**FDA Circular**
**No. 2013 - 2013-014**

**SUBJECT: List of Products Requiring Bioequivalence (BE) Studies as Part of the Application for Marketing Authorization in Addition to Rifampicin and the 11 Products Listed in Bureau Circular No. 2006-008**

## I. Background/Rationale

In line with the mandate of the Food and Drug Administration of ensuring the availability of safe, efficacious and quality pharmaceutical products in the Philippines, Administrative Order No. 67 s. 1989: *Revised Rules and Regulations on Registration of Pharmaceutical Products* and Bureau Circular No. 01 s. 1997: *Enforcement of the Requirement for Bioavailability Studies for Registration of Products Included in the List B' (Prime) under Administrative Order No. 67 s. 1989* were issued to introduce the concept of Bioavailability/Bioequivalence to all stakeholders, highlight the importance of establishing interchangeability between innovator (originator) and multisource (generic) pharmaceutical products, and correspondingly require the submission of satisfactory BA/BE Study Reports.

However, due to the unavailability of Philippine-based testing facilities and/or bioanalytical test methods used in the conduct of the studies then, a selective moratorium on this requirement was imposed with the issuance of Bureau Circular No. 13-A s. 1999. This left the mandatory BE Study Report submission applicable only to Rifampicin-containing oral preparations.

In 2006, by virtue of Bureau Circular No. 2006-008, the moratorium was lifted paving the way for the imposition of the BE Study Report requirement to 11 more drug molecules, namely Atenolol, Metoprolol, Propranolol, Nicardipine, Nifedipine, Diltiazem, Gliclazide, Metformin, Phenytoin, Pyrazinamide and Theophylline.

With the introduction of many off-patent, multisource pharmaceutical products in the market, particularly those with known or potential bioavailability problems, whether manufactured locally or sourced abroad, and have not undergone *in vivo* BE Studies or even *in vitro* multipoint dissolution testing, FDA recognizes the need to ensure that these products perform similarly as the innovator drug, and are interchangeable (i.e. therapeutically equivalent) in clinical practice.

For this reason, it is imperative that the existing list of products requiring BE Studies as part of the application for marketing authorization be **expanded**.

## II. Implementing Details

### A. Products requiring the submission of satisfactory BE Study Reports (in addition to Rifampicin and the 11 products listed in Bureau Circular No. 2006-008)

1. Class 4 drugs (low solubility, low permeability) based on the revised World Health Organization (WHO) criteria for Biopharmaceutics Classification System (BCS)

2. Class 2 drugs (high permeability, low solubility) **not eligible for biowaiver** based on the revised WHO criteria for BCS

3. Subsequent generic products to be marketed after the patent expiration of the innovator

   *Principle: The innovator drug has proven its safety and efficacy in view of available satisfactory clinical data/studies. When its patent expires, pharmaceutical manufacturers may produce generic versions of the innovator product, provided they can establish product interchangeability through **BE Studies or Biowaiver**, whichever is applicable.*

4. All modified-release pharmaceutical products for oral administration designed to act systemically

### B. Products that may avail of Biowaiver provided they meet all applicable WHO criteria for application of the Biowaiver procedure (including certain products covered in Bureau Circular No. 2006-008)

*Principle: An applicant should be able to provide documented evidence (either through peer-reviewed scientific literature or in its absence, actual laboratory*

*testing) that a product may avail of Biowaiver based on the solubility and permeability of its API, and the dissolution characteristics of the dosage form. Otherwise, submission of a satisfactory BE Study Report is* ***required****.*

1. Class 1 drugs (high permeability, high solubility) based on the revised WHO criteria for BCS

2. Class 2 drugs (high permeability, low solubility) **with weak acidic properties** based on the revised WHO criteria for BCS

3. Class 3 drugs (low permeability, high solubility) based on the revised WHO criteria for BCS

For illustration purposes, the attached ***Annex A*** features selected drugs belonging to the WHO Model List of Essential Medicines (EML) with the appropriate BCS classification. This list is **not exhaustive** and is only meant to guide the applicants on whether certain products require outright BE Study Reports or may avail of Biowaiver.

**C. Other Considerations**

1. For new and pending applications for initial and renewal registration scheduled for or with on-going BE Studies

   a. A marketing authorization with limited validity shall be issued to the applicant provided there is prior compliance with the requirements and conditions stipulated in Bureau Circular No. 2006-008-A: **Amendment to Bureau Circular No. 008 s. 2006, the Subject of which is the "Lifting of Moratorium on the Conduct of Bioavailability/Bioequivalence Studies for Selected Pharmaceutical Products" and Bureau Circular No. 2007-005 or the "Supplemental Guidelines for the Processing of Principal Certificate of Product Registration", and Providing for the Procedures and/or Guidelines thereof**.

2. For studies to be conducted abroad:

   a. All BE Study Reports shall be accompanied by a copy of the valid Certificate of Accreditation of the foreign BA/BE testing center which conducted the study, issued by the governing regulatory authority or in its absence, an independent accrediting body. The BA/BE testing center's

accreditation shall be based on satisfactory compliance with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) principles.

**b.** The reference (comparator) drug to be used shall be the one determined by this Office. Generally, this is the innovator drug registered and marketed in the Philippines. In its absence, the market leader or the generic drug product(s) registered after the innovator shall serve as the alternate reference drug.

**c.** If a study has already been done using the same reference drug recognized by this Office but of a different manufacturer or manufacturing site, a multipoint comparative dissolution profile between the reference drugs from 2 different manufacturers/manufacturing sites shall be provided together with the BE Study Report. The test shall be performed following the WHO *in vitro* testing guidelines (e.g. using pH 1.2 HCl solution, pH 4.5 acetate buffer and pH 6.8 phosphate buffer in immediate-release oral dosage forms).

**3.** Reporting Format: The BE Study Report shall follow the ASEAN Bioequivalence Study Reporting Format, as agreed and adopted at the 15th Meeting of the ASEAN Consultative Committee for Standards and Quality – Pharmaceutical Product Working Group (ACCSQ-PPWG) [Refer to ***Annex B***].

## III. Repealing Clause

Pertinent sections and provisions of existing Circulars and Memoranda in conflict with this Circular are hereby revised and modified accordingly.

## IV. Effectivity

This Circular shall take effect beginning 01 July 2013, wherein the BE Study requirement shall initially be implemented in BCS Class 4 drugs. By 01 January 2014, the BE Study requirement shall be expanded to cover the remaining product categories mentioned in Section II. A. of this Circular.

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Acting Director IV

**ANNEX A**

**Classification of Selected Drugs Belonging to the World Health Organization (WHO) Model List of Essential Medicines (EML) Based on the Biopharmaceutics Classification System**

1. Class 4 drugs (low solubility, low permeability) based on the revised WHO criteria for BCS

   **a.** Substances on the WHO-EML
   - a.1 Acetazolamide
   - a.2 Albendazole (chewable tablet)
   - a.3 Artemether + Lumefantrine
   - a.4 Azithromycin
   - a.5 Cefixime
   - a.6 Clofazimine
   - a.7 Diloxanide furoate
   - a.8 Efavirenz
   - a.9 Erythromycin stearate and Erythromycin ethylsuccinate
   - a.10 Furosemide
   - a.11 Glibenclamide
   - a.12 Haloperidol
   - a.13 Indinavir sulfate
   - a.14 Ivermectin
   - a.15 Lopinavir + Ritonavir
   - a.16 Mebendazole (chewable tablet)*
   - a.17 Mefloquine hydrochloride
   - a.18 Nelfinavir mesilate
   - a.19 Niclosamide (chewable tablet)*
   - a.20 Pyrantel embonate (chewable tablet)*
   - a.21 Pyrimethamine
   - a.22 Retinol palmitate
   - a.23 Ritonavir
   - a.24 Saquinavir
   - a.25 Spironolactone
   - a.26 Sulfasalazine**
   - a.27 Triclabendazole

   **b.** Substances on the Complementary List of the WHO-EML
   - b.1 Artesunate
   - b.2 Azathioprine sodium
   - b.3 Ciclosporin
   - b.4 Etoposide
   - b.5 Mercaptopurine

b.6 Mifepristone
b.7 Oxamniquine
b.8 *p*-Aminosalicylic acid
b.9 Sulfadiazine
b.10 Pyrimethamine in Sulfadoxine + Pyrimethamine

2. Class 3 drugs (low permeability, high solubility) based on the revised WHO criteria for BCS

**a.** Substances on the WHO-EML

a.1 Abacavir
a.2 Aciclovir
a.3 Amodiaquine
a.4 Atenolol
a.5 Clavulanic acid in Amoxicillin + Clavulanic acid
a.6 Benznidazole
a.7 Biperiden hydrochloride
a.8 Chloramphenicol
a.9 Chlorphenamine hydrogen maleate
a.10 Chlorpromazine hydrochloride
a.11 Ciprofloxacin hydrochloride
a.12 Clomifene citrate
a.13 Clomipramine hydrochloride
a.14 Cloxacillin sodium
a.15 Codeine phosphate
a.16 Didanosine (buffered chewable, dispersible tablet)
a.17 Enalapril
a.18 Ergocalciferol
a.19 Ethambutol hydrochloride
a.20 Ethinylestradiol
a.21 Ethinylestradiol in Ethinylestradiol + Levonorgestrel
a.22 Ethinylestradiol in Ethinylestradiol + Norethisterone
a.23 Ferrous salt
a.24 Ferrous salt + Folic acid
a.25 Folic acid
a.26 Glyceryl trinitrate (sublingual application)
a.27 Hydralazine hydrochloride
a.28 Hydrochlorothiazide
a.29 Isoniazid
a.30 Isoniazid + Ethambutol
a.31 Isosorbide dinitrate (sublingual application)*
a.32 Levamisole hydrochloride
a.33 Carbidopa in Levodopa + Carbidopa
a.34 Levothyroxine sodium
a.35 Metformin hydrochloride

a.36 Methyldopa
a.37 Metoclopramide hydrochloride
a.38 Morphine sulfate
a.39 Neostigmine bromide
a.40 Nifurtimox
a.41 Penicillamine
a.42 Pyrazinamide
a.43 Ranitidine hydrochloride
a.44 Isoniazid in Rifampicin + Isoniazid
a.45 Isoniazid in Rifampicin + Isoniazid + Pyrazinamide
a.46 Isoniazid in Rifampicin + Isoniazid + Pyrazinamide + Ethambutol
a.47 Ethambutol in Rifampicin + Isoniazid + Pyrazinamide + Ethambutol
a.48 Thiamine hydrochloride
a.49 Zinc sulfate

**b.** Substances on the Complementary List of the WHO-EML

b.1 Chlorambucil
b.2 Cycloserine
b.3 Ethionamide
b.4 Ethosuximide
b.5 Flucytosine
b.6 Levamisole hydrochloride
b.7 Methotrexate sodium
b.8 Pentamine
b.9 Procarbazine hydrochloride
b.10 Pyridostigmine bromide
b.11 Quinidine sulfate
b.12 Sulfadoxine in Sulfadoxine + Pyrimethamine

**3.** Class 2 drugs (high permeability, low solubility) **not eligible for biowaiver** based on the revised WHO criteria for BCS

**a.** Substances on the WHO-EML

a.1 Carbamazepine
a.2 Dapsone
a.3 Griseofulvin
a.4 Iopanoic acid
a.5 Nevirapine
a.6 Nitrofurantoin
a.7 Praziquantel
a.8 Sulfamethoxazole + Trimethoprim
a.9 Trimethoprim

a.10 Verapamil hydrochloride

4. Class 2 drugs (high permeability, low solubility) **with weak acidic properties** based on the revised WHO criteria for BCS

   **a.** Substances on the WHO-EML
   - a.1 Ibuprofen
   - a.2 Phenytoin sodium

5. Class 1 drugs (high permeability, high solubility) based on the revised WHO criteria for BCS

   **a.** Substances on the WHO-EML
   - a.1 Acetylsalicylic acid
   - a.2 Allopurinol
   - a.3 Amiloride hydrochloride
   - a.4 Amitriptyline hydrochloride
   - a.5 Amlodipine
   - a.6 Amoxicillin
   - a.7 Ascorbic acid
   - a.8 Chloroquine phosphate and Chloroquine sulfate
   - a.9 Diazepam
   - a.10 Digoxin
   - a.11 Doxycyline hydrochloride
   - a.12 Fluconazole
   - a.13 Lamivudine
   - a.14 Levonorgestrel
   - a.15 Lithium carbonate
   - a.16 DL-Methionine
   - a.17 Metronidazole
   - a.18 Nicotinamide
   - a.19 Norethisterone
   - a.20 Paracetamol
   - a.21 Phenobarbital
   - a.22 Phenoxymethyl penicillin potassium
   - a.23 Potassium iodide
   - a.24 Prednisolone
   - a.25 Primaquine diphosphate
   - a.26 Proguanil hydrochloride
   - a.27 Promethazine hydrochloride
   - a.28 Propranolol hydrochloride
   - a.29 Propylthiouracil
   - a.30 Pyridoxine hydrochloride
   - a.31 Quinine bisulfate and Quinine sulfate
   - a.32 Riboflavin

a.33 Salbutamol sulfate
a.34 Stavudine
a.35 Valproic acid sodium
a.36 Warfarin sodium
a.37 Zidovudine

**b.** Substances on the Complementary List of the WHO-EML

b.1 Calcium folinate
b.2 Clindamycin
b.3 Cyclophosphamide
b.4 Diethylcarbamazine dihydrogen citrate
b.5 Levofloxacin
b.6 Ofloxacin
b.7 Prednisolone
b.8 Tamoxifen citrate

* Dissolution test for biowaiver is not applicable (locally acting, systemic absorption from the oral cavity or dosage form not designed for immediate-release)

** Dissolution test for biowaiver is not relevant (locally acting, no significant systemic absorption)

**ANNEX B**

# ASEAN Bioequivalence Study Reporting Format

[This format has been agreed and adopted at the 15th ASEAN Consultative Committee for Standards and Quality – Pharmaceutical Product Working Group (ACCSQ-PPWG) Meeting]

## 1. Title Page

1.1 Study Title

1.2 Name and Address of Sponsor

1.3 Name, Person-in-Charge and Address of Institution

1.4 Name and Address of Principal Investigator

1.5 Name of Medical/Clinical Investigator

1.6 Name, Person-in-Charge and Address of Clinical Laboratory

1.7 Name, Person-in-Charge and Address of Analytical Laboratory

1.8 Name,Person-in-Charge and Address for Data Management, Pharmacokinetics and Statistical Analysis

1.9 Name and Address of Other Investigator(s) and Study Personnel

1.10 Start and End Date of Clinical and Analytical Study

1.11 Signature of Investigator(s), (Medical Writer, QA Manager – if applicable) and Date

## 2. Study Synopsis

## 3. Table of Contents

## 4. Abbreviation and Definition of Terms

## 5. Introduction

5.1 Pharmacology

5.2 Pharmacokinetics

5.3 Adverse Events

## 6. Objective(s)

## 7. Product Information

7.1 Test Product Information

- Trade Name
- Active Ingredient, Strength and Dosage Form
- Batch Number, Manufacturing Date and Expiry Date
- Batch Size Compliance (can be directly provided by sponsor)

- Product Formulation (can be directly provided by sponsor)
- Finished Product Specifications (can be directly provided by sponsor)
- Name and Address of Manufacturer

7.2 Reference Product Information

- Trade Name
- Active Ingredient, Strength and Dosage Form
- Batch Number, Manufacturing Date and Expiry Date
- Name and Address of Manufacturer
- Name and Address of Importer or Authorization Holder

7.3 Pharmaceutical Equivalence Data

- Comparing Content of Active Ingredient/Potency
- Uniformity of Dosage Units

7.4 Comparison of Dissolution Profiles (can be directly provided by sponsor)

7.5 Letter with a signed statement from the applicant/sponsor confirming that the test product is the same as the one that is submitted for marketing authorization

**8. Investigational Plan**

8.1 Clinical Study Design

- Study Design (crossover, parallel)
- Fed, Fasted
- Inclusion, Exclusion, Restriction
- Standardization of Study Condition
- Drug Administration
- Removal of Subject from Assessment
- Health Screening
- Subject Detail, Number of Subjects, Deviation
- Sampling Protocol/Time, Sample Preparation/Handling, Storage, Deviation
- Volume of Blood Collected
- Subject Monitoring
- Genetic Phenotyping (if applicable)

8.2 Study Treatments

- Selection of Doses (single, multiple)

- Identity of Investigational Products, Dosing
- Randomization
- Blinding
- Washout Period
- Water Intake Volume

8.3. Clinical and Safety Records
- Adverse Event(s)
- Drug-related Adverse Drug Reaction(s)

8.4 Pharmacokinetic Parameters and Tests
- Definitions and Calculation

8.5 Statistical Analyses
- Log-transformed Data Analysis (AUC, $C_{max}$)
- Sampling Time Adjustments
- $t_{max}$
- $t_{½}$
- Acceptance Criteria for Bioequivalence
- ANOVA Presentation
- Power

8.6 Assay Methodology and Validation
- Assay Method Description
- Method of Detection
- Validation Procedure and Summary Results
  - Specificity
  - Accuracy
  - Precision
  - Recovery
  - Stability
  - LOQ
  - Linearity

8.7 Data Quality Assurance

**9. Results and Discussion**

9.1 Clinical Study Results
- Demographic Characteristics of the Subjects

- Details of Clinical Activity
- Deviation from Protocol (if any)
- Results of Drug/Alcohol/Smoking Usage, Medical History and Medical Examination, Vital Signs and Diagnostic Laboratory Tests of Subjects
- Adverse Event/Reaction Reports for Test Product and Reference Product

9.2 Summary of Analytical Results

9.3 Pharmacokinetic Analyses

- Drug Levels at Each Sampling Time, Descriptive Statistics
- Table of Individual Subject Pharmacokinetic Parameters, Descriptive Statistics
- Figure of Mean Plasma or Urine Concentration-Time Profile
- Figure of Individual Subject Plasma or Urine Concentration-Time Profile

9.4 Statistical Analyses

- Statistical Considerations
- Time Points Selected for $K_{el}$, $t_{½}$
- Summary Statistics of Pharmacokinetic Parameters: $AUC_t$, % AUC extrapolated, $AUC_\infty$, $C_{max}$, $t_{max}$, $t_{½}$
- Summary of Statistical Significance for AUC and $C_{max}$ (based on log-transformed data calculated as 90 % CI of test/reference Geometric Means) and for $t_{max}$ (based on non-transformed data calculated as p-value)
- SimilarCalculation for Urine Data: Ae and dAe/dt [Ae corresponds to AUC; $(dAe/dt)_{max}$ corresponds to $C_{max}$]
- Intra-Subject Variability
- Power of Study
- Assessment of Sequence, Period and Treatment Effects
- Table: Analysis of Variance, Geometric Least-Squares Means for Each Pharmacokinetic Parameter
- Table: Calculation of 90% Confidence Interval for the Ratio of Pharmacokinetic Parameters under Consideration in Logarithmic Transformation

## 10. Conclusions

## 11. Appendices

11.1 Protocol and Approval

- Letter of Approval from Drug Regulatory Authority (if applicable)
- Study Protocol and its Amendments together with Institutional Review Board/Ethical Committee Approvals
- Informed Consent Form
- Protocol Deviation Listing
- Adverse Event Listing
- Finished Product Specifications and Certificate of Analysis

11.2 Validation Report (including 20% of Raw Chromatograms)

11.3 Analytical Report (including 20% of Raw Chromatograms)

11.4 Certificate of Accreditation of Clinical Facility, Clinical Laboratory and Analytical Laboratory

11.5 Dose Proportionality Comparative Dissolution Profiles between Various Strengths (when BE study investigating is only for one strength but the application for registration consists of several strengths) [can be directly provided by sponsor]