FDA CIRCULAR
No. _____

SUBJECT : **Application Process and Requirements for Post-Approval Changes of Biological Products Adopting the World Health Organization Guidelines for Changes to Approved Vaccines and Biotherapeutic Products for Human Use**

I. BACKGROUND

By virtue of Administrative Order (A.O.) No. 47-a, series of 2001 entitled "Rules and Regulations on the Registration, Including Approval and Conduct of Clinical Trials, and Lot or Batch Release Certification of Vaccines and Biological Products", the Annex 4 of World Health Organization (WHO) Technical Report Series (TRS) No. 993 and Annex 3 of 1011 serve as the standard for the evaluation of applications for the registration of vaccines and biotherapeutic products.

With the intent to harmonize regulatory requirements for pharmaceutical products, including vaccines and biotherapeutic products, among ASEAN member states, AO No. 2013-0021 entitled "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" was issued. Relative thereto, the Food and Drug Administration (FDA) issued FDA Circular (FC) No. 2014-008 entitled "Application Process and Requirements for Post-Approval Changes of Pharmaceutical Products" which became effective on 01 April 2014 to promulgate the revised application process and requirements for instituting Post-Approval Changes (PAC) to registered pharmaceutical products, which covered both 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 FC 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 FC No. 2016-017, "Additional Post-Approval Changes for Pharmaceutical Products" effective 03 October 2016.

The above regulations are intended to provide supportive information on the process and requirements for changes to small molecule/chemically-synthesized drug products. However, given the complexity and current challenges of global life-cycle management of vaccines and biotherapeutic

products, the need to develop a specific and pertinent guideline for changes to approved biological products is imperative.

II. OBJECTIVES

The objectives of this Circular are:

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

III. SCOPE

This circular shall apply to all Marketing Authorization Holders (MAHs) of biological products.

IV. DEFINITION OF TERMS

A. Biological drug product or biological product or biologic or biotherapeutic product refers to any product of biological origin, prepared with biological processes, derived from blood and plasma, or manufactured by biotechnology, consisting of substances of higher molecular weight whose purity, potency, and composition cannot readily and reliably be determined by chemical or physicochemical analysis. Examples of this group include vaccines, blood products, modified animal tissues, high molecular weight hormones, allergens, and the products of genetic engineering or other newer biotechnological techniques. This definition does not include antibiotics and substances that, although of biological origin, are of low molecular weight and can be isolated as pure substances, such as purified steroids and alkaloids.

B. Major Variation refers to 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. Master Cell Bank (MCB) refers to a quantity of well-characterized cells of animal or other origin, derived from a cell seed at a specific Population Doubling Level (PDL) or passage level, dispensed into multiple containers, cryopreserved and stored frozen under defined conditions, such as the vapour or liquid nitrogen in aliquots of uniform composition.

D. Master Seed Lot (MSL) refers to a lot or bank of cells or viruses from which all future vaccine production will be derived. The MSL represents a well-characterized collection of cells or viruses or bacteria of uniform composition.

E. Minor Variation refers to 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.

F. Vaccine refers to a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from the weakened or killed forms of the microbe, its toxins or one of its surface proteins.

G. Variation/Post-Approval Change refers to 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.

V. IMPLEMENTING DETAILS

A. Eligibility

Any MAH of biological products may apply for PAC, provided that:

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

B. Classification of Variations

All PACs shall be based on the latest version of the WHO Guidelines for Changes to Approved Vaccines and Biotherapeutic Products and country-specific regulations. The list of PACs with their corresponding codes and classifications shall be included in the Philippine Variation Guideline for Biological Products (PVGB) as Annex 1 of this Circular. This list shall be updated whenever the adopted guidelines and regulations have been revised which shall be released through an FDA Advisory. The classification of variations are as follows:

1. WHO Guidelines for Changes to Approved Biological Products
    a. Major Variation (BMaV)
    b. Minor Variation (BMiV)
        i. Prior Approval (BMiV-PA)
        ii. Notification (BMiV-N)
2. Country-Specific Guideline for Post-Approval Changes to Biological Products
    a. Major Variation (BMaV) – BMaV-PH
    b. Minor Variation (BMiV)
        i. Prior Approval (BMiV-PH)
        ii. Notification (BMiV-PH-N)
3. Other changes not covered by the PVGB (B-OTH)

The FDA reserves the right to correct the filed categorization of PAC application, according to the set guidelines, where deemed necessary. This may render the application unsatisfactory, wherein an appropriate response will be issued by this 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 the validity of the CPR.

1. Pre-Assessment

   Applications for PAC shall undergo pre-assessment to ensure the completeness of submitted applications and documentary requirements. The pre-assessment of applications shall be done within the prescribed working days and office hours of the FDA. Schedule of submissions shall follow the latest guidelines or through established on FDA online submission platform once available and implemented.

2. Application Process
   a. Major Variation, Minor Variation-Prior Approval and Other changes not covered by the PVGB (BMaV, BMaV-PH, BMiV-PA, BMiV-PH and B-OTH) – These applications shall follow the submission process as prescribed in the latest FDA issuance.
   b. Minor Variation-Notification (BMiV-N and BMiV-PH-N)
      i. Applications for variation-notification shall be submitted to the FDAC via email, fdac.pacd.cdrr@fda.gov.ph, every Tuesday and Wednesday 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-acknowledgment evaluation
      iii. For notification submissions that are appropriate, complete, and satisfactory, the CDRR shall inform the applicant through the Document Tracking System (DTS). For deficient documentary requirements and/or inappropriate variation and its classification (e.g., variation should be prior approval or major variation), the CDRR shall impose appropriate regulatory actions such as, but not limited to, issuance of Letter of Disapproval (LOD). 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.

Any BMiV-N and BMiV-PH-N application with accompanying BMaV, BMaV-PH, BMiV-PA, BMiV-PH or B-OTH application/s shall not be processed as per Section V.C.1.b and shall be filed separately as per process under Section V.C.1.a.

c. The changes requiring a new product registration leading to issuance of a new CPR under a new drug registration number are:

i. Changes to the API:
(1) change of the API to a different API including change in salt or isomer form of the API
(2) inclusion of an additional API to a single component or multicomponent product
(3) removal of API from a multicomponent product
(4) change in the strength of one or more APIs
(5) 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 involve addition and/or removal of excipient

v. Addition of new primary packaging material/presentation for a registered drug product, including its attached device, delivery system

vi. Change/addition of new cell substrate/viral or bacterial seeds that are unrelated to the licensed master cell bank (MCB)/master seed lot (MSL) or pre-MCB/MSL material (for biotherapeutic drug products)

vii. Addition/replacement/deletion of component(s) (for drug kits)

Applications with change/s mentioned in Sections V.C.1.c.i to V.C.1.c.v shall be submitted and processed under Initial or Monitored Release (MR) (whichever is applicable), depending on the current registration status of the drug product, whereas those from Sections VI.C.1.c.vi to VI.C.1.c.vii shall be processed as PAC following the PVGB.

3. Requirements

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

a. All PAC application submissions shall include the following country-specific requirements:

i. Signed Integrated Application Form (IAF), 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. Certificate of approval from the national regulatory authority (NRA) of the exporting country or the country of origin (where applicable)

b. All submissions for BMaV, BMaV-PH, BMiV-PA, BMiV-PH and B-OTH shall also include the following requirements, aside from those cited under Section V.C.2.a:

i. Notarized letter of PAC Request following Annex 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. Complete documentary requirements and pertinent evidence supporting the change/s as per the latest version of the PVGB

c. All submissions for BMiV-N and BMiV-PH-N shall also include the following requirements, aside from those cited under Section V.C.2.a:

i. Hard Copy:
   - Two (2) original copies of notarized Notification Form for Minor Variation following Annex 2

ii. Soft/Electronic Copy:
   - Notarized Annex 2
   - For variations of Certificate of Listing of Identical Product (CLIDP), copy of the Principal Certificate of Product Registration (PCPR) variation approval/acknowledgment (where applicable)
   - Complete documentary requirements and pertinent evidence supporting the change/s as per the latest version of the PVGB

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 the product shall be applied following the corresponding PAC Classification, whichever is

applicable. 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.

If the PAC application under notification is disapproved and the MAH already implemented the changes, the MAH shall report to the FDA for actions regarding cease of implementation.

4. Authorization

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

d. For BMaV, BMaV-PH, BMiV-PA, BMiV-PH and B-OTH applications, a variation Certificate shall be issued by FDA indicating each PAC approved.
e. For BMiV-N and BMiV-PH-N applications, an acknowledgment receipt and signed notification form with assigned DTN shall be issued.
f. For PACs listed in Sections V.C.1.c., a CPR with a new validity shall be issued.

On the other hand, this Office may also issue a Letter of Disapproval (LOD), stating the reasons or grounds for the disapproval of the application based on the variation and submission guidelines.

5. Fees

The appropriate fees and charges as specified under existing regulations shall apply, including a Legal Research Fee (LRF), or any amendment or latest issuance thereafter.

The payment shall be based on **each drug product and variation code**. This does not apply to those not covered by the PVGB, i.e B-OTH, wherein payment should be on **per change** basis.

VI. 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 shall not be covered by this Circular.

VII. SEPARABILITY CLAUSE

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

VIII. REPEALING CLAUSE

Any provisions in previous circulars and memoranda inconsistent with this Circular are hereby withdrawn, repealed, and/or revoked accordingly.

IX. EFFECTIVITY

This Circular shall take effect fifteen (15) calendar days after publication in one (1) newspaper of general circulation and upon filing with the University of the Philippines, Office of the National Administrative Register (ONAR).

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Director General