Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

28 February 2014

**FDA CIRCULAR**
No. 2014-008

**SUBJECT: Application Process and Requirements for Post-approval Changes of Pharmaceutical Products**

## I. BACKGROUND/RATIONALE

Prior to the full adoption and implementation of the Association of Southeast Asian Nations (ASEAN) Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR), Marketing Authorization Holders (MAHs) referred to the provisions of PSD Memo 02-05, "Updated Checklist of Requirements for Request of Amendment and Revalidation", FDA Circular No. 2011-002, "Application for Revisions/Updates in the Package Insert, Patient Leaflet Information, Prescribing Information, Core Data Sheet, and Basic Succinct Statement", and other national regulations to support post-approval changes to their registered products. However, the said regulations proved to be insufficient to cover many other possible post-approval change scenarios. Therefore, a more comprehensive guideline is needed to address in detail the requirements and application process for post-approval changes.

The ASEAN Variation Guideline (AVG) for Pharmaceutical Products was established (a) to take into account technical and scientific progress of pharmaceutical products after they have been approved for marketing by the Drug Regulatory Authority (DRA) and (b) to support any post-approval changes that may be required to enable the pharmaceutical products to be manufactured. The AVG is intended to provide supportive information on the requirements for submission of variation application to implement a change to a pharmaceutical product. Although the AVG is a comprehensive guideline, some post-approval changes not covered here are subject to country-specific requirements.

In line with the provisions of Administrative Order No. 2013-021, "Adoption of the Association of Southeast Asian Nations (ASEAN) Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR) for the Registration of Pharmaceutical Products for Human Use", the Food and Drug Administration hereby promulgates the revised application process and requirements for instituting Post-Approval Changes (PACs) to registered pharmaceutical products, which shall cover both the AVG and country-specific requirements.

## II. OBJECTIVES

The objectives of this Circular are:

1) To promulgate the revised requirements in instituting post-approval changes to registered pharmaceutical products, incorporating the AVG and country-specific requirements; and
2) To provide the application process for instituting post-approval changes.

## III. SCOPE

This Circular shall apply to all manufacturers, traders and distributors (e.g. exporters, importers and wholesalers) of pharmaceutical products covered by ACTD/ACTR. In the absence of a more specific regulation, the provisions of this Circular also serve as the requirements for manufacturers, traders and distributors of single and multi-component vitamin and mineral products, vaccines and biologics, traditional medicines, over-the-counter preparations, household remedies, medical gases, and veterinary products.

## IV. IMPLEMENTING DETAILS

### A. *Eligibility*

Any MAH of a pharmaceutical product may apply for PAC, provided:

1. The MAH has a valid License to Operate (LTO); and
2. The pharmaceutical product is covered by a valid Certificate of Product Registration (CPR); provided further, that if the CPR has already expired, the pharmaceutical product is applied for regular renewal registration.

### B. *Classification*

Post-approval changes may be classified according to reference:

(a) ASEAN Variation Guideline
- Major Variation (MaV)
- Minor Variation (MiV)
  - Prior Approval (MiV-PA)
  - Notification (MiV-N)

(b) Country-Specific Requirements
- MaV
  - Additional route of administration
  - Change of manufacturing site (same subsidiary) of the drug product
- MiV-PA

- Change of capsule color
- Change of brand name
- Change of MAH
- Reclassification (ex. Over-the-counter [OTC] to Prescription, OTC to household remedy [HR])

- Such other PACs not covered by AVG

C. *Application Process*

An application for PAC may be submitted any time during the validity of the CPR; provided, that if such application is submitted at the end of the CPR validity, it shall be incorporated in the application for regular renewal registration.

All applications for PACs shall follow the submission process and requirements as prescribed in the latest issuance of FDA.

D. *Requirements*

The requirements shall follow the AVG, latest revision, which shall be posted and made available at the FDA website. For changes requiring prior approval (i.e., AVG/Country-Specific Requirements MaV and MiV-PA), a Letter of Request for Post-Approval Change shall be included in the application, indicating the specific type of PAC and all affected products. A template Letter of Request is attached as Annex A.

For changes classified under minor variation-notification, application is on a per product submission. A notification form shall be included in the application, in addition to the requirements of AVG. A template Notification is attached as Annex B.

For PACs following Country-Specific Requirements, the requirements are attached as Annex C. For other PACs that may arise and are not covered by this Circular, the requirements shall be determined by FDA as deemed appropriate/applicable.

All PACs to a specific product may be submitted under a single application. In case of recurring documentary requirements, a single copy may be submitted.

For verification purposes, FDA may require additional information, as deemed necessary, to ensure that the product maintain its safety, efficacy, and quality.

E. *Approval*

A Certificate/Clearance shall be issued by FDA indicating each PAC approved.

F. *Fees*

The appropriate fees as prescribed under existing regulations shall apply, including the Legal Research Fund (LRF). The payment shall be on a per product, per change basis. A matrix of fees is attached as Annex D.

The fees for the following PACs shall be equivalent to **initial registration** schedule of fees:

- MaV-1: Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product
- MaV-4: Addition or replacement of the manufacturing site of the drug product
- MaV-10: Qualitative or quantitative change of excipient
  a) For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)
  b) For modified release oral dosage forms
  c) For other critical dosage forms such as sterile preparations
- MaV-11: Quantitative change in the coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form
- MaV-12: Change in primary packaging material for sterile product
  a) Qualitative and quantitative composition and/or
  b) Type of container and/or
  c) Inclusion of primary packaging material
- MaV-13: Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for a sterile solid and liquid drug product (unless the change is dimension, i.e. wide-mouth bottles vs. narrow-mouth bottles)
- MiV-PA15: Qualitative or quantitative change of excipient
  a) For immediate release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline)
  b) For other non-critical dosage forms (e.g. oral liquid, external preparation)
- MiV-PA16: Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral dosage form

- MiV-PA17: Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]
- MiV-PA28: Change in primary packaging material for non-sterile product
  a) Qualitative and quantitative composition and/or
  b) Type of container and/or
  c) Inclusion of primary packaging material
- Change of manufacturing site (same subsidiary) of the drug product

FDA, from time to time, may prescribe changes in fees, which shall be promulgated in an appropriate regulation.

## V. TRANSITORY PROVISIONS

The revised requirements and application process for post-approval changes shall only apply to incoming post-approval change applications; all pending applications and their compliances shall not be covered by this Circular.

## VI. REPEALING CLAUSE/SEPARABILITY CLAUSE

Provisions in previous 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.

## VII. EFFECTIVITY

This Circular shall take effect 01 April 2014.

**KENNETH Y. HARTIGAN-GO, MD**
Acting Director General

# ANNEX A
## Letter of Request for Post-approval Change/s

KENNETH Y. HARTIGAN-GO, MD
Acting Director General
Food and Drug Administration
Civic Drive, Filinvest Corporate City
Alabang, Muntinlupa City

| **DTN** | |
|---|---|
| | |
| Date | |

Attention: Licensing and Registration Division
Center for Drug Regulation and Research

Sir/Madam,

We would like to submit our application for Post-approval Change/s, (*type of Post Approval Change as per AVG or Country-specific requirements*) for the following product/s:

| Product Name/Strength and Form | CPR Validity/Drug Registration Number | Current | Proposed Change/s | Classification/ Specific Type of PAC/s |
|---|---|---|---|---|
| | | | | e.g. AVG MaV-1 |
| | | | | |

For your approval.

Very truly yours,

*Company representative name and signature*
*Position*

# ANNEX B
# NOTIFICATION FOR MINOR VARIATION

Republic of the Philippines
Department of Health
**FOOD AND DRUG ADMINISTRATION**

**NOTIFICATION FOR MINOR VARIATION/S OF REGISTERED PHARMACEUTICAL PRODUCT**

**Date:** _____

| | |
|---|---|
| **NOTIFICATION NUMBER:** | |
| | |
| **MARIA LOURDES C. SANTIAGO, MSc, MM**<br>OIC, Center for Drug Regulation and Research | |
| **DTN:** | |
| **Amount Paid:** | |
| **OR No.:** | |
| **OR Date Issued:** | |

**KENNETH Y. HARTIGAN-GO, MD**
Acting Director General
Food and Drug Administration
Civic Drive, Filinvest Corporate City
Alabang, Muntinlupa City

Attention: CENTER FOR DRUG REGULATION
AND RESEARCH

Sir/Madam:

In accordance with Administrative Order No. 2013-0021 and related issuances, we wish to apply and notify FDA of our intention to make Minor Variation/s to our pharmaceutical product described below:

**PRODUCT PARTICULARS**

**Generic Name:** _____
**Dosage Strength/Form:** _____
**Brand Name** _____

**Approved Shelf-life:** _____
**Storage Condition:** _____
**Packaging/Presentation:** _____

**FDA Registration No.:** _____ **CPR No.:** _____ **Validity:** _____
**Registration Status:** ☐ **Monitored Release** ☐ **Initial** ☐ **Renewal**

## COMPANY PARTICULARS

**Manufacturer:** _____

_____

**Trader :** _____

_____

**Importer:** _____

_____

**Distributor:** _____

_____

**Packer / Repacker:** _____

_____

## POST-APPROVAL CHANGES PARTICULARS

| Table of Changes | | |
|---|---|---|
| **Current** | **Proposed Changes** | **Specific Type of Minor Variation** |
| | | e.g. MiV-N1 |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

## DECLARATION

In support of our notification, I, the undersigned, hereby declare under oath that:

1. I am duly authorized to bind the establishment I represent pursuant to the authority attached to this Notification for Minor Variation Form (Board Resolution in case of corporation and Special Power of Attorney in all other cases both of which should be duly notarized);
2. In behalf of my company, the pharmaceutical product identified in the notification meets all the legal requirements, and conforms to existing standards and specification requirements applicable to the said product;
3. The particulars given in this notification are true and all data and information of relevance in relation to the notification have been supplied and that the documents enclosed are authentic or true copies;
4. I agree that the grant of acceptance shall be automatically revoked by FDA in the event that there is subsequent findings of misrepresentation in any of the data indicated in the required documents or any of the said documents is subsequently found to be falsified of fraudulently filed; and/or in case the samples of the identified pharmaceutical product collected through post marketing surveillance shall be found not to conform to the product's registered specifications or approved labeling.
5. The company I represent shall automatically cease and desist from further distributing the identified pharmaceutical product subject of revocation upon receipt of the notice of revocation and pending any administrative proceeding until further notice from FDA.
6. I, or my company undertake to:
   a) Ensure the identified pharmaceutical product's technical and safety information is made readily available to FDA anytime when requested, and to keep records of the distribution of the products for product recall purposes;
   b) Notify FDA as soon as possible by telephone, facsimile transmission, email, or in writing, and in any case, no later than 7 calendar days after first knowledge of any fatal or life threatening serious adverse events if the cause, whether proximate or otherwise, of such adverse events is the use of the identified pharmaceutical product;
   c) Report to FDA of all other serious adverse events that are not fatal or life threatening as soon as possible, and in any case, no later than 15 calendar days after first knowledge, whether proximate or otherwise, of such adverse events is the use of the identified pharmaceutical product.
   d) Keep or hold FDA free and harmless against any and all third party claims arising from the above adverse events; and
   e) Respond to and cooperate fully with Food-Drug Regulation Officers with regard to any subsequent post-marketing activity initiated by FDA.
7. I understand that our company or establishment cannot place reliance on the acceptance of the notification by FDA in any legal proceedings concerning the above product, in the event that the identified product has failed to conform to any standards or specifications previously declared to FDA.

COMPANY PHARMACIST

**Signature:** _____
**Name:** _____
**Designation:** _____
**Date:** _____

## ACKNOWLEDGEMENT

SUBSCRIBED AND SWORN TO BEFORE ME this _____ personally appeared the following:

| Name | Residence Certificate | Date Issued | Place Issued |
|---|---|---|---|
| | | | |
| | | | |

Known to me and to me known to be the same persons who executed the foregoing instrument and they acknowledged to me that the same is their free and voluntary act and deed.

WITNESS MY HAND AND SEAL on the date and place first above written.

Doc No. _____
Page No. _____
Book No. _____
Series of _____

# ANNEX C
# Requirements for Philippines Specific Post-Approval Change/s

| Additional route of administration | |
|---|---|
| C | 1. A new proposed route of administration in addition to the existing approved route.<br>2. Product formulation remains the same as the initially approved formulation. |
| D | 1. Currently approved product labeling.<br>2. Proposed product labeling, a clean and annotated version highlighting the changes made.<br>3. Justifications for the changes proposed.<br>4. Clinical expert reports and/or clinical trial reports (where applicable)<br>5. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable).<br>6. Approval letters from reference regulatory authorities or the country of origin which have approved the new route of administration (where applicable).<br>7. Clinical documents as per ASEAN Common Technical Dossier (ACTD) part IV (where applicable). |

| Change of Manufacturing Site of the Drug Product(as per Memo: PSD02-05) | |
|---|---|
| C | 1. The proposed manufacturing site is under the same subsidiary<br>2. There is no change in formulation, equipment, and manufacturing procedure |
| D | 1. Proof that the proposed site is appropriately authorized for the pharmaceutical form concerned such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification.<br>2. Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action).<br>3. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).<br>4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).<br>5. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission.<br>6. Comparative dissolution profile data manufactured in the currently approved and proposed manufacturing site for oral solid dosage forms as per compendium and validated dissolution test method.<br>7. Product formula.<br>8. Release and shelf-life specifications of drug product.<br>9. Batch numbering system (where applicable).<br>10. Specification of drug substance.<br>11. Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).<br>12. In case of a contract manufacturer, letter of appointment and letter of acceptance for the proposed site to manufacture the product and stating the types of activity to be performed (where applicable). |

| Change of capsule color (as per BFAD Memo Circular No. 15 s. 1994) | |
|---|---|
| C | 1. Capsule color change where colorant used is not novel.<br>2. Capsule shell is from the same source or manufacturer. |
| D | 1. Justifications for the changes proposed.<br>2. BSE/TSE-free certificate for gelatin capsules of animal origin.<br>3. Certification from capsule shell supplier that change in color will not change the product's physical and chemical properties or technical specification.<br>4. Letter of commitment that the new capsule color will be used only when the product batches bearing the old color are consumed. |

| Change of brand name (as per Memo: PSD02-05) | |
|---|---|
| C | 1. Change from unbranded to branded drug.<br>2. Change to a different brand name.<br>3. Change from branded drug to unbranded drug (deletion of brand name). |
| D | 1. Complete labeling materials with proposed brand name. |

| Change of MAH (as per Memo: PSD02-05) | |
|---|---|
| C | 1. The source of the pharmaceutical product (foreign manufacturer/exporter, local manufacturer) remains the same.<br>2. Administrative change referring only to change of local trader/importer/distributor. |
| D | 1. Copy of valid License to Operate.<br>2. Termination of Contract/Deed of Assignment.<br>3. Agreement between manufacturer and the new trader/importer/distributor.<br>4. Complete labeling materials reflecting the change of trader/importer/distributor. |

| Reclassification from Prescription to Over-the-counter (OTC) | |
|---|---|
| C | 1. Drug is time-tested and has undergone thorough investigation and extensive clinical use<br>2. Drug has been in the international market for 20 years (for imported products) and 10 years in the Philippine market<br>3. The product is recognized to contain API(s) with proven safety and efficacy in use (wide margin of safety and high therapeutic index) even without professional supervision as proven by adverse drug reaction (ADR) monitoring<br>4. The drug is neither with bioequivalence (BE) problems nor classified as a prohibited, regulated or an internationally controlled drug product<br>5. Classified and marketed as OTC from the country of origin and marketed as OTC in at least 2 of the following countries: Australia, Canada, Japan, Sweden, United Kingdom, United States of America |
| D | 1. Complete technical profile of product, including description, formulation, indication, and directions for use<br>2. Currently approved product labelling<br>3. Proposed product labeling, a clear and annotated version highlighting the changes made.<br>4. Classification of the product from the country of origin<br>5. List of countries where the product is currently marketed and the corresponding classification of the product<br>6. Clinical documents as per ASEAN Common Technical Dossier (ACTD) Part IV (where applicable).<br>7. ADR Report showing low occurrence of drug interaction (clinically insignificant) |

| Reclassification from OTC to Household Remedy (HR) (as per A.O. No. 117 s. 1992 and M.C. No. 17 s. 1992) | |
|---|---|
| C | 1. Drug has no history of or recognized ADR when used according to its indication for 20 years<br>2. Drug must be included in the list of HR drugs as per A.O. No. 117 s. 1992 |
| D | 1. Complete technical profile of the product, including description, formulation, indication, and directions for use<br>2. Currently approved product labelling<br>3. Proposed product labeling, a clean and annotated version highlighting the changes made<br>4. Classification of the product in the country of origin<br>5. List of countries where the product is currently marketed and the corresponding classification of the product<br>6. Local Post-Marketing Surveillance (PMS) Report |

# ANNEX D
# Matrix of Fees

| Type of PAC | Fee per product per PAC |
|---|---|
| Regular PACs, including change of capsule color | P500 + LRF |
| With FDA Clinical Review for revision/update of PI, PIL, Prescribing Information, Core Data Sheet and Basic Succint statement | P500 + LRF |
| With FDA Clinical Review for additional indication<br>With Subsequent Labeling Amendment (per product/strength) | P2,500 + LRF<br>+P500 + LRF |
| Change or addition of brand name | P2,500 + LRF + P510 (for each brand name proposed) |
| Shelf life extension/reduction | P1,000 + LRF |
| Equivalent to **Initial Registration**, including Additional Route of Administration | |
| Unbranded | P10,000 + LRF |
| Branded | P15,000 + LRF |
| Monitored Release Status | P20,000 + LRF (for three years) + P20,000 + LRF (for additional two years as per FDA Circular 2013-004) |
| Reclassification | P3,000 + LRF |