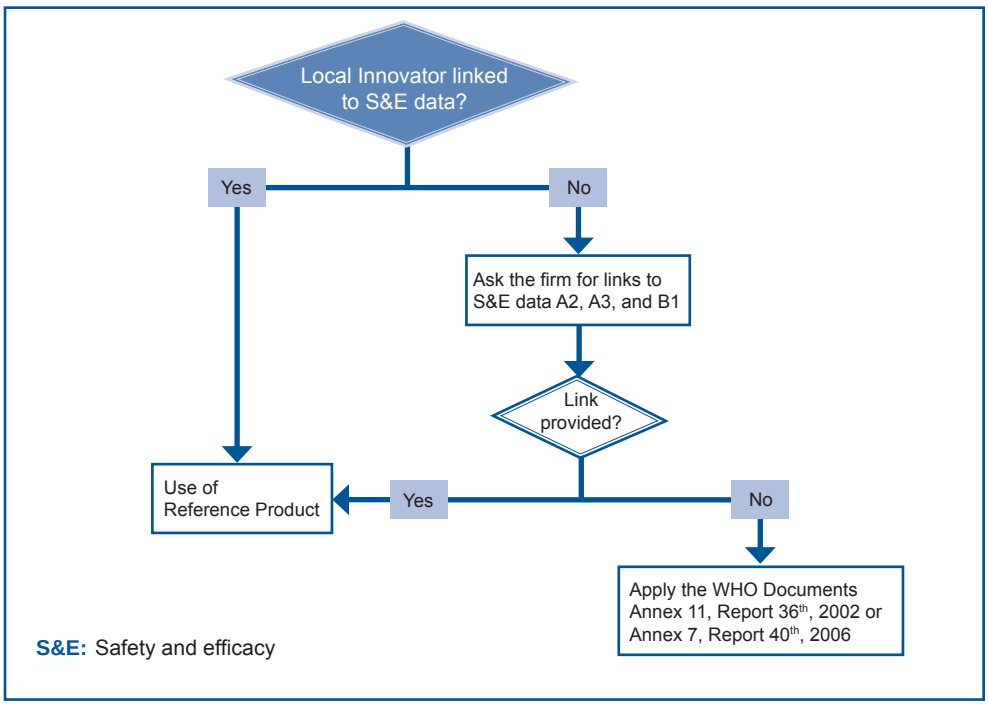
1. Ask the innovator if data (SUPAC or BE studies) are available to link the locally marketed product to clinical S&E information of the product registered and marketed in the original country. If yes, use it as reference.
2. If not (includes Scenario C1/C2), find a comparator product that is reliably linked to the original clinical data (see WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-sixth Report, Annex 11, WHO 2002; or, Fortieth Report, Annex 7, WHO 2006).

   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

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.

Figure II. **Decision Tree to Guide in the Selection of Comparator Products in the Region**



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 the Annex (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*

   - Guideline on Preparation of DIN Submissions (February 22, 1995). Available at: *http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guideld/din/pre_din_ind_e.html.*
   - Conduct and analysis of bioavailability and bioequivalence studies Part A: Oral Dosage Formulations Used for Systemic Effects. Available at: *http://www.hcsc.gc.ca/hpfb-dgpsa/tpd-dpt/bio-a_e.html*.

- Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations. Available at: *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: 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 on 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 certificat on 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, a document “The Inscription, Medicines Control, Importation and Publicity Regulation” (Decree N°: 28466-S) was published. That regulation incorporated criteria of application and exemption of BE for pharmaceutical products of diverse origins. That requirement was implemented six months after publishing in the Official Newspaper (La Gaceta).The Prioritized Active Pharmaceutical Ingredients (PAPIs) List and Reference Products List.

In 2000, national regulatory agency (NRA) created an advisory commission in the quality of medicines (industry, academy, regulators), directed to develop proposals of the regulation and to evaluate the qualification needs.

Working groups were created to work in priority subjects (GMP, BE, Stability, Analytical Methods Validation etc.). National BE WG analyzed different regulations and criteria published by agencies with greater experience in subject: USA, Brazil, EMEA, Canada, other Latin American countries, WHO publications and technical papers. They developed a basic APIs List candidates requiring *in vivo* BE studies, this included different risk criteria: pharmacokinetic, physico-chemical, NTI, and population consumption. In 2001, a first list of 7 PAPIs with BE: valproic acid, phenytoin, carbamazepin, cyclosporin, digoxin, levothyroxine and verapamil was published.

In 2005, a document “Regulation for the Sanitary Registry of Medicines that Require to demonstrate Therapeutic Equivalence” (Decree N°:32470-S) was published, this included aspects about logistics of implementation, technical and legal documents necessary to register, selection of reference product and waiver criteria.

In the year 2008, the Technical Council of Inscriptions resolved to extend the PAPIs list (PAPs) (Resolution CTI-001-07) that require to demonstrate Therapeutic Equivalence, and included the following: nelfinavir, cyclosporine, didanosine, lamotrigine, levodopa + carbidopa, anastrozole, tamoxifen, zidovudine, and warfarin.

A transitory decree was published (Decree N°33076-S reformed) that defined the period of time required for the application of bioequivalence tests or dissolution tests following a gradual implementation by groups of PAPIs. A cumulative list of Reference Products for all formulations registered in the country and related to PAPIs was published as well (Resolution DRC-560-08).

The approved modifications to the Decree of GMP are being currently studied, as is the publication of documents that complement the application of BE: technical guidelines for industry, elaboration of instruments for the presentation of the application and of the study results, a new list of PAPIs for the year 2009, updating the reference products list, and also the development and maintenance of an official website concerning actual regulation on BE, a list of approved bioequivalent products for interchangeability, etc.

We are visualizing the need to have a generics policy, the assurance of additional resources to develop technical and educational topics, and a BE Unit within the NRA. The participation of Costa Rica in the BE working group in the PANDRHA network has allowed the NRA to develop educational activities with national and international experts, and we emphasize our disposition to share our experience and regulatory harmonization with other Central-American and Caribbean authorities.

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.

PARF Series Technical Document Nº 8 Framework for Implementation of Equivalence Requirements for Pharmaceutical Products

ISBN 978-92-75-13222-7