Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

25 OCT 2016

FDA CIRCULAR
No. 2016-019

SUBJECT: Revised Guidelines on the Submission of Equivalence Evidence for Registration of Pharmaceutical Products

I. OBJECTIVE AND APPLICABILITY

The objective of this Circular is (a) to establish the specific requirements in the submission of *in vitro* or *in vivo* equivalence evidence in the registration of pharmaceutical products; and (b) to rationalize the scope of requiring product interchangeability based on product risk.

Consistent with Administrative Order No. 2013-0021, relative to FDA Circular No. 2013-014[1] and pursuant to FDA Circular No. 2015-012[2], the following guidelines are hereby imposed:

A. For Renewal Applications:

All applications for renewal registration shall be issued a CPR with a validity of five (5) years, *provided* that the following conditions shall be fulfilled:

1. *Mandatory submission of in vivo/in vitro equivalence study (whichever is applicable) upon renewal shall apply to the following:*

    a) Biopharmaceutics Classification System (BCS) Class 2 and Class 4 oral immediate-release pharmaceutical products with systemic action;
    b) Modified-release pharmaceutical products designed to act systemically;
    c) Pharmaceutical products containing drug/s with narrow therapeutic index (NTI);
    d) Fixed-dose combination (FDC) products with systemic action where at least one of the drug substances requires an *in vivo* study; and
    e) Additional strengths of a pharmaceutical product, wherein the reference, usually the highest strength, has demonstrated *in vivo* equivalence with the comparator drug

[1] "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"
[2] "Additional Requirements for the Effective Implementation of FDA Circular No. 2013-014, 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"

The required equivalence study shall be submitted at the time of filing of the application for renewal registration together with the other applicable documentary requirements.

2. *Conditional approval of incoming renewal applications shall be applicable to the following:*

   a) Pharmaceutical products containing a Class 1 or 3 drugs based on the BCS; and
   b) FDC products containing substances under BCS Class 1 and/or 3 only

   Upfront submission of the satisfactory equivalence study may not be required. *Provided*, however, at the time of filing of the application for renewal registration, the applicant company shall provide documents substantiating the BCS Class of the drug substance/s as stated in the succeeding Part III (Implementing Details), Section C of this Circular together with the other applicable documentary requirements.

   Provided further, the required biowaiver/equivalence study shall be submitted within three (3) years after the issuance of the renewed Certificate of Product Registration (CPR). Non-submission shall be a ground for recall and/or seizure of products and other appropriate legal action by the FDA.

3. *Approval of renewal registration shall be allowed without the upfront submission of BE study or biowaiver to the following renewal applications:*

   a) Over-the-Counter (OTC) drugs;
   b) Single and multi-component vitamin and mineral preparations;
   c) Single and multi-component preparations containing amino acids; and
   d) Household Remedies (HR)

   Provided, that the other documentary requirements for renewal registration are submitted. *Provided further,* that the FDA shall not be precluded to impose the requirement of interchangeability on the above products as it deems necessary.

B. For Initial and Variation Applications:

From the effectivity of this Circular all application dossiers for initial as well as certain post-approval changes of drug products covered in this Circular shall include a complete and detailed *in vivo* or *in vitro* equivalence evidence, whichever is applicable. Submission of the study schedule in lieu of the actual study report, as well as any requests for extension for whatever reason shall not be accepted.

II. SCOPE

This Circular shall apply to all manufacturers, traders and distributors (exporters, importers and wholesalers) of all drug products, except:

1. Traditional/Herbal medicines;
2. Biological products;
3. Medical oxygen;
4. Veterinary drugs; and
5. Stem cell products

In the meantime, however, this will not cover manufacturers, traders and distributors (exporters, importers and wholesalers) of the following:

1. Over-the-Counter (OTC) drugs;
2. Single and multi-component vitamin and mineral preparations;
3. Single and multi-component preparations containing amino acids; and
4. Household Remedies (HR)

III. IMPLEMENTING DETAILS

All pharmaceutical products covered in this Circular shall strictly follow the latest ASEAN and World Health Organization (WHO) Guidelines. The FDA may further broaden the product coverage, as deemed necessary, to ensure interchangeability of multisource/generic pharmaceutical products.

A. *Products requiring in vivo equivalence studies*

Applications for registration of the following products are required to submit *in vivo* equivalence studies:

1. Biopharmaceutics Classification System (BCS) Class 2 and Class 4 oral immediate-release pharmaceutical products with systemic action;
2. Modified-release pharmaceutical products designed to act systemically;
3. Pharmaceutical products containing drug/s with narrow therapeutic index (NTI); and
4. Fixed-dose combination (FDC) products with systemic action where at least one of the drug substances requires an *in vivo* study

B. *Products qualified to conduct in vitro equivalence studies*

The following products shall be eligible for a biowaiver, provided they meet the criteria stated in the ASEAN and World Health Organization (WHO) Guidelines:

1. Pharmaceutical products containing a Class 1 or 3 drugs based on the BCS;
2. FDC products containing substances under BCS Class 1 and/or 3 only; and
3. Additional strengths of a pharmaceutical product, wherein the reference, usually the highest strength, has demonstrated *in vivo* equivalence with the comparator drug

C. *Determination of BCS Class of a drug substance*

In the submission of BCS-based biowaivers, the applicant company shall determine the aqueous solubility and intestinal permeability of the drug by providing references such as sound peer-reviewed literature and results from a validated method to determine the BCS Class of a drug substance.

D. *Comparator drug products*

The comparator drug to be used for equivalence studies shall be determined by this Office based on the selection criteria of ASEAN comparator product. A list of comparator drugs according to the drug substance and the corresponding dosage form/s and strength/s shall be provided by this Office. This list shall be updated periodically.

If an equivalence study used the same comparator drug recognized by this Office but with different manufacturing site, the applicant company shall provide the results of *in vitro* dissolution between the comparator drugs in addition to the original equivalence study.

In case a comparator drug is not available in or was acquired outside the Philippines, the comparator drug should be purchased from a well regulated market with stringent regulatory authority such as ICH member countries.

The applicant company shall provide the following documents to confirm the source and use of the comparator drug for equivalence studies:

1. Copy of the labeling materials of the comparator drug. Pertinent information such as the name of the product, name and address of the manufacturer, batch number and expiry date shall be clearly visible on the labels;
2. Copy of invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice;
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation; and
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive responsible in the application for registration of the drug product.

For BE Studies of FDC products, the multisource pharmaceutical product shall be compared with the respective innovator FDC product. In case no innovator FDC product is available in the market, the comparator drugs of the individual components administered in loose combination shall be used.

E. *Foreign studies*

In case a BE Study is conducted outside the Philippines, the applicant company shall provide a copy of the valid Certificate of Accreditation and/or inspection report of the foreign BE Study Site issued by regulatory agencies to confirm compliance with Good Clinical Practice (GCP) and Good Laboratory Practices (GLP).

F. *Equivalence study method*

The analytical method used for the equivalence study shall be well-documented and validated following the existing guidelines.

G. *Reporting Format*

The *in vivo* equivalence study report shall follow the ASEAN Bioequivalence Study Reporting Format. For *in vitro* studies, no specific reporting format is required, provided that the dissolution protocol and report shall indicate the procedure and results of the study following the latest ASEAN and WHO Guidelines.

IV. REPEALING AND SEPARABILITY CLAUSE

Provisions in previous FDA circulars and memoranda that are inconsistent with this Circular are hereby withdrawn, repealed and/or revoked accordingly.

If any provision in this Circular, or application of such provision to any circumstances, is held invalid, the remainder of the provisions in this Circular shall not be affected.

V. EFFECTIVITY

This Circular shall take effect immediately.

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