Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

FDA Circular
No. 2020-002

06 FEB 2020

SUBJECT: GUIDELINES ON THE REGISTRATION OF HUMAN INFLUENZA VACCINES

I. BACKGROUND/RATIONALE

The World Health Organization (WHO) defines influenza as a contagious, acute respiratory illness caused by influenza viruses, usually influenza A or B subtypes. Influenza viruses can infect humans and other animals. Viruses that infect humans circulate in seasonal epidemics, although some tropical regions experience endemic influenza circulation. An influenza pandemic or global epidemic may occur when a novel influenza virus strain appears which is significantly different from circulating strains and against which almost no one is immune.

Influenza can cause severe illness or death, especially in people at high risk and vaccination is the most effective way to prevent infection and severe outcomes caused by influenza viruses.

Every year, seasonal influenza vaccines are reviewed and updated as needed, based on each virus types' prevalence, and the success rate of the previous vaccine. It consists of strains recommended by WHO, either for northern or southern hemisphere, that aims to protect against currently circulating influenza viruses.

Pursuant to Republic Act No. 3720, known as the "Food, Drug and Cosmetics Act" as amended by Executive Order No. 175 and Republic Act No. 9711, also known as the "Food and Drug Administration (FDA) Act of 2009" and Department Circular No. 2011-0101 "The Rules and Regulations Implementing RA 9711" to establish an effective regulatory system for authorization and monitoring of health products and with the promulgation of Administrative Order (A.O.) No. 47-a, series of 2001 "Rules and Regulations on the Registration, Including Approval and Conduct of Clinical Trials, and Lot or Batch Release Certification of Vaccine and Biologic Products" to establish a specific list of requirements, rules and regulations for the registration of influenza vaccines that is aligned with international best practices, and to ensure access of these vaccines in the country.

II. SCOPE

This Circular shall apply to all manufacturers and distributors (e.g. importers and wholesalers) of influenza vaccines for human use.

III. OBJECTIVES

This Circular aims to provide clarity on the registration of new influenza vaccines, as well as regulatory guidance and requirements for the variation application of influenza vaccine strains with the view of streamlining the registration process in the Center for Drug Regulation and Research (CDRR).

IV. REGISTRATION

A. Procedures and Requirements

1. Procedures and General Considerations

a. All applications shall follow the submission process as prescribed in the latest issuance of the FDA.

b. All influenza vaccines shall be given a Monitored Release (MR) status.

c. Applications for strain variation shall be classified as major variation and shall be processed under the code, MaV-SC (Major Variation – Strain Clearance).

In the event that the WHO recommended strains remain the same for the following year, an application shall be filed under Minor Variation – Strain Clearance (MiV-SC).

d. Applications for MaV-SC and MiV-SC may be submitted any time during the validity of the Certificate of Product Registration (CPR).

An application for MaV-SC or MiV-SC received after the date of expiration of the CPR shall be subject to a surcharge or penalty equivalent to twice the MR registration fee and an additional 10% per month or a fraction thereof of continuing non-submission of such application up to a maximum of one hundred twenty (120) days. Any application for MaV-SC or MiV-SC filed thereafter shall be considered invalid and the application shall undergo the MR registration filing and evaluation procedure.

e. Consequential changes that are related to the strain change may be filed together with MaV-SC under a single Document Tracking Number (DTN). Any changes [including, but are not limited to, changes in the manufacturing processes, posology, product labelling information of influenza vaccines] that are not related to the annual strain update shall not be processed, in which the said changes shall follow the normal categorization procedure and shall be filed as a separate variation application with a new set of documents under a new DTN. Corresponding fees shall apply for additional changes.

Non-consequential changes for influenza vaccines shall be assigned a new code, "Flu–[variation code]" (e.g. Flu–MaV–1) (Refer to Appendix 4), and shall follow the documentary requirements based on the ASEAN Variation Guideline (AVG) and WHO Technical Report Series (TRS) 993 Annex 4 and WHO TRS 1011 Annex 3.

2. Requirements

Requirements for MR registration, MaV-SC and MiV-SC shall follow AO No. 47-A s. 2001 and AO No. 2013-0021 "Adoption of the Association of Southeast Asian Nations (ASEAN) Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR)" on the presentation and format of the dossier [ACTD or ICH Common Technical Dossier (CTD)] (refer to Appendix 1).

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

B. Validity

1. A CPR for influenza vaccines with one (1) year validity shall be issued.

2. MaV-SC applications shall be issued a new CPR reflecting the new strain(s) and new validity, while retaining the registration number.

3. MiV-SC applications shall be issued a new CPR reflecting the old strain(s) and new validity, while retaining the registration number.

C. Fees

The appropriate fees as prescribed under existing regulations shall apply, including the Legal Research Fund (LRF). The payment for the additional consequential changes shall be on **per product, per change** basis and shall follow the existing regulation on fees as per FDA Circular No. 2014-008 "Application Process and Requirements for Post-approval Changes of Pharmaceutical Products".

Application Type	**Fees**
Monitored Release	
Registration	Php 20,000[i] + LRF
Clinical Review	Php 5,000[ii] + LRF
Brand Name (if any)	Php 500[iii] + LRF
Variation	
Major Variation – Strain Clearance (MaV-SC)	Php 20,000[#] + LRF
Minor Variation – Strain Clearance (MiV-SC)	Php 500 + LRF

LRF is equivalent to one percent (1%) of the filing fee imposed, but in no case lower than ten pesos.
[#]Fee reflected does not include consequential changes filed together with MaV-SC.

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 human influenza vaccine shall only apply to incoming MR registration, MaV-SC and MiV-SC applications.

VI. REPEALING/SEPARABILITY CLAUSE

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

VII. EFFECTIVITY

This Circular shall take effect immediately.

ROLANDO ENRIQUE D. DOMINGO, MD, DPBO
Undersecretary of Health
Officer-in-Charge, Director General

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[i]Item 1.1, Section B. Fees for Registration of Products Regulated by BFAD, AO No. 50 s. 2001 "Revised 2001 Schedule of Fees and Charges for the Corresponding Services Rendered by the Bureau of Food and Drugs"

[ii]Item 7.8.2, Section B. Fees for Registration of Products Regulated by BFAD, AO No. 50 s. 2001 "Revised 2001 Schedule of Fees and Charges for the Corresponding Services Rendered by the Bureau of Food and Drugs"

[iii]Annex D - Matrix of Fees, FC No. 2014-008

Appendix 1

CENTER FOR DRUG REGULATION AND RESEARCH
LIST OF REQUIREMENTS FOR THE REGISTRATION OF HUMAN INFLUENZA VACCINES

No.	Parameters	Requirements		
		MR	MaV-SC (Only relevant and adequate sections of the ACTD/CTD should be submitted. All sections not felt to be necessary should however be justified adequately in the Summary/Overview)	MiV-SC
Part I	Administrative Data and Product Information			
Sec. A	Introduction	✓	✓	
Sec. B	Table of Contents	✓	✓	
Sec. C	Guidance on the Administrative Data and Product Information			
	1. Integrated Application Form (with proof of payment)	✓	✓	✓
	2. Letter of Authorization (where applicable)	✓		
	3. Certifications			
	For contract manufacturing a. License of pharmaceutical industries and contract manufacturer b. Contract manufacturing agreement c. GMP certificate of contract manufacturer	✓	✓	✓
	For manufacturing "under-license" a. License of pharmaceutical industries b. GMP certificate of the manufacturer c. Copy of "under-license" agreement	✓	✓	✓
	For imported products			
	a. Foreign GMP Clearance	✓	✓	✓
	b. License of pharmaceutical industries/importer/wholesaler (country specific)	✓	✓	✓
	c. Certificate of Pharmaceutical Product (CPP) issued by the competent authority in the country of origin to the current WHO format	✓	✓	
	If the product is not marketed in the country of origin the following should be submitted: c.1 CPP indicating that the product is for export only or Certificate of Export; and c.2 Authenticated Certificate of Free Sale (CFS)			

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	or CPP where it is marketed; *If the country of origin does not issue a CPP the following should be submitted:* c.3 Justification that the country of origin does not issue a CPP; and c.4 Authenticated CFS or CPP where it is marketed			
	4. Site Master File	✓		
	5. Labeling	✓	✓ [new strain(s)]	✓
	6. Product Information a. Package Insert b. Summary of Product Characteristics (Product Data Sheet)	✓	✓	✓
Part II	Quality			
Sec. A	Table of Contents	✓	✓	
Sec. B	Quality Overall Summary (QOS)	✓	✓ (addendum to "previous" QOS)	
Sec. C	Body of Data Drug Substance (S)			
S 1	General Information			
	S 1.1. Nomenclature	✓		
	S 1.2. Structural Formula	✓		
	S 1.3. General Properties	✓		
S 2	Manufacture			
	S 2.1. Manufacturer(s)	✓	✓	
	S 2.2. Description of Manufacturing Process and Process Controls	✓	✓	
	S 2.3. Control of Materials	✓	✓	
	- seed lots: history:	✓	✓	
	- passage level	✓	✓	
	- characterization of Haemagglutinin and Neuraminidase	✓	✓	
	- analytical protocols (including test results on seed lots)*	✓	✓	
	S 2.4. Control of Critical Steps and Intermediates	✓	✓	
	S 2.5. Process Validation and/or Evaluation	✓	✓	
	- monovalent bulks:	✓	✓	
	- manufacturing process strain specific changes	✓	✓	
	- validation of critical manufacturing steps (e.g. inactivation, splitting efficiency)	✓	✓ [new strain(s)]	
	S 2.6. Manufacturing Process Development	✓		
S 3	Characterization			

	S 3.1. Elucidation of Structure and Characteristics	✓	✓	
	S 3.2. Impurities	✓	✓	
S 4	Control of Drug Substance			
	S 4.1. Specifications	✓	✓	
	S 4.2. Analytical Procedures	✓	✓	
	S 4.3. Validation of Analytical Procedures	✓	✓	
	- validation study reports and summaries of test method [e.g. validation of Single Radial Diffusion (SRD) test]	✓	✓ [new strain(s)]	
	S 4.4. Batch Analyses	✓	✓	
	- results of monovalent bulks: results (including test for neuraminidase):	✓	✓	
	- each working seed lot of a new master seed lot of new strain(s)		✓	
	- each working seed lot from previously approved master seed lot where the procedure of working seed lot preparation is different from the approved procedure		✓	
	S 4.5. Justification of Specifications	✓		
S 5	Reference Standards or Materials	✓		
S 6	Container Closure System	✓		
S 7	Stability	✓	✓	
	(Stability tests on the active substances: results from monovalent bulks where they are used for more than one year)	✓	✓	
	Drug Product (P)			
P 1	Composition	✓	✓	
P 2	Pharmaceutical Development			
	P 2.1. Information on Development Studies	✓		
	P 2.2. Components of the Drug Product	✓	✓	
	P 2.2.1. Active Ingredients	✓	✓	
	- formulation development [actual formula and Certificate of Analysis (CoA) of batch(es) used in clinical trial(s) when available (either in quality or in clinical submission)]	✓	✓ [new strain(s)]	
	P 2.2.2. Excipients	✓		
	P 2.3. Finished Product	✓		
	P 2.3.1. Formulation Development	✓		
	P 2.3.2. Overages	✓		
	P 2.3.3. Physicochemical and Biological Properties	✓		
	P 2.4. Manufacturing Process Development	✓		
	P 2.5. Container Closure System	✓		
	P 2.6. Microbiological Attributes	✓		
	P 2.7. Compatibility	✓		
P 3	Manufacture			
	P 3.1. Batch Formula (actual formula)	✓	✓	
	P 3.2. Manufacturing Process and Process Control	✓		
	P 3.3. Controls of Critical Steps and Intermediates	✓		
	P 3.4. Process Validation and/or Evaluation	✓		

P 4	Control of Excipients				
	P 4.1. Specifications	✓			
	P 4.2. Analytical Procedures	✓			
	P 4.3. Excipients of Human and Animal Origin	✓			
	P 4.4. Novel Excipients	✓			
P 5	Control of Finished Product				
	P 5.1. Specifications	✓	✓		
	P 5.2. Analytical Procedures	✓	✓		
	P 5.3. Validation of Analytical Procedures	✓	✓		
	[validation of SRD test (either the final bulk or drug product)]	✓	✓ [new strain(s)]		
	P 5.4. Batch Analyses	✓	✓		
	P 5.5. Characterization of Impurities	✓	✓		
	P 5.6. Justification of Specifications	✓			
P 6	Reference Standards or Materials	✓			
P 7	Container Closure System	✓			
P 8	Product Stability	✓	✓		
	- stability data from previous season and available stability data of current strain(s)	✓	✓ [new strain(s)]		
	- stability commitment(s) to complete the on-going stability studies to support approved shelf-life	✓	✓		
	- post-approval stability protocol for the final lot stability	✓	✓		
Part III	Nonclinical Document				
Sec. A	Table of Contents	✓			
Sec. B	Nonclinical Overview	✓			
	1. General Aspect	✓			
	2. Content and Structural Format	✓			
Sec. C	Nonclinical Written and Tabulated Summaries	✓			
	1. Nonclinical Written Summaries	✓			
	1.1 Introduction	✓			
	1.2. General Presentation Issues	✓			
	2. Content of Nonclinical Written and Tabulated Summaries	✓			
	2.1. Pharmacology	✓			
	2.1.1. Written Summary	✓			
	2.1.1.1. Primary Pharmacodynamics	✓			
	2.1.1.1.1. Immunogenicity Studies	✓			
	2.1.1.2. Secondary Pharmacodynamics	✓			
	2.1.1.3. Safety Pharmacology	✓			
	2.1.1.4. Pharmacodynamic Drug Interactions	✓			
	2.1.2. Tabulated Summary	✓			
	2.2. Toxicology	✓			
	2.2.1. Written Summary	✓			
	2.2.1.1. Single-Dose Toxicity	✓			
	2.2.1.2. Repeat-Dose Toxicity	✓			
	2.2.1.3. Genotoxicity	✓			

	2.2.1.4. Carcinogenicity	✓			
	2.2.1.5. Reproductive and Developmental Toxicity	✓			
	2.2.1.5.1. Fertility and Early Embryonic Development	✓			
	2.2.1.5.2. Embryo-Foetal Development	✓			
	2.2.1.5.3. Prenatal and Postnatal Development	✓			
	2.2.1.6. Local Tolerance	✓			
	2.2.1.7. Other Toxicity Studies (if available)	✓			
	2.2.2. Tabulated Summary	✓			
	3. Nonclinical Tabulated Summaries	✓			
Sec. D	Nonclinical Study Reports	✓			
	1. Table of Contents	✓			
	2. Pharmacology	✓			
	2.1. Written Study Reports	✓			
	2.1.1. Primary Pharmacodynamics	✓			
	2.1.2. Secondary Pharmacodynamics	✓			
	2.1.2.1. Immunogenicity Studies	✓			
	2.1.3. Safety Pharmacology	✓			
	2.1.4. Pharmacodynamic Drug Interactions	✓			
	3. Toxicology	✓			
	3.1. Written Study Reports	✓			
	3.1.1. Single-Dose Toxicity	✓			
	3.1.2. Repeat-Dose Toxicity	✓			
	3.1.3. Genotoxicity	✓			
	3.1.3.1. In vitro Reports	✓			
	3.1.3.2. In vivo Reports	✓			
	3.1.4. Carcinogenicity	✓			
	3.1.4.1. Long Term Studies	✓			
	3.1.4.2. Short or Medium Term Studies	✓			
	3.1.4.3. Other Studies	✓			
	3.1.5. Reproductive and Developmental Toxicity	✓			
	3.1.5.1. Fertility and Early Embryonic Development	✓			
	3.1.5.2. Embryo-Foetal Development	✓			
	3.1.5.3. Prenatal and Postnatal Development	✓			
	3.1.5.4. Studies in which the Offspring are Dosed and/or further Evaluated	✓			
	3.1.6. Local Tolerance	✓			
	3.1.7. Other Toxicity Studies (if available)	✓			
	3.1.7.1. Antigenicity	✓			
	3.1.7.2. Immunotoxicity	✓			
	3.1.7.3. Dependence	✓			
	3.1.7.4. Metabolites	✓			
	3.1.7.5. Impurities	✓			
	3.1.7.6. Other	✓			
Sec. E	List of Key Literature References	✓			

Part IV	Clinical Document		**		
Sec. A	Table of Contents	✓	✓		
Sec. B	Clinical Overview	✓	✓		
	1. Product Development Rationale	✓	✓		
	2. Overview of Biopharmaceutics	✓	✓		
	3. Overview of Clinical Pharmacology	✓	✓		
	4. Overview of Efficacy	✓	✓		
	5. Overview of Safety	✓	✓		
	6. Benefits and Risks Conclusions	✓	✓		
Sec. C	Clinical Summary	✓			
	1. Summary of Biopharmaceutic Studies and Associated Analytical Methods	✓			
	1.1. Background and Overview	✓			
	1.2. Summary of Results of Individual Studies	✓			
	1.3. Comparison and Analyses of Results across Studies	✓			
	Appendix 1	✓			
	2. Summary of Clinical Pharmacology Studies	✓			
	2.1. Background and Overview	✓			
	2.2. Summary of Results of Individual Studies	✓			
	2.3. Comparison and Analyses of Results across Studies	✓			
	2.4. Special Studies	✓			
	Appendix 2	✓			
	3. Summary of Clinical Efficacy	✓			
	3.1. Background and Overview of Clinical Efficacy	✓			
	3.2. Summary of Results of Individual Studies	✓			
	3.3. Comparison and Analyses of Results across Studies	✓			
	3.3.1. Study Populations	✓			
	3.3.2. Comparison of Efficacy Results of all Studies	✓			
	3.3.3. Comparison of Results in Sub-populations	✓			
	3.4. Analysis of Clinical Information Relevant to Dosing Recommendations	✓			
	3.5. Persistence of Efficacy and/or Tolerance Effects	✓			
	Appendix 3	✓			
	4. Summary of Clinical Safety	✓			
	4.1. Exposure to the Drug	✓			
	4.1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies	✓			
	4.1.2. Overall extent of Exposure	✓			
	4.1.3. Demographic and Other Characteristics of Study Population	✓			
	4.2. Adverse Events	✓			
	4.2.1. Analysis of Adverse Events	✓			
	4.2.1.1. Common Adverse Events	✓			
	4.2.1.2. Deaths	✓			
	4.2.1.3. Other Serious Adverse Events	✓			
	4.2.1.4. Other Significant Adverse Events	✓			

	4.2.1.5. Analysis of Adverse Events by Organ System or Syndrome	✓		
	4.2.2. Narratives	✓		
	4.3. Clinical Laboratory Evaluations	✓		
	4.4. Vital Signs, Physical Findings, and Other Observations Related to Safety	✓		
	4.5. Safety in Special Groups and Situations	✓		
	4.5.1. Patient Groups	✓		
	4.5.2. Drug Interactions	✓		
	4.5.3. Use in Pregnancy and Lactation	✓		
	4.5.4. Overdose	✓		
	4.5.5. Drug Abuse	✓		
	4.5.6. Withdrawal and Rebound	✓		
	4.5.7. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability	✓		
	4.6. Post-Marketing Data	✓		
	Appendix 4	✓		
	5. Synopses of Individual Studies	✓		
Sec. D	Tabular Listing of All Clinical Studies	✓	✓	
Sec. E	Clinical Study Reports (if applicable)	✓	✓	
	- reports of efficacy and safety studies	✓	✓	

*Where the seed virus is tested for extraneous agents using Polymerase Chain Reaction (PCR), these data should be included in this application.

**Results of clinical studies with the new influenza vaccine are to be submitted including (if any):

1. Raw data
2. Characteristics of the trial population (demography, co-morbidity, co-medication) standardized tables for immunogenicity and reactogenicity

Additional Requirements

Parameters	Requirements		
	MR	MaV-SC	MiV-SC
1. Representative Sample (w/ CoA) may be submitted at a later date, e.g. when the application has already been decked as indicated in the Document Tracking System.	✓	✓	✓
2. Risk Management Plan (RMP)	✓	✓	✓
3. Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER)	✓	✓	✓
4. List of Countries where the product is already licensed and the date of approval	✓	✓	✓
5. Names of the medical director of the importer/distributor and local manufacturer who will monitor event/s reactions and prepare appropriate report to be submitted to FDA	✓		
6. Person/s responsible for production and control of the product (Name/s Position, Department, and sample of signature)	✓		
7. Information on the number system of the lots or batches	✓	✓	
8. System for the re-processing of the product in event of rejection of the lot or batch by the manufacturer's QA/QC	✓		
9. Summary Lot Protocol	✓	✓	✓
10. Lot to Lot Consistency from three (3) consecutive batches	✓	✓	

11. Description of the cold-chain procedures employed from the origin to the port of entry and in the Philippines (how and where)	✓		
12. Copy of valid CPR		✓	✓
13. Notarized Letter of Request for Major Variation – Strain Clearance (refer to Appendix 2) indicating the affected product, as well as declaration that there is/are no other change/s except from the update on the annual strain. This shall be signed by the Head of Regulatory Office.		✓	
14. Notarized Letter of Request for Minor Variation – Strain Clearance (refer to Appendix 3) indicating the affected product, as well as declaration that there is/are no other change/s. This shall be signed by the Head of Regulatory Office.			✓
14. Adverse event following immunization report (summary of annual reports)	✓	✓	✓

Appendix 2

Letter of Request for Major Variation – Strain Clearance

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, Major Variation – Strain Clearance (MaV-SC), for the following product:

Product Name/Strength and Form	CPR Validity/ Drug Registration Number	Current Strain(s)	Proposed Strain(s)
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

For your approval.

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

Very truly yours,

Click or tap here to enter text.
Click or tap here to enter text.
Company representative name and signature
Position

DECLARATION

In support of our post-approval change 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 Major Variation - Strain Clearance (MaV-SC) (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 influenza vaccine 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 has been checked in reference to the currently approved data in the system;
3. All conditions for MaV-SC 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 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;
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 influenza vaccine'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 Following Immunization (AEFI) 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. 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.

COMPANY PHARMACIST

Signature: Click or tap here to enter text.
Name: Click or tap here to enter text.
Designation: Click or tap here to enter text.
Date: Click or tap here to enter text.

SUBSCRIBED AND SWORN TO BEFORE ME this Click or tap here to enter text. Personally appeared the following:

Name	Residence Certificate	Date Issued	Place Issued
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

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.: Click or tap here to enter text.
Page No.: Click or tap here to enter text.
Book No.: Click or tap here to enter text.
Series of: Click or tap here to enter text.

Appendix 3

Letter of Request for Minor Variation – Strain Clearance

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, Minor Variation – Strain Clearance (MiV-SC), for the following product:

Product Name/Strength and Form	CPR Validity/ Drug Registration Number	Strain(s)
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

For your approval.

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

Very truly yours,

Click or tap here to enter text.
Click or tap here to enter text.
Company representative name and signature
Position

DECLARATION

In support of our post-approval change 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 Minor Variation - Strain Clearance (MiV-SC) (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 influenza vaccine 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 has been checked in reference to the currently approved data in the system;
3. All conditions for MiV-SC 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 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;
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 influenza vaccine'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 Following Immunization (AEFI) 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. 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.

COMPANY PHARMACIST

Signature: Click or tap here to enter text.
Name: Click or tap here to enter text.
Designation: Click or tap here to enter text.
Date: Click or tap here to enter text.

SUBSCRIBED AND SWORN TO BEFORE ME this Click or tap here to enter text. Personally appeared the following:

Name	Residence Certificate	Date Issued	Place Issued
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.
Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.

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.: Click or tap here to enter text.
Page No.: Click or tap here to enter text.
Book No.: Click or tap here to enter text.
Series of: Click or tap here to enter text.

Appendix 4

List of Variation Codes Specific for Human Influenza Vaccines

Variation Code	Classification
Major Variation	
Flu-MaV-1	Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product
Flu-MaV-2	Change of content of product labeling
Flu-MaV-3	Change of manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
Flu-MaV-4	Replacement of the manufacturing site of the drug product
Flu-MaV-5	Replacement of site for the primary packaging (direct contact with drug product)
Flu-MaV-6	Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
Flu-MaV-7	Change of batch size of sterile drug product
MaV-8	Change of batch size of non-sterile drug product **(Not applicable for Human Influenza Vaccines)**
Flu-MaV-9	Change in the manufacturing process for the drug product
Flu-MaV-10	Qualitative or quantitative change of excipient
MaV-11	Quantitative change in the coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form **(Not applicable for Human Influenza Vaccines)**
Flu-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
Flu-MaV-13	Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product
MaV-14	Inclusion or replacement of the solvent/diluent for the drug product **(Not applicable for Human Influenza Vaccines)**
Flu-MaV-15	Extension of shelf-life of the drug product
Flu-MaV-16	Change of storage conditions of the drug product (Lowering from the approved storage condition)
Minor Variation	
Flu-MiV-PA1	Change of drug product name
Flu-MiV-PA2	Change of product labeling (in accordance to country specific labeling requirement)
Flu-MiV-PA3	Replacement of the company or party responsible for batch release

Variation Code	Classification
Flu-MiV-PA4	Change of manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
Flu-MiV-PA5	Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
Flu-MiV-PA6	Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
Flu-MiV-PA7	Change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
Flu-MiV-PA8	Change of the specification of drug substance
Flu-MiV-PA9	Change of the test procedure of non-compendial drug substance
Flu-MiV-PA10	Change of shelf-life or retest period for drug substance
Flu-MiV-PA11	Change of storage condition for drug substance
Flu-MiV-PA12	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
MiV-PA13	Change of batch size of non-sterile drug product **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA14	Reduction or removal of overage
Flu-MiV-PA15	Qualitative or quantitative change of excipient **(Not applicable for Human Influenza Vaccines)**
MiV-PA16	Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral dosage form **(Not applicable for Human Influenza Vaccines)**
MiV-PA17	Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)] **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA19	Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)
MiV-PA20	Minor change of the manufacturing process for non-sterile product **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA21	Change of specifications of an excipient
Flu-MiV-PA22	Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure
MiV-PA23	Change in the source of empty hard capsule **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA24	Change of release and shelf-life specifications of the drug product
MiV-PA25	Change of imprints, bossing or other markings on the tablets or printing on capsules including addition or change of inks used for product marking **(Not applicable for Human Influenza Vaccines)**
MiV-PA26	Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA27	Change in the test procedure of the drug product (including replacement or addition of a test procedure)

Variation Code	Classification
MiV-PA28	Change in primary packaging material for non-sterile product **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA29	Replacement of a manufacturer for secondary packaging
MiV-PA30	Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA33	Addition or replacement of measuring device for oral liquid dosage forms and other dosage form **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA34	Reduction of shelf-life of the drug product
Flu-MiV-PA35	Change of storage conditions of the drug product (Increasing from the approved storage condition)
Minor Variation – Notification	
Flu-MiV-N1	Change in name and/or address of the marketing authorization holder (MAH)
Flu-MiV-N2	Change of product owner
Flu-MiV-N3	Change in ownership of manufacturer
Flu-MiV-N4	Change of the name or address (for example: postal code, street name) of the manufacturer of drug product
Flu-MiV-N5	Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release
Flu-MiV-N6	Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance
Flu-MiV-N7	Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)
Flu-MiV-N8	Renewal of European Pharmacopoeial Certificate of Suitability (CEP)
Flu-MiV-N9	Change of release and shelf-life specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium
Flu-MiV-N10	Deletion of pack size for a product
Country Specific Variation (Prior Approval)	
Flu-MaV-PH1	Additional route of administration
Flu-MaV-PH2	Change of manufacturing site of the drug product (proposed manufacturing site is under the same subsidiary)
MiV-PH1	Change of capsule color **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PH2	Change of brand name
Country Specific Variation-Notification	
Flu-MiV-PH-N1	Change of product labeling a) Change/s in packaging design (no change in text) b) Change/s in layout (positioning of graphic designs) c) Printing of product information inside the carton d) Addition of Global Product Identification Number (GPIN)
Flu-MiV-PH-N2	Change/addition of QC/stability testing site/s (different from batch release site)

Variation Code	Classification
Flu-MiV-PH-N3	Change/inclusion of distributor (no change in MAH)
Flu-MiV-PH-N4	Addition/change of supplier of drug substance/excipient
Flu-MiV-PH-N5	Addition/change of supplier of packaging materials
Flu-MiV-PH-N6	Administrative changes affecting entities other than the MAH
MiV-PH-N7	Addition of pack size for non-sterile drug product **(Not applicable for Human Influenza Vaccines)**
Variations Reclassified as Prior Approval to Notification	
Flu-MiV-PH3	Change of MAH
MiV-PA18	Deletion of the solvent/diluent for the drug product **(Not applicable for Human Influenza Vaccines)**
Flu-MiV-PA31	Change of outer carton pack sizes for a drug product
Flu-MiV-PA32	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)
Others (Prior Approval)	
Flu-MiV-PH6	Changes not covered by AVG

Codes are subject to change which shall be promulgated in an appropriate regulation.