



REPUBLIC OF THE PHILIPPINES
DEPARTMENT OF HEALTH
BUREAU OF FOOD AND DRUGS

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Alabang, Muntinlupa City



MALAYA AT MALUSOG
NA PAMAYAHAN

27 April 2006

Bureau Circular
No. 108 s. 2006

Subject: Lifting of Moratorium on the Conduct of Bioavailability/ Bioequivalence Studies for Selected Pharmaceutical Products

Pursuant to the Bureau's mandate of ensuring the safety, efficacy, purity and quality of pharmaceutical products, and considering that bioanalytical methods to be used in the conduct of Bioequivalence (BE) studies of some products are now available, the requirement of submission of satisfactory results of Bioequivalence studies for selected pharmaceutical products is now resumed.

In addition to Rifampicin-containing products, applications covered by any of the conditions stated herein shall be required to include a BE report satisfying all the requirements of this Bureau to establish therapeutic equivalence and product interchangeability. All reports submitted shall follow the recommended BA/BE report format of this Bureau.

I. Definition of Terms

- a. Reference Drug – Reference drug is either the innovator pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety, and quality (according to requirements at the time of authorization) or the product which is the market leader.
- b. Generic Products – also referred to as multisource pharmaceutical product is considered to be essentially similar or bioequivalent to an innovator product. Generic products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Generic products that are therapeutically equivalent are interchangeable.

II. Products Requiring the Submission of In Vivo Bioequivalence Study

A. Initial Registration

Based on the capability of the BFAD accredited Bioavailability Centers, all applications for initial registration of drug products listed below with their corresponding reference drugs shall include a satisfactory BE report.

ACTIVE INGREDIENT	DOSAGE FORM	REFERENCE DRUG	COMPANY
Atenolol	Tablet	Tenormin Tablet	AstraZeneca Pharmaceutical (Phils),Inc
Diltiazem	Tablet, Capsule	Dilzem Tablet	Pfizer, Inc.
Gliclazide	Tablet	Diamicron Tablet	Servier Phils, Inc
Metformin	Tablet	Glucophage Tablet	Merck, Inc
Metoprolol	Tablet	Betaloc Tablet	AstraZeneca Pharmaceutical (Phils),Inc
Nicardipine	Tablet, Capsule	Cardipine Tablet	LR Imperial
Nifedipine	Tablet, Capsule	Adalat Softgel Capsule	Bayer Phils, Inc
Phenytoin	Tablet, Capsule	Dilantin Capsule	Pfizer, Inc
Propranolol	Tablet, Capsule	Inderal Tablet	AstraZeneca Pharmaceutical (Phils),Inc
Pyrazinamide	Tablet, Suspension, Granules for Suspension	PZA-Ciba Tablet, Suspension	Novartis Healthcare Phils, Inc
Theophylline	Tablet, Capsule	Theodur Tablet	AstraZeneca Pharmaceutical (Phils),Inc

B. Renewal Registration

1. Applications for renewal registration of drug products listed above, which were previously approved without the submission of the BE

studies, shall include a satisfactory BE report in addition to other requirements during the renewal of its registration.

In cases that no BE studies has been conducted for an applicant's product, a schedule of the BE study issued by an accredited Bioavailability Center will be accepted and a Certificate of Product Registration (CPR) with one (1) year validity shall be issued. The CPR issued is subject to revalidation until and upon the submission of the BE report. Such revalidation, however, will not be automatic and shall be subject to further review by BFAD and that the applicants will still be required to resubmit application requirement once the one (1) year validity period expires.

2. The above provisions shall also apply to pending applications for renewal registration with BFAD, for products listed above.
- C. The Bureau shall issue CPRs with a full validity period (based on fees paid) if the applicant has submitted a satisfactory BE report and has been approved by BFAD.
 - D. For studies done abroad, the reference drug to be used must be the reference drug determined by this Bureau. The reference drug must be the drug that has been approved for marketing in the Philippines. In addition, all reports must be accompanied by an authenticated Certification of Accreditation of the BA/BE Center where the study is to be or has been conducted, issued by the drug regulatory authority or any independent accrediting body.

This Circular takes effect on 01 June 2006.


Prof. LETICIA BARBARA B. GUTIERREZ, M.S.
DIRECTOR

FORMAT AND CONTENTS OF BIOEQUIVALENCE STUDY REPORT

I. TITLE PAGE:

- Study Title
- Name of Sponsor
- Name and address of Clinical & Analytical Laboratory
- Name of Principal and Clinical Investigators
- Dates of Clinical Study (start and completion)
- Signature of Principal and Clinical Investigators (with date)

II. TABLE OF CONTENTS

III. STUDY RESUME

- Product Information
- Summary of Bioequivalence Study
- Summary of Bioequivalence Data
 - Plasma
 - Urinary Excretion
- Figure of Mean Plasma Concentration-Time Profile
- Figure of Mean Urinary Excretion Rates

IV. PROTOCOL AND APPROVAL

- Protocol
- Informed Consent Form
- Letter of Approval from the Institutional Review Board
- List of Members of the Institutional Review Board

V. CLINICAL STUDY

- Summary of the Study
- Details of the Study
- Demographic Characteristics of the Subjects
- Subject Assignment in the Study
- Mean Physical Characteristics of Subjects Arranged by Sequence
- Details of the Clinical Activity
- Deviations from the Protocol
- Vital Signs of the Subject
- Adverse Reactions Report

VI. ASSAY METHODOLOGY AND VALIDATION

- Assay Method Description

- Validation Procedure
- Summary of Validation
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- Data on Interday Precision and Accuracy
- Data on Intraday Precision and Accuracy
- Figure for Standard Curve(s) for low/high ranges
- Chromatograms of Standard and Quality Control of Samples
- Sample Calculation

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- Definition and Calculations
- Statistical Tests
- Drug Levels at each Sampling Time and Pharmacokinetic Parameters
- Figure of Mean Plasma Concentration-Time Profile
- Figures of Individual Subject Plasma Concentration-Time Profiles
- Figure of Mean Cumulative Urinary Excretion
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- Figure of Mean Urinary Excretion Rates
- Figures of Individual Subject Urinary Excretion Rates
- Tables of Individual Subject Data Arranged by Drug/Period, Drug Sequence

VIII. STATISTICAL ANALYSIS

- Statistical Considerations
- Summary of Statistical Significance
- Summary of Statistical Parameters
- Analysis of Variance, Least Squares Estimates and Least Square Means

IX. APPENDICES

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- Sample Identification Codes
- Analytical Raw Data
- Chromatograms of at least 20% of Subjects
- Medical Record and Clinical Reports
- Clinical Facilities Description
- Analytical Facilities Description
- Curricula vitea of the Investigators

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- Dissolution Assay Methodology
- Content Uniformity Testing
- Potency Determination

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- Quantitative Formulation