# 4th Meeting of the Working Group on Bioequivalence

Mexico City
4 -5, August, 2003

***Minutes***

**PARTICIPANTS**

*Members*

- Justina Molzon FDA, Coordinator
- Ricardo Bolaños, ANMAT/Argentina
- Salomon Stavchansky, Univ. Texas
- Irene Goncalves, INH Venezuela
- Pamela Milla, ISP-Chile. In lieu of Regina Pezoa
- Conrad Pereira, Health Canada
- Silvia Storpitis, ANVISA/Brazil
- Silvia Chiarcovich, ALIFAR
- Loreta Marquez, FIFARMA
- Lidiette Fonseca, University /MOH, Costa Rica (Absent)
- Roger Williams, USP (Absent)

*Secretariat (PAHO/WHO)*: R. D'Alessio

*Technical Ressource:* Lizzie Sanchez (FDA)

**MINUTES**

1. **Update on SC and Working Groups.** *Rosario D'Alessio & Justina Molzon*

Rosario provided an update on PANDRH activities including the last meeting of the SC and other working groups. The first page of the PANDRH website was introduced emphasizing that people outside PANDRH WGs will be able to access the information through the Internet. The August 2003 update was provided.
Justina centered her discussion on ICH's Global Cooperation Group and the importance of the PANDRH and BE/WG and set the foundation for discussions for the next two days. She also stated the importance of seeking comments on PANDRH documents from countries in the Americas. Justina emphasized the activities of the BA/BE WG indicating that the topic of BE has not been yet been addressed by ICH, and that if the PANDRH model is successful, it could be implemented in other harmonization processes areas of the world.

2. **Science based criteria for products requiring in vitro and/or in vivo BE studies and those not requiring BE studies**. *Salomon Stavschansky*. (Annex # 1).

General comments:

- Drug regulatory authorities (DRA) should make sure that generic drug products conform to the same standards of quality, efficacy and safety required from innovator drug products. Therefore, regulatory frameworks should be

established to show that generic drug products are therapeutically equivalent and interchangeable with their associated innovator's product. Such regulatory frameworks would necessitate proof of bioequivalence. In the absence of such a regulatory framework, PANDRH's Bioeqivalence Working Group makes the following recommendations: When bioequivalence is the main mechanism used to link the generic product to the innovator's original documentation of safety and efficacy, a framework is proposed to assist drug regulatory authorities to establish requirements for proof of interchangeability by describing when is bioequivalence testing required for multisource products. Further, it also delineates the type of testing, in vivo and/or in vitro, which should be submitted for marketing approval.

- A decision tree provides criteria with illustrative lists for prioritization and implementation.

- BA should be deleted from the document. However, it could be used by the DRA in the implementation and to provide flexibility when there is no regulation for GENERICS.

- Patient safety is of paramount importance.

- There is a need to develop scientific criteria to establish when BE is needed and when it is not. Therefore, there is a need for special considerations of food effects for products requiring in vivo studies.

- Implementation issues can be done through a subcommittee of DRA working with completed document to focus on ramifications and considerations for implementation.

- On the question of relative or comparative BA, some members of the group are of the opinion that it should be left to market forces and that the DRA should not go after companies that have products on the market. It was pointed out that only Mexico and Brazil have generic drug systems. Products currently on the market may not have to be withdrawn. A coding system that describes whether BE information has been provided for that product could be implemented, to inform health professionals and the public of the interchangeability of the product with respect to the reference product.

- On Biopharmaceutics Classification System (BCS): a BCS working group was formed by the Special Interest Group (SIG) on BA/BE of the FIP. The WG is gathering and evaluating reliable published data to support waivers of in-vivo testing based on BCS and developing a standardized protocol to carry out Caco-2 cells permeability studies. This was announced on the FIP Newsletter of July 2003. This information is posted in the FIP WebPage and the

objective is to develop an IBSCDAB International BCS Database.

- "Productos similares" should be defined and included in the glossary to be used in the document the WG/BE is writing for the Americas.

3. **Develop priorized lists (core nucleus and recommended) of pharmaceutical products where in vivo BE are necessary.** *Ricardo Bolanos.* (Annex #2)

Dr. Bolanos provided background on the document "*Propuesta de criterios para la selección de productos farmacéuticos y lista de principios activos a los que se les debería exigir estudios de bioeequivalencia*". He described the categories of health risk, i.e. high, intermediate and low, and the situation that exists in various countries of Latin America in terms of Bioequivalence.

Discussion

- How to utilize the information and lists provided:
    - It was suggested that the lists developed be mapped to the criteria for BE discussed previously (prepared by Dr. Stavchanski) in order to provide a framework to justify the concern for the products placed on the list.
    - Lists could be broken down into the criteria and serve to illustrate the products for each criteria.
    - It should be noted that the list of drugs associated with each criterion is not exhaustive but illustrative.
    - The lists need to be flexible and should be updated when new information is obtained from various agencies. It was pointed out that there are many products that need to be included on the list. The countries have not considered their inclusion and therefore, they are not on the list.
    - It should be considered as a base list and it should include more recently introduced products.
    - By definition, BE is for products off patent. Therefore, products should only be on this list if they are off patent.
    - The difficulty of maintaining the list was discussed. We will never have a perfect list due to the fact that a product's patent expires every month.

- The list will distract from the intent to require BE studies for high-risk products and it will endanger the report to the IV Conference.

- It was suggested to provide the list to the countries, in alphabetical order, to determine what needs to be done and also to add an additional column with criteria: Criteria won't change, the List will.

- Consider adding the WHO list (made from Canada, Germany, USA).

- Criteria:

  - It may have more than one category on criteria. An illustrative list can be used.

  - After discussing weighting based on which countries require BE study, it was decided that once the criteria is described (Health risk from the document), prioritization will be on expanding scale for health risk. It should be deleted information.

  - A Matrix should be created so that each country can make its own conclusions.

  - The most critical drugs should be used to start the process. Health risk is the most important criteria. Each country should decide what they need to do.

  - There is a need for scientific basis for each list. Each country can choose percentile based on their capacity.

  - Only Mexico and Brazil have generic regulations laws. Once other countries have laws it will no longer be necessary to decide sanitary risk as studies will be required. The list is only temporary to help solve the problem of "productos similares" currently on the market.

- Number of drugs in the list

  - It was noted that there are too many drugs in the list.

  - Quadrant approach: High sanitary risk and high risk of bio-inequivalence.

  - Developed sanitary risk column and ranked. Develop higher risk of bio-inequivalence to cut down the size of the list in order to come up with minimum points to start to require BE of products on the market and those being introduced into the market.

- A mechanism to cut down the list and add an element of risk evaluation.

- The country list just confirms sanitary risk conclusion. Won't change ranking.

- How to weight criteria. A lot of these criteria came to exist as ways to decide if met criteria should be discussed individually. Look at the drug and look at the characteristics and the factors to determine if they are on the list or not. It was not meant to focus on the factors individually. Critical or not critical drug yes/no. See Canada's document that defines the factors to be considered to assess the need for in vivo bioequivalence assessment for drugs or drug products.

- Once decide critical drug use work already done.

- Summary

  - The WG/BE needs to decide which documents will be used. The Secretariat (PAHO) will take care of work—need decision. How do we combine the documents: Ricardo will work with Salomon to get documents together. They will consolidate the criteria and will consolidate the two documents. By the end of the year the new document should be ready for discussion during the next meeting of the WG.

  - The new document will be sent out for comments.

  - Draft an implementation plan.

    - Loreta—guide in EMEA document includes decision tree format in implementation, -Not accepted by the group.

    - The group agreed to deal with the scientific issues first and address the implementation issues later on.

    - Decision tree for implementation: Harmonization registration strategies amongst the countries so they don't have to repeat the studies.

4. **Implementation of Technical seminars: programs, schedules, participants and speakers**. *Lizzie Sanchez*

DISCUSSION:

- Module 1&2:

- Only Modules 1+2 were developed. The training has been provided only in Caracas and Costa Rica. At the moment the FDA is in the process of revising the materials.

- It is necessary to select the next country where the training will take place. The possibility of implementing the training in Mexico will be discussed with Mexico authorities next week. There is a high possibility that the seminar will be implemented in October this year. Mexico—easier to organize. The Fall could be a good time for them.

- The subregional seminar for MERCOSUR, was programmed to take place in Argentina. For different reasons this seminar was postponed several times. Two considerations: To define if Argentina (ANMAT) will offer the seminar or if the location should be changed to another MERCOSUR country. Ricardo Bolanos will communicate this to ANMAT authorities and will inform the Secretariat accordingly. However, it does not seem feasible that the seminar will be offered before the end of the year. There is also a possibility to move the training to another MERCOSUR country, such as Brazil, where the National Congress will take place (October 1-3). The Course could be offered before or after the Congress. The professors could come from other MERCOSUR countries. Two professors from Chile and two from Argentina already participated at the AA meeting. Therefore, they could also assume the responsibility for helping with the implementation of the meeting.

- English speaking staff could do the course for the CARICOM in a 2-day seminar. Maybe Larry Lesko would be interested. Since it is a subregional activity, high cost is involved due to travel costs. Key countries that must participate: Guyana, Trinidad, Jamaica, Barbados, and Santa Lucia.

• Module 3&4

- Assistance from senior staff from the FDA will be required to organize Modules 3&4. The modules will only be given in English and, therefore, translation to Spanish will be necessary.

- Module 3 in English at the regional level could possibly be worked out with DIA.

- Module 4 will need to be more practical with hands on experience.

- It can be programmed in English only. The people selected could be train in data analysis in a central location. For example, Pharsight software sessions gratis—output more user friendly; FDA then focuses on

regulatory decisions in training. Module 4 should be offered in a location where computers are available. Spread sheets for pk data and ANOVA. The training should focus to those with good PK and PCOL background and good math skills. Could use help from others. Perhaps Canada could help with the training since the system is similar to FDA.

- General comments:

  - o It was emphasized that the training is to strengthen DRA ability to analyze BE submissions. All training is open to the private sector but will don't charge much for the program.

  - o In the past the tuition has been $200. It needs to be increased. All activities have selected number of registration fees waived from government's representatives.

  - o DRA is responsible for selecting the participants from regulatory agencies. There is a need for selecting the best candidates. Problems have risen when participants are not the most suitable candidates to reproduce the activity. Participants should also include University Professors to help implement/reproduce the program.

  - o Given materials need to be done to help the countries.

  - o The WG/BE needs to find the way to disseminate the work to justify the effort. It is the responsibility of the group to help promote the network. The work of the group should be cited in conferences, speeches and other presentations attended by the members of the group at national or international activities outside PANDRH. There is also a need to change the culture of MOH to recognize this important initiative by PANDRH.

  - o Loreta and Sol will design the strategic plan—to create identity.

**5. Status of the working Plan. Review & Pending issues:**

5.1 Develop a list of pharmaceutical products where in vivo BE studies are not necessary

- o The needed information is already provided and included in the Criteria document
- o It will be completed by information provided by Lizzie (Annex #3) and incorporated into Sol's document.

5.2 Develop a list of comparator drug products for use in the American Region

- The letter sent by WHO on this issue has been obtained.
- The SC suggested holding a meeting in Washington DC at PAHO HQ before December 2003 with responsible participants: PAHO, FIFARMA, ALIFAR, USP, and FDA.
- For that meeting, it is necessary to have the consolidated document Salomon and Ricardo are working on and the list of products to come up with the comparators.
- During the discussion it was pointed out that in the WHO algorithm—the innovator must solve the problem if not marketed in every country. Example of problem in Mexico--Zantac by national brand—innovator not in the country. When the innovator requested marketing approval, Mexico opted for changing the reference product to the innovator product—uses international index.

5.3 Questionnaire for updated BE situation in the Americas.

- The Secretariat will send the last questionnaire to Silvia (ALIFAR). They will develop a DRAFT by Sept 15.
- The Diagnostic Survey will be sent by the Secretariat with other surveys from other WGs since they are directed to the same DRA.
- Strategies for implementation. Will be discussed at the next meeting.

**6. The next Meeting of the Group will be the IV Conference. *The Secretariat***

- It was recommended by the SC that the BE group should meet twice a year.
- In accordance to the Meeting Plan approved by the SC, the next meeting of the BE should be in January. However, a possibility of holding the meeting next June is being considered, to allow the WG members to participate at the annual meting of DIA. This meeting will be held in Washington, DC, in June 2004. The Secretariat is considering this possibility jointly with the DIA and the Coordinator of the BE Group. The Secretariat will inform the WG as soon as the decision is made.
- The agenda for the next meeting will include the materials and the agenda for the IV Conference.

- The second meeting of 2004 should take place after the IV Conference.

**ANNEX # 1**

**Proposed criteria for bioequivalence testing (in vitro and in vivo) and for waivers of in vivo testing of generic drug products. Draft Prepared by Salomon Stavchansky, Ph.D.**

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*Introduction*

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

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

1. Guidelines Published by the Food and Drug Administration

2. Health Canada's Guideline on Preparation of DIN Submissions.

3. The WHO document (1999) entitled Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: a Manual for Drug Regulatory Authorities; Annex 3: *Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability.

4. ICH documents

The mission of the taskforce on Bioavailability and Bioequivalence appointed by PAHO-BE workgroup is to develop a set of criteria for bioequivalence-bioavailability testing of generic drug products, similar products (productos similares), and multisource products.

*Oral Drugs/drug products for which in vivo documentation of equivalence is considered especially important*

The following are factors and oral drugs/drug products that should be considered when requesting in vivo documentation of equivalence.

1. Oral immediate release pharmaceutical products with systemic action when one or more of the following criteria apply:

    - indicated for serious conditions requiring assured therapeutic response,

    - narrow therapeutic window/safety margin; critical drugs, steep dose-response curve; drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening events.

Some factors to take into account when considering these drug products are:

2. serious dose-dependent adverse effects exist close to the dosing range,

3. narrow therapeutic range or narrow tolerance range,

4. requirement for blood level monitoring to control and individualize treatment; this is the standard of care or normal condition of use,

5. dosing based on body weight or other highly individualized dosing requirement,

6. serious clinical consequences of overdosing (toxicity) or under-dosing (lack of effect),

7. steep dose response relationship for efficacy and/or toxicity,

8. pharmacokinetics complicated by variable or incomplete absorption or absorption window, nonlinear pharmacokinetics, pre-systemic elimination/high first-pass metabolism >70% and or complicated metabolic pathways,

9. unfavorable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability, etc.,

10. documented evidence for bioavailability problems related to the drug or drugs of similar chemical structure or formulations,

11. where a high ratio of excipients to active ingredients exists,

12. Non-oral and non-parenteral pharmaceutical products designed to act by systemic absorption (such as transdermal patches, suppositories, etc.),

13. Sustained or otherwise modified release pharmaceutical products designed to act by systemic absorption,

14. Fixed combination products (see WHO Technical Report Series No. 825, 1992) with systemic action,

15. Non-solution pharmaceutical products which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc. application) and are intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence. This does not, however, exclude the potential need for drug concentration measurements in order to assess unintended partial absorption.

In cases (1) to (14) plasma concentration measurements over time (bioequivalence) are normally sufficient proof for efficacy and safety. In case (15) the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence.

*Criteria recommended for waiver of evidence of in vivo bioavailability or bioequivalence*

Generally, for orally administered drug products both in-vivo and in-vitro testing are necessary. In-vivo testing is required for all generic drug products with some exceptions. It is possible for regulatory agencies to waive the requirement for bioavailability or bioequivalence.

A drug product's in vivo bioavailability or bioequivalence may be waived if the product meets one of the following criteria:

The drug product:

1. is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution. When multisource pharmaceutical products are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations,

2. are solutions for oral use, contain the active substance in the same concentration, and do not contain an excipient that is known or suspected to affect gastro-intestinal transit or absorption of the active substance,

3. are powders for reconstitution as a solution and the solution meets either criterion (1) or criterion (2) above,

4. contains the same active and inactive ingredients in the same concentration as the designated reference product,

5. is administered by inhalation as a gas, e.g., a medicinal or an inhalation anesthetic and contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application,

6. is a solution for application to the skin, an oral solution, elixir, syrup, tincture, or similar other solubilized form. Contains an active drug ingredient in the same concentration and dosage form as the reference drug product that is the subject of an approved full new drug application, and contains no inactive ingredient or other change in formulation from the drug product that is

the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety,

7. drug products for inhalation and nasal sprays for use with or without a device, presented in an aqueous solution and containing the same drug, at the same concentration of the reference drug product and excipients of same function, with compatible concentration levels,

8. oral drug products containing active ingredients that are designed not to be absorbed in the gastrointestinal tract.

It is incumbent upon the applicant to demonstrate that the excipients in the drug product are essentially the same and in comparable concentrations as those in the reference product. In the event this information about the reference product cannot be provided by the applicant and the drug regulatory authority does not have access to these data, in vivo studies should be performed.

*For certain drug products, bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data.*

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

a) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the following conditions are met:

1. The bioavailability of this other drug product has been demonstrated;
2. Both drug products meet an appropriate in vitro test approved by FDA; and
3. The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.
4. This subparagraph does not apply to enteric coated or controlled release dosage forms.
5. The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.
6. The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for

which the same manufacturer has obtained approval and the following conditions are met:

a) The bioavailability of the other product has been demonstrated;

b) Both drug products meet an appropriate in vitro test approved by the Regulatory Agency.

7. Regulatory Agencies, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability if waiver is compatible with the protection of the public health.

8. Regulatory Agencies, for good cause, may require evidence of in vivo bioavailability or bioequivalence for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product.

*In-Vitro Testing. New Paradigm*

*Biopharmaceutics Classification System*

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

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

In addition, immediate release solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo. However, when the in vivo dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of in vivo Bioavailability or Bioequivalence may not be necessary for drug products containing Class 1 drug

substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach can be used to justify biowaivers for highly soluble and highly permeable drug substances (i.e., Class 1) in Immediate release solid oral dosage forms that exhibit rapid in vitro dissolution using USP recommended test methods. The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

*Solubility*

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

*Permeability*

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

*Dissolution*

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

Under certain circumstances, product quality, Bioavailability and Bioequivalence can be documented using in vitro approaches. For highly soluble, highly permeable, rapidly dissolving, and orally administered drug products, documentation of Bioequivalence using an in vitro approach (dissolution studies) is appropriate based on the biopharmaceutics classification system.

This approach may also be suitable under some circumstances in assessing Bioequivalence during the initial registration period, and in the presence of certain post-approval changes to approved applications. In addition, in vitro approaches to documenting Bioavailability for **productos similares** approved before the new bioequivalence and bioavailabililty requirements of the new health law.

Dissolution testing is also used to assess batch-to-batch quality, where the dissolution tests, with defined procedures and acceptance criteria, are used to allow batch release.

Dissolution testing is also used to:

1. Provide process control and quality assurance,

2. Assess whether further BE studies relative minor post-approval changes be conducted, where dissolution can function as a signal of bioinequivalence,

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

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

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

**For new drug products applications and Similar Products (productos similares):**

4. The pH solubility profile of the drug substance

5. Dissolution profiles generated at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm) for U.S. Pharmacopoeia (USP) Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle))

6. Dissolution profiles generated on all strengths in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants are recommended.

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

**For Generic Products**

**For immediate-release drug products**:
It is recommended that the appropriate USP method be submitted. If there is no USP method available, the Regulatory Agency's method for the reference drug product drug is used. If the USP and/or Regulatory Agency methods are not available, a dissolution method development report can be submitted.

**For modified-release products**:

1. dissolution profiles using the appropriate USP method (if available) can be submitted. If there is no USP method available, the Regulatory Agency's method for the reference drug product is used.

2. profiles using at least three other dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) and water would be provided.

Three batches for both new drug applications and generic drug applications are used to set dissolution specifications for modified-release dosage forms, including extended-release dosage forms.

*Illustrative List of products for which in-vivo BE studies are not necessary*

A. Injectable, Ophthalmic and Otic Solutions, provided that the active and inactive ingredients are qualitatively and quantitatively the same as the reference listed drug (RLD)

B. Oral and Topical solutions- provided that differences in inactive ingredients are characterized and do not affect the absorption of the active ingredient of the product.

C. Immediate release drug products with a determination of efficacy, which are not known to have bioproblems. The Regulatory Agency may request in vitro dissolution testing for oral solid dosage forms - Examples include
Acetaminophen and codeine tablets, folic acid tablets, Hydrocortisone cream and ointment, Triamcinolone ointment, Cytarabine injectable, dacarbazine injectable.

D. Biopharmaceutics Classification System (BCS) class 1:
Example: Metoprolol

*Food Effects*

1. For uncomplicated Drugs in Immediate-Release Dosage Forms bioequivalence must be demonstrated under fasted conditions

2. For complicated Drugs in Immediate-Release Dosage Forms (e.g., narrow therapeutic range drugs (drugs with a steep dose -response curve, critical drugs), highly toxic drugs and non-linear drugs). Bioequivalence must be demonstrated under both fasted and fed conditions.

3. Non-Linear Drugs
   Bioequivalence must be demonstrated under both fasted and fed conditions unless the non-linearity occurs after the drug enters the systemic circulation and there is no evidence that the product exhibits a food effect.

4. Drugs in Modified-Release Dosage Forms
   BE must be demonstrated under both fasted and fed conditions.

The test meal employed in comparative Bioavailability studies conducted in the fed state should be of a nature and content that would promote the maximal perturbation in Bioavailability of the drug from the drug product. This would be accomplished by administration of a meal of known and fixed high fat and high caloric content. As the test meal for Bioequivalence purposes is usually administered as a breakfast, an example would be: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash browns and 8 ounces of whole milk. Sponsors must be able to justify the choice of meal in a fed bioequivalence study and relate the specific components and timing of food administration.

*Special Regional Considerations*

*Brazilian regulation*

The following situations are particular to the Government of Brazil:

1. The following drugs are classified by the Brazilian regulation as type I drugs. Companies with products classified as type I drugs by the Brazilian Government have a short deadline to present studies to prove their bioequivalence to the reference drug product:

1. Valproic acid
2. Aminophylline
3. Carbamazepine
4. Cyclosporine
5. Clindamicyne

6. Clonidine
7. Clozapine
8. Digoxin
9. Disopyramide
10. Phenytoin
11. Lithum
12. Isotretinoin
13. Minoxidil
14. Oxcarbazepine
15. Prazosin
16. Primidona
17. Procainamide
18. Quinidine
19. Theophylline
20. Verapamil
21. Warfarin

2. Solid dosage forms containing acetylsalicylic acid, acetaminophen, dipyrone or ibuprofen, exempt from medical prescription, will be waived from the bioequivalence study if the dissolution profiles are comparable to the reference drug products

*References*


1. Requirements for Bioequivalence Testing

A. United States Code of Federal Regulations, Title 21 (21 CFR 314 and 320):
21 CFR 314. 94(a) (7) Content and format of an abbreviated drug application- establishes the requirement for BE in ANDAs
http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfrv5_02.html
(Click on 314, then on 314.94) Click on 320 for regulations on BA/BE)

21 CFR 320.1 provides definitions of BA/BE, drug product, pharmaceutical equivalents, pharmaceutical alternatives and BE requirement.
320.21 Requirements for submission of in vivo BA and BE data.
320.23 Basis for demonstrating in vivo BA or BE
320.24 Types of evidence to establish BA or BE

3. Guidances
4. 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 Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation

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

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

**ANNEX # 2**

**Propuesta de criterios para la selección de productos farmacéuticos y lista de principios activos a los que se les debería exigir estudios de bioequivalencia**. Borrador preparado por: Ricardo Bolaños, Ana María Concha e Irene Goncalves.

***TABLA DE CONTENIDOS***

## 1.- Introducción

En el mes de enero del año 1999, se realizó en Caracas, Venezuela, una reunión de expertos de la región en temas de bioequivalencia. De dicha reunión surgió un documento denominado *"Consultation of Experts on Bioequivalence of Pharmaceutical Products, June 1999"*. En el mencionado documento, en las conclusiones, punto 3), último párrafo, se establece que cuando los países no pueden aplicar totalmente el estándar (de bioequivalencia), se recomienda que se aplique gradualmente.

Los países de la Región, se encuentran en esta situación planteada, es decir, no pueden, por diferentes razones operativas y administrativas, aplicar plenamente el estándar de exigencia de estudios de bioequivalencia a todos los productos.

Esta situación plantea una cuestión de relevante importancia, pues no pudiendo aplicarse plenamente el estándar, debe procederse a una selección *racional* de principios activos a los que se les debería exigir estudios de bioequivalencia.

La selección de principios activos para exigencia de estudios de bioequivalencia, es una decisión de salud pública y como tal debe tener en cuenta la relación Beneficio/Riesgo de los principios activos.

Ante esta situación surge el concepto de Riesgo Sanitario, es decir qué principios activos son más riesgosos para la salud pública.

Un acercamiento posible es tener en cuenta qué principios activos, por sus características farmacológicas, deben ser controlados mediante determinaciones en sangre **(Tabla I).**

### 1.1 Drogas habitualmente monitoreadas en sangre

**Tabla I.- RANGOS TERAPÉUTICOS DE FÁRMACOS HABITUALMENTE MONITORIZADOS** (FLOREZ,J: FARMACOLOGÍA HUMANA. 2a.Ed. Edit. Masson, Barcelona, 1992).

| DROGA | TER.MIN. | TER.MAX. | TOX.MIN. | TOX.MAX. | UNIDADES |
|---|---|---|---|---|---|
| AMIKACINA | 1-4 | 20-25 | >10 | >30-35 | ug/ml |
| AMITRIPTILINA + NORTRIPTILINA | 150-250 | - | >300 | - | ng/ml |
| CARBAMEZEPINA | 4-8 | 8-12 | >8 | >15 | ug/ml |
| CICLOSPORINA | 150-300 | - | >300 | - | ng/ML |
| CLORAMFENICOL | 10 | 20 | - | >25 | ug/ml |
| CLORPROMAZINA | 100-200 | - | >500 | - | ng/ml |
| DESMETIILIMI-PRAMINA | 125-300 | - | - | - | ng/ml |
| DIGOXINA | 0.5-1.5 | - | >2 | - | ng/ml |
| ETOSUXIMIDA | 40-80 | - | >150 | - | ug/ml |
| FENITOÍNA | 10-20 | - | >20 | - | ug/ml |
| FENITOÍNA (ANTIARR.) | 10 | 20 | - | >20 | ug/ml |
| FENOBARBITAL | 15-25 | - | >30 | - | ug/ml |
| GENTAMICINA | 0.5-1 | 6-8 | >2 | >10-12 | ug/ml |
| HALOPERIDOL | 10-15 | - | >10 | - | ng/ml |
| IMIPRAMINA+DES-METILIMIPRAMINA | 150-250 | - | - | - | ng/ml |
| LIDOCAÍNA | 2 | 5 | - | >5 | ug/ml |
| LITIO | 0.8-1.2 | - | >1.5 | - | mEq/L |
| METOTREXATO (48hs) | - | - | $>10^{-6}$ | - | mol/L |
| NETILMICINA | 0.5-1 | 6-8 | >2 | >10-12 | ug/ml |
| **DROGA** | **TER.MIN.** | **TER.MAX.** | **TOX.MIN.** | **TOX.MAX.** | **UNIDADES** |
| ***NORTRIPTILINA*** | 50-150 | - | - | - | ng/ml |
| PRIMIDONA | 5-10 | - | >10 | - | ug/ml |
| PROCAINAMIDA | 4 | 8 | - | >10 | ug/ml |
| QUINIDINA | 3 | 5 | - | >6 | ug/ml |
| SALICILATOS | 150 | 300 | - | >300 | ug/ml |
| TEOFILINA | 10 | 20 | - | >20 | ug/ml |
| TIOPENTAL (INF.CONTINUA) | 2.5-5 | - | - | - | mg/100ml |
| TOBRAMICINA | 0.5-1 | 6-8 | >2 | >10-12 | ug/ml |
| VALPROATO (Na) | 50-100 | - | >100 | - | ug/ml |
| VANCOMICINA | 5-10 | 25 | >13 | >25 | ug/ml |

En el recién nacido es importante el monitoreo de aminoglucósidos, cloramfenicol, digoxina y teofilina; en el niño: antiepilépticos y teofilina y en el anciano: digoxina, psicofármacos y teofilina y en la mujer embarazada: aminoglucósidos, antiepilépticos, digoxina, teofilina y litio en los casos excepcionales en que pueda utilizarse.

En la insuficiencia renal, es de importancia la monitorización de aminoglucósidos, vancomicina y litio. En la insuficiencia cardíaca: digoxina, aminoglucósidos, teofilina y

antiarrítmicos. En las alteraciones hepáticas: teofilina y lidocaína.

Desde el punto de vista médico sanitario, puede considerarse el Riesgo, teniendo en cuenta qué consecuencias para la salud tiene el hecho que el principio activo se encuentre por fuera de la ventana terapéutica (entendiendo por tal a la razón entre Concentración Máxima no tóxica y Concentración Mínima efectiva). En este orden de ideas, surgen tres niveles de Riesgo: Alto, Intermedio y Bajo, como se describe a continuación:

### 1.2 Categorías de Riesgo Sanitario

**RIESGO SANITARIO ALTO:** Es la probabilidad de aparición de complicaciones de la enfermedad amenazantes para la vida o para la integridad psicofísica de la persona y/o de reacciones adversas graves (muerte, hospitalización del paciente, prolongación de la hospitalización, discapacidad significativa o persistente, incapacidad o amenaza de muerte) cuando la concentración sanguínea de la droga no se encuentra dentro de la ventana terapéutica.

**RIESGO SANITARIO INTERMEDIO:** Es la probabilidad de aparición de complicaciones de la enfermedad no amenazantes para la vida o para la integridad psicofísica de la persona y/o de reacciones adversas no necesariamente graves cuando la concentración sanguínea de la droga no se encuentra dentro de la ventana terapéutica.

**RIESGO SANITARIO BAJO:** Es la probabilidad de aparición de una complicación menor de la enfermedad y/o de reacciones adversas leves cuando la concentración sanguínea de la droga no se encuentra dentro de la ventana terapéutica.

## 2.- La situación de Exigencia de Estudios de Bioequivalencia en diferentes Países de Latinoamérica

Se ha procedido a revisar la información disponible de 6 países de Latinoamérica: Argentina (A), Brasil (B), Chile (Ch), Colombia (C), Cuba (Cu) y Venezuela (V). Se procedió a excluir aquellos principios activos que se utilizan en formas farmacéuticas excluidas de los estudios de Bioequivalencia (por ejemplo soluciones inyectables). La situación actual, se muestra en las tablas II y III.

**Tabla II.- Principios activos a los que se les exigen estudios de bioequivalencia en diferentes países de Latinoamérica.**

| Droga | Países | | | | | | Exigencia en países |
|---|---|---|---|---|---|---|---|
| | Venezuela | Argentina | Brasil | Chile | Colombia | Cuba | |
| 6-mercaptopurina | X | | X | | | X | 3 |
| Acetazolamida | | | X | | | X | 2 |
| Ácido nalidíxico | | | | | | X | 1 |
| Ácido valproico | X | X | X | X | X | X | 6 |
| Alopurinol | | | X | | | X | 2 |
| Amicacina | | | X | | | | 1 |
| Amitriptilina | | | X | | | | 1 |
| Antirretrovirales | | X | | | | | 1 |
| Atenolol | | | X | | | | 1 |
| Azatioprina | | | | X | | X | 2 |
| Biperideno | | | | | | X | 1 |
| Carbamazepina | X | X | X | X | X | X | 6 |
| Carbonato de litio | X | X | X | X | | X | 5 |
| Ciclofosfamida | | | | | | X | 1 |
| Ciclosporina | X | X | X | X | X | X | 6 |
| Ciprofloxacino | | | | | | X | 1 |
| Clomifeno | | | | | | X | 1 |
| Clozapina | X | | X | | | | 2 |
| Co-trimoxazol | | | | | | X | 1 |
| Desipramina | | | X | | | | 1 |
| Dexametasona | | | X | | | | 1 |
| Digoxina | X | X | X | X | | | 4 |
| Dihidroergotamina | | | X | | | | 1 |
| Diltiazem | X | | | | | | 1 |
| Dinitrato de isosorbide | X | | X | X | | X | 4 |
| Doxiciclina | | | X | | | X | 2 |
| Espiranolactona | | | X | X | | X | 3 |
| Etambutol | | | | | | X | 1 |
| Etinilestradiol | X | | | X | | X | 3 |
| Etopósido | X | | X | | | X | 3 |
| Etosuximida | | X | X | | | | 2 |
| Fenitoína | X | X | X | X | X | X | 6 |
| Fenobarbital | | | X | | | | 1 |
| Flucitosina | | | | | | X | 1 |
| Fludrocortisona | | | | | | X | 1 |
| Flutamida | X | | X | | | | 2 |
| Furosemida | | | | X | | X | 2 |
| Gentamicina | | | X | | | | 1 |
| Glibenclamida | | | X | X | | | 2 |
| Griseofulvina | | | X | X | | | 2 |
| Hidroclorotiazida | | | X | X | | | 2 |
| Imipramina | | | X | X | | | 2 |
| Indometacina | | | X | | | | 1 |
| Insulinas | X | X | | | | X | 3 |
| Isotretinoína | | X | | | | | 1 |
| Ketoconazol | | | | X | | X | 2 |
| Levamisol | | | | | | X | 1 |
| Levodopa + IDDC | | X | X | | | | 2 |

**Tabla II (continuación).- Principios activos a los que se les exigen estudios de bioequivalencia en diferentes países de Latinoamérica.**

| Droga | Países | | | | | | Exigencia en países |
|---|---|---|---|---|---|---|---|
| | Venezuela | Argentina | Brasil | Chile | Colombia | Cuba | |
| Levonorgestrel | X | | | | | | 1 |
| Levotiroxina | X | | | | | | 1 |
| Lidocaína | | | X | | | | 1 |
| Mebendazol | | | | | | X | 1 |
| Mefloquina | | | | | | X | 1 |
| Metoprolol | X | | | | | | 1 |
| Metotrexato | X | | X | X | | X | 4 |
| Metronidazol | | | | X | | X | 2 |
| Micofenolato | | | X | | | | 1 |
| Nifedipina | X | | | X | | X | 3 |
| Nitroglicerina | X | | | X | | | 2 |
| Noretisterona | X | | | | | | 1 |
| Nortriptilina | | | X | | | | 1 |
| Olanzapina | X | | X | | | | 2 |
| Oxcarbazepina | X | X | X | | X | | 4 |
| Oxcazepam | | | X | | | | 1 |
| Pindolol | | | X | | | | 1 |
| Pirazinamida | | | | | | X | 1 |
| Piridostigmina | | X | | | | | 1 |
| Pirimetamina | | | | | | X | 1 |
| Prednisolona | | | X | | | | 1 |
| Primidona | | | X | | | | 1 |
| Procainamida | X | | X | | | X | 3 |
| Procarbazina | | | | | | X | 1 |
| Propranolol | | | X | X | | X | 3 |
| Quinidina | X | X | X | | | | 3 |
| Rifampicina | | | | | | X | 1 |
| Salbutamol, sulfato (oral) | | | | X | | X | 2 |
| Sirolimus | | | X | | | | 1 |
| Sulfasalazina | | | | X | | X | 2 |
| Tacrolimus | | | X | | | | 1 |
| Tamoxifeno | X | | | X | | X | 3 |
| Teofilina | X | X | X | X | | | 4 |
| Terbutalina | | | X | | | | 1 |
| Tobramicina | | | X | | | | 1 |
| Tolbutamida | X | X | X | X | | X | 5 |
| Verapamilo | X | X | X | | | X | 4 |
| Warfarina | X | X | X | | | | 3 |

**Tabla III.- Principios Activos a los que se les exige bioequivalencia en Latinoamérica (ordenamiento por cantidad de países)**

Exigencia en 6 países
- Ácido valproico (Venezuela, Argentina, Brasil, Chile, Colombia, Cuba)
- Carbamazepina (Venezuela, Argentina, Brasil, Chile, Colombia, Cuba)
- Ciclosporina (Venezuela, Argentina, Brasil, Chile, Colombia, Cuba)
- Fenitoína (Venezuela, Argentina, Brasil, Chile, Colombia, Cuba)

*Exigencia en 5 países*
- Carbonato de litio (Venezuela, Argentina, Brasil, Chile, Cuba)
- Tolbutamida (Venezuela, Argentina, Brasil, Chile, Cuba)

Exigencia en 4 países
- Digoxina (Venezuela, Argentina, Brasil, Chile)
- Dinitrato de isosorbide (Venezuela, Brasil, Chile, Cuba)
- Metotrexato (Venezuela, Brasil, Chile, Cuba)
- Oxcarbazepina (Venezuela, Argentina, Brasil, Colombia)
- Teofilina (Venezuela, Argentina, Brasil, Chile)
- Verapamilo (Venezuela, Argentina, Brasil, Cuba)

Exigencia en 3 países
- 6- mercaptopurina (Venezuela, Brasil, Cuba)
- Espironolactona (Brasil, Chile, Cuba)
- Etinilestradiol (Venezuela, Chile, Cuba)
- Etopósido (Venezuela, Brasil, Cuba)
- Insulinas (Venezuela, Argentina, Cuba)
- Nifedipina (Venezuela, Chile, Cuba)
- Procainamida (Venezuela, Brasil, Cuba)
- Propranolol (Brasil, Chile, Cuba)
- Quinidina (Venezuela, Argentina, Brasil)
- Tamoxifeno (Venezuela, Chile, Cuba)
- Warfarina (Venezuela, Argentina, Brasil)

Exigencia en 2 países
- Acetazolamida (Brasil, Cuba)
- Alopurinol (Brasil, Cuba)
- Azatioprina (Chile, Cuba)
- Clozapina (Venezuela, Brasil)
- Doxiciclina (Brasil, Cuba)
- Etosuximida (Argentina, Brasil)
- Flutamida (Venezuela, Brasil)
- Furosemida (Chile, Cuba)
- Glibenclamida ( Brasil, Chile)
- Griseofulvina (Brasil, Chile)
- Hidroclorotiazida (Brasil, Chile)
- Imipramina (Brasil, Chile)
- Ketoconazol (Chile, Cuba)
- Levodopa + IDDC (Argentina, Brasil)
- Metronidazol (Chile, Cuba)
- Nitroglicerina (Venezuela, Chile)
- Olanzapina (Venezuela, Brasil)
- Salbutamol, Sulfato (oral) (Chile, Cuba)
- Sulfasalazina (Chile, Cuba)

Exigencia en 1 país
- Ácido nalidíxico (Cuba)
- Amikacina (Brasil)
- Amitriptilina (Brasil)

- Antirretrovirales (Argentina)
- Atenolol (Brasil)
- Biperideno (Cuba)
- Ciclofosfamida (Cuba)
- Ciprofloxacino (Cuba)
- Clomifeno (Cuba)
- Co-trimoxazol (Cuba)
- Desipramina (Brasil)
- Dexametasona (Brasil)
- Dihidroergotamina (Brasil)
- Diltiazem (Venezuela)
- Etambutol (Cuba)
- Fenobarbital (Brasil)
- Flucitosina (Cuba)
- Fludrocortisona (Cuba)
- Gentamicina (Brasil)
- Indometacina (Brasil)
- Isotretinoína (Argentina)
- Levamisol (Cuba)
- Levonorgestrel (Venezuela)
- Levotiroxina (Venezuela)
- Lidocaína (Brasil)
- Mebendazol (Cuba)
- Mefloquina (Cuba)
- Metoprolol (Venezuela)
- Micofenolato (Brasil)
- Noretisterona (Venezuela)
- Nortriptilina (Brasil)
- Oxazepam (Brasil)
- Pindolol (Brasil)
- Pirazinamida (Cuba)
- Piridostigmina (Argentina)
- Pirimetamina (Cuba)
- Prednisolona (Brasil)
- Primidona (Brasil)
- Procarbazina (Cuba)
- Rifampicina (Cuba)
- Sirolimus (Brasil)
- Tacrolimus (Brasil)
- Terbutalina (Brasil)
- Tobramicina (Brasil)

## 3.- Propuesta de metodología para la selección de principios activos a los que se deberían exigir estudios de bioequivalencia

Si bien es cierto que existen otros factores a considerar como los parámetros fisicoquímicos y farmacocinéticos, desde el punto de vista de la Salud Pública el elemento más importante a tener en cuenta es el Riesgo Sanitario, habida consideración de la *realidad observada* en los países de la Región. Por esta razón es que se optó por elegir un Modelo Ponderado en el cual se tuvieron en cuenta ambos aspectos: Riesgo Sanitario y Realidad Observada, pero dándole una ponderación diferente a cada uno. De esta manera surge el siguiente Modelo:

**Puntaje Total = (Riesgo Sanitario x 3) + (Nº de países que exigen estudios x 1).**

**Riesgo Sanitario:** se procedió a asignarle 3 puntos a Riesgo Sanitario Alto, 2 punto a Riesgo Sanitario Intermedio y 1 punto a Riesgo Sanitario Bajo.
Tomando como ejemplo a la Fenitoína se obtiene lo siguiente:
Riesgo Sanitario : Alto (3 puntos)

Nº de países en que se exigen estudios de bioequivalencia: 6
Puntaje Total = (3 x 3) + (6 x 1) = 15 puntos.
A los efectos de proceder a la selección final y tomando criterios estadísticos, se procedió a utilizar el Percentilo.

De esta manera, ordenados los principios activos por su puntaje de mayor a menor, se encontró que el Percentilo 20 (20% de los principios activos), da la posición 15, ello corresponde a Puntaje Total= 10. Con esto se decide que en la primera etapa de exigencia los principios activos a los que debería exigírseles estudios de bioequivalencia son los siguientes (Tabla IV):

**Tabla IV.- Principios activos seleccionados para la realización de estudios de Bioequivalencia.**

| **Principio activo** | ***Puntaje*** |
|---|---|
| Fenitoína | 15 |
| Carbamazepina | 15 |
| Ácido Valproico | 15 |
| Ciclosporina | 15 |
| Tolbutamida | 14 |
| Carbonato de litio | 14 |
| Verapamilo | 13 |
| Teofilina | 13 |
| **Digoxina** | 13 |
| Oxcarbazepina | 13 |
| Procainamida | 12 |
| Warfarina | 12 |
| Quinidina | 12 |
| Etosuximida | 11 |
| Metotrexato | 10 |

Estos resultados surgen del análisis que se muestra en las Tablas V y VI.

**Tabla V:- Ordenamiento de principios activos de acuerdo a su puntaje**

| DROGA | RIESGO SANITARIO | PONDERA-CIÓN | RIESGO PONDER. | EXIGENCIA PAÍSES | PONDERA-CIÓN | EXIGENCIA PONDER. | PUNTAJE TOTAL |
|---|---|---|---|---|---|---|---|
| Fenitoína | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Carbamazepina | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Ácido Valproico | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Ciclosporina | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Tolbutamida | 3 | 3 | 9 | 5 | 1 | 5 | 14 |
| Carbonato de litio | 3 | 3 | 9 | 5 | 1 | 5 | 14 |
| Verapamilo | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Teofilina | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Digoxina | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Oxcarbazepina | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Procainamida | 3 | 3 | 9 | 3 | 1 | 3 | 12 |
| Warfarina | 3 | 3 | 9 | 3 | 1 | 3 | 12 |
| Quinidina | 3 | 3 | 9 | 3 | 1 | 3 | 12 |
| Etosuximida | 3 | 3 | 9 | 2 | 1 | 2 | 11 |
| Metotrexato | 2 | 3 | 6 | 4 | 1 | 4 | 10 |
| 6-Mercaptopurina | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Etopósido | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Etinilestradiol | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Tamoxifeno | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Propranolol | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Azatioprina | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Salbutamol, sulfato | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Levodopa + Inhib.DDC | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Nitroglicerina | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Dinitrato de isosorbide | 1 | 3 | 3 | 4 | 1 | 4 | 7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Biperideno | 2 | 3 | 6 | 1 | 1 | 1 | 7 |

Tabla V:- Ordenamiento de principios activos de acuerdo a su puntaje (continuación)

| DROGA | RIESGO SANITARIO | PONDERA-CIÓN | RIESGO PONDER. | EXIGENCIA PAÍSES | PONDERA-CIÓN | EXIGENCIA PONDER. | PUNTAJE TOTAL |
|---|---|---|---|---|---|---|---|
| Desipramina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Etambutol | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Fludrocortisona | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Flucitosina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Nortriptilina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Isotretinoína | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Levotiroxina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Metoprolol | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Levonorgestrel | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Norestisterona | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Amitriptilina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Atenolol | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Fenobarbital | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Nifedipina | 1 | 3 | 3 | 3 | 1 | 3 | 6 |
| Espironolactona | 1 | 3 | 3 | 3 | 1 | 3 | 6 |
| Glibenclamida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Doxiciclina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Alopurinol | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Furosemida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Griseofulvina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Imipramina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Ketoconazol | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Metronidazol | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Sulfasalazina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Hidroclorotiazida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Acetazolamida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |

Tabla V:- Ordenamiento de principios activos de acuerdo a su puntaje (continuación).

| DROGA | RIESGO SANITARIO | PONDERA-CIÓN | RIESGO PONDER. | EXIGENCIA PAÍSES | PONDERA-CIÓN | EXIGENCIA PONDER. | PUNTAJE TOTAL |
|---|---|---|---|---|---|---|---|
| Flutamida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Clozapina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Olanzapina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Ciclofosfamida | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Ciprofloxacino | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Clomifeno | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Dexametasona | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Dihidroergotamina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Indometacina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Levamisol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Mebendazol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Mefloquina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Ácido Nalidixico | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Oxazepam | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Pindolol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Pirazinamida | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Pirimetamina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Prednisolona | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Primidona | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Procarbazina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Rifampicina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Co-trimoxazol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Piridostigmina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Diltiazem | 1 | 3 | 3 | 1 | 1 | 1 | 4 |

Tabla VI.- Ordenamiento alfabético de principios activos.

| DROGA | RIESGO SANITARIO | PONDERA-CIÓN | RIESGO PONDER. | EXIGENCIA PAÍSES | PONDERA-CIÓN | EXIGENCIA PONDER. | PUNTAJE TOTAL |
|---|---|---|---|---|---|---|---|
| 6-Mercaptopurina | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Acetazolamida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Ácido Nalidixico | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Ácido Valproico | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Alopurinol | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Amitriptilina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Atenolol | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Azatioprina | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Biperideno | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Carbamazepina | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Carbonato de litio | 3 | 3 | 9 | 5 | 1 | 5 | 14 |
| Ciclofosfamida | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Ciclosporina | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Ciprofloxacino | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Clomifeno | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Clozapina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Co-trimoxazol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Desipramina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Dexametasona | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Digoxina | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Dihidroergotamina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Diltiazem | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Dinitrato de isosorbide | 1 | 3 | 3 | 4 | 1 | 4 | 7 |
| Doxiciclina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Espironolactona | 1 | 3 | 3 | 3 | 1 | 3 | 6 |
| Etambutol | 2 | 3 | 6 | 1 | 1 | 1 | 7 |

Tabla VI.- Ordenamiento alfabético de principios activos (continuación).

| DROGA | RIESGO SANITARIO | PONDERA-CIÓN | RIESGO PONDER. | EXIGENCIA PAÍSES | PONDERA-CIÓN | EXIGENCIA PONDER. | PUNTAJE TOTAL |
|---|---|---|---|---|---|---|---|
| Etinilestradiol | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Etopósido | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Etosuximida | 3 | 3 | 9 | 2 | 1 | 2 | 11 |
| Fenitoína | 3 | 3 | 9 | 6 | 1 | 6 | 15 |
| Fenobarbital | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Flucitosina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Fludrocortisona | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Flutamida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Furosemida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Glibenclamida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Griseofulvina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Hidroclorotiazida | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Imipramina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Indometacina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Isotretinoína | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Ketoconazol | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Levamisol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Levodopa + Inhib.DDC | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Levonorgestrel | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Levotiroxina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Mebendazol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Mefloquina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Metoprolol | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Metotrexato | 2 | 3 | 6 | 4 | 1 | 4 | 10 |
| Metronidazol | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Nifedipina | 1 | 3 | 3 | 3 | 1 | 3 | 6 |

Tabla VI.- Ordenamiento alfabético de principios activos (continuación).

| DROGA | RIESGO SANITARIO | PONDERA-CIÓN | RIESGO PONDER. | EXIGENCIA PAÍSES | PONDERA-CIÓN | EXIGENCIA PONDER. | PUNTAJE TOTAL |
|---|---|---|---|---|---|---|---|
| Nitroglicerina | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Norestisterona | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Nortriptilina | 2 | 3 | 6 | 1 | 1 | 1 | 7 |
| Olanzapina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Oxazepam | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Oxcarbazepina | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Pindolol | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Pirazinamida | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Piridostigmina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Pirimetamina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Prednisolona | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Primidona | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Procainamida | 3 | 3 | 9 | 3 | 1 | 3 | 12 |
| Procarbazina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Propranolol | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Quinidina | 3 | 3 | 9 | 3 | 1 | 3 | 12 |
| Rifampicina | 1 | 3 | 3 | 1 | 1 | 1 | 4 |
| Salbutamol, sulfato | 2 | 3 | 6 | 2 | 1 | 2 | 8 |
| Sulfasalazina | 1 | 3 | 3 | 2 | 1 | 2 | 5 |
| Tamoxifeno | 2 | 3 | 6 | 3 | 1 | 3 | 9 |
| Teofilina | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Tolbutamida | 3 | 3 | 9 | 5 | 1 | 5 | 14 |
| Verapamilo | 3 | 3 | 9 | 4 | 1 | 4 | 13 |
| Warfarina | 3 | 3 | 9 | 3 | 1 | 3 | 12 |

**4.- Bibliografía consultada**

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- Resolución Número 01400 de 2001. Por la cual se establece la Guía de Biodisponibilidad y de Bioequivalencia de Medicamentos que trata el Decreto 677 de 1995. Diario Oficial de la República de Colombia Nº 44554. Septiembre 17 de 2001.

**Annex # 3**

## Criteria for bioequivalence testing (in-vivo and in-vitro) and for waivers of in-vivo testing of generic products approved by the Food and Drug Administration. (Lizzie/FDA)

In vivo and/or in-vitro BE testing is required for most generic drug products submitted for marketing approval in Abbreviated New Drug Applications (ANDAs). A proposed generic drug product submitted in an ANDA must be compared to the officially designated reference listed drug (RLD) in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book).

Products approved before 1938 were "grandfathered" and ANDAs are not accepted for these products. Products approved between 1938 and 1962 were evaluated for efficacy in the "Drug Efficacy Study Implementation" (DESI) review. For those products found to be effective for the labeled indication during this review, ANDAs are accepted by the FDA. The Orange Book includes all products approved after 1962 (based on evidence of safety and efficacy) and DESI products with a determination of efficacy.

Generally, for orally administered drug products both in-vivo and in-vitro testing are necessary. In-vivo testing is required for all generic drug products with the following exceptions:

- 21 CFR Sec. 320.22: Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:
(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

(2)The drug product:

(i) Is administered by inhalation as a gas, e.g., a medicinal or an inhalation anesthetic; and

(ii) Contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application.

(3) The drug product:

(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, or similar other solubilized form.

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and

(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety.

(c) FDA shall waive the requirement for the submission of evidence demonstrating the in vivo bioavailability of a solid oral dosage form (other than an enteric coated or controlled release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or which is identical, related, or similar to such a drug product under Sec. 310.6 of this chapter unless FDA has evaluated the drug product under the criteria set forth in Sec. 320.32, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential bioequivalence problem. A drug product so rated reflects a determination by FDA that an in vivo bioequivalence study is required.

(d) For certain drug products, bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the drug product meets one of the following criteria:

(1) [Reserved]

(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

(i) The bioavailability of this other drug product has been demonstrated;

(ii) Both drug products meet an appropriate in vitro test approved by FDA; and

(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(iv) This subparagraph does not apply to enteric coated or controlled release dosage forms.

(3) The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.

(4) The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met:

(i) The bioavailability of the other product has been demonstrated; and

(ii) Both drug products meet an appropriate in vitro test approved by FDA.

(e) FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability if waiver is compatible with the protection of the public health. For full new drug applications, FDA may defer a requirement for the submission of evidence of in vivo bioavailability if deferral is compatible with the protection of the public health.

(f) FDA, for good cause, may require evidence of in vivo bioavailability or bioequivalence for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product.

**In-Vitro Testing: (Excerpt from the revised BA/BE guidance)**

Under certain circumstances, product quality BA and BE can be documented using in vitro approaches (21 CFR 320.24(b)(5) and 21 CFR 320.22(d)(3)). For highly soluble, highly permeable, rapidly dissolving, and orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) is

appropriate based on the biopharmaceutics classification system.[5] This approach may also be suitable under some circumstances in assessing BE during the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved NDAs and ANDAs. In addition, in vitro approaches to documenting BE for *nonbioproblem* drugs approved before 1962 remain appropriate (21 CFR 320.33).

Dissolution testing is also used to assess batch-to-batch quality, where the dissolution tests, with defined procedures and acceptance criteria, are used to allow batch release. We recommend that dissolution testing is also used to (1) provide process control and quality assurance, and (2) assess whether further BE studies relative to minor postapproval changes be conducted, where dissolution can function as a signal of bioinequivalence. In vitro dissolution characterization is encouraged for all product formulations investigated (including prototype formulations), particularly if in vivo absorption characteristics are being defined for the different product formulations. Such efforts may enable the establishment of an in vitro-in vivo correlation. When an in vitro-in vivo correlation or association is available (21 CFR 320.24(b)(1)(ii)), the in vitro test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform in vivo. The following guidance provide recommendations on the development of dissolution methodology, setting specifications, and the regulatory applications of dissolution testing: (1) *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*; and (2) *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*.

We recommend that the following information generally be included in the dissolution method development report for solid oral dosage forms:

For an NDA:

- The pH solubility profile of the drug substance
- Dissolution profiles generated at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm) for U.S. Pharmacopoeia (USP) Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle))
- Dissolution profiles generated on all strengths in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants are recommended.

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

For ANDAs:

- For immediate-release drug products, we recommend that the appropriate USP method be submitted. If there is no USP method available, we recommend that the FDA method for the reference listed drug be used. If the USP and/or FDA methods are not available, the dissolution method development report described above can be submitted.
- For modified-release products, dissolution profiles using the appropriate USP method (if available) can be submitted. If there is no USP method available, we recommend that the FDA method for the reference listed drug be used. In addition, profiles using at least three other dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer) and water would be provided.

The guidance recommends that dissolution data from three batches for both NDAs and ANDAs be used to set dissolution specifications for modified-release dosage forms, including extended-release dosage forms.

**Illustrative List of products for which in-vivo BE studies are not necessary:**

A. Injectable, Ophthalmic and Otic Solutions, provided that the active and inactive ingredients are qualitatively and quantitatively the same as the reference listed drug (RLD)

B. Oral and Topical solutions- provided that differences in inactive ingredients are characterized and do not affect the absorption of the active ingredient of the product.

C. DESI immediate release (IR) drug products with a determination of efficacy, which are not known to have bioproblems. We request in vitro dissolution testing for oral solid dosage forms - Examples include drugs coded as AA, AT, AP in the Orange Book:

AA: Acetaminophen and codeine tablets, folic acid tablets,

AT: Hydrocortisone cream and ointment, Triamcinolone ointment

AP: Cytarabine injectable, dacarbazine injectable

See more products in the Orange Book at: http://www.fda.gov/cder/ob/

Also see list 8-1 for DESI products list at: http://www.fda.gov/cder/ob/docs/preface/ecbioava.htm

D. Biopharmaceutics Classification System (BCS) class 1: Example: Metoprolol

**References:**

1. Requirements for Bioequivalence Testing

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

- 21 CFR 314. 94(a) (7) Content and format of an abbreviated drug application- establishes the requirement for BE in ANDAs http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfrv5_02.html

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

- 21 CFR 320.1 provides definitions of BA/BE, drug product, pharmaceutical equivalents, pharmaceutical alternatives and BE requirement.
- 320.21 Requirements for submission of in vivo BA and BE data.
- 320.23 Basis for demonstrating in vivo BA or BE
- 320.24 Types of evidence to establish BA or BE

2. Guidances: 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 Questions and Answers about SUPAC-IR Guidance
- 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 Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation
- Changes to an Approved NDA or ANDA

- Changes to an Approved NDA or ANDA: Questions and Answers