POST-REGISTRATION VARIATION GUIDELINES FOR PHARMACEUTICAL AND BIOLOGICAL PRODUCTS

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This draft guideline is uploaded on official website of DRAP dated 4th July, 2023, for seeking comments and suggestions from stakeholders on the draft document. Stakeholders can submit their comments and suggestions within15 days of uploading this document using the prescribed format to submit comments (link to access the le of comments), and forward via email to muneeb.cheema@dra.gov.pk, copying at zeeshan.nazir@dra.gov.pk, or can post at mailing address Director, Pharmaceutical Evaluation & Registration 4th floor TF Complex, 7th Mauve Area, G-9/4, Islamabad.

Drug Regulatory Authority of Pakistan
Islamabad-Pakistan

1. HISTORY

This is the second edition of these guidelines**.**

2. APPLICATION-Guideline for Industry

This document applies to the industry for post registration variations in the pharmaceutical and biological drug 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 drug products. It includes categories of variations and the required documentation & procedures for submission of an application for a particular variation.

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4. INTRODUCTION

Registration / Marketing Authorization holders are responsible for the safety, efficacy, and quality of drug products that are placed on the market throughout their approved life cycle. The technical and scientific advancements in the pharmaceutical sector require to make changes in the drug products on the market in order to improve their desired action. Such changes, regardless of the nature of the change, are referred to as variations, which may require either approval before implementation or only intimation with relevant documentation as per their relevant types and classification. These guidelines retain the essentials of the previously published guidelines and have been extended with new terminology of types of variations and documentation required to support a specific change.

Moreover, certain major variations are now categorized as minor variations which require prior approval before implementation and certain minor variations requiring prior approval before implementation have now been considered as minor variations requiring notification only after implementation (tell & do).

5. BACKGROUND

These guidelines have been technically and structurally inspired by ASEAN Variation Guideline for Pharmaceutical Products (Revision 2) and WHO guidelines on variations to a prequalified product (WHO TRS 981,2013). The first edition was prepared keeping in view 1) the technical requirements entailed by European Union guidelines on the various categories of variations to the terms of marketing authorizations for medicinal products for human and veterinary medicinal products and 2) the procedures devised by Registration Board of DRAP in its various meeting for approval of variations applied for the registered drug products. This guidance document supersedes the first edition published in 2022.

6. GENERAL CONSIDERATIONS

The registration / marketing authorization 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.

7. SCOPE OF GUIDELINES

This guidance document is applicable to APIs and excipients manufactured by chemical synthesis or semi-synthetic processes and biological processes and the drug products containing such APIs & excipients.

APIs, excipients and drug products of biological, and biotechnological origin shall be treated as special cases and the applicant may be asked to provide any additional documentation, if required by the Biological Evaluation & Research (BE&R) Division.

8. GLOSSARY

API	Active Pharmaceutical Ingredient
BAN	British Approved Name
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
C	Conditions to be fulfilled
CAS	Chemical Abstract Service
CEP	Certificate of Suitability
CoA	Certificate of Analysis
CPP	Critical Process Parameters
CQA	Critical Quality Attribute
CTD	Common Technical Document
D	Documents to be submitted
DML	Drug Manufacturing License
DRAP	Drug Regulatory Authority of Pakistan
EPAR	European Public Assessment Report
FDA	Food & Drug Administration of United States
GCP	Good Clinical Practices
GLP	Good laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
INN	International nonproprietary name
IR	Infrared
JP	Japanese Pharmacopoeia
LR&A	Licensing, Registering & Advertising
MaV	Major Variation
MiV-N	Minor Variation (Notification)
MiV-PA	Minor Variation (Prior Approval)
MS	Mass Spectrometry

NMR	Nuclear Magnetic Resonance
OSD	Oral Solid Dosage form
PAR	Public Assessment Report
Ph.Eur	European Pharmacopoeia
Ph.Int	International Pharmacopoeia
RRA	Reference Regulatory Authority
SAE	Serious Adverse Events
TSE	Transmissible Spongiform Encephalopathies
USAN	United States Adopted Name
USP	United States Pharmacopoeia
WHO	World Health Organization

9. CLASSIFICATION OF VARIATIONS

9.1 Minor Variation (MiV-N, MiV-PA)

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

9.2 Major variation (MaV)

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

10. PROCEDURE AND TIMELINES

Variation application shall be submitted in name of Secretary Registration Board along with a declaration letter by the registration holder or authorized person in his behalf which shall declare there is no other change except for the proposed variation.

10.1. Minor Variation-Notification (MiV-N)

MiV-N are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the finished product. Such notifications do not require prior approval but must be notified to Authority immediately after implementation.

Minor Variation-Notification (MiV-N)	
Procedure	Notification "Do & Tell" The registration holder shall submit notification for the change as per conditions and supporting documents as described under MiV-N. Such changes can be implemented immediately at the time of submission, and it can be considered accepted if an objection is not issued by the Authority within 30 working days of the date of submission of valid application.

10.2. Minor Variation - Prior Approval (MiV-PA)

MiV-PA are changes that may have minor effects on the overall safety, efficacy and quality of the finished product. Such notifications require prior approval of the Authority before implementation.

Minor Variation - Prior Approval (MiV-PA)	
Procedure	**Prior Approval** If the application fulfils the requirements (conditions and supporting documents) as described under MiV-PA, the Authority shall issue an approval for acceptance of the proposed change.
Timeline for evaluation of application	The Authority shall communicate decision on application within 45 working days from the date of submission of valid application.

10.3. Major Variation (MaV)

Major variations (MaV) are changes that could have major effects on the overall safety, efficacy and quality of the drug product. Such notifications require prior approval of the Authority before implementation.

Major Variation (MaV)	
Procedure	**Prior Approval** If the application fulfills the requirements (conditions and supporting documents) as described under MiV-PA, the Authority shall issue an approval for acceptance of the proposed change.
Timeline for evaluation of application	The Authority shall communicate the decision on application within 60 working days from the date of submission of valid application.

11. SUBMISSION OF APPLICATION FOR A VARIATION

11.1. General requirements

The following documents are required to be submitted for all types of variation applications:

i. Application by a registration/ market authorization holder or any authorized person on his behalf for the proposed change on Form provided in ***Appendix-I*****.**
ii. Submission of applicable fee depending on the type of variation.
iii. Copy of registration letter and renewal status along with any previous variation already informed/approved.
iv. In general, the registration holders are required to submit data related to variation as per relevant section of Form-5F (CTD).
v. Notarized approval/ acceptance of variation/ Certificate of Pharmaceutical Product (CPP) by the concerned regulatory authority of country in case of imported drug products as per their applicable guidelines/ regulations.
vi. Notarized valid GMP certificate with GMP inspection report by concerned regulatory authority of country of origin for imported drugs and for local products valid GMP certificate with GMP inspection report by DRAP.
vii. Declaration letter stating that there is no other change except for the proposed variation and the information provided is true and correct.

11.2. Conditions to be fulfilled (C)

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 affect the quality, safety and efficacy (QSE) of the drug product.

11.3. Documents to be submitted (D)

The list of documents 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 if required may be asked from the applicant. Regardless of the documents specified, applicants shall ensure that one has provided all relevant information to support the applied 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 and in case of imported drugs, these alternative approaches are accepted and the variations were approved on these alternative approaches.

12. TYPES OF VARIATIONS, CONDITIONS AND DOCUMENTS REQUIRED

12.1. Minor Variation-Notification

Minor Variation-Notification (MiV-N)	
MiV-N1	**Change in the name of Active Pharmaceutical Ingredient / Drug Substance, while the drug substance remain the same molecule(s)**
C	1. The active pharmaceutical ingredient / drug substance shall remain the same molecule(s).
D	1. Proof of acceptance by WHO or copy of the latest version of International Nonproprietary Names (INN) list mentioning proposed name of API/DS.
MiV-N2	**Minor change in the manufacturing process of an immediate release solid oral dosage form, semi solid or oral solutions**
C	1. The change includes following: i. Change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients. ii. Change to alternative equipment of the same design and operating principles of the same or of a different capacity. iii. Process changes including changes such as mixing times and operating speeds within application/validation ranges. 2. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 3. The manufacturing principle for individual manufacturing steps remain unchanged, e.g., there are no changes in the processing intermediates and manufacturing solvent(s) used in the process. 4. The proposed process must be controlled by relevant in-process controls used in the approved process and no changes (widening or deletion of limits) are required for these controls.

	5. The specifications of the finished product and/or process intermediates remain unchanged. 6. The proposed process must lead to an identical product regarding all aspects of quality, safety and efficacy.
D	1. Amendment of the relevant section(s) of the dossier, as appropriate, including a direct comparison of the approved and proposed processes. 2. Copy of approved drug product specifications. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the approved and the proposed process. 4. A declaration/ undertaking from registration holder that: i. Batch analysis data on the next two full production batches shall be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action). ii. The relevant stability studies of the drug product shall be started and that the relevant stability studies shall be finalized; data shall be provided only if outside specification (with proposed action).
MiV-N3	**Change in any part of the (primary) packaging material not in contact with the finished product formulation such as color of flip-off caps, color code rings on ampoules, change of needle shield (different plastic used).**
C	1. The change shall not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
D	1. Amendment of the relevant section(s) of the dossier (Form-5F or CTD), including revised product labeling as appropriate.
MiV-N4	**Changes in Labelling & Prescribing Information.**
C	1. The changes shall be in accordance with labelling and prescribing information of the innovator products as approved by the Reference Regulatory Authorities designated by the Registration Board.
D	1. Previously approved product labelling (SmPC, PIL etc) if any. 2. Proposed product labeling, a clean and annotated version highlighting the changes made.

	3. Copy of approved PI/SmPC/PIL from an approved reference regulatory agency. 4. Justifications for the changes proposed. 5. Approval letters from reference countries or countries of origin which have approved the proposed indication or dosing regimen etc., for Innovator product.

12.2. Minor Variation-Prior Approval

Minor Variation-Prior Approval (MiV-PA)	
MiV-PA1	**Change in name/ title of registration/ market authorization holder.**
C	1. The name change refers to the renaming of a company or organization. 2. The change shall not include transfer of marketing authorization to another company. 3. The manufacturing site shall remain unchanged. 4. No legal case / proceeding is pending at any forum / court of law concerning with the proposed change.
D	1. Copy of approval letter of change of name / title of firm/company from Licensing Division DRAP. 2. In case of imported drug products following documents are required: i. Copy of revised Drug Sale License (DSL) issued by respective provincial governments indicating same proprietor and address as on previous issued DSL. ii. Notarized agency agreement in name of new/revised DSL holder by the market authorization holder abroad.
MiV-PA2	**Change of name/ title in case of contract manufacturing/ analysis**
C	1. The name change refers to the renaming of a manufacturer. 2. The manufacturing site shall remain unchanged. 3. No legal case / proceedings is pending at any forum / court of law concerning with the proposed change.

D	1. Copy of approval letter of change of name / title of firm/company from Licensing Division DRAP. 2. Revised contract agreement as per applicable contract manufacturing policy i.e., Rule 20-A of Drug (Licensing, Registering & Advertising) Rules 1976.
MiV-PA3	**Change in name and/or address (for example: postal code, street name) of the marketing authorization holder in exporting country in case of imported drug product.**
C	1. The name change refers to the renaming of a company or organization. 2. The change shall not include transfer of marketing authorization to another company. 3. The manufacturing site shall remain unchanged.
D	1. Legalized CoPP/ document from the relevant authority confirming the change with the proposed name and/or address. 2. Notarized sole agency agreement from marketing authorization holder in name of registration holder.
MiV-PA4	**Change of the name or address (for example: postal code, street name) of the manufacturer of drug product in exporting country in case of imported drug product.**
C	1. The manufacturing site shall remain unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug product.
D	1. Legalized CoPP/ document from the relevant authority confirming the change with the proposed name and/or address. 2. Notarized sole agency agreement from marketing authorization holder in name of registration holder.
MiV-PA5	**Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release in exporting country.**
C	1. The manufacturer of the drug product shall remain unchanged. 2. The batch release site shall remain unchanged.
D	1. Legalized CoPP/ document from the relevant authority confirming the change with the proposed name and/or address.

	2. Notarized sole agency agreement from marketing authorization holder in name of registration holder.
MiV-PA6	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product.**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product).
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized for the packaging activity of the drug product concerned such as CoPP (legalized) which covers GMP certification. 3. Validation scheme and/or report of the manufacturing process to the proposed change of alternative site for primary packaging (where applicable). 4. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 5. A letter of commitment from marketing authorization holder to conduct long term and accelerated stability studies for the first three batches of drug product packed at the proposed site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
MiV-PA7	**Change of drug product name**
C	1. There shall be no change except for the product name change. 2. No litigation shall be pending at any forum / court of law concerning with the proposed change. 3. No confusion with another drug product either when spoken or written. 4. The proposed name shall not: i. suggest greater safety or efficacy than supported by clinical data ii. imply a therapeutic use iii. imply superiority over another similar product iv. imply the presence of substance(s) present or not present in the product.

D	1. Information regarding previous approvals of change of brand name since registration of drug product. 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 and 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. Line extension 4. Legalized CoPP where applicable in case of imported drug products. 5. For establishing brand name resemblance with any other registered drug product, a unit carton/ any other information as evidence of resemblance shall be provided. 6. Revised draft package insert and labeling incorporating the proposed variation.
MiV-PA8	**Change of importer/ MA holder in Pakistan**
C	1. The manufacturing site remains unchanged. 2. No litigation shall be pending at any forum / court of law concerning with the proposed change.
D	1. Termination letter (original) from marketing authorization holder/ manufacturer for previous importer. 2. Legalised Authority letter/sole agent letter (original) from marketing authorization holder/ manufacturer in name of new importer. 3. No Objection Certficate (issued within last 6 Months) from existing registration holder in name of applicant for registration of drug product. 4. Revised drafts of the package insert and labeling incorporating the proposed variation. 5. Legalized Certficate of Pharmaceutical Product (CoPP) or other relevant documents as defined by Registration Board.
MiV-PA9	**Change in Market Authorization Holder (MAH) in exporting country.**
C	1. The manufacturing site remains unchanged.

	2. The registration holder shall remain the same. 3. Undertaking from MA holder in exporting country that No litigation is pending at any forum / court of law concerning with the proposed change
D	1. Legalised authority letter/sole agent letter (original) from new Market Authorization Holder (MAH) abroad. 2. Approval of new MAH from regulatory body of exporting country or Legalized Certificate of Pharmaceutical Product (CoPP) mentioning new Market Authorization Holder (MAH).
MiV-PA10	**Change of batch size of non-sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 3. Shelf-life specifications of drug product remain unchanged. 4. This is applicable to change of batch size up to 10-fold compared to the approved batch size. 5. The manufacturing process shall remain unchanged
D	1. Comparative tabulated format of approved and proposed batch size. 2. Validation scheme and/or report of the manufacturing process of the proposed batch size should be provided upon submission. 3. Revised CTD Section P3.1-3.4 (where applicable) 4. Specifications of the drug product shall remain the same 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to approved and proposed batch sizes. 6. Stability data of at least six months (accelarted & real time) in accordance with applicable guidelines and report if any results fall outside shelf-life specifications (with proposed action).
MiV-PA11	**Minor change of the manufacturing process for non-sterile product**
C	1. The manufacturing site remains unchanged. 2. The overall manufacturing principle remains unchanged. 3. The change does not cause negative impact on the quality, safety and efficacy of the drug product.

	4. The dissolution profile of the proposed product is comparable to that of the approved product. 5. Specifications of drug product remain unchanged.
D	1. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms 2. Description of the proposed manufacturing process and technical justification for the change. 3. Comparative tabulated format of approved and proposed process with changes highlighted. 4. For semi solid and suspension products, validation scheme and/or report of the manufacturing process. 5. Copy of approved shelf life specifications. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one batch manufactured to both the approved and the proposed process; 7. A declaration/undertaking that: i. Batch analysis data on the next two full production batches should be made available upon request. ii. Stability studies of the drug product have been started and shall be reported only if outside specification (with proposed action).
MiV-PA12	**Quantitative change in coating of tablets and/or size of capsule shell for immediate release oral solid dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the approved product. 2. Specifications of the drug product remain unchanged except for the weight and/or size.
D	1. Comparative tabulated format of approved and proposed product and batch manufacturing formula.

	2. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms. 3. A declaration/ undertaking that: i. The change does not interfere with the drug product specifications test method. ii. The relevant stability studies of the drug product have been started and will be reported if any results fall outside specifications (with proposed action).
MiV-PA13	**Change in primary packaging material for non-sterile product** **a. Qualitative and quantitative composition and/or** **b. Type of container and/or** **c. Inclusion of primary packaging material**
C	1. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 2. Specifications of drug product remain unchanged.
D	1. Revised drafts of the package insert incorporating the proposed variation (where applicable). 2. Justification for the change in packaging material and appropriate scientific studies on the proposed packaging. 3. For semi-solid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). Container-Content compatability studies 4. Comparative tabulated format of the approved and proposed specifications of the primary packaging material (where applicable). 5. Revised CTD Sections P3 and/or P7 (where applicable). 6. Six month stability data and with undertaking to report if any results fall outside specifications (with proposed action) upto the proposed shelf life.

MiV-PA14	**Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries.**
C	1. There will be no qualitative or quantitive change in API.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Detailed drawing or written description of the approved and proposed appearance. 3. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed dimensions/shape for oral solid dosage forms. 4. For scored tablets, data on test of uniformity of the subdivided parts of tablets at release as conformed to compendial requirement. 5. Specifications of the drug product with proposed dimension and/or shape.
MiV-PA15	**Change of Secondary packaging materials**
C	1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties
D	1. Justification of proposed change, with tabulated differences between existing and proposed information. 2. An undertaking that: a. Proposed label complies all provisions of the Drugs (Labeling & Packing) Rules, 1986. b. The proposed color scheme / label has no resemble with already registered Products. In case of resemblance, new label will be changed immediately. c. No case is pending at any forum / court of law regarding this matter. d. Undertaking that the real time stability studies will be performed and the report will be submitted
MiV-PA16	**Change in the design or color scheme of packaging material.**
C	1. The proposed packaging design/color scheme must not resemble to already registered product. 2. Packaging material shall remain same.

D	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 in case of imported drug. 3. An undertaking/ declaration that: a. No case is 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. The proposed label complies all provisions of Drugs (Labeling & Packing) Rules, 1986.
MiV-PA17	**Standardization of formulation in accordance with the innovator's product/ approvals of reference regulatory authorities/ pharmacopeias.**
C	1. Existing formulation shall remain the same
D	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 as adopted by Registration Board / innovator product and/ or Pharmacopeias. 4. Undertaking that the provided information/ documents are true/ correct
MiV-PA18	**Grant of additional pack size for locally manufactured veterinary products (excluding injectables)**
C	None
D	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 local availability of applied additional pack sizes. 5. Approval of pack by regulatory authority of exporting country in case of imported drugs.
MiV-PA19	**Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product**
C	1. The change only concerns the same packaging type and material.

	2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Change in the dimension of the primary packaging (where applicable). 4. Specifications of the drug product remain unchanged.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification for the proposed pack size. 3. Revised CTD Sections P3 and/or P7 (where applicable). 4. A declaration/undertaking that the relevant stability studies of the drug product have been started and that the relevant stability studies shall be finalized; data shall be provided only if outside specification (with proposed action). 5. The proposed change complies to all provisions of Drugs (Labeling & Packing) Rules, 1986
MiV-PA20	**Change of the colouring agent /capsule shell colour of the product**
C	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring agents /capsule shell must not have been rejected for pharmaceutical use. 3. The specifications of the drug product remain unchanged, except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable).
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Revised product formulation and batch manufacturing formula. 3. Qualitative and quantitative information of the approved and proposed colouring agent/flavouring agent/capsule shell colour in a comparative table. 4. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the

	issuing country and/or documentary evidence from the supplier (where applicable). 5. Revised specifications of the drug product. 6. Certificate of Analysis of proposed coloring agent/flavoring agent/capsule shell (where applicable). 7. A declaration/ undertaking that: i. The proposed colouring agent/flavouring agent/capsule shell colour does not interfere with the drug product specifications test method. ii. A letter of commitment from marketing authorization holder to inform users of the relevant change (where applicable). iii. Stability study has been started and report if any results fall outside drug product specifications (with proposed action).
MiV-PA21	**Addition/ change of flavouring agent of the product e.g oral liquid/ dry powder suspension/sachet.**
	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring flavouring agents must not have been rejected for pharmaceutical use. 3. The specifications of the drug product remain unchanged, except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable).
	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Revised product formulation and batch manufacturing formula. 3. Qualitative and quantitative information of the approved and proposed colouring agent/flavouring agent/capsule shell colour in a comparative table. 4. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable).

	5. Revised specifications of the drug product. 6. Certificate of Analysis of proposed flavoring agent (where applicable). 7. A declaration/ undertaking that: i. The proposed colouring agent/flavouring agent/capsule shell colour does not interfere with the drug product specifications test method. ii. A letter of commitment from marketing authorization holder to inform users of the relevant change (where applicable). iii. Stability study has been started and report if any results fall outside drug product specifications (with proposed action).
MiV-PA22	**Change of specifications and/or test procedure of the drug product and/or drug substance and/or excipient, following the updates in the Official Pharmacopeia.**
C	1. Applicable to compendia specifications and/or test procedure only. 2. Change shall be made exclusively to comply with an update of the relevant monograph within the same Official Pharmacopeia**.**
D	1. Tabulation of the approved and proposed specifications and/or test procedure of the drug product with changes highlighted. 2. Batch analysis data (in comparative tabulated format) of the drug product for all tests in the proposed specification of at least two batches and/or certificate of analysis of excipient and/or drug substance. 3. Revised drug product specifications. 4. For change in test procedure, appropriate verification data of the proposed test procedure (where applicable).

12.3. Major Variation

Major Variation (MaV)	
MaV-1	**Addition or replacement of manufacturer/ site of drug substance or API used in locally manufactured product**
C	1. Specifications of drug substances remain unchanged.
D	1. Complete CTD section S1-S7 as per DRAP guidance document on CTD (Form-5F) 2. Comparative tabulated format of the approved and proposed drug substance manufacture information (where applicable). 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. 4. A letter of commitment from marketing authorization/ registration holder to conduct long term and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
MaV-2	**Change or addition in the source of half-finished products i.e. pellets / granules / ready to fill bulk etc.,**
C	1. Specifications of drug substances remain unchanged.
D	1. Data submission on applicable CTD Sections along with fee. 2. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches from the approved and proposed manufacturing sites. 3. A letter of commitment from marketing authorization/ registration holder to conduct long term and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.

MaV-3	Change of the manufacturing site of drug product
C	1. There is no legal case / proceeding is pending at any forum / court of law concerning with the proposed change. 2. The registration holder (importer) shall remain the same. 3. Market Authorization Holder abroad shall remain the same. 4. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place.
D	a. **Locally manufactured drug products** 1. Application on Form 5F (CTD) for human drug products and on Form-5 for veterinary drug products along with the fee. 2. Proof that the proposed site/ manufacturer is appropriately authorized for the pharmaceutical form concerned i.e., approval of manufacturing facility from Licensing Division and having valid GMP certificate. 3. In case of contract manufacturing, contract agreement with proposed manufacturer as per requirements laid down in SRO 1347(I)/2021 and contract termination letter with previously approved manufacturer by the MA holder. 4. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the previous approved and proposed manufacturing site for oral solid dosage forms. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches from the proposed site and last three batches from the approved site. stability and validation of the product and all other quality assurance specifications 6. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). **b**. **Imported drug products** 1. Application on Form 5F (CTD) for human drug products and Form 5A for veterinary drug products along with fee.

	2. Proof that the proposed site is appropriately authorized for the manufacturing of drug product concerned such as a valid legalized Certificate of Pharmaceutical Product (CoPP) which covers GMP certification. 3. Revised agency agreement and/or any proof / evidence of the contract between market authorization holder & proposed manufacturer where the manufacturer and market authorization holder are different entities. 4. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the previously approved and proposed manufacturing site for oral solid dosage forms. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches from the proposed site and last three batches from the approved site. Validation studies 6. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MaV-4	**Addition or replacement of site for primary packaging (direct contact with drug product) for sterile imported product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. No change in nature and material of container/closure system
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized for the packaging activity of the drug product concerned such as Legalized Certificate of Pharmaceutical Product (CPP) which covers GMP certification 3. Validation protocol and/or report on primary packaging processes at the proposed site should be provided upon submission. 4. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 5. Stability data of at least six months and report if any results fall outside shelf-life specifications (with proposed action).

MaV-5	**Change of specifications to officially recognized pharmacopeia standards.**
C	1. No legal case / proceeding is pending at any forum / court of law concerning with the proposed change. 2. The change is made exclusively to comply with the officially recognized pharmacopoeia.
D	1. Copy of the proposed drug product specifications dated and signed by authorized personnel and a comparative table of approved and proposed specifications. 2. Certificate of analysis of at least one batch and comparative summary of results, in tabular format, for one batch using current and proposed procedures. Validation studies 3. Demonstration of suitability of the monograph to control the drug product. 4. Time line for change 5. Undertaking that: i. The change is made exclusively to comply with the pharmacopeia of reference regulatory authorities. 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.
MaV-6	**Change in analytical procedures for drug product**
C	1. New analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 2. The change does not concern sterility testing. 3. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns. 4. No new impurities have been detected. 5. There is no legal case / proceeding pending at any forum / court of law concerning with the proposed change

D	1. Copy of the proposed drug product specifications dated and signed by authorized personnel and a comparative table of approved and proposed specifications. 2. Comparative table of approved and proposed procedure. 3. Copies/ summaries of validation reports. 4. Certificate of analysis of at least one batch and comparative summary of results, in tabular format, for one batch using current and proposed procedures. 5. Undertaking that: i. No case is pending at any forum / court of law regarding this product. ii. 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.
MaV-7	**Qualitative or quantitative change of excipients** **a. For immediate release oral dosage forms** **b. For modified release oral dosage forms** **c. For other critical dosage forms such as sterile preparations.**
C	1. Specifications of drug product remain unchanged, excluding product description except for update of product description with respect to appearance/odor/taste as a consequence of the change (where applicable). 2. Replacement of an excipient with a comparable excipient of the same functional characteristics. 3. The dissolution profile of the proposed product is comparable to that of the approved product. 4. Process validation scheme and/or report is available, or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed product formula.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

	2. A declaration that the proposed excipient does not interfere with the drug product specifications and test method (where applicable). 3. Justification for the change must be given by appropriate development of pharmaceutics. 4. Comparative tabulated format of the approved and proposed product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight (where applicable). 5. Comparative dissolution profile data of at least one batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms. 6. Revised batch manufacturing formula. 7. Validation scheme and/or report of the manufacturing process appropriate to the proposed change in product formula should be provided upon submission. 8. Revised CTD Section P3.1 to P3.4 (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminant's source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). 11. Drug product specifications 12. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on at least two production batches according to approved and proposed product formula. 13. Stability data of at least six months and to report if any results fall outside shelf-life specifications (with proposed action). 14. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).

MaV-8	**Change in shelf life of drug product (extension or reduction)**
C	1. No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage. 2. Stability data were generated in accordance with the currently accepted stability protocol. 3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
D	1. Copy of the currently accepted shelf-life specifications. 2. Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two production-scale batches for a period sufficient to support the proposed shelf-life. 3. Updated post-acceptance stability protocol and stability commitment. 4. Approval of regulatory body of country of origin (in case of imported products).
MaV-9	**Change of storage conditions of the drug product**
C	1. The studies must show conformance to the approved shelf-life specification.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long term stability studies covering the duration of approved shelf-life (at proposed storage condition) of the product and in the authorized packaging material and results of microbiological testing should be included (where appropriate).
MaV-10	**Change in primary packaging material for sterile product.** **a. Qualitative and quantitative composition and/or** **b. Type of container and/or** **c. Inclusion of primary packaging material**
C	1. Specifications of the drug product remain unchanged.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

	2. Appropriate scientific data on proposed packaging (comparative data on permeability, e.g. moisture, O2, CO2). 3. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 4. Validation scheme and/or report of the manufacturing and sterilization process. 5. Comparative tabulated format of specifications of the approved and proposed primary packaging material. 6. Revised CTD Sections P3 and/or P7 (where applicable). 7. Stability data of at least six months and to report if any results fall outside shelf-life specifications (with proposed action). 8. Evidence of such change in country of origin in case of imported drug
MaV-11	**Major change in the manufacturing process of the finished drug product**
C	1. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 2. The manufacturing site remains unchanged.
D	1. Description of the proposed manufacturing process and technical justification for the change. 2. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms 3. Validation scheme and/or report of the proposed manufacturing process. 4. Copy of approved specifications with copy of proposed specifications that supports that the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy needs trials. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product for a minimum of one production batch manufactured according to approved and proposed processes. 6. Stability data of at least six months and to report if any results fall outside shelf-life specifications (with proposed action) 7. Evidence of such change in country of origin

MaV-12	**Change of batch size of sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 3. Shelf-life specifications of drug product remain unchanged.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Validation scheme and/or report of the manufacturing process of the proposed batch size should be provided upon submission. 3. Specifications of the drug product. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to approved and proposed batch sizes. 5. Stability data of at least six months and to report if any results fall outside shelf-life specifications (with proposed action).
MaV-13	**Change of shape or dimension of container or closure for sterile solid and liquid drug product**
C	1. The packaging material remains unchanged. 2. Specifications of the drug product are not affected except shape and dimensions
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Validation data of the manufacturing process, sterilization and container closure system (where applicable). 3. Stability data and to report if any results fall outside shelf-life specifications (with proposed action).
MaV-14	**Quantitative change in coating of tablets and/or size of capsule shell for modified release oral dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the approved product. 2. The specifications of the drug product remain unchanged except for the weight and/or size (where applicable).

D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. Comparative tabulated format of approved and proposed product and batch manufacturing formula. 3. Comparative dissolution profile data of at least one production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms. 4. Specifcations of drug product. 5. The stability data of the drug product and to report if any results fall outside shelf-life specifications (with proposed action).
MaV-15	**Inclusion or replacement of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product. 2. The diluent/ solvent is added/ replaced in line with the innovator.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation. 2. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 3. A declaration/ undertaking from the marketing authorization holder that shelf-life specifications of drug product are not affected. 4. In addition to section P for the solvent/diluent and reconstitution stability data, section S is also required.

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. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

The following changes are considered as new product registration:

13.1. Changes to the Active Pharmaceutical Ingredient (API) / Drug Substance

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.

13.2. Changes to the Pharmaceutical Form /Dosage Form

i. Change from an immediate-release product to extended or delayed release dosage form and vice versa.

ii. Change from a liquid to a powder for reconstitution, or vice versa.

13.3. Changes in the route of administration

13.4. Additional volume of already registered injectable drug products

14. 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. WHO Guidelines on variations to a prequalified product, WHO Technical Report Series, No. 81, 2013.

vii. ASEAN Variation Guideline for Pharmaceutical Products Revision 2 (2021).

viii. Decisions of Registration Board related to Post Registration Variations.

APPENDIX-I

FORM FOR SUBMISSION OF POST-REGISTRATION VARIATION APPLICATION

1. GENERAL INFORMATION

Name and address of the Applicant / Registration Holder:			
Name and address of contact person:			
E-mail:		**Contact:**	

a. Variation procedure number:
b. Type of Application (tick all applicable options)

- ☐ MiV- N
- ☐ MiV- PA
- ☐ MaV-
- ☐ Single variation
- ☐ Group of variations

c. Change(s) concern(s) (for Minor Variation (Prior Approval) and MaV variations only, tick all changes applicable):

- ☐ Safety
- ☐ Quality
- ☐ Other

2. PRODUCT CONCERNED BY THIS APPLICATION

Registration Number		**Brand Name**		
Pharmaceutical form (Dosage form with complete description)			**Strength**	
Registration Date			**Renewal status**	
Active Pharmaceutical Ingredient (s)				
Name of excipients				
Registration/ MA Holder Name		**Manufacturer Name** (If different from Registration/ MA holder name)		
Drug Manufacturing License (DML)		**Drug Sale License (DSL)**		
Shelf life & storage conditions				
Container closure details				

2. VARIATIONS INCLUDED IN THIS APPLICATION

Number and title of variation, as per the classification guideline		Procedure Type
☒ a)	Specific variation applied for, as per the classification guideline	Type

3. PRECISE SCOPE AND BACKGROUND FOR CHANGE AND JUSTIFICATION

(*Include a description and background of all the proposed changes. In the case of a group of variations, a justification should be provided in a separate paragraph. If a variation concerns an unforeseen change, include a justification for its proposed classification).*

5. COMPARISION

PRESENT	PROPOSED

Declaration of the Applicant:
I hereby submit an application for the above-mentioned variation/change in accordance with the proposals given above. I declare that (*Please tick the appropriate declarations*):

- ☐ There are no other changes than those identified in this application
- ☐ Where applicable, all prerequisites/documents as set for the variation(s) concerned are fulfilled;
- ☐ For type minor variation notifications (MiV-N): where applicable, the required documents as specified for the changes concerned have been submitted;

Change(s) will be implemented from ☐ Next production run/next printing
☐ Date: _____

Authorized Signatory		**Status (Job title)**	
Name		**Date**	

DRUG REGULATORY AUTHORITY OF PAKISTAN
Telecom Foundation Complex, G-9/4, Islamabad, Pakistan
Email: addl-dir.per@dra.gov.pk Ph: +92 51 9107313
www.dra.gov.pk