



POST REGISTRATION VARIATION GUIDELINES FOR PHARMACEUTICAL AND BIOLOGICAL PRODUCTS

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Drug Regulatory Authority of Pakistan
Islamabad - Pakistan.

HISTORY

This is the first edition of these guidelines.

APPLICATION-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.

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. These guidelines will:-

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

This guideline is expected to be regularly updated, in light of revision of Registration Board's decision, taking into account the recommendations and scientific or technical progress in the reference regulatory authorities.

These guidelines conform to 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 products.

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INTRODUCTION

Registration / marketing authorization (MA) holder of pharmaceutical/biological drug products for human and veterinary use (also referred as applicant) is 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 and some may require approval of Drug Regulatory Authority of Pakistan (DRAP) before implementation while others only require intimation with relevant documentation as per applicable standard operating procedures (SOPs).

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.

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. Registration / MA holder should know that some variation generate subsequent / consequential variations that might require to be applied separately.

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

GLOSSARY

ACRONYMS

BE&R	Biological Evaluation & Registration Division
BSE	Bovine Spongiform Encephalopathy
DML	Drug Manufacturing License
DS	Drug Substance
FDP	Finished Drug Product
MAH	Marketing Authorization Holder
NOC	No Objection Certificate
OOS	Out of Specifications
PE&R	Pharmaceutical Evaluation & Registration Division
QSE	Quality, Safety and Efficacy
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.

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	<p>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.</p> <p>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.</p>
Excipient	Anything other than the active 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 by the Registration Board set up under the Drugs Act, 1976, as a certificate of drug registration.

Marketing Authorization Holder/Registration Holder Any person or legal entity 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 Pharmacopoeia (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.

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 declared / approved in 249th and 275th meetings of the Registration Board.

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 drug regulatory agency 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, 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.

SCOPE OF GUIDELINE

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 & registration holders on the regulation of changes to the original registration / Market Authorization or registered products in terms of:

- a) Procedures and criteria for the appropriate categorization, reporting of changes and subsequent approval as required.
- b) 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 & veterinary use.

TYPES & CLASSIFICATION

Variations are either:-

- an administrative change such as a change of company name and/or address
- a change to the characteristics of a product that can affect its quality, such as a change to its composition
- 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.

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:-

a) 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 e.g. change in management of the manufacturer / MA holder firm.

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 02 month of implementation of change.

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

DRAP will acknowledge the receipt of notification / intimation. In specific circumstance, change application may be rejected with the consequence that the registration holder must cease to apply the already implemented variation.

b) 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 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.

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 a registered biological FDP / DS or excipient is categorized as major change. In case a product registration / MA holder is unclear about the categorization of a particular variation, firm may contact to Secretary Registration Board for clarification. 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.

CHANGES LEADING TO A NEW PRODUCT REGISTRATION

The following changes are considered as new product registration:-

- 1. Changes to the Active Pharmaceutical Ingredient (API) / DS**
 - a) Change of the API to a different API including change in the salt or isomer form of the API;
 - b) Inclusion of an additional API to a multicomponent product;
 - c) Removal of one API from a multicomponent product;
 - d) Change in the strength of one or more APIs;
- 2. Changes to the pharmaceutical form/dosage form**
 - a) Change from an immediate-release product to a slow-or delayed release dosage form and vice versa;
 - b) Change from a liquid to a powder for reconstitution, or vice versa.
- 3. Changes in the route of administration**
- 4. Case of additional flavor**

PROCEDURE FOR SUBMISSION OF APPLICATION:

Marketing authorization/ registration holder/ importer of finished pharmaceutical/ biological drug products can apply for approval of post registration variation to their registered products accompanied with non-refundable processing fee specified in the relevant updated version of fee schedule (i.e. Schedule “F” as amended time to time).

Variation application will be submitted along with a declaration letter undersigned by the Head of Regulatory Officer that declares there is no other change except for the proposed variation.

Application shall be submitted via R&I, DRAP, addressing to the concerned section.

CONDITIONS TO BE FULFILLED

For each variation, attempts have been made to identify particular conditions or circumstance that need to be fulfilled. 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 Finished Drug Product.

DOCUMENTATION REQUIRED

The list of documentation 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. It should be noted that DRAP reserves the right to request further information not explicitly described in these guidelines. It is also important to note that DRAP may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy and quality of product.

Type of Variation	Minor Variation (MiV)-Type I		Major Variation (MaV) Type-II
	Type IA	Type IB	
Procedure	<ul style="list-style-type: none"> MA holder will implement the change and intimate the relevant section ,DRAP. If the intimation fulfils the requirements (conditions and required supporting documents), DRAP shall issue acknowledgement. 	<ul style="list-style-type: none"> MA holder will submit prior application to DRAP. If the application fulfils the requirements (conditions and required supporting documents), DRAP shall issue an approval for the proposed change. 	<ul style="list-style-type: none"> MA holder will submit prior application to DRAP. If the application fulfils 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.

PROCEDURE FOR ASSESSMENT OF APPLICATION

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 appropriate.

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

Once the application is thoroughly reviewed and evaluated, it is included as agenda for the upcoming Post registration Variation Committee (PRVC) / Registration Board (RB) meeting. The PRVC / RB discuss the cases, and gives recommendatory decision on each case.

Issuance of Approval Letters

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

A ADMINSTRATIVE CHANGES

A.1 Change in Name / Title of Manufacturer	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture Products	1,2	1,2,6,7	MiV-1B
B. For Import Products	1,2	1,2,3,4,5,7	

CONDITIONS

1. There is no legal case/ proceeding is pending at any forum / court of law concerning with the proposed change.
2. The manufactuirng site remain the same.

DOCUMENTATION

1. Application on firm's letter head for proposed change with applicable fee.
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 Or any legalized document of concerned regulatory authority confirming 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. Evidence of the contract between registration / MA holder & manufacturer (with changed / new name), where the manufacturer and product license holder are different entities.
6. Approval of new name / title from CLB.
7. An undertaking that:
 - a) The formulation, API source & Specifications, manufacturing process, release & shelf life specifications have not changed.
 - b) Provided information is true & correct.

A.2 Change in the (Proprietary / Brand) Name of Finished Drug Product	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture Products	1,2,3,4	1,2,3,4,5,8	MiV-1B
B. For Import Products	1,2,3,4	1,2,3,4,5,6,8	

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. Application on firm's letter head for proposed change with justification and applicable fee (however, in case of similarity / resemblance with already registered drug, fee will not be required).
2. Copy of registration letter and last renewal status.
3. Information regarding previous change of brand name since registration of drug.
4. Details (batch number, date of manufacture, quantity and stock position) regarding last batch manufactured / imported.
5. 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.
6. 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.
7. 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.
8. Undertaking that provided information/ documents are correct.

A.3 Registration of Product from one importer to another importer with no change in manufacturing site.	Conditions to be fulfilled	Required Documents	Category
A. For Import Products	1	1,2,3,4,5,6,7	MiV-1B
Conditions			
<ol style="list-style-type: none"> 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			
<ol style="list-style-type: none"> 1. Application on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate, with amendments of the relevant section(s) of the 			

dossier and applicable fee.
2. Copy of registration letter and last renewal status.
3. Termination letter (original) from manufacturer for previous importer.
4. Authority letter/sole agent letter (original) from manufacturer.
5. Document confirming NOC (issued within last 6 Months) from existing registration holder permitting for registration of product to another importer.
6. 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.
7. Undertaking that the provided information/ documents are true/ correct.

A.4 Change in Name / Address of importer (MAH) of Drug Product with No Change of Proprietor	Conditions to be fulfilled	Required Documents	Category
A. For Import Products	1,2	1,2,3,4,5,6,7	MiV-1B
Conditions			
<ol style="list-style-type: none"> The registration holder / MA holder shall remain the same legal entity. The manufacturing site remains same. 			
Documentation			
<ol style="list-style-type: none"> Application on firm's letter head for proposed change with applicable fee. Copy of registration letter and last renewal status. Copy of Drug Sale License with new name. Approval of new name by SECP / registrar of firm. Sole Agency agreement with new name of importer by Manufacturer or product License Holder. Undertaking by the firm that no case is pending at any forum / court of law regarding previous name. Undertaking that the provided information/ documents are true/ correct. 			

A.5 Change in the name of manufacturer of the Active Pharmaceutical Ingredients / Drug Substance.	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1	1,2,3,5	MiV-1A
B. For import products	1	1,2,4,5	MiV-1A
Conditions			

1. The manufacturing site and all manufacturing operations shall remain the same.
Documentation
<ol style="list-style-type: none"> 1. Intimation on the firm's letter head for proposed change with the applicable fee. 2. Copy of registration letter and last renewal status. 3. Approval of new name by SECP / registrar of firm, 4. In case of imported products any formal document from a relevant official body in which the new name is mentioned. 5. Relevant section(s) of the dossier, presented in the prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate.

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	1,2,3,4	MiV-1A

Conditions
1. The active pharmaceutical ingredient / drug substance shall remain the same molecule(s).
Documentation
<ol style="list-style-type: none"> 1. Intimation on the firm's letter head for proposed change with the applicable fee. 2. Copy of registration letter and last renewal status. 3. Proof of acceptance by WHO or copy of the INN list. 4. Relevant section(s) of the dossier, presented in the prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate.

B

QUALITY CHANGES

B.1 Registration of Product from One Manufacturer to another Manufacturer with Change in Manufacturing Site.	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1,2	1,2,3,4,5,6,7,8,9	MaV-II
Conditions			
<ol style="list-style-type: none"> 1. Both manufacturers must have valid Drug Manufacturing License of manufacturing sites. 2. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change. 			
Documentation			
<ol style="list-style-type: none"> 1. Application on the prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate, with applicable fee. 2. Copy of registration letter and last renewal status. 3. Copy of approved section by Central Licensing Board or panel inspection report conducted for renewal of DML as evidence of approved sections (in cases of DML before 2005). 4. Copy of last inspection report conducted by DRAP within last 12 months of proposed manufacturing site. 5. NOC (issued within last 6 Months) from existing manufacturer / registration holder permitting for grant of registration of product to another manufacturer. 6. Statement / undertaking that applicant do not have registration of same products. If so, it will have to apply for cancellation of product. 7. Undertaking that firm will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug. 8. An Undertaking that: <ol style="list-style-type: none"> a. Validated method of analysis, master formula and product development data will be provided. 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. Undertaking that the provided information is true & correct. 			

B.2 Change of Manufacturing Site for imported finished drug products.	Site for	Conditions to be fulfilled	Required Documents	Category
A. For Import Products		1,2	1,2,3,4,5,6,7	MaV-II
Conditions				
<ol style="list-style-type: none"> 1. The registration holder / MA holder (importer) shall remain the same. 2. Product License Holder / MAH in abroad shall remain the same. 				
Documentation				
<ol style="list-style-type: none"> 1. Application on the prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate, with applicable fee. 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. 6. Proof / evidence of the contract between Product License Holder & manufacturer (with changed/ new name), where the manufacturer and product license holder are different entities. 7. Undertaking that the provided information/ documents are true/ correct. 				

B.3 Change 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 local manufacture products		1,2,3,4,5,6,7,8	MaV-II
B. For import products		1,2,3,4,5,6,7,8	MaV-II
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" manufacturers. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. 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 			

<p>per conditions of zone IV-A or zone IV-B on 3 commercial scale batches.</p> <ol style="list-style-type: none"> 5. Certificate of analysis by the manufacturer of AS / Half finished products (pellets / granules / ready to fill bulk). 6. 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. 7. Valid & legalized GMP certificate issued by regulatory authority of exporting country if not already submitted in DRAP during last 1 year. 8. An Undertaking that :- <ol style="list-style-type: none"> 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. That the provided information is true & correct.

B.4 Change (Addition / deletion / substitution) in excipients (inactive) including Colour.	Conditions to be fulfilled	Required Documents	Category
	1	1,2,3,4,5,6,7	MiV-IB
Conditions			
1. There will be no qualitative or quantities change in API.			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" excipients with justification for change. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. Specification of existing and proposed excipients / Colour. 5. Document confirming that proposed excipient / inactive is of pharmaceutical grade. 6. 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. Description and composition of the FPP including Batch formula, description of manufacturing process and process controls, if different from previous one. 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	1,2,3	MiV-IB
Conditions			
<ol style="list-style-type: none"> 1. There will be no qualitative or quantitative change in API. 2. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change. 			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" shape, colour or size, with justification for change. 2. Copy of registration letter and last renewal status. 3. Undertaking that: <ol style="list-style-type: none"> i. Other specification 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 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. iv. The provided information/ documents are true/ correct. 			

B.6 Standardization of formulation in accordance with the innovator's Product / Pharmacopeias / Product approved in Reference Regulatory Authorities.	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1	1,2,3,4	MiV-II

B. For import products	1	1,2,3,4	MiV-II
Conditions			
1. There will be no qualitative or quantitative change in API or DS.			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" formulation. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. Document in support of proposed correction/evidence of approval status by Reference Regulatory Authorities/ innovator product and/ or Pharmacopeias as adopted by Registration Board. 5. Undertaking that the provided information/ documents are true/ correct. 			

B.7 Change of Finished Drug Product Specifications*	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1	1,2,3,4,5	MaV-II
B. For import 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			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" specifications. 2. Copy of registration letter and last renewal status. 3. Document in support of proposed change including evidence to comply with the specifications of official monograph of recognized pharmacopeia. 4. Analytical reports as per proposed monograph of FPP. 5. Undertaking that : <ol style="list-style-type: none"> 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.
 iv. The provided information/ documents are true/ correct.

***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.8 Change in shelf life	Conditions to be fulfilled	Required Documents	Category
For extension in shelf life:			
A. For local manufacture products	1	1,2,3,4,7	MaV-II
B. For import products	1	1,2,3,4,5,7	
For reduction in shelf life			
A. For local manufacture products	1	1,2,3,4,6,7	MaV-II
B. For import 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. Application on firm’s letter head with applicable fee, clearly outline the proposed change as “present” and “proposed” shelf life. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. Proposed change in shelf-life with justification and 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. 5. Approval of regulatory body of country of origin or Original and legalized Certificate of Pharmaceutical Product as per WHO format.			

6. If the reduction in shelf life is necessitated because of stability concerns, declaration of reason for reduction in shelf life.
7. 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.
 - d) Provided information is true & correct.

B.9 Change in Labeled Storage Conditions	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1	1,2,3,4,5	MaV-II
B. For import products	1	1,2,3,4,5	
Conditions			
1. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.			
Documentation			
1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" storage condition. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. Proposed change is supported by documentary evidence from reference regulatory authorities and/ or innovator product. 5. Undertaking that: <ol style="list-style-type: none"> 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 			

<p>reason for change in storage condition.</p> <p>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.</p> <p>e. Provided information is true & correct</p>
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B.10 Change in the shape or dimensions of the container closure system.	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1,2	1,2,3,4,5	MiV-1A
B. For import products	1,2	1,2,3,4,5	
Conditions			
<ol style="list-style-type: none"> 1. No change in the qualitative or quantitative 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			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" shape or dimension of container closure system. 2. Copy of registration letter and last renewal status. 3. Justification for proposed change in shape or dimension of container closure system. 4. Information on the proposed container-closure system (e.g. description, materials of construction, and specifications). 5. Undertaking that: <ol style="list-style-type: none"> 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. Revalidation studies will be conducted in the case of terminally sterilized products. 			

<p>The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.</p> <p>vi. 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.</p> <p>vii. The provided information/ documents are true/ correct.</p>

B.11 Change in primary packaging material/Container closure system	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1	1,2,3,4,5,6,7,8,10	MaV-II
B. For import products	1	1,2,3,4,5,6,7,8,9,10	
Conditions			
1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" packaging material / container closure system. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. 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, O₂,CO₂ etc), demonstrating equivalent or superior protection compared to the current packaging system. Quality testing of packaging material by supplier/manufacturer and acceptance criteria for release. Information on the proposed primary packaging type such as description, material of construction of primary packaging, specifications etc, comparative table of the current and proposed immediate packaging specifications. For changes to functional packaging related to container closure (e.g. MDIs etc), data to demonstrate the functioning of the new packaging. 5. 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 			

<p>Authorities. Registration Board shall be informed immediately and along with market withdrawal in case of any significant change about result of stability studies.</p> <p>6. Shelf life of the drug product supported with justification.</p> <p>7. 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.</p> <p>8. If the proposed change requires change in manufacturing section / facility, then a new registration application with prescribed fee shall be submitted.</p> <p>9. An undertaking:</p> <ol style="list-style-type: none"> To perform stress studies. 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. Provided information is true & correct.

B.12 Change of Secondary packaging materials	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1	1,2,3,4,5,6,8	MiV-1B
B. For import products	1	1,2,3,4,5,6,7,8	
Conditions			
1. The proposed packaging material must be at least equitant to the approved material in respect of its relevant properties.			
Documentation			
<ol style="list-style-type: none"> Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" packaging material. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. Copy of registration letter and last renewal status. Justification of proposed change. Difference between existing and proposed information in tabulated form. Confirmation and undertaking that proposed label complies all provisions of Drugs (Labeling & Packing) Rules, 1986. Regulatory approval of change from country of export. An undertaking that: <ol style="list-style-type: none"> The proposed colour scheme / label has no resemble with already registered 			

<p>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.</p> <p>b. Dosage, administration, indication & direction for use etc. on the label be in line with marketing authorization.</p> <p>c. Undertaking that the provided information/ documents are true/ correct.</p>

B.13 Change in the manufacturing process of the finished drug product	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1,2,3	1,2,3,4	MiV-1B
B. For import products	1,2,3	1,2,3,4	MiV-1B
Conditions			
<ol style="list-style-type: none"> 1. There is no change in qualitative and 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			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" manufacturing process. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. An undertaking that :- <ol style="list-style-type: none"> 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. 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 in 276th meeting. Description and composition of the FPP including Batch formula, description of manufacturing process and process controls. 			

d. The provided information/ documents are true/ correct.

B.14 Addition / Deletion / change of the diluent / solvent container from the pack	Conditions to be fulfilled	Required Documents	Category
		1,2,3,4	MiV-<u>1B</u>
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" diluent / solvent. 2. Copy of registration letter and last renewal status. 3. Justification for the addition / deletion of solvent / diluent, to ensure quality, safety and effectiveness of the drug product. 			

B.15 Change to in-process tests or limits applied during the manufacture of the finished product	Conditions to be fulfilled	Required Documents	Category
	1,2	1,2,3,4	MiV-<u>IB</u>
Conditions			
<ol style="list-style-type: none"> 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			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" in-process tests or limits. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. Comparative table of current and propose in-process tests and limits. 5. 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. 6. Justification of the new in-process tests and limits. 			

B.16 Change in test procedure for the finished product	Conditions to be fulfilled	Required Documents	Category
	1,2	1,2,3,4	MiV-1B
Conditions			
<ol style="list-style-type: none"> 1. There have been no changes of the total impurity limits, no new unqualified impurities are detected. 2. The method of analysis should remain same (e.g. a change in column length or temperature, but not different type of column or method). 			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" test procedure for finished drug product. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. Comparative validation studies showing that updated test procedure are equivalent or better to former test procedure. 			

B.17 Grant of Additional pack size for Veterinary Products (excluding Injectable)	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products		1,2,3,4,5,7	MiV-IB
B. For import products		1,2,3,6,7	MiV-IB
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee 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. GMP inspection conducted by DRAP during last 12 months. 6. Evidence of availability of demanded pack size in country of origin. 7. Undertaking that the provided information/ documents are true/ correct. 			

B.18 Change from Bulk Concentrate to ready to fill bulk or vice versa	Conditions to be fulfilled	Required Documents	Category
A. For local manufacture products	1	1,2,3,4,5,7	MaV-II
B. For import products	1	1,2,3,6,7	MaV-II
Conditions			
1. The manufacturing site of drug substance shall remain the same.			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" manufacturers. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products as appropriate. 3. Copy of registration letter and last renewal status. 4. 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. 5. Certificate of analysis by the manufacturer of DS. 6. Documents confirming that the proposed source has valid permission for manufacturing of DS by the regulatory authority of country of origin. 7. Valid & legalized GMP certificate issued by regulatory authority of exporting country if not already submitted in DRAP during last 1 year. 8. An Undertaking that :- <ol style="list-style-type: none"> 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. That the provided information is true & correct. 			

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
		1,2,3,4,5,6,7,8,9	MaV-II
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" Prescribing information. 2. Relevant section(s) of the dossier, on prescribed format i.e. Form-5F for human products, or Form-5/5A for veterinary products, as appropriate. 3. Copy of registration letter and last renewal status. 4. Difference between existing and proposed information in tabulated form. 5. Justification of proposed changes. 6. Reference of prescribing information approved by Reference Regulatory Authorities and innovator product. 7. Copy of approval from regulatory agency / authority from country of origin for innovator's product 8. Copy of label outer pack in case of changes in indication/ dose/ administration etc. 9. Undertaking that the provided information is true & correct. 			

C.2 Change in the Summary of Product Characteristics, Labelling or Patient information Leaflet	Conditions to be fulfilled	Required Documents	Category
	1	1,2,3,4	MaV-II
Conditions			
<ol style="list-style-type: none"> 1. The change is resulted from sequentiaial of the variartion or change for which data is submitted to DRAP. 			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, clearly outline the proposed change as "present" and "proposed" changes in SmPC 2. Copy of registration letter and last renewal status. 3. Revised product information. 			

C.3 Introduction or changes in Pharmacovigilance system.	Conditions to be fulfilled	Required Documents	Category
	1	1,2,3,	MiV-1B
Conditions			
<ol style="list-style-type: none"> 1. The pharmacovigilance system of MAH is assessed by the Pakistan National Pharmacovigilance Cell 			
Documentation			
<ol style="list-style-type: none"> 1. Application on firm's letter head with applicable fee, 2. Copy of registration letter and last renewal status. 3. Changes in the Pharmacovigilance system of MAH. 			

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REFERENCES:

1. The DRAP Act, 2012.
2. The Drugs Act 1976.
3. The Drugs (Licensing, Registering and Advertising) Rules, 1976.
4. The Drugs (Specifications) Rules 1978.
5. The Drugs (Labelling & Packing) Rules, 1986.
6. EU guidelines on the various categories of variations to the terms of marketing authorizations for medicinal products for human and veterinary medicinal products.
7. Decisions of Registration Board.

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