POST REGISTRATION VARIATION GUIDELINES FOR PHARMACEUTICAL AND BIOLOGICAL PRODUCTS

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1. HISTORY

This is the first edition of these guidelines.

2. APPLICATION[1]-Guideline for Industry and Regulators

This document is applicable to Industry and Regulators with regards to provide guidance for post registration variations to the registered drug products submitted by the registrations / market authorization holders (importers, exporters, manufacturers, etc.) of pharmaceutical and biological products both for human and veterinary use.

3. PURPOSE

This guideline is intended to provide information for submission of post registration variation application by the registrations / marketing authorization holders of the finished drug products. It includes relevant requirements and procedures for submission of an application for variation. Purpose of these guidelines is as follows:

i. Facilitate the interpretation of the relevant regulations and decisions of Registration Board regarding post registration variations of registered drug products.
ii. Assist applicants with the classification of changes entailing prior approval or intimation.
iii. Provide guidance as per applicable SOPs on the conditions and other data requirements to support variance application.

These guidelines conform to DRAP Act 2012, Drugs Act 1976 and rules framed there under and some parts such as classification, definitions, and description etc., have been adopted from WHO guidelines on variations of drug products.

[1] The Guidance document is prepared by Drug Regulatory Authority of Pakistan for better illustration of classification, procedures and requirement for carrying out variations in the registered drug products. However, content of guidance document only reflects the current thinking perspective of the Authority.

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4. INTRODUCTION

Registration / Marketing Authorization (MA) holders of Pharmaceutical / Biological drug products for human and veterinary use (also referred as applicant) are responsible for the safety, efficacy and quality of a finished pharmaceutical / biological drug product that is placed on the market throughout its approved life cycle. Therefore, the applicant is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the registered product. Such changes, regardless of the nature of the change, are referred to as variations, which may require either approval of Drug Regulatory Authority of Pakistan (DRAP) before implementation or only intimation with relevant documentation as per their relevant Types and Classification.

5. BACKGROUND

Section 7 (c) (ix) of DRAP Act 2012, mandated the systematic implementation of internationally recognized standards of World Health Organization, International Conference on Harmonization (ICH), and Food and Drug Administration guidelines etc.

In this context, Registration Board in its various meetings has devised procedures for variance to the registered products. This document transforms the said procedures into a guidance document to provide information for both regulators and applicants.

6. GLOSSARY

ACRONYMS

BE&R	Biological Evaluation & Registration Division
BSE	Bovine Spongiform Encephalopathy
CoPP	Certificate of Pharmaceutical Product
CLB	Central Licensing Board
CTD	Common Technical Document
DML	Drug Manufacturing License
DRAP	Drug Regulatory Authority of Pakistan
DS	Drug Substance
FDP	Finished Drug Product
FPP	Finished Pharmaceutical Product
MAH	Marketing Authorization Holder
MaV	Major Variation
MiV	Minor Variation
NOC	No Objection Certificate
OOS	Out of Specifications
PE&R	Pharmaceutical Evaluation & Registration Division
PRVC	Post Registration Variation Committee
QSE	Quality, Safety and Efficacy
RB	Registration Board
SOP	Standard Operating Procedure
TSE	Transmissible Spongiform Encephalopathy

DEFINITIONS

The definitions provided below apply to the terms used in this document. They may have different meanings in other contexts or documents.

Drug Substance/Active Pharmaceutical Ingredient (API)	A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).
Container closure system	A primary container closure system is a packaging component (for example, a vial) that is in, or may come into, direct contact with the final product dosage form, or components that contribute to the container/closure integrity of the primary packaging material for a sterile product. A secondary container closure system is a packaging component (for example, a carton) that is not, and will not be, in direct contact with the dosage form.
Excipient	Anything other than the drug substance in the dosage form.
Finished Product	A product that has undergone all stages of production, including packaging in its final container and labeling.
Half Finished Product	Any material or mixture of materials that has to undergo further manufacture.
Marketing Authorization (MA)	A document issued after the approval of the Registration Board set up under the Drugs Act, 1976, as a certificate of drug registration.
Marketing Authorization Holder/Registration Holder	Legal entity/ Firm that has received marketing authorization/ registration to manufacture and/or distribute a finished drug product. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or registration. Also referred to as the "manufacturer" or "applicant" in this document, if both are same.
Officially Recognized Pharmacopoeia (Or Compendium)	The International Pharmacopoeia (Ph. Int.) or such other specifications as published by the World Health Organization, the European Pharmacopoeia (Ph. Eur.), the United States Pharmacopeia (USP), the British Pharmacopoeia (BP), the British Pharmaceutical Codex, the United States

	National Formulary, the Japanese Pharmacopoeia (JP) and such other publications as may be prescribed or pharmacopeia of Reference Regulatory Authorities (RRA) as adopted by Registration Board.
Packaging Material	Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding, any outer packaging used for transportation or shipment and packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
Pharmaceutical Product	Any drug intended for human use or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form.
Post Registration Variation Committee (PRVC)	Registration Board has constituted a Post Registration Variation Committee (PRVC) to perform such functions for which Registration Board has authorized its Chairman. The members of committee are: Director (PE&R) / Chairman Registration Board. Additional Director (PE&R)/Secretary Registration Board. Deputy Director (concerned section) and/ or Assistant Director (concerned section).
Reference Regulatory Authorities (RRA)	As adopted authority by the Registration Board in its 275th meeting.
Registration Board (RB)	A board set up under Section 7 of the Drugs Act, 1976.
Reference Medicinal Product (RMP)	The reference medicinal product is a drug product having same molecules / formulation in the same dosage form which has been granted a market authorization by any of reference regulatory authority as adopted by the Registration Board.
Specification	A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of

	criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use. OR Requirements with which the products or materials used or obtained during manufacture must conform as specified in the Drugs (Specifications) Rules 1978.
Validation	Documented act of proving that any procedure, process, equipment, material, activity or system works correctly and actually leads to the expected result.
Variation	A change to any aspect of a pharmaceutical product quality safety & efficacy, including but not limited to the change of use of a starting material, a change to a formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labeling and product information.

7. GENERAL CONSIDERATIONS

The registration / marketing authorization (MA) holder shall consider the potential impact of variation upon the quality, safety and efficacy of drug product. Some variation may require that the effect of variation to be assessed through appropriate studies prior to implementation of change.

This guideline applies to all variations whether from the applicant's initiative or requested by the DRAP.

8. SCOPE OF GUIDELINES

This guidance document covers the variation applications submitted by the product registration / MA holder of pharmaceutical and biological products for human use and veterinary Use. However, for biological products, some variation may require more extensive data to assess the impact of variation.

This document aimed for guidance to regulators and registration holders on the regulation of changes to the original registration / Market Authorization or registered products in terms of:

i. Procedures and criteria for the appropriate categorization, reporting of changes and subsequent approval as required.

ii. Data required to evaluate the impact of the proposed / intended change on the quality, safety and efficacy of the locally manufactured / imported finished pharmaceutical and biological drug products intended for human and veterinary use.

9. TYPES AND CLASSIFICATIONS

Post Registration Variations are of following types:-

i. An administrative change such as a change of company name and/or address

ii. A change to the characteristics of a product that can affect its quality, such as a change to its composition

iii. A change to the safety, efficacy or pharmacovigilance of the product

Types of changes are classified as Minor and Major. Minor changes are designated as Type I and further divided into 1A and 1B. Major changes are designated as Type II.

9.1.MINOR VARIATIONS (MiV)-Type-I

Variation to a registered finished product in terms of changes which has minimal or insignificant impact on the aspects of efficacy, quality, and safety. Minor variations are further divided into following: -

9.1.1. MiV-Type IA change

Type IA changes have little or no impact on the quality, safety or efficacy of the product, for example administrative modifications

Type IA procedures are classed a 'do-and-tell' procedure, means registration holder should implement the change and intimate / notify to DRAP by fulfilling the conditions and supporting documents. Applicant should ensure this notification/intimation must reach relevant section of DRAP within two month of implementation of change for DRAP's record.

Applicant must ensure the validity of the manufacturer's license and registration status prior to implementation of change.

9.1.2. MiV-Type IB change

If the change is more significant than IA change but it does not fall under type II or Major variation category, it is considered as type IB change. These changes need prior approval from DRAP before implementation. (e.g. Change in brand/proprietary name, title of firm, etc.)

Registration holder MA holder is required to submit an application for proposed change to relevant section of DRAP i.e. Secretary, Registration Board / Assistant Director (PRV), along with supporting documents and fulfill the conditions as described in these guidelines.

If the application fulfills the prescribed criteria, DRAP shall issue an approval for the proposed change.

9.2.MAJOR VARIATIONS (MaV)- TYPE II

These changes are more complex and may have a significant impact on the quality, safety and/or efficacy of the product i.e. change in manufacturing site, container closure system, etc.,

Registration holder needs to seek prior approval for major variations before they are made. Registration holder MA holder is required to submit an application for proposed change to relevant section of DRAP i.e. Secretary, Registration Board / Assistant Director (PRV), along with supporting documents and fulfill the conditions as described in these guidelines.

Upon receipt of an application, it will take 90 to 120 days to assess the application depending on urgency or complexity of changes, excluding time taken to address deficiency or answer the queries raised by assessor.

Important Note: Any variation to biological FDP / DS or its excipient with known effect, shall be categorized as major change. In case a product registration / MA holder is unclear about the categorization of a specific variation, firm may contact to Secretary Registration Board for clarification. However, DRAP reserves the right to re-categorize the application type, where deem appropriate. Furthermore, re-categorization may require the MA holder to withdraw the original application and resubmit a new application according to the correct category, if required.

No.	Description of Post-registration Changes	Procedure Type	Approval required	Intimation only
	A. ADMINISTRATIVE CHANGES			
A1	Change in the Name / Title of Manufacture or Registartion Holder	**MiV-1B**	✔	
A2	Change in the (Proprietary / Brand) Name of Finished Drug Product	**MiV-1B**	✔	
A3	Registration of Product from one importer to another importer	**MiV-1B**	✔	
A4	Change in Marketing Authroization (MA) or Product License (PL) in exporting country.	**MiV-1B**	✔	
A5	Change in Name or Address of importer/ registartion holder of Product with No Change of Proprietor	**MiV-1B**	✔	
A6	Change in the name of Active Pharmaceutical Ingredient / Drug Substance, while the drug substance remain the same molecule(s)	**MiV-1A**		✔
A7	Change in the design or color scheme of packaging material.	**MiV-1B**	✔	
A8	Standardization of Formulation In Accordance With the Innovator's Product/ Reference Regulatory Authorities and Pharmacopeias	**MiV-1B**	✔	
A9	Grant of Additional Pack Size for Locally Manufactured Veterinary Products (Excluding Injectables)	**MiV-1B**	✔	
A10	Change of Address of Manufacturing Site/Source / Marketing Authorization Holder (MAH).	**MiV-1B**	✔	
	B. QUALITY CHANGES			
B1	Change in Manufacturing Site or Registration of Product from One Manufacturer to another Manufacturer .	**MaV-II**	✔	
B2	Change of Manufacturing Site for imported finished drug products.	**MaV-II**	✔	
B3	Change or addition in the Source of Active Pharmaceutical Ingredient / Drug Substance or Half-	**MaV-II**	✔	

	Finished Products i.e. Pellets / Granules / Ready to Fill Bulk etc.			
B4	Change (Addition / deletion / substitution) of excipients or inactive ingredients including Colour.	**MiV-1B**	✔	
B5	Change in shape / color / size of Tablet or Capsule.	**MiV-1B**	✔	
B6	Change of Specifications or Method of Analysis of Finished Drug Product	**MaV-II**	✔	
B7	Change in shelf life, extension or reduction	**MaV-II**	✔	
B8	Change in Labeled Storage Conditions	**MaV-II**	✔	
B9	Change in the shape or dimensions of the container closure system	**MiV-1A**		✔
B10	Change in primary packaging material / Container closure system	**MiV-1B**	✔	
B11	Change of Secondary packaging materials	**MiV-1B**	✔	
B12	Change in the manufacturing process of the finished drug product	**MiV-1B**	✔	
B13	Addition / Deletion / change of the diluent / solvent container	**MiV-1A**		✔
B14	Change to in-process tests or limits applied during the manufacture of the finished product	**MiV-1B**	✔	
B15	Change from Bulk Concentrate to ready to fill bulk or vice versa	**MaV-II**	✔	
C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES				
C1	Change in Prescribing Information (PI), including changes in Indications, Contraindications, dosage etc.	**MaV-II**	✔	

C2	Change in the Summary of Product Characteristics, Labelling or Patient information Leaflet	**MiV-1B**	✔	
C3	C.3 Introduction or changes in Pharmacovigilance system.	**MiV-1B**	✔	

10. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

The following changes are considered as new product registration: -

10.1. Changes to the Active Pharmaceutical Ingredient (API) / DS

i. Change of the API to a different API including change in the salt or isomer form of API;
ii. Inclusion of an additional API to a multicomponent product;
iii. Removal of one API from a multicomponent product;
iv. Change in the strength of one or more APIs;

10.2. Changes to the Pharmaceutical Form /Dosage Form

i. Change from an immediate-release product to a slow-or delayed release dosage form and vice versa;
ii. Change from a liquid to a powder for reconstitution, or vice versa.

10.3. Changes in the Route of Administration

10.4. Case of Additional Flavor of already Registered Drug Product

10.5. Additional Volume of already Registered Injectable Drug Products

11. PROCEDURE FOR SUBMISSION OF APPLICATION

11.1. General Requirements

Marketing authorization / registration holders of finished pharmaceutical / biological drug products can apply for approval of post registration variation to their registered products. Following will be general requirements for all types of variation applications: -

i. Application (or intimation if applicable) on firm's letter head for proposed change accompanied with non-refundable processing fee challan as specified in the relevant updated version of fee schedule (i.e. Schedule "F" as amended time to time, or, whichever is applicable).
ii. Copy of registration letter and last renewal status of drug product.
iii. Declaration letter signed by the head of regulatory officer/ authorized officer, declaring that there is no other change except for the proposed variation and the information provided is true and correct.
iv. In general, MA holders / registration holders are encouraged to submit data related to variation as per relevant section of Form-5F (SRO No. 713/(I)/2018 dated 8th June, 2018), whereas, the aforementioned CTD format is mandatory for variations where it has been specified in this guidelines, or for the products which were initially registered on the basis of Form-5F / CTD dossiers applications.

Application shall be supported with the assurance that relevant conditions and documents required as identified in this guideline has been fulfilled for proposed variations, as below mentioned explained.

11.2. Conditions To Be Fulfilled

For each variation, attempts have been made to identify conditions or circumstance that need to be fulfilled for submitting variation application. For all changes, it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not adversely effect on the quality, safety and efficacy (QSE) of the drug product.

11.3. Documentation Required

The list of documentation required to be submitted along with application is identified for each variation in this guideline; however, this list is not intended to be exhaustive and further documentation may be required. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation. Alternative

approaches to the principles and practices described in this document may be acceptable provided that such variations / changes / practices or proposed alternatives are being supported with adequate scientific justification & applicable data integrity guidelines.

11.4. Submission of Application

Application shall be submitted through R&I section, DRAP, addressing to the concerned section of PE&R & BE&R Division.

Type of Variation	**Minor Variation (MiV)-Type I**		**Major Variation (MaV) Type-II**
	Type IA	**Type IB**	
Procedure	• MA holder will implement the change and intimate the relevant section of concerned division. • If the intimation fulfills the requirements (conditions and required supporting documents), DRAP shall issue acknowledgement.	• MA holder will submit prior application to DRAP. • If the application fulfills the requirements (conditions and required supporting documents), DRAP shall issue an approval for the proposed change.	• MA holder will submit prior application to DRAP. • If the application fulfills the requirements (conditions and required supporting documents), DRAP shall issue an approval for the proposed change.
Timelines	Within 01 month of receipt of intimation.	02 months of provision of complete information and documentation.	03 months of provision of complete information and documentation.

12. PROCEDURE FOR ASSESSMENT OF APPLICATION

12.1. Completion of Application

On receipt of application, it shall be evaluated on preliminary basis by the concerned section for completion of pre-requisites. Deficiencies are communicated to the applicant for completion of application. Complete applications are evaluated in light of SOPs approved by the Registration Board and are processed for inclusion in the agenda of PRVC or RB, as per authorization.

12.2. Meeting of Post Registration Variation Committee (PRVC) / Registration Board (RB)

The PRVC / RB shall discuss the cases and shall give decision on each case.

12.3. Issuance of Approval Letter

After the meeting, draft minutes are prepared for approval and thereafter, the decision on each case is communicated to registration / MA holders through approval letters.

A ADMINSTARTIVE CHANGES

A.1 Change in the Name / Title of Manufacture or Registartion Holder	Conditions to be fulfilled	Required Documents	Category
A. For Locally Manufactured Products	**1,2**	**1,2,5**	**MiV-1B**
B. For Imported Products	**1,2**	**3,4,5**	

CONDITIONS

iv. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change.

v. The manufactuirng site shall remain the same.

DOCUMENTATION

1. Copy of approval letter of new name / title of firm/company from CLB.
2. Evidence of the contract between registration / MA holder and manufacturer (with changed / new name), if the manufacturer and product license/registration holder are different entities.
3. Original legalized CoPP as per WHO format for new manufacturer's name, or Original legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin Or any legalized document of concerned regulatory authority confirming the change of name of Manufacturer/ Marketing Authorization Holder without change in manufacturing site.
4. Revised Sole Agency Agreement when there is change in MAH.
5. An undertaking that the formulation, API source & Specifications, manufacturing process, release & shelf life specifications have not changed.

A.2 Change in the (Proprietary / Brand) Name of Finished Drug Product	Conditions to be fulfilled	Required Documents	Category
A. For Locally Manufactured Products	**1,2,3,4**	**1,2,3**	**MiV-1B**
B. For Imported Products	**1,2,3,4**	**1,2,3,4**	

Conditions

1. There is no legal case/proceeding is pending at any forum / court of law concerning with the proposed change.

2. The registration / MA holder will check the suitability of proposed names to ensure that no resemblance or phonetic matching with already registered products.
3. The proposed names should not be liable to cause confusion in print, handwriting or speech with the (Proprietary / brand) name of another registered product.
4. The proposed name should not convey misleading therapeutic, pharmaceutical and/or promotional connotations.

Documentation

1. Information regarding previous change of brand name since registration of drug.
2. Details (batch number, date of manufacture, quantity and stock position) regarding last batch manufactured / imported.
3. An undertaking that the proposed names do not resemble with already registered brands. In case of resemblance /similarity with already registered drug, the applicant will be liable to change immediately. Moreover, no case is pending at any forum / court of law regarding this matter.
4. Original and legalized Certificate of Pharmaceutical Product as per WHO format for new brand name OR Original and legalized GMP certificate of new brand name with free sale certificate from regulatory body of country of origin.
5. For reports regarding brand name resemblance, following documents / information will be required:
   a) Unit carton/ any other information as evidence of resemblance which is being reported.

A.3 Registration of Product from one importer to another importer.	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Imported Products	**1,2**	**1,2,3,4,5**	**MiV-1B**

Conditions

1. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change.
2. There is no change in manufacturing site.

Documentation

1. Application on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate.
2. Termination letter (original) from manufacturer for previous importer.
3. Authority letter/sole agent letter (original) from manufacturer.
4. Document confirming NOC (issued within last 6 Months) from existing registration holder permitting for registration of product to another importer.

5. Original and legalized Certificate of Pharmaceutical Product as per WHO format for new manufacturer's name OR Original and legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin.

A.4 Change in Marketing Authroization (MA) or Product License (PL) in exporting country	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Imported Products	**1,2**	**1,2,3**	**MiV-1B**
Conditions			
1. There is no change in manufacturing site. 2. The registration holder / MA holder (importer) shall remain the same.			
Documentation			
1. Legalized authority letter/sole agent letter (original) from new MA /PL holder abroad. 2. Approval of new MA/PL holder from regulatory body of exporting country. 3. Original and legalized Certificate of Pharmaceutical Product as per WHO format for new MA/PL name			

A.5 Change in Name or Address of importer/ registartion holder of product	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Imported Products	**1,2**	**1,2,3,4**	**MiV-1B**
Conditions			
1. The importer / registration holder / MA holder shall remain the same legal entity. 2. The manufacturing site remains same.			
Documentation			
1. Copy of Drug Sale License with new name or address of registration holder. 2. Approval of new name by SECP / registrar of firm, as applicable. 3. Sole Agency agreement with new name of importer by Manufacturer and/or Product License Holder abroad. 4. An undertaking that the firm that no case is pending at any forum / court of law regarding previous name and/or address.			

A.6 Change in the name of Active Pharmaceutical Ingredient / Drug Substance, while the drug substance remain the same molecule(s).	**Conditions to be fulfilled**	**Required Documents**	**Category**
	1	**1**	**MiV-1A**

Conditions

1. The active pharmaceutical ingredient / drug substance shall remain the same molecule(s).

Documentation

1. Proof of acceptance by WHO or copy of the latest version of International Nonproprietary Names (INN) list mentioning proposed name of API/DS.

A.7 Change in the design or color scheme of packaging material.	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Locally Manufactured Products	**1,2**	**1,3**	**MiV-1B**
B. For Imported Products	**1,2**	**1,2,3**	

Conditions

1. The proposed packaging design/color scheme must not resemble to already registered product.
2. Packaging material shall remain same.

Documentation

1. Justification of proposed change with comparison of differences between existing and proposed design and other information in a tabulated form.
2. Regulatory approval of change from country of export.
3. An undertaking that:
    a. There is no case pending at any forum / court of law regarding this matter.
    b. Dosage, administration, indication & direction for use etc. on the label be in line with the registration / marketing authorization.
    c. Confirmation and undertaking that proposed label complies all provisions of Drugs (Labeling & Packing) Rules, 1986.

A.8 Standardization of Formulation In Accordance With the Innovator's Product/ Reference Regulatory Authorities and Pharmacopeias	**Conditions to be fulfilled**	**Required Documents**	**Category**
A) For Locally Manufactured Products	**1**	**1,2,3,4**	**MiV-1B**
B) For Imported Products	**1**	**1,2,3,4**	

Conditions

1. Existing formulation shall remain the same

Documentation

1. Application with required fee as per relevant SRO.
2. Copy of registration letter and last renewal status.
3. Document in support of proposed correction/evidence of approval status by Reference Regulatory Authorities/ innovator product and/ or Pharmacopeias as adopted by Registration Board.
4. Undertaking that the provided information/ documents are true/ correct.

A.9 Grant of Additional Pack Size for Locally Manufactured Veterinary Products (Excluding Injectables)	**Conditions to be fulfilled**	**Required Documents**	**Category**
A) For Locally Manufactured Products	**1**	**1,2,3,4,5,6**	**MiV-1B**

Conditions

1. The applied product(s) should be other than injectable dosage form.

Documentation

1. Application with required fee as per relevant SRO.
2. Copy of registration letter and last renewal status.
3. Detail of previously granted pack sizes.
4. Generic status/ evidence of availability of applied additional pack sizes.
5. Undertaking that the provided information/ documents are true/ correct.
6. GMP inspection conducted by DRAP during last 3 years.

A.10 Change of Address of Manufacturing Site/Source / Marketing Authorization Holder (MAH)	Conditions to be fulfilled	Required Documents	Category
A) For Imported Products	**1,2**	**1,2,3,4,5**	**MiV-1B**

Conditions

1. The manufacturer / MA holder (abroad) shall remain the same legal entity.
2. The manufacturing site shall remain the same.

Documentation

1. Application with required fee as per relevant SRO.
2. Copy of registration letter and last renewal status.
3. Original and legalized Certificate of Pharmaceutical Product as per WHO format for new manufacturer's name OR Original and legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin.
4. Site master file of new manufacturing site in case of change of manufacturing site/ source.
5. Revised Sole Agency Agreement when there is change in MAH. f) Proof/ evidence of the contract between Product License Holder & manufacturer (with changed/ new name), where the manufacturer and product license holder are differed.

B QUALITY CHANGES

B.1 Change in Manufacturing Site or Registration of Product from One Manufacturer to another Manufacturer with.	Conditions to be fulfilled	Required Documents	Category
A. For Locally Manufactured Products	**1,2**	**1,2,3,4,5,6,7**	**MaV-II**

Conditions

1. Both manufacturers must have valid Drug Manufacturing License of manuafcturing sites.
2. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change.

Documentation

1. Application on the prescribed format i.e. Form-5F for human products or Form-5/5A for veterinary products, as appropriate.

2. Copy of approved section of relevant pharmaceutical form by CLB or panel inspection report conducted for renewal of DML as evidence of approved sections (in cases of DML before 2005), along with copy of last inspection report conducted by DRAP within last 12 months of proposed manufacturing site.
3. NOC (issued within last 6 Months) from existing manufacturer / registration holder permitting for grant of registration of product to another manufacturer.
4. Validation data or validation protocol to be submitted and where relevant, batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the
5. Comparative manufacturing process at the two sites.
6. Batch analysis data of three production batches and comparative data on the last three batches from the previous site.
7. An Undertaking that:
    a. firm will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug.
    b. Validated method of analysis, master formula and product development data will be provided.
    c. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to registration board and all the stock will be recalled from the market immediately.
    d. Applicant do not have registration of same products. If so, it will have to apply for cancellation of product.

B.2 Change of Manufacturing Site for imported finished drug products.	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Imported Products	**1,2**	**1,2,3,4,5**	**MaV-II**

Conditions

1. The registration holder / MA holder (importer) shall remain the same.
2. Product License Holder / MAH in aboroad shall remain the same.

Documentation

1. Original and legalized Certificate of Pharmaceutical Product as per WHO format for new manufacturer's name OR Original and legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin.
2. Site master file of new manufacturing site.

3. Revised Sole Agency Agreement and any proof / evidence of the contract between Product License Holder & manufacturer (with changed/ new name), where the manufacturer and product license holder are different entities. 4. Comparative manufacturing process at the two sites. 5. Batch analysis data of three production batches and comparative data on the last three batches from the previous site.

B.3 Change or addition in the Source of Active Pharmaceutical Ingredient / Drug Substance or Half-Finished Products i.e. Pellets / Granules / Ready to Fill Bulk etc.	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Locally Manufactured Products		**1,2,3,4,5,6**	**MaV-II**
B. For imported products		**1,2,3,4,5,6**	**MaV-II**
Documentation			
1. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites. 2. Both real time & accelerated stability studies of AS / Half finished products (pellets / granules / ready to fill bulk) conducted by manufacturer of AS / half finished product as per conditions of zone IV-A or zone IV-B on 3 commercial scale batches. 3. Certificate of analysis by the manufacturer of AS / Half finished products (pellets / granules / ready to fill bulk). 4. Documents confirming that the proposed source has valid permission for manufacturing of AS / pellets / granules / ready to fill bulk by the regulatory authority of country of origin. 5. Valid & legalized GMP certificate issued by regulatory authority of exporting country if not already submitted in DRAP during last 1 year. 6. An Undertaking that :- a. Shelf life of finished product would be assigned after conducting product development studies, real time and accelerated stability studies. b. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.			

B.4 Change (Addition / deletion / substitution) of excipients or inactive ingredients including Colour.	**Conditions to be fulfilled**	**Required Documents**	**Category**
	1,2	**1,2,3,4,5,6,7**	**MiV-IB**

Conditions

1. There will be no qualitative or quantities change in API.
2. The dissolution profile of the proposed product is comparable to that of the current approved product.

Documentation

1. Justification for the change/choice of excipients, etc. must be given by appropriate information from pharmaceutical development. (including stability aspects and antimicrobial preservation where appropriate).
2. Specification of existing and proposed excipients / Colour, with confirmation that proposed excipient / inactive is of pharmaceutical grade.
3. Comparative tabulated format of the current and revised product formulation with calculated changes highlighted.
4. Results of stability testing (as per conditions of zone IV-A) with a minimum of 3 months of accelerated and 3 months of long-term testing on 03 lab scale batches or developmental scale batches as specified by Registration Board.
5. Description and composition of the FPP including Batch formula, description of manufacturing process and process controls, if different from previous one.
6. Drug product release and shelf-life specifications.
7. An undertaking that:
   a. The provided information is true & correct.
   b. There is no change in specifications of FPP.
   c. All excipients are of Pharmacopeial grade.
   d. All excipients do not include the use of materials of human or animal origin for which TSE/BSE risk assessment/safety data is required.
   e. That the new excipient does not interfere with the analytical procedures for the FPP.
   f. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.

B.5 Change in shape / color / size of Tablet or Capsule.	**Conditions to be fulfilled**	**Required Documents**	**Category**
	1,2	**1,2,3,1**	**MiV-IB**

Conditions

1. There will be no qualitative or quantitive change in API.
2. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change.

Documentation
1. Justification for the change must be given by appropriate information from pharmaceutical development. 2. Dissolution profile or Disintegration time whichever is appropriate, for new one comparable with old one. 3. Comparison of relase and shelf life specification of product. 4. Undertaking that: a. Other specification of the product remains the same. b. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.

B.6 Change of Specifications or Method of Analysis of Finished Drug Product *	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Locally Manufactured Products	**1**	**1,2,3,4,5**	**MaV-II**
B. For imported products	**1**	**1,2,3,4,5**	**MaV-II**

Conditions
1. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change.

Documentation
1. Document in support of proposed change including evidence to comply with the specifications of official monograph of recognized pharmacopeia. 2. Comparative table of current and proposed specifications. 3. Analytical reports as per proposed monograph of FPP. 4. Undertaking that : i. The change is made exclusively to comply with the pharmacopeia of Reference Regulatory Authorities or as per Innovator's product specifications. ii. No case is pending at any forum / court of law regarding this product. iii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.

***Important Note: Registration / MA holders of all such products which were initially registered as per Manufacturers / In-house / Innovator's specifications are required to immediately apply for change of finished product specifications as the official monograph for**

such products appears in any of the recognized official Pharmacopeias. However, if the manufacturer specifications are more stringent than Pharmacopeial specifications, in such cases MA holders will provide relevant data etc. for approval of Registration Board.

B.7 Change in shelf life	**Conditions to be fulfilled**	**Required Documents**	**Category**
For extension in shelf life			
A. For Locally Manufactured Products	**1**	**1,2,3,4,7**	**MaV-II**
B. For imported products	**1**	**1,2,3,4,5,7**	
For reduction in shelf life			
A. For Locally Manufactured Products	**1**	**1,2,3,4,6,7**	**MaV-II**
B. For imported products	**1**	**1,2,3,4,5,6,7**	

Conditions

1. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.

Documentation

1. Justification for proposed change in shelf-life with data of long-term real time stability testing (as per conditions of zone IV-A) including chromatograms for a minimum of 3 commercial scale batches or development scale batches as set by Registration Board, in an authorized packing material and /or after first opening or reconstitution, as appropriate.
2. Approval of regulatory body of country of origin or Original and legalized Certificate of Pharmaceutical Product as per WHO format.
3. If the reduction in shelf life is necessitated because of stability concerns, declaration of reason for reduction in shelf life.
4. An undertaking that*:
    a) There is no change to the primary packaging type that is in direct contact with the FPP and to the recommended conditions of storage.
    b) There is no change in formulation and specification either of finished product, API and excipients etc.

    *(In case both the above conditions are involved then applicant will submit complete requisite information as per procedure for these variations.)
    c) In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.

B.8 Change in Labeled Storage Conditions	Conditions to be fulfilled	Required Documents	Category
A. For Locally Manufactured Products	1	1,3	MaV-II
B. For imported products	1	1,2,3	

Conditions

1. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.

Documentation

1. Justification for proposed change in storage condition with data of long-term real time stability testing (as per conditions of zone IV-A) including chromatograms for a minimum of 3 commercial scale batches or development scale batches as set by Registration Board, in an authorized packing material and /or after first opening or reconstitution, as appropriate.
2. Proposed change is supported by documentary evidence from reference regulatory authorities and/ or innovator product.
3. Undertaking that:
    a. The change is in accordance with innovator's product/ Reference Regulatory Authorities.
    b. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.
    c. If the change is necessitated because of stability concerns, declaration of relevant reason for change in storage condition.
    d. In case of any quality complaint/ OOS result observed by the marketing authorization holder, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.

B.9 Change in the shape or dimensions of the container closure system.	Conditions to be fulfilled	Required Documents	Category
A. For Non sterile medicinal products	1,2	1,2,4,	MiV-1A
B. For Sterile medicinal prodcts	1,2	1,2,3,4	

Conditions

1. No change in the qulitative or quantitive composition of the container or closure.

2. The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FDP.

Documentation

1. Justification for proposed change in shape or dimension of container closure system.
2. Information on the proposed container-closure system (e.g. description, materials of construction, and specifications).
3. Re-validation studies performed in case of sterile products which are terminally sterilized.
4. Undertaking that:
   i. Other specifications of the product would remain the same.
   ii. There is no change in the qualitative & quantitative composition of the product and manufacturer will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug.
   iii. In the case of changes to the thickness of a packaging component or for sterile FPPs: stability data (as per conditions of zone IV-A), where applicable, results of photo-stability studies will be conducted on 03 lab scale batches or developmental scale batches.
   iv. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies to ensure appropriate delivery.
   v. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.

B.10 Change in primary packaging material / Container closure system	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Locally Manufactured Products	**1**	**1,2,3,4,5,6,7**	**MaV-II**
B. For imported products	**1**	**1,2,3,4,5,6,7**	

Conditions

1. The proposed packaging material must be at least equivalent to the existing material in respect of its relevant properties.

Documentation

1. Justification of proposed change including data on the suitability of the container-closure system (e.g. extractable / leachable testing (where applicable), permeation testing (light transmission, moisture permeation, O_2,CO_2 etc), demonstrating equivalent or superior

protection compared to the existing packaging system. Quality testing of packaging material by supplier/manufacturer and acceptance criteria for release.

2. Comparative table of the current and proposed immediate packaging specifications and appropriate Information on the proposed container closure / primary packaging type such as description, material of construction of primary packaging, specifications etc, For changes to functional packaging related to container closure (e.g. MDIs etc), data to demonstrate the functioning of the new packaging.
3. If the container closure system of applied formulation is different from that of the reference product, manufacturer will place first three lab scale batches or developmental scale batches as set by Registration Board, at 3 months of accelerated and 3 months of real time studies(alongwith stability protocol, pharmacopeial reference and certificate of analysis/data sheet for each point of time) for compatibility of applied formulation with container closure system as directed by Pharmacopeia of Reference Regulatory Authorities. Registration Board shall be informed immediately and along with market withdrawal in case of any significant change about result of stability studies.
4. Shelf life of the drug product supported with justification.
5. Existing and proposed container closure system with differences (e.g. description, materials of construction of primary packaging components, specifications, if appropriate) highlighted in tabular form.
6. If the proposed change requires change in manufacturing section / facility, then a new registration application with prescribed fee shall be submitted.
7. An undertaking:
    a. To perform stress studies.
    b. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to registration board and all the stock will be recalled from the market immediately.

B.11 Change of Secondary packaging materials	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Locally Manufactured Products	**1**	**1,3**	**MiV-1B**
B. For imported products	**1**	**1,2,3**	

Conditions

1. The proposed packaging material must be at least equilant to the approved material in respect of its relevant properties.

Documentation

1. Justification of proposed change, with tabulated differences between existing and proposed information.
2. Regulatory approval of change from country of export.
3. An undertaking that:
    a. Proposed label complies all provisions of the Drugs (Labeling & Packing) Rules, 1986.
    b. The proposed colour scheme / label has no resemble with already registered Products. In case of resemblance, new label will be changed immediately. Moreover, no case is pending at any forum / court of law regarding this matter.
    c. Dosage, administration, indication & direction for use etc. on the label be in line with the registration / marketing authorization.

B.12 Change in the manufacturing process of the finished drug product	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Locally Manufactured Products	**1,2,3**	**1,2,3,4,5**	**MiV-1B**
B. For imported products	**1,2,3**	**1,2,3,4,5**	**MiV-1B**

Conditions

1. There is no change in qualitative or quantitative impurity profile or in physiochemical properties.
2. The specifications of the FDP remains unchanged.
3. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.

Documentation

1. Justification for propose change with relevant data from pharmaceutical development.
2. Dissolution profile of at least one representative production batch and comparative data of the last three batches from the previous process.
3. Description and composition of the FPP including Batch formula, description of manufacturing process and process controls in comparative tabulated form.
4. Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process.
5. An undertaking that :-
    a. There is no change in the qualitative & quantitative composition of the product and manufacturer will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug.

b. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately. c. The stability testing (as per conditions of zone IV-A) with a minimum of 3 months of accelerated and 3 months of long-term testing on 03 lab scale batches or developmental scale batches as specified by Registration Board in 276th meeting has been started and result will be submitted.

B.13 Addition / Deletion / change of the diluent / solvent container from the pack	**Conditions to be fulfilled**	**Required Documents**	**Category**
		1	**MiV-1A**
Documentation			
1. Justification for the addition / deletion of solvent / diluent, to ensure quality, safety and effectiveness of the drug product.			

B.14 Change to in-process tests or limits applied during the manufacture of the finished product	**Conditions to be fulfilled**	**Required Documents**	**Category**
	1,2	**1,2,3**	**MiV-IB**
Conditions			
1. The change does not result from unexpected events arises during manufacture e.g. change in total impurity limits. 2. The test procedure remain the same, or changes in the test procedure are minor.			
Documentation			
1. Comparative table of current and propose in-process tests and limits. 2. Comparative dissolution profile data or disintegration for the finished drug product on at least one pilot batch manufactured using current and new in-process test, where appropriate. 3. Justification of the new in-process tests and limits.			

B.15 Change from Bulk Concentrate to ready to fill bulk or vice versa.	**Conditions to be fulfilled**	**Required Documents**	**Category**
A. For Locally Manufactured Products	**1**	**1,2,3,5**	**MaV-II**
B. For imported products	**1**	**1,2,3,4,5**	**MaV-II**

Conditions

1. The manufacturing site of drug substance shall remain the same.

Documentation

1. Both real time & accelerated stability studies of DS conducted by manufacturer of DS as per conditions of zone IV-A or zone IV-B on 3 commercial scale batches.
2. Certificate of analysis by the manufacturer of DS.
3. Documents confirming that the proposed source has valid permission for manufacturing of DS by the regulatory authority of country of origin.
4. Valid & legalized GMP certificate issued by regulatory authority of exporting country if not already submitted in DRAP during last 1 year.
5. An Undertaking that :-
    a. Shelf life of finished product would be assigned after conducting product development studies, real time and accelerated stability studies.
    b. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same will be reported to Registration Board and all the stock will be recalled from the market immediately.

C SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.1 Change in Prescribing Information (PI), including changes in Indications, Contraindications, dosage etc.	Conditions to be fulfilled	Required Documents	Category
		1,2,3,4	MaV-II

Documentation

1. Justification of proposed changes and difference between existing and proposed information in tabulated form.
2. Reference of prescribing information approved by Reference Regulatory Authorities and innovator product.
3. Copy of approval from regulatory agency / authority from country of origin for innovator's product.
4. Copy of label outer pack in case of changes in indication/ dose/ administration etc.

C.2 Change in the Summary of Product Characteristics, Labelling or Patient information Leaflet	Conditions to be fulfilled	Required Documents	Category
	1	1,2	MiV-IB

Conditions

1. The change is resulted from sequentaial of the variartion or change for which data is submitted to DRAP.

Documentation

1. Revised product information, Patient Leaflet etc.
2. Copy of approval of variation(s) granted.

C.3 Introduction or changes in Pharmacovigilance system.	Conditions to be fulfilled	Required Documents	Category
	1	1	MiV-1B

Conditions

1. The pharmcovigilance system of MAH is assessed by the Paksitan National Pharmacovigilance Cell

Documentation
1. Detail of changes in the pharmacovigilance system of product by registration / MA holder.

Important Note:
This list of variations provided above is not exhaustive and expected to be amended from time to time as and when the need arises. Any variations not yet listed in this guideline should be justified and decided by Registration Board and will be incorporated in this document accordingly

13. REFERENCES

i. The DRAP Act, 2012.

ii. The Drugs Act 1976.

iii. The Drugs (Licensing, Registering and Advertising) Rules, 1976.

iv. The Drugs (Specifications) Rules 1978.

v. The Drugs (Labeling & Packing) Rules, 1986.

vi. EU guidelines on the various categories of variations to the terms of marketing authorizations for medicinal products for human and veterinary medicinal products.

vii. WHO guidelines on variations to a prequalified product, WHO Technical Report Series, No. 81, 2013.

viii. Minutes of Registration Board having decisions related to Post Registration Variations.

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