FDA CIRCULAR
No. _____

SUBJECT : **Implementing Rules and Regulations on Revised Application Process and Requirements for Post-Approval Changes of Pharmaceutical Products, and Institutionalization of the Philippine Variation Guidelines**

I. BACKGROUND/RATIONALE

In line with the provisions of Administrative Order (A.O.) No. 2013-0021, "Adoption of the Association of Southeast Asian Nations (ASEAN) Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR) for Registration of Pharmaceutical Products for Human Use", the Food and Drug Administration (FDA), in February 2014, issued FDA Circular No. 2014-008, "Application Process and Requirements for Post-Approval Changes of Pharmaceutical Products". The Circular, which became effective on 01 April 2014, was created to promulgate the revised application process and requirements for instituting Post-Approval Changes (PAC) to registered pharmaceutical products, which covered both the latest version of the ASEAN Variation Guidelines (AVG) for Pharmaceutical Products and country-specific regulatory requirements.

The application process and requirements for PAC of pharmaceutical products have then evolved with the implementation of FDA Circular No. 2014-008-A, "Amendment to Annex B, Notification for Minor Variation of FDA Circular No. 2014-008 entitled "Application Process and Requirements for Post-Approval Changes of Pharmaceutical Products", specifically on Section IV, C, D, and E for Minor Variation-Notification "effective 01 July 2016, and FDA Circular No. 2016-017, "Additional Post-Approval Changes for Pharmaceutical Products" effective 03 October 2016.

In the exigency of service, the FDA hereby enforces the Implementing Rules and Regulations on the Revised Application Process and Requirements for Post-Approval Changes of Pharmaceutical Products, and Institutionalization of the Philippine Variation Guidelines following the latest version of the ASEAN Variation Guidelines for Pharmaceutical Products and consistent with country-specific regulations and the provisions as stated in Administrative Order (A.O.) No. 67 s. 1989, "Revised Rules and Regulations on Registration of Pharmaceutical Products", Administrative Order (A.O.) No. 2013-0021, "Adoption of the Association of Southeast Asian Nations (ASEAN) Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR) for Registration of Pharmaceutical Products for Human Use", and Bureau Circular No. 5 s. 1997, "Revised Checklist of Requirements and the 1997 Guidelines for the registration of Pharmaceutical Products".

II. OBJECTIVES

This Circular aims:

1. To provide a comprehensive guideline on the application process for post-approval changes.
2. To promulgate the additional requirements in instituting post-approval changes to registered pharmaceutical products, incorporating AVG and country-specific requirements in form of the Philippine Variation Guidelines.
3. To serve as a guidance document in the implementation of the adopted AVG for Pharmaceutical Products incorporating country-specific variations.

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 shall also serve as the requirements for manufacturers, traders, and distributors (e.g. exporters, importers, and wholesalers) of single- and multi-component vitamin and mineral products, traditional medicines, over-the-counter preparations, household remedies, medical gases, vaccines and biologicals and veterinary products.

IV. DEFINITION OF TERMS

A. Variation/Post-Approval Change
   A change to any aspect of a pharmaceutical product, including but not limited to change in the method and site of manufacture, specifications for the finished pharmaceutical product and ingredients, container, labeling and product information.

B. Major Variation
   Post-Approval Change to a registered pharmaceutical finished product that may affect significantly and/or directly the aspects of quality, safety and efficacy and it does not fall within the definition of minor variation and new registration.

C. Minor Variation
   Post-Approval Change to a registered pharmaceutical finished product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of quality, safety, and efficacy.

V. ABBREVIATIONS/ACRONYMS

A. ASEAN Variation Guideline for Pharmaceutical Products
   1. Major Variation (MaV)
   2. Minor Variation (MiV)

a. Prior Approval (MiV-PA)
b. Notification (MiV-N)

3. Conditions to be fulfilled – C
4. Documents to be submitted – D
5. Package Insert – PI
6. Summary of Product Characteristics – SPC/SmPC
7. Patient Information Leaflet – PIL
8. Certificate of Pharmaceutical Product – CPP

B. Country-Specific Guideline for Post-Approval Changes to Pharmaceutical Products

1. Major Variation – MaV-PH
2. Minor Variation
    a. Prior Approval (MiV-PH)
    b. Notification (MiV-PH-N)

VI. IMPLEMENTING DETAILS

A. Eligibility

Any Marketing Authorization Holder (MAH) of a pharmaceutical product may apply for PAC, provided that:

1. The MAH has a valid License to Operate (LTO); and
2. The pharmaceutical product has a valid Certificate of Product Registration (CPR).

B. Classification

All PACs shall be based on the latest version of the ASEAN Variation Guidelines and country-specific regulations. The list of PACs with their corresponding codes and classifications shall be included in the Philippine Variation Guidelines, which shall be updated whenever the adopted guidelines and regulations have been revised.

1. ASEAN Variation Guideline for Pharmaceutical Products
    a. Major Variation (MaV)
    b. Minor Variation (MiV)
        i. Prior Approval (MiV-PA)
        ii. Notification (MiV-N)
2. Country-Specific Guideline for Post-Approval Changes to Pharmaceutical Products
    a. Major Variation (MaV) – MaV-PH
    b. Minor Variation (MiV)
        i. Prior Approval (MiV-PH)
        ii. Notification (MiV-PH-N)

FDA reserves the right to correct the filed categorization of PAC application, where deemed necessary, according to the set guidelines. This may render the application unsatisfactory, wherein an appropriate response

will be issued by the Office, and the MAH shall be required to submit a new application under a new Document Tracking Number (DTN).

C. Procedure and Requirements

An application for PAC may be submitted any time within validity of the CPR. In addition, no requests for PAC shall be incorporated with the corresponding Renewal and Monitored Release (MR)/Monitored Release Extension (MRE) to Initial registration, as these applications shall be submitted and processed separately and independently.

All applications for PAC shall be submitted to the Food and Drug Action Center (FDAC) following the schedule prescribed in the latest FDA guidelines. Applicants shall have a limit of **ten (10) variation applications/DTNs per MAH per day**.

1. Application Process
    a. Major Variation and Minor Variation-Prior Approval (MaV, MaV-PH, MiV-PA and MiV-PH) – These applications shall follow the submission process as prescribed in the latest FDA issuance.
    b. Minor Variation-Notification (MiV-N and MiV-PH-N)
        i. Applications for variation-notification shall be submitted to the FDAC officer through walk-in or email without the need for prior appointment.
        ii. Upon receipt of the application, a DTN and Acknowledgment Receipt shall be issued to the applicant as proof of acceptance of the notification.
        iii. The application shall then be endorsed to the Center for Drug Regulation and Research (CDRR) for post-acknowledgement evaluation.
        iv. For notification submissions that are appropriate, complete, and satisfactory, CDRR shall inform the applicant through Document Tracking System (DTS) and store the notification documents for updating the product file accordingly. For violative notifications, i.e., deficient documentary requirements and/or inappropriate variation and its classification (e.g., variation should be prior approval or major variation), CDRR shall impose appropriate regulatory actions such as, but not limited to, issuance of Warning Letters and/or Reports of Violation (ROV). As a consequence, the notification shall be deemed cancelled. This shall also mean forfeiture of payment and shall not be subject for refund and/or transfer of payment to other transactions within FDA.

This Office shall strictly implement that only up to **three (3) variations to a specific product shall be submitted in a single application under a given DTN**. Then, additional PAC for the same product, including consequential changes, shall be filed under another DTN/s. In such

cases, cross-referencing of variation applications for a specific product should be done.

This Office shall only process the first three (3) proposed PAC declared in the application per DTN.

In case of recurring documents for multiple PAC, a single copy may be submitted.

Any MiV-N and MiV-PH-N application with accompanying MaV, MaV-PH, MiV-PA or MiV-PH application/s shall not be processed as per Section VI.C.1.b and shall be filed separately as per process under Section VI.C.1.a.

c. Changes leading to a new product registration leading to issuance of a new CPR under a new drug registration number
    i. Changes to the Active Pharmaceutical Ingredient (API)
        - Change of the API to a different API including change in salt or isomer form of the API
        - Inclusion of an additional API to a single component or multicomponent product
        - Removal of API from a multicomponent product
        - Change in the strength of one or more APIs
        - Increase in overage
    ii. Changes to the pharmaceutical form/dosage form
    iii. Changes in the route of administration (exception for parenteral route)
    iv. Change of drug product formulation which involves addition and/or removal of excipient
    v. Replacement/inclusion/deletion of delivery system of the drug product
    vi. Addition/replacement/deletion of component/s in an existing or to form a new product containing all its individual components, e.g. Combination pack and Kit
    vii. Change of primary packaging material that is less protective than the approved material in respect of its relevant properties
    viii. Change from a currently approved contract manufacturer or own plant to another contract manufacturer. For change of manufacturing site to a subsidiary manufacturing site, refer to MaV-4
    ix. Addition of a new manufacturing site to the currently approved site for the same manufacturing activity
    x. Addition of bulk product manufacturer
    xi. Addition of alternative manufacturer/site of drug substance to the currently approved site for the same manufacturing activity
    xii. Addition of a new primary packaging material/presentation for a registered drug product,

including its attached device, delivery system, diluent/solvent among others

xiii. Change or addition of primary packaging type for a registered drug product, e.g. from blister pack to bottle

xiv. Addition of a new flavor for a registered drug product

Applications with change/s mentioned in Sections VI.C.1.c.i to VI.C.1.c.viii shall be submitted and processed under Initial or Monitored Release (whichever is applicable), depending on the current registration status of the drug product, whereas those from Sections VI.C.1.c.ix to VI.C.1.c.xiv shall be processed as PAC following the Philippine Variation Guidelines, wherein the Initial dossier as well as variation-specific documents shall be submitted.

2. Requirements

The requirements shall follow the latest version of the AVG and country specific regulations, which shall be posted and made available at the FDA website.

a. **ALL** PAC application submissions shall include the following country-specific requirements:
    i. Signed Integrated Application Form (IAF), Annexes 1 and 4, in both Portable Document Format (PDF) and Microsoft Excel (XLS/XLSX) Format
    ii. Copy of valid Certificate of Product Registration (CPR) and/or proof of CPR renewal
    iii. Copy of previously approved/acknowledged PACs (if not yet incorporated in the current CPR)
    iv. Proof of payment, i.e. copy of official receipt (OR) and/or Assessment Slip
    v. Amended relevant section/s of the dossier following ACTD or national requirements (where applicable)

b. All submissions for MaV, MaV-PH, MiV-PA and MiV-PH shall also include the following requirements, aside from those cited under Section VI.C.2.a:
    i. Notarized letter of PAC Request (refer to Attachment 1) indicating the specific type of PAC and the affected product, as well as declaration that there is/are no other change/s except those mentioned in the letter of request. This shall be signed by the Head of Regulatory Office.
    ii. Documentary requirements as per the latest version of the AVG and country-specific regulations (refer to the Philippine Variation Guidelines)

c. All submissions for MiV-N and MiV-PH-N shall also include the following requirements, aside from those cited under Section VI.C.2.a:
    i. Hard Copy:
        - Two (2) original copies of notarized Notification Form for Minor Variation (refer to Attachment 2)
    ii. Soft/Electronic Copy:
        - Notarized Attachment 2

- For variations of Certificate of Listing of Identical Product (CLIDP), copy of the Principal Certificate of Product Registration (PCPR) variation approval/acknowledgement (where applicable)
- Complete documentary requirements and pertinent evidence supporting the change/s (refer to the Philippine Variation Guidelines)

The applicant shall indicate the specific type of PAC, the complete, detailed information/description on the proposed changes and the affected product/s in the Letter of PAC Request and Notification Form. For items that are not applicable, these shall be written as "N/A". After the last entry in the table of changes, the applicant shall indicate "NOTHING FOLLOWS".

All variations made to/proposed for (whichever is applicable) the product shall be applied following the corresponding PAC Classification. The applicant must ensure that all changes declared in the application are substantiated with the documentary requirements per PAC based on the current guidelines. Any changes, which are not included in the application, observed in the documents shall not be processed, in which the said PAC shall be filed as a separate application with a new set of documents under a new DTN.

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

For already implemented PAC under notification, if the application is disapproved, the applicant shall report to FDA for actions regarding cease of implementation.

3. Authorization

Once the variation application is considered approved/acknowledged, this Office shall issue the following:

a. For MaV, MaV-PH, MiV-PA and MiV-PH applications, a variation Certificate shall be issued by FDA indicating each PAC approved.
b. For MiV-N and MiV-PH-N applications, an acknowledgement receipt and signed notification form with assigned DTN shall be issued.
c. For PACs listed in Sections VI.C.1.c.i to VI.C.1.c.vi, a CPR with a new validity shall be issued.
d. For PACs listed in Sections VI.C.1.c.vii to VI.C.1.c.xiv, a CPR retaining the validity of the previous drug product registration shall be issued.

On the other hand, this Office may also issue a Letter of Disapproval (LOD), Warning Letter, or Report of Violation (ROV), whichever is

applicable, stating the reasons or grounds for the non-acceptance of the application based on the variation and submission guidelines.

4. Fees

   The appropriate fees as prescribed under existing regulations shall apply, including the Legal Research Fee (LRF). The payment shall be based for **each drug product and variation code**. This does not apply to those not covered by ASEAN or country-specific variation guidelines, e.g. MiV-PH4, wherein payment should be on a **per change** basis. A matrix of fees is attached (refer to the Philippine Variation Guidelines).

   The fees for the PAC listed in Section VI.C.1.c shall be equivalent to **initial registration** schedule of fees based on the previous registration status of the drug product (when applicable). The distinction in fees for the aforementioned PAC is in line with the complexity of the proposed change/s. In accordance with Sections VI.C.3.c and VI.C.3.d, these types of changes, when approved, will be issued a CPR.

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

VII. TRANSITORY PROVISIONS

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

VIII. REPEALING/SEPARABILITY CLAUSE

PSD Memo 02-05, FDA Circular No. 2011-02, FDA Circular No. 2014-008, FDA Circular No. 2014-008-A, FDA Circular No. 2016-017 and other provisions in previous circulars and memoranda 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.

IX. EFFECTIVITY

This Circular shall take effect immediately.

ROLANDO ENRIQUE D. DOMINGO, MD
Director General

Keywords	Prior Approval, Notification, Variation, Post-approval Changes, PAC, AVG, ASEAN Variation Guideline
Related Issuances, laws, directives from other government agencies	RA 3720, RA 9711, AO 2013-0021, FC 2014-008, FC 2014-008-A, FC 2016-017

Attachment 1
Letter of Request for Post-Approval Change/s

Letter of Request for Post-approval Change/s

DTN	
Date:	

FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City
Alabang, Muntinlupa City

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

We, *(company name)*, declare that there is/are no other change/s to the drug product registration aside from what is/are specified above.

For your approval.

Very truly yours,

(Company representative name and signature)
(Position)

DECLARATION

In support of our post-approval change/s application, 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 Letter of Request for Post-Approval Change/s (Board Resolution in case of corporation and Special Power of Attorney in all other cases both of which should be duly notarized).
2. On behalf of my company, the pharmaceutical product identified in the letter of request meets all the legal requirements and conforms to existing standards and specification requirements applicable to the said product, and that the proposed change/s has/have been checked in reference to the currently approved data in the system.
3. All conditions for the post-approval changes have been fulfilled and all required supporting documents are submitted.
4. The particulars given in this application are true and all data and information of relevance in relation to the request have been supplied and that the documents enclosed are authentic or true copies.
5. I agree that the approval of the variation/s shall not preclude the Food and Drug Administration (FDA) in imposing appropriate regulatory actions in the event that there is/are outright negligence on the conditions for variation and explicit misdeclaration of the applied changes as variation; lacking and deficient documentary requirements as stipulated in current Circulars on Post-Approval Changes; 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.
6. 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.
7. I, or my company undertake to:
    a. All the conditions.
    b. 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.
    c. Notify FDA of any adverse events consistent with the requirements of pharmacovigilance.
    d. Respond to and cooperate fully with Food-Drug Regulation Officers (FDROs) regarding any subsequent post-marketing activity initiated by FDA.
    e. Exhaust the remaining stocks of **labeling materials and products** bearing the old product information up to a maximum of one (1) year from the date of receipt of the certification, at the manufacturing level.
    f. Submit a commercial sample of the first batch of manufacturing/importation/packaging/repackaging of the subject product, for all pack sizes, including the package insert or patient information leaflet (whichever is applicable) reflecting the proposed change, as soon as available.
8. I understand that our company or establishment cannot place reliance on the acceptance of the post-approval change 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.

HEAD OF REGULATORY OFFICE COMPANY PHARMACIST

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

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 met hat 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 _____

Attachment 2
Notification Form

Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

NOTIFICATION FORM FOR MINOR VARIATION/S OF REGISTERED PHARMACEUTICAL PRODUCT

Date: _____

FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City
Alabang, Muntinlupa City

DOCUMENT TRACKING NUMBER (DTN)	
TO BE FILLED OUT BY FDA	
Received by:	
Signature:	
Date:	
PAYMENT DETAILS	
Amount Paid:	
OR No.:	
OR Date Issued:	

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

Details should be consistent with the current CPR/CLIDP.

Generic Name _____
Dosage Strength and Form _____
Brand Name _____
_____
Approved Shelf-life _____
Storage Condition _____
Packaging/Presentation _____

FDA Registration No. _____ **Validity** _____
Registration Status _____
State the validity or the DTN of the renewal application, if the CPR/CLIDP has not yet been renewed

COMPANY PARTICULARS

Details should be consistent with the current CPR/CLIDP. Complete name/s and address/es of the involved establishment/s should be reflected.

Manufacturer _____
_____
Trader _____
_____
Importer _____
_____
Distributor _____
_____
Packer/Repacker _____
_____

DTN	
Received by:	

POST-APPROVAL CHANGES PARTICULARS

Table of Changes		
Current	**Proposed Changes**	**Specific Type of Variation** *For MiV-PH-N7, indicate the original variation code applied for the PCPR, e.g. MiV-PH-N7 (MaV-15)*

***** NOTHING FOLLOWS *****

DTN	
Received by:	

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 Form for Minor Variation/s of registered pharmaceutical product (Board Resolution in case of corporation and Special Power of Attorney in all other cases both of which should be duly notarized).
2. On behalf of my company, the pharmaceutical product identified in the notification form meets all the legal requirements, and conforms to existing standards and specification requirements applicable to the said product.
3. All conditions for the variations have been fulfilled and all required supporting documents are submitted.
4. 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.
5. I agree that the acknowledgement of this notification shall not preclude the Food and Drug Administration (FDA) in imposing appropriate regulatory actions in the event that there is/are outright negligence on the conditions for minor variation – notification and explicit misdeclaration of the applied changes as notification; lacking and deficient documentary requirements as stipulated in current Circulars on Post-Approval Changes; 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.
6. 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.
7. 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 of any adverse events consistent with the requirements of pharmacovigilance.
   c) Respond to and cooperate fully with Food-Drug Regulation Officers (FDROs) with regard to any subsequent post-marketing activity initiated by FDA.
   d) Exhaust the remaining stocks **of labeling materials and products** bearing the old product information up to a maximum of one (1) year from the date of receipt of the notification, at the manufacturing level.
   e) Submit a commercial sample of the first batch of manufacturing/importation/packaging/repackaging of the subject product, for all pack sizes, including the package insert or patient information leaflet (whichever is applicable) reflecting the notified change, as soon as available.
8. 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.
9. There is/are no other change/s made to/proposed for the drug product aside from what is/are specified in the Post-Approval Changes Particulars of this Notification Form.

DTN	
Received by:	

HEAD OF REGULATORY OFFICE

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

COMPANY PHARMACIST

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

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 _____