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REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

GUIDELINE FOR SUBMISSION OF VARIATION APPLICATIONS FOR REGISTERED MEDICINES

JANUARY, 2024

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HPT/PER/GUD/015	**Guideline for Submission of Variation Applications for Registered Medicines**	**Revision No. 4**	**Effective Date:** 30/01/2024 **Review Date:** 29/01/2029

Prepared by: Deputy Director Product Evaluation and Registration

Sign.....

Date...16/01/2024.....

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Date...19/01/2024.....

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ACRONYMS AND ABBREVIATIONS

AN	Annual Notification
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Classification
BSE/TSE	Bovine Spongiform Encephalopathy/ Transmissible Spongiform
CEP	European Pharmacopoeial Certificate of Suitability
CTD	Common Technical Document
DMF	Drug Master File
DRA	Drug Regulatory Authority
EMA	European Medicines Agency
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
IN	Immediate Notification
INN	International Non-proprietary Name
KIPI	Kenya Intellectual Property Institute
MAH	Marketing Authorisation Holder
MAH	Marketing Authorisation Holder
Mj	Major Variation
Mn	Minor variation
PIL	Patient Information Leaflet
PPB	Pharmacy and Poisons Board
QC	Quality Control
SmPC	Summary of Product Characteristics
VarT No.	Variation Type Number
WHO	World Health Organisation

DEFINITIONS

A variation is a post-approval amendment that details the proposed change(s) to information appertaining to approved documentation for updating the details of the Marketing authorization license issued by the Pharmacy and Poisons Board, the National Drug Regulatory Authority.

Major variation: Major variations are changes that could have major effects on the overall safety, efficacy, and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by PPB is required before the changes can be implemented. An approval of changes will be issued by PPB for all major variations if and when the variation is considered acceptable.

Minor variation: Minor variations are changes that may have minor effects on the overall safety, efficacy, and quality of the FPP.

Such variations can only be implemented on receipt of a letter of acceptance from PPB.

Notification: Notifications are changes that could have minimal or no effects on the overall safety, efficacy, and quality of the FPP. Such notifications do not require prior approval but must be notified to PPB immediately after implementation (Immediate Notifications) or within 12 months following the implementation of the change (Annual Notifications). E.g Periodic Safety Update Reports.

Annual notification (AN): Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. ANs should be submitted to PPB within 12 months of implementation of the changes. For convenience, applicants may group several AN changes as a single submission.

Immediate notification (IN): Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted within 30 calendar days of the date of acknowledgment of receipt of the application.

The active substance may mean an active pharmaceutical ingredient (API) or active biological/immunological substance, where it's not clearly expressed.

Variation Reference: where reference has to be made to specific variations in this guideline, the proposed variation should be quoted using the Variation type number (VarT No.). If a variation type is not captured within this document the applicant shall refer to the WHO Variation guidelines (latest Technical Reference Series).

ACKNOWLEDGEMENT

The Registrar, Pharmacy, and Poisons Board would like to thank the following persons for their comments and contributions to the development of this guideline.

INTRODUCTION

Background

This guideline is meant to inform the applicant on how to submit variation applications of registered human products as per Cap 244 laws of Kenya to the Pharmacy and Poisons Board. This document will simplify and streamline the process for submitting post-approval changes.

Applicants should start by reading through this document with reference to the conditions and documentation required. Thereafter applicants should submit a variation application form using the application template in Annex 1.

This is a living document and will be updated frequently as experience is gained through the processing of variations.

LEGAL FRAMEWORK

Cap 244 Section 3 B, subsection (2) (i) empowers the board to consider applications for approval and alterations of dossier intended for use in marketing authorization of medicinal substances

SCOPE

This guideline primarily covers the conditions to be fulfilled, documentation required, and the format of submission of variations applications for registered medicines. This guideline does not apply to vaccines and biological products.

PPB may request the applicant to furnish additional information, material, or define conditions not provided for in this guideline that may be deemed necessary to assist in the evaluation of submitted variations.

PAYMENT OF FEES

Every application shall be accompanied by requisite fees at the time of application except for PSURS. Any application that will not be accompanied by requisite fees will not be accepted.

Mode of Payment: Payments by crossed or bankers' cheque shall be made payable to **PHARMACY AND POISONS BOARD**. Any variation irrespective of whether a notification, minor or major variation will attract a fee as prescribed by the Board as per the service charter.

Timelines for Evaluations of applications for Variations

Information on timelines for evaluations of variation applications is available in the Pharmacy and Poisons Board service charter.
https://web.pharmacyboardkenya.org/download/customers-service-delivery-charter/.

Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to PPB within 12 months of implementation of the changes.

Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by the Authority within 30 working days from the date of acknowledgement of receipt of the application.

Minor variation (Vmin)

Minor variations are changes that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

Minor variations shall be reviewed as per the customer service delivery charter available on the board's website.

Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by PPB is required before the changes can be implemented. An approval of the change will be issued for all major variations when the variation is considered acceptable. Major variations shall be reviewed as per the customer service delivery charter available on the board's website.

The applicant(s) are advised that all variations to registered products must be submitted in strict accordance with this guideline. If the applicant is uncertain about the classification of a variation, seek clarification via email from the PPB prior to submission. Any application found to be misclassified with a lower variation risk to bypass regulatory scrutiny will be rejected. The applicant will be required to reapply and pay the initial application fee in full.

It is encouraged that all queries raised are addressed comprehensively. If the change is not considered satisfactory, within three cycles of the additional review after first assessment, the application will be rejected and the applicant will be required to make a new application. This will be notified, through email correspondence to the applicant.

Reliance mechanisms in handling variations.

For an application to be assessed through reliance, the change must be approved by WHO listed authority (WLA) following conditions and documentation shall be fulfilled.

a. All Conditions and documentation will be required as per variations codes selected along with a copy of the reference SRA/ WHO decision or other document confirming the final decision of the reference SRA/WHO.

b. Confirmation letter that the information (variation dossier) submitted to the PPB is the same as that submitted to reference SRA/WHO for the variation.

Whenever FPPs have been registered on the basis of approval by a WHO listed authority (WLA) (innovator products or generic products) or WHO prequalification, subsequent applications for variations should also be approved by the same WLA and WHO PQP, respectively, and the Board shall be notified of the approval of the changes and the applicant shall submit proof of approval of such changes from the respective agency, if applicable.

For products formerly registered by PPB and subsequently approved by WLAs, the variation(s) shall be approved based on submission of letter of approval of the variation(s), from the WLAs.

VARIATIONS

ADMINISTRATIVE CHANGES

VarT No.	Description of change	Condition(s)	Documentation	Variation Type
A1	**Change in the name and/or address of the MAH**	1	1,2	IN

Condition

The MAH shall remain the same legal entity.

Documentation

1. A letter or any formal document from a relevant official institution (e.g. a Regulatory authority from the country of origin or official body dealing with registration of business names) in which the new name or new address is mentioned).
2. Revised product information.

VarT No.	Description of change	Condition(s)	Documentation	Variation Type
A2	**Change in the (invented) name of the medicinal product**	1	1,2	Mn

Condition

Check by PPB on the acceptability.

Documentation

1. A statement on rationale justifying the change
2. Revised product information.

VarT No.	Description of change	Condition (s)	Documentation	Variation Type
A3	**Change in the name of the API**	**1**	**1,2**	**Mn**

Condition

The API shall remain the same

Documentation

1. A statement of rationale justifying the change
2. Revised product information.

VarT No.	Description of change	Condition(s)	Documentation	Variation Type
A4	**Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the API, starting material, reagent or intermediate used in the manufacture of the API (where specified in the product dossier) where no EU CEP, WHO APICPQ or EAC APIMF is part of the approved dossier in the name of the API**	1	1,2,3	IN

Condition

The manufacturing site and all manufacturing processes shall remain the same.

Documentation

1. A letter or any formal document from a relevant official institution (e.g. a

   Regulatory authority from the country of origin or official body dealing with registration of business names) in which the new name or new address is mentioned).
2. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
3. An updated letter of access, in case of change in the name of the holder of the APIMF".

VarT No.	Description of change	Condition(s)	Documentation	Variation Type
A5	**Change in the name and/or address of the FPP manufacturer including QC sites**			
I	Manufacturer involved in Batch release	1	1,2,3	IN
II	Manufacturer involved in any other activity	1	1,2	IN

Condition

The manufacturing site and all manufacturing processes shall remain the same.

Documentation

1. A letter or any formal document from a relevant official institution (e.g. a Regulatory authority from the country of origin or official body dealing with registration of business names) in which the new name or new address is mentioned).
2. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
3. Revised product information as relevant, may include revision of PIL, primary and secondary packs

VarT No.	Description of change	Condition(s)	Documentation	Variation Type
A6	**Change in ATC code**	1	1,2,3	Mn

Condition

Approval of change by WHO ATC code

Documentation

1. Proof of approval of the ATC code change by the WHO code list
2. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format.

3. Revised product information as relevant, may include revision of PIL, primary and secondary packs.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
A7	**Deletion of manufacturing sites (including for an API, intermediate or FPP, packaging site, manufacturer responsible for batch release, batch control site, or supplier of a starting material, reagent or excipient (stated in the dossier) involved in:**			
I	Production of the API starting material	1,2	1,2,3	AN
II	Production or testing of the API Intermediate or API	1,2	1,2,3	IN
III	Production, packaging or testing of the intermediate or FPP	1,2	1,2,3	IN

Conditions

1. It should be evidenced that at least one site or manufacturer, as previously authorized, remains to perform the same function as the one (s) concerned by the deletion.
2. The deletion should not be due to critical deficiencies in any way in manufacturing activities.

Documentation

1. The variation application form should clearly outline the "current" and "proposed" manufacturers.
2. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format.

3. Revised product information as relevant, may include revision of PIL, primary and secondary packs.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
A8	**Change of Local Technical Representative (LTR)**	1,2	1,2,3	Mn

Documentation

A legal (notarized) contractual agreement between the proposed LTR and MAH

1. a) A letter of no objection from the current LTR should be submitted within 21 calendar days of application, OR
   b) If there is an objection, the current LTR should submit documentation that includes a court injunction/tribunal ruling stopping the transfer of the products to the proposed LTR within 21 calendar days of application
2. Where the documentation in section 2(b) is not provided within 21 calendar days, the. The board shall proceed and effect the transfer of LTR as applied for by MAH

VarT No.	Description of change	Condition(s)	Documentation	Variation type
A9	**Change in Marketing Authorization Holder**			
I	Change of ownership of registered products	1	1,2,3,4	Mn
II	Change in the name or address of the Marketing authorization Holder	1	2,3,4	Mn

Condition

The manufacturing site and all manufacturing processes shall remain the same.

Documentation

1. An authorization letter from the current MAH
2. A letter or any formal document from a relevant official institution

(e.g. a Regulatory authority from the country of origin or official body dealing with the registration of business names) in which the new name or new address is mentioned.

3. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format

4. Revised product information as relevant, may include revision of PIL, primary and secondary packs

VarT No.	Description of change	Condition(s)	Documentation	Variation type
A10	**Change in the name and/or address of the MAH resulting from sale or legal transfer of an Entity**	1	1,2,3	Mn

Condition

There is the transfer of legal entity.

Documentation

1. A letter or any formal document from a relevant official institution (e.g. a regulatory authority from the country of origin and official body dealing with the registration of business names) in which the new name or new address is mentioned.
2. Legal transfer documents signed by the two entities and notarized.
3. Revised product information.

A CHANGES AFFECTING QUALITY

B1. API

NB:

1. An introduction or deletion of an API from combination products would require a submission of a new CTD application as opposed to a variation.
2. Similarly, a change in salt form or polymorphic form of an API would require a submission of a new CTD application as a new product.

B1.a Manufacturing

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.a.i	**Change in the manufacturer of a starting material/reagent/intermediate used in the manufacture of the API or change in the manufacturer (including where relevant QC sites) of the API**			
A	The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	1,2,3	1 to 7	Mn
B	Introduction of a new manufacturer of the API that is supported by an APIMF	1,2,3	1 to 7	Mj
C	The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions that could impact important quality attributes of the API, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.	1,2,3	1 to 7	Mj
D	New manufacturer of material requiring viral safety and/or TSE risk assessment	1,2,3	1 to 7	Mj
E	Change that relates to a biologically active substance (including a starting material/reagent/ intermediate used in the manufacture of a biological/immunological product).	1,2,3	1 to 7	Mj
F	Changes to QC testing site (s) for the API- replacement/deletion or addition of a site where batch control/testing takes place	2,4	1,5	Mn

Conditions

1. For starting materials and reagents, the specifications (including in IPQC, and methods of analysis) are currently approved.
2. For intermediates and APIs, the specifications (including in IPQC, methods of analysis), method of preparation (including batch size), and detailed route of synthesis are currently approved.
3. The API is not a biological/immunological substance or sterile

4. In the case of manufacturing involving the use of materials of human or animal origin, the manufacturer does not use any new supplier for which assessment is required of viral safety or TSE/BSE safety.
5. Analytical method(s) transfer from the old to the new site has been completed.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. A declaration by the MAH or the APIMF holder, that the synthetic route (or in the case of herbal medicinal products, where appropriate that the method of preparation, geographical source, production of herbal drug, and manufacturing route), QC procedures, and specifications of the API and the starting material/reagent/intermediate in the manufacturing process of the API (if applicable) are as currently approved.
3. A TSE/BSE certificate including the name of manufacturer, species, and tissues from which the material is a derivative, country of origin of the source animals, its use, and previous acceptance
4. Batch analysis data (in a comparative tabular format) for at least two batches of the API from the current and proposed manufacturers/ manufacturing sites.
5. The variation application form should clearly outline the "current" and "proposed" manufacturers/manufacturing sites.
6. A declaration by the QP of each of the MAH listed in the application where the API is used as a starting material and a declaration by the QP of each of the manufacturing Authorization holders listed in the application as responsible for batch release stating that the API manufacturer(s) referred to in the application operate in compliance with GMP.
7. Where relevant, a commitment by the API manufacturer to inform the MAH of any changes to the manufacturing process, specifications, and test procedures of the API.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.a.ii	**Changes in the manufacturing process of the API**			
A	Minor change in the manufacturing process of the API	1 to 7	1 ,2,3	Mn
B	Major changes to the manufacturing process of the API could impact significantly the quality, safety, or efficacy of the product. NB: For chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may impact important quality attributes of the API, such as qualitative and/or quantitative impurity profile requiring qualification, or Physico-chemical properties impacting on bioavailability.	1 to 7	1 ,2,3	Mj
C	Change to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological product that is not related to a protocol.	1 to 7	1 ,2,3	Mj
D	Change to an herbal medicinal product (including a change to geographical source, manufacturing route or production).	1,2,3	1 to 7	Mj
E	Minor change to the restricted part of APIMF.	1,2,3	1 to 4	Mn
F	Change in the manufacturing process	None	1 to 3	Mj

Conditions

1. There should be no adverse change in qualitative and/or quantitative impurity profile in the physicochemical properties.
2. The synthetic route remains the same including starting materials, catalysts, and reagents.

3. In the case of herbal products, the geographical source, production of the herbal substance, and the manufacturing route of the herbal product remain the same.
4. The API or intermediates' specifications remain the same.
5. The change is fully described in the open ("applicant's") part of an APIMF, if applicable.
6. The active substance is not a biological/immunological substance
7. The change does not refer to the geographical source, manufacturing route, or production of an herbal medicinal product.
8. The change does not refer to the restricted part of an APIMF.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Batch analysis data (in a comparative tabular format) for at least two batches of the API from the current and proposed manufacturers/ manufacturing sites.
3. A copy of the approved (dated and signed) API specifications
4. A declaration from the MAH or the APIMF holder, where applicable, that there is no change in qualitative and quantitative impurity profile or physicochemical properties, that the synthetic route remains the same and that the specifications of the API or intermediates are unchanged.

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B1.a.iii	Change in batch size/batch size ranges of API or intermediate			
A	Up to 10-fold increase to the currently approved batch size	1 to 8	1 ,2,5	AN
B	Reduction in batch size	1 to 5	1 ,2,5	AN

C	Change requiring assessment of the comparability of a biological/immunological active substance.	1,2,4, 5	1 ,2,5	Mj
D	Greater than 10-fold increase to the currently approved batch size	1 to 5	1 to 4	Mn
E	Decrease/increase in the scale for a biological/immunological active substance without process change (e.g., line duplication).	1,2,4, 5	1 to 4	Mn

Conditions

1. Changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.
2. At least two BMRs (tested according to the specifications) should be available for the proposed batch size.
3. The API is not a biological/immunological substance
4. The change should be validated to ensure that it does not adversely affect process reproducibility
5. The change should not be the result of deficiencies (unexpected events) arising during manufacture or because of stability concerns.
6. The API or intermediate specifications is unchanged
7. The API is not sterile
8. The currently approved batch size was not approved through a minor variation application

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Batch numbers (of tested batches) of the proposed batch sizes
3. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch, manufactured to both the currently approved and the proposed sizes.
4. A commitment to providing batch data on the next two production batches.

5. Stability data- Provide a commitment to place one batch per year on stability for the proposed batch size. Any OOS or atypical trend is to be immediately reported to the Pharmacy and Poisons.
6. A copy of the approved (dated and signed) API/intermediates specifications
7. A declaration by the MAH or the APIMF holder, that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, that the change does not adversely affect process reproducibility, that it is not the result of unexpected events during manufacture or because of stability concerns and that the specifications of the API/intermediates remain unchanged.

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B1.a.iv	**Change to in-process tests/limits applied during the manufacture of the API**			
A	Tightening of IPQC limits	1 to 4	1 ,2	AN
B	Addition of IPQC tests or limits	1,2,5,6	1,2,3,4,6	AN
C	Deletion of non-significant IPQC tests	1,2	1 ,2,5	IN
D	Widening of the approved IPQC test limits, which may have a significant effect on the overall quality of the API	1 to 5	1 to 4	Mj
E	Deletion of the approved IPQC test limits, which may have a significant effect on the overall quality of the API	1,2,4, 5	1 to 4	Mj
F	Addition or replacement/deletion of an IPQC test due to safety or quality concern	1,2,4, 5	1,2,3,4,6	Mn

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during manufacture e.g. change in impurity profile, or total impurities.
3. The change should be within currently approved limits
4. The test procedure remains the same (or with insignificant changes)
5. The test procedure is not a novel method or an old method used in a nonstandard way
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biologically active substance (Standard pharmacopoeial microbiological methods are exempt)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
2. Comparative data between the current and proposed test methods in a tabular format
3. Details of the new non-pharmacopeia method with validation protocol and data
4. Batch analysis data on two production batches (three for biologicals) of the API for all specifications parameters
5. Justification through risk assessment from MAH/APIMF holder showing that the test parameter is insignificant
6. Justification from MAH/APIMF holder for the new IPQC tests and/or limits

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.a.v	**Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine e.g., human influenza vaccines**			
A	Replacement of strain			Mj

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data between the current and proposed strain
3. Revision of product information including the SmPC

B1.b Control of API

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.b.i	**Change in the specification parameters and/or limits of an API, starting material / intermediate / reagent used in the manufacture of the API**			
A	Tightening of specification limits	1 to 4	1,2	AN
B	Introduction of a new specification parameter with an accompanying test method	1, 2, 5, 6,7	1, 2, 3, 4, 7	AN
C	Deletion of a non-significant specification parameter (e.g., an obsolete parameter)	1,2	1,2,6	AN
D	Deletion of a specification parameter which could impact significantly on the quality of the API and/or the FPP	1,2	1,2,6	Mj
E	Change in the specification parameter limits outside the approved specification limits range for the API	1,2	1,2,6	Mj

F	Widening of the approved specifications limits that may impact on the quality of the API and/or the FPP	1,2	1,2,6	Mj
G	Addition or replacement of a specification parameter due to safety or quality concern (excludes biological/ immunological substance)	1,2	1to7	Mn

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during manufacture e.g. changes in impurity profile, or total impurities.
3. The change should be within currently approved limits
4. The test procedure remains the same (or with insignificant changes)
5. The test procedure is not a novel method or an old method used in a nonstandard way
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biologically active substance (Standard pharmacopoeial microbiological methods are exempt)
7. The change does not concern a genotoxic impurity

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data between the current and proposed test methods in a tabular format
3. Details of the new non-pharmacopeia method with validation protocol and data
4. Batch analysis data on two production batches (three for biologicals) of the API for all specifications parameters

5. Comparative dissolution profile, where applicable, of the FPP of at least one pilot batch each containing the API complying with the current and proposed API specifications.
6. For herbal products, comparative disintegration data is to be provided.
7. Justification through risk assessment from MAH/APIMF holder showing that the test parameter is insignificant
8. Justification from MAH/APIMF holder for the new IPQC tests and/or limits

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B1.b.ii	**Change in test procedure for API or starting material/ reagent/intermediate used in the manufacture of the API**			
A	Minor changes to already approved test Procedure	1 to 4	1,2	Mn
B	Deletion of a test procedure when an alternative test procedure is approved	7	1	Mn
C	Other changes to a test procedure on a reagent which has no significant effect on the quality of the API	1,2,4,6	1,2	Mn
D	Change to a biological /immunological/ immunochemical test or a method using a biological test reagent	1,2,4,6	1,2	Mj
E	Other changes to a test procedure for an API/starting material/intermediate	1,2,4,6	1,2	Mn

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and the currently approved method.

2. There are no changes in total impurities and no new (unqualified) impurities
3. The analytical method should essentially remain the same with minor changes, such as a change in column length and not column type for HPLC methods.
4. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biologically active substance (Standard pharmacopeia microbiological methods are exempt)
5. The test procedure is not a novel method or an old method used in a nonstandard way
6. The active substance is not biological or immunological
7. An alternative test procedure is already approved (should not have been approved through a minor variation)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data between the current and proposed test methods in a tabular format (this is not a requirement in case of the addition of a test method)

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B1.b.iii	**Change in test procedure used to control the API by the FPP manufacturer involving: -**			
A	Change in the analytical procedures as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled	None	1-3	IN
B.i	Addition of an analytical procedure	1-3	1-3	AN
Bii	Addition of an analytical procedure	3,8	1-3,5	IN

Biii	Addition of an analytical procedure	8	1-3,5	Mn
Biv	Addition of an analytical procedure	None	1-3	Mj
Ci	Replacement of an analytical procedure	1-6	1-4	AN
Cii	Replacement of an analytical procedure	2-3, 5-6, 8	1-5	IN
Ciii	Replacement of an analytical procedure	1-3,5-6	1-4	Mn
Civ	Replacement of an analytical procedure	5-6, 8	1-5	Mn
Cv	Replacement of an analytical procedure	None	1,6	Mj
Di	Deletion of an analytical procedure	6-7	1,6	AN
Dii	Deletion of an analytical procedure	6,8	1,5,6	IN
Diii	Deletion of an analytical procedure	None	1,6	Mj

Conditions

1. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
2. The change is not necessitated by the failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. No new impurities have been detected as a result of the use of the new analytical method.
4. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method) and no new impurities are detected.
5. Comparative studies are available demonstrating that the proposed analytical
6. The change does not concern sterility testing.
7. The deleted analytical procedure is an alternative method and is equivalent to the currently accepted method

8. The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF.

Documentation

1. Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used.
3. Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or significantly modified analytical procedures are used.
4. Comparative analytical results demonstrate that the proposed analytical
5. A copy of the APIMF acceptance letter.
6. Justification for the deletion of the analytical procedure, with supporting data.

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B1.b.iv	**change or addition of a manufacturing block or unit at a currently accepted site of API manufacture**			
A	change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	1-5	No variation required; Changes are to be handled through APIMF procedure (if applicable)	
B	change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	1,3-5	1-4	IN

Conditions

1. The API is non-sterile.

2. The API manufacturing block or unit is currently accepted through the APIMF procedure.
3. The same quality system covers currently accepted and proposed units or blocks
4. For low-solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API lot used in the preparation of the bio batch.
5. No change in the route of synthesis, quality control procedures, and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable). Minor changes in the equipment are acceptable.

Documentation required

1. A declaration from the supplier of the FPP that the route of synthesis, quality control procedures, and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
2. A valid name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s)).
3. Description of the batches, copies of certificates of analysis, and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed units or blocks.
4. A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

B1.c Container closure system

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.c.i	**Change in the primary packaging of the API**			
A	Qualitative and/or quantitative composition	1,2,3	1,2,3,4,6	Mn

B	Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances	1,2,3	1,2,3,4,6	Mj
C	Non-Sterile Liquid APIs	1,2,3	1,2,3,5,6	Mn

Conditions

1. Prove equivalence between the currently approved and the proposed immediate packaging
2. Relevant stability studies under ICH conditions, evaluating all relevant test parameters (on at least two pilot scale batches and one production scale batch)
3. Sterile, liquid and biological/immunological active substances are excluded

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data (e.g. permeability data on O2, CO2, moisture) between the current and proposed packaging in a tabular format
3. Where appropriate, provide proof of no interaction between the packaging and the active substance
4. A declaration by the MAH or APIMF holder that the stability studies have been appropriately carried out
5. Stability data
6. Comparison (in tabular format) of the current and proposed packaging specifications

VarT No.	**Description of change**	**Condition (s)**	**Documentation**	**Variation type**
B1.c.ii	**Change in the specification parameters and/or limits of the primary packaging of the API**			

A	Tightening of specification limits	1,2,3,4	1,2	AN
B	Addition of specification parameters with accompanying test method(s)	1,2,5	1,2,3,4,6	AN
C	Deletion of a non-significant specification parameter	1,2	1,2,5	AN
D	Addition/Replacement of a test parameter due to safety or quality concern	1,2	1,2,3,4,6	Mn

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during the manufacture of the packaging or storage of the API.
3. Any change should be within the currently approved packaging specification limits
4. The test procedure is unchanged (minor changes to the procedure could be exempted but need approval in addition)
5. The test procedure is not a novel method or an old method used in a non-standard way.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparison of the currently approved and the proposed specifications in tabular format
3. New analytical method details and validation data
4. Batch analysis data (of two batches) between the currently approved and proposed primary packaging for all specification parameters
5. Justification (through risk assessment) from MAH or APIMF holder that a specification parameter is not significant

6. Justification from MAH or APIMF holder for new specification parameter(s) and/or limits.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.c.iii	**Change in test procedure for the Primary packaging of the API**			
A	Minor changes to already approved test procedure	1 to 3	1,2	AN
B	Other changes to a test procedure (including Addition/deletion)	1,3,4	1,2	AN
C	Deletion of a test procedure (if there is an already approved test method)	5	1	AN

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and the currently approved method.
2. The analytical method should essentially remain the same with minor changes, such as a change in column length and not column type for HPLC methods.
3. The test procedure is not a novel method or an old method used in a non-standard way
4. The active substance is not biological or immunological
5. An alternative test procedure is already approved (should not have been approved through a minor variation)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative validation data between the current and proposed test methods in a tabular format (this is not a requirement in case of the addition of a test method)

B1.d API Stability

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.d. i	**Change in the re-test period/shelf life or storage conditions of the API**			
A	Re-test period or shelf life			
	1. Reduction	1	1 to 3	IN
	2. Extension of the re-test period through data extrapolation (not in accordance to ICH)	1	1 to 3	Mj
	3. Extension of shelf life of a biological /Immunological active through data extrapolation (not in accordance to ICH) NB: There is no re-test period for biological/immunological active	1	1 to 3	Mj
	4. Extension of a re-test period or shelf life using real time stability data	1	1 to 3	Mn
B	Storage Conditions			
	1. Change to more restrictive conditions	1	1 to 3	IN
	2. Change in storage conditions of biological/ immunological active when the stability studies have not been performed according to a currently approved stability protocol			Mj
	3. Change in storage conditions			Mn

Condition

The change is not due to unexpected events during manufacture or due to stability concern.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format

2. Stability data showing stability studies were done according to the approved protocol meeting all the test specifications
3. A copy of the approved (signed and dated) specifications

B1.e API design space/facilities

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B1.e.i	**Introduction of a new design space or extension of an approved design space for the API, excluding biologicals**			
A	Description of the design space in tabular format		1,2	Mj

Documentation

Amendment of the relevant section(s) of the dossier presented in the PPB-CTD

B2 Finished Pharmaceutical Product

B2.a FPP Description and Composition

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.a.i	**Change or addition of imprints, embossing or other markings including replacement or addition of inks used for product marking.**			
A	Change in imprints/embossing/other markings	1 to 3	1,2	Mn
B	Change in scoring/break lines intended to divide into equal doses	1 to 3	1 to 3	Mn/Mj

Conditions

1. FPP release and shelf-life specifications remain unchanged except concerning appearance
2. Any ink must conform to the relevant international guidelines
3. The proposed scoring/break lines are not intended to divide into equal doses

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Samples are to be provided, as appropriate
3. Data demonstrating the equivalence of doses

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.a.ii	**Change i n the shape or dimensions of the**			
A	Immediate release tablets, capsules, suppositories & pessaries	1 to 3	1,4	Mj
B	Gastro-resistant, modified or prolonged release dosage forms & scored tablets intended to be divided into equal doses	1 to 4	1 to 5	Mj

Conditions

1. Dissolution profiles are comparable between the new and old pharmaceutical forms.
2. In the case of herbal products, the disintegration time compares between the old and new pharmaceutical forms.
3. Release and shelf life specifications remain the same except for dimensions
4. The qualitative and quantitative composition remains unchanged
5. The change is not on a scored tablet already approved to be divided into equal doses

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative dissolution data of at least one pilot batch demonstrating dissolution equivalence between the currently approved and proposed pharmaceutical form
3. Justification for not submitting a BE study (Biopharmaceutical classification rationale or any justifiable reason)
4. Samples of the FPP were justifiable
5. Results showing dose equivalence

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B2.a.iii	**Changes in the Excipients Composition**			
A	**Change in flavors/colors**			
	1. Change in flavors addition/deletion/replacement	1 to 7, 9	1 to 6	Mn
	2. Change in colors Increase/reduction	1 to 4	1,2,4	Mn
	3. Biological VET products for oral use where the coloring or flavoring agent is critical for uptake	1 to 4	1,2,4	Mj
B	**Other Excipients**			
	1. Minor quantitative change	1, 2, 4, 8, 9, 10	1,2,7	Mn
	2. Qualitative and/or quantitative changes of one or more excipients that may have significant impact affecting quality, efficacy and safety of the FPP	1, 2, 4, 8, 9, 10	1,2,7	Mj

	3. Change relating to a biological/immunological FPP	1, 2, 4, 8, 9, 10	1,2,7	Mj
	4. Change relating to any excipient that requires viral safety or BSE/TSE assessment	1, 2, 4, 8, 9, 10	1,2,7	Mj
	5. Change supported through BE	1, 2, 4, 8, 9, 10	1,2,7	Mj
	6. Replacement of only one excipient with a comparable excipient that has the same functional characteristics and at a similar quantity	1, 2, 4, 8, 9, 10	1, 3 to 10	Mn

Conditions

1. No change in functional characteristics between the currently approved and proposed formulation
2. Any minor changes in formulation to vary the weight minimally should be done on the excipient making the biggest part of the formulation e.g. diluents.
3. The FPP specification has only been updated in respect of appearance/odor/taste and if relevant, deletion of an identification test.
4. Stability studies as per ICH conditions (on at least two pilot batches and one production batch)
5. The proposed component must comply with international guidelines on safety.
6. The proposed component does not include the use of materials of human or animal origin for which assessment is required of viral safety or BSE/TSE.
7. The change does not affect strength differentiation and palatability, especially in pediatric medicines.
8. The dissolution is comparable between the currently approved and the proposed formulations while for herbal products, disintegration is comparable.

9. The change is not a consequence of stability problems and no strength differentiation issue could impact on safety.
10. The product is not a biological/immunological product.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format.
2. A declaration by the MAH or manufacturer that stability was carried out in accordance to ICH requirements.
3. Stability data.
4. Sample of the new Product.
5. A BSE/TSE certificate (that includes: name of manufacturer, species, and tissues from which the material is a derivative, country of origin of the source animals, and the material use)
6. Analytical data demonstrating that the new excipient does not interfere with the finished product specification test methods, if appropriate.
7. Justification for change (Pharmaceutical development data)
8. Comparative dissolution profile between the currently approved and the proposed formulations while for herbal products, comparative disintegration data.
9. Justification for not submitting a BE study (Biopharmaceutical classification rationale or any justifiable reason)
10. For VET medicines intended for use in food-producing animal species data demonstrating food safety should be submitted.

#Reference to the SUPAC-IR: Immediate-Release Solid Oral Dosage Forms guidelines with regard to change in excipients

Components & composition

1. Level 1 change:

Changes that are unlikely to have any detectable impact on formulation quality and performance e.g.

a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
b. Changes in excipients expressed as a percentage (w/w) of the total formulation, less than or equal to the accepted percent ranges (see table in the slides below): The total additive effect of all excipient changes should not be more than 5%.

Condition: No BE documentation required. No dissolution documentation (only pharmacopoeial requirements)

2. Level 2 change:

Changes that could have a significant impact on formulation, quality, and performance. Tests and documentation for a Level 2 change vary depending on three factors: therapeutic range, solubility, and permeability.

E.g.

a) Change in the technical grade of an excipient. (Example: Avicel PH102 vs. Avicel PH200.)
b) Changes in excipients expressed as percent (w/w) of the total formulation, greater than those listed for a Level 1 change but less than or equal to the accepted percent ranges (which represent a two-fold increase over Level 1 changes) as per the table in slides below.

Conditions

1. The total additive effect of all excipient changes should not change by more than 10%.
2. No, BE documentation is required.
3. Dissolution documentation required viz:-
    a. Case A: High Permeability, High Solubility Drugs Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C

b. Case B: Low Permeability, High Solubility Drugs. Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

c. Case C: High Permeability, Low Solubility Drugs. Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of the drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.

3. Level 3 change:

Changes that are likely to have a significant impact on formulation quality and performance. Tests and documentation vary depending on the following three factors: therapeutic range, solubility, and permeability.

E.g.:

(Conditions)

1. Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted under level 1 (example 2).

2. All other drugs not meeting the dissolution criteria under level 2 (2; dissolutions Cases A, B, or C)

3. Changes in the excipient ranges of low solubility, and low permeability drugs beyond those listed under level 1(example 2).

4. Changes in the excipient ranges of all drugs beyond those listed under level 2(example 2)

Dissolution documentation (dissolution profile as described under case B level 2).

BE full BE study. **Exemption: I*VIV* correlation is acceptable.**

Composition	**Change Level**	
	Level 1	Level 2
Filler	±5	±10
Disintegrant		
Starch	±3	±6
Other	±1	±2
Binder	±0.5	±1
Lubricant		
Calcium or magnesium stearate	±0.25	±0.5
Other	±1	±2
Glidant		
Talc	±1	±2
Other	0.1	±0.2
Film coat	±1	±2

NB

1. Please note that the above percentages assume that the drug substance in the product is formulated to 100% potency (label claim).
2. The total additive effect of all excipient changes should not exceed 5% for level 1 change and 10% for level 2 change.
3. The components (active/s and excipients) in the formulation should have numerical targets which represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based.

4. Allowable changes in the composition should be based on the approved target composition and not on previous Level changes in the composition.
5. Level 3 change is as described in the four options.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.a.iv	**Change in coating weight of oral dosage forms or change in weight of capsule shells**			
A	Oral solid dosage forms	1 to 4	1 to 3	Mn
B	Gastro-resistant, modified or prolonged release dosage forms with a functional coat (coating is critical for the release mechanism).	1 to 4	1 to 3	Mj

Conditions

1. The dissolution profile is comparable between the currently approved and the proposed formulations (done on at least two pilot batches) while for herbal products, disintegration is comparable.
2. The coating (either functional or non-functional) does not critically affect drug release and/or release mechanism
3. The FPP specification has only been updated in respect of weight and dimensions, if applicable
4. Stability studies as per ICH conditions (on at least two pilot batches and one production batch)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. A declaration by the MAH or manufacturer that stability was carried out in accordance with ICH requirements
3. Stability data

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.a.v	**Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same.**			Mj

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Revised product information

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.a.vi	**Deletion of the solvent / diluent container from the pack**			Mn

Conditions

1. Justification for the deletion and in addition, a statement on alternative means to
2. obtain the solvent/diluent as required for the safe and effective use of the medicinal product

Documentation

1. Justification for the deletion and in addition, a statement on alternative means to obtain the solvent/diluent as required for the safe and effective use of the medicinal product
2. Revised product information

B2.b FPP Manufacture

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.b.i	**Replacement or addition of a manufacturing site for part or all of the manufacturing processes of the FPP**			
A	Secondary Packaging site	1,2	1,3,7	Mn
B	Primary Packaging site	1 to 5	1 to 4, 7, 8	Mn
C	Site where any manufacturing operation(s) take place, EXCEPT batch release, batch control, and secondary packaging for **biological/ immunological** FPPs.	1 to 5	1 to 4, 7, 8	Mj
D	Site which requires an	1 to 5	1 to 4, 7, 8	Mj
E	Site where any manufacturing operation(s) take place, EXCEPT batch-release, batch control,	1 to 5	1 to 8	Mn
F	Site where any manufacturing operation(s) take place, EXCEPT batch release, batch control, and secondary packaging for **sterile FPPs manufactured using an aseptic method EXCLUDING biological/ immunological medicinal products.**	1 to 5	1 to 7	Mn
G	Site where all manufacturing processes take place including batch release for both **Non-Sterile and sterile products EXCLUDING biological/ immunological medicinal products.**	1 to 5	1 to 7	mj

NB: Please Note that an FPP manufacturing site refers to the following:-

1. A manufacturing site refers to a specific block/s for Non-Biological and Non-sterile products.

2. A manufacturing site refers to a specific manufacturing line for Biological and sterile Products.

Conditions

1. Satisfactory GMP inspection as evidenced by a PPB cGMP certificate
2. Manufacturing license from the relevant drug regulatory authority.
3. The product is not sterile
4. Validation by the relevant validation protocol(s) at the new site
5. The product is not biological or immunological

Documentation

1. A cGMP from PPB for the manufacturing site
2. Validation protocol and validation report that has at least three validation batches
3. The variation application form should clearly outline the "present" and "proposed" FPP manufacturing site (s)
4. A copy/copies of approved (signed and dated) release and shelf-life specifications
5. Batch analysis data (in a comparative tabular format) for at least two pilot batches and one production batch from the new site and three production batches from the currently approved manufacturing site(s).
6. For liquid formulations (& semisolids) in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
7. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.
8. Information on API suppliers for the new or additional site and their respective DMFs. Must include information on the API manufacturer of the API lot used in the manufacture of bio batch.
9. Signed, Version numbered FPP and API manufacturer API specification from the new or additional sites.
10. Master Batch Record and executed batch record from both or new site.

11. Comparative stability data from current and proposed sites.
12. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.b.ii	Change to batch release arrangements and QC testing of the FPP			
A	Replacement or addition of a site where batch control/testing takes place	1 to 3	1,2,4	Mn
B	Replacement or addition o f a manufacturer responsible for batch release	1 to 3	1,2,4	Mn
	1. Not including batch control/testing	1,2	1 to 4	Mn
	2. Including batch control/testing	1 to 3	1 to 4	Mn
	3. Including batch control/testing for a biological/immunological product and one of the test methods performed at that site is a biological / immunological / immunochemical method.	1 to 3	1 to 4	Mj

Conditions

1. The site should be appropriately authorized; a relevant cGMP from PPB
2. The product is not biological/immunological
3. Method transfer including QC analytical should be completed

Documentation

1. Provide a copy of cGMP from PPB

2. The variation application form should clearly outline the “present” and “proposed” FPP manufacturing site (s)
3. A declaration by the Qualified Person (QP) responsible for batch certification stating that the API manufacturer(s) referred to in the marketing Authorization operates in compliance with international guidelines on GMP for starting materials.
4. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B2.b.iii	Change in the manufacturing process of the FPP			
A	Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions.	1 to 7	1, 3, 4, 6, 7, 8	Mn
B	Substantial changes in the manufacturing process that could significantly impact on the quality, safety and efficacy of the FPP	1 to 7	1, 3, 4, 6, 7, 8	Mj
C	The product is a biological/immunological product and the change require an assessment of comparability.	1 to 7	1, 3, 4,6, 7, 8	Mj
D	Introduction of a non-standard terminal sterilization method	1 to 7	1, 3, 4,5, 6, 7, 8	Mj
E	Introduction/ increase in the overage	1 to 7	1, 3, 4, 6, 7, 8	Mn
F	Minor change in the manufacturing process of an aqueous oral suspension.	1 to 7	1, 2, 4, 6, 7, 8	
G	Minor changes in the manufacturing process of a dry powder Inhaler or metered dose inhaler	1 to 7	1, 3, 4, 6, 7, 8	Mn
H	Major changes in the manufacturing process of a dry powder Inhaler or metered dose inhaler	1, 2, 4, 5,6,7	1, 3, 4, 6, 7, 8,9	Mj

Conditions

1. There should be no adverse change in qualitative and/or quantitative impurity profile or physicochemical properties.
2. The active substance is not a biological/immunological/herbal medicinal product
3. The manufacturing process remains unchanged
4. The currently registered manufacturing process is well controlled through IPQC tests without widening the IPQC test parameters
5. The FPP or intermediate specifications remain unchanged
6. The new process leads to an identical product regarding quality, efficacy, and safety
7. Relevant stability studies as per ICH requirements (for at least three production batches)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. For liquid formulations (& semisolids) in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
3. For Solid dosage forms comparative dissolution profiles in tabulated form between the currently approved and proposed process on at least three production batches
4. Justification for a BE study exemption
5. Validation data in case of a sterilization method change
6. A copy of the approved (dated and signed) FPP release and shelf-life specifications
7. Batch analysis data in comparative tabular format (between the proposed and the current)
8. Stability data on at least three batches
9. Validation data including in vitro tests on powder deposition, aerodynamic diameters/aerosol velocity for metered dose inhalers, etc.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.b.iv	Change in batch size/batch size ranges of FPP			
A	Up to 10-fold increase to the currently approved batch size	1 to 7	1,4	Mn
B	Reduction in batch size	1 to 6	1,4	Mn
C	The change relates to all other pharmaceutical complex manufacturing processes	1 to 6	1,4	Mj
D	Change requiring assessment of the comparability of a biological/immunological active substance.	1 to 6	1,4	Mj
E	Greater than 10-fold increase to the currently approved batch size	1 to 6	1 to 6	Mj
F	Decrease/increase in the scale for a biological/ immunological active substance without process change (e.g. line duplication).	1 to 6	1 to 6	Mn

Conditions

1. The change doesn't affect reproducibility
2. The change relates to standard immediate release dosage forms or non-sterile liquid dosage forms
3. Changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.
4. Reproducibility should be evidenced through validation of the manufacturing process (at least three production batches of the proposed batch size)
5. The product is not a biological/immunological product
6. The change should not be the result of deficiencies (unexpected events) arising during manufacture or because of stability concerns.
7. The currently approved batch size was not approved through a minor variation application

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch, manufactured to both the currently approved and the proposed sizes.
3. A commitment to providing batch data on the next two production batches.
4. A copy of the approved (dated and signed) release and shelf-life specifications of the FPP
5. Batch numbers (of tested batches) of the proposed batch sizes
6. Validation results (at least three batches)
7. Stability studies data (at least three production batches)

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B2.b.v	**Change to in-process tests or limits applied**			
A	Tightening of IPQC limits	1 to 4	1 ,2	AN
B	Addition of IPQC tests or limits	1,2,5,6	1 to 5,7	AN
C	Deletion of non-significant IPQC tests	1,2	1 ,2,6	AN
D	Widening of the approved IPQC test limits, which may have a significant effect on the overall quality of the FPP	1,2	1 ,2,6	Mj
E	Deletion of the approved IPQC test limits, which may have a significant effect on the overall quality of the FPP.	1,2	1 ,2,6	Mj
f	Addition or replacement/deletion of an IPQC test due to safety or quality concern	1,2	1 to 5,7	Mn

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during manufacture e.g. change in impurity profile, or total impurities.
3. The change should be within currently approved limits
4. The test procedure remains the same (or with insignificant changes)
5. The test procedure is not a novel method or an old method used in a non-standard way
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biologically active substance (Standard pharmacopoeial microbiological methods are exempt)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
2. Comparative data between the current and proposed test methods in a tabular format
3. Details of the new non-pharmacopeia method with validation protocol and data
4. Batch analysis data on three production batches of the FPP for all specifications parameters
5. Comparative dissolution profile data for the FPP on at least one pilot batch manufactured using the currently approved and new in-process tests while for herbal medicinal products, comparative disintegration data may be allowed.
6. Justification through risk assessment from MAH/Manufacturer showing that the test parameter is insignificant
7. Justification from MAH/manufacturer for the new IPQC tests and/or limits

B2.c Control of Excipients

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.c.i	**Change in the specification parameters and/or limits of the excipients**			
A	Tightening of specification limits	1,2,3,4	1,2	AN
B	Addition of specification parameters with accompanying test method(s)	1,2,5,6,7	1, 2, 3, 4, 6, 8	AN
C	Deletion of a non-significant specification parameter	1,2	1,2,7	AN
D	Change outside the approved specification limits	1,2	1,2,7	Mn
E	Deletion of a specification which may have impact on product quality	1,2	1,2,7	Mj
F	Addition/Replacement of a test parameter (excludes biological/immunological product) due to safety or quality concern	1,2	1, 2, 3, 4, 5, 6, 8	Mn
G	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	1	2	AN

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during the manufacture of the packaging or storage of the API.
3. Any change should be within the currently approved packaging specification limits
4. The test procedure is unchanged (minor changes to the procedure could be exempted but need approval in addition)
5. The test procedure is not a novel method or an old method used in a non-standard way

6. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent (standard pharmacopoeial microbiological methods are exempt)
7. The change does not involve a genotoxic impurity

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
2. Comparison of the currently approved and the proposed specifications in tabular format
3. New analytical method details and validation data
4. Batch analysis data (of three batches) of the formulation containing the excipient on all specification parameters
5. Comparative dissolution profile data for the FPP of the formulation containing the excipient with currently approved and proposed specifications while for herbal medicinal products, comparative disintegration data may be allowed.
6. Justification for not providing BE studies data
7. Justification (through risk assessment) that a specification parameter is not significant
8. Justification of new specification parameter(s) and/or limits

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B2.c.ii	**Change in test procedure for API or starting material/reagent/intermediate used in the manufacture of the FPP**			
A	Minor changes to already approved test procedure	1 to 4	1,2	Mn
B	Deletion of a test procedure when an alternative test procedure is approved	5	1	Mn

C	Change to a biological/immunological/immunochemical test or a method using a biological test reagent	5	1	Mj
D	Other changes to a test procedure for starting material/ reagent/Intermediate	5	1,2	Mn

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and the currently approved method.
2. There are no changes in total impurities and no new (unqualified) impurities
3. The analytical method should essentially remain the same with minor changes, such as changes in column length and not column type for HPLC methods.
4. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biologically active substance (Standard pharmacopeia microbiological methods are exempt)
5. An alternative test procedure is already approved (should not have been approved through a minor variation)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data evidencing equivalence between the currently approved and proposed test methods in a tabular format (this is not a requirement in case of addition of a test method)

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**

B2.c.iii	Change in source of an excipient or reagent with TSE risk			
A	Change from a TSE risk material to a vegetable or synthetic source			
	Excipients used in the manufacture of a biological or immunological active substance or used in the manufacture of a biological/immunological product	1	1	Mn
	Excipients NOT used in the manufacture of a biological or immunological active substance or used in the manufacture of a biological/immunological product	1	1,2	Mn
B	Change or addition of a TSE risk material, without a CEP	1	1,2	Mj

Condition

The FPP release and shelf-life specifications remain unchanged

Documentation

1. Declaration from the manufacturer or the marketing Authorization holder of the material that it is purely of vegetable or synthetic origin.
2. Comparative data evidencing equivalence between the currently approved and proposed material e.g. dissolution data of the FPP made of the currently approved and proposed material.

VarT No.	**Description of change**	**Condition (s)**	**Documentation**	**Variation type**
B2.c.iv	**Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier)**			
A	Minor change in synthesis or recovery of a non-pharmacopoeial excipient	1,2	1 to 4	Mn

B	The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished product.	1,2	1 to 4	Mj
C	The excipient is a biological/immunological substance	1,2	1 to 4	Mj

Conditions

1. The synthetic routes are identical and there are no changes in total impurities and no new (unqualified) impurities
2. Adjuvants are excluded

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Batch analysis data (of three batches) of the formulation containing the excipient manufactured according to the old and proposed process
3. Comparative dissolution profile data for the FPP of the formulation containing the excipient with currently approved and proposed specifications while for herbal medicinal products, comparative disintegration data may be allowed.
4. Copy of the approved and proposed excipient specifications

B2.d Control of FPP

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.d.i	**Change in the specification parameters and/or limits of the FPP**			
A	Tightening of specification limits	1 to 4	1,2	AN
B	Introduction of a new specification parameter with an accompanying test method	1, 2, 5, 6,7	1, 2, 3, 4, 7	Mn

C	Deletion of a non-significant specification parameter (e.g. an obsolete parameter)	1,2	1,2,6	AN
D	Change in the specification parameter limits outside the approved specification limits range	1,2,4,5,7	1,2,3,4,5,6,7	IN
E	Deletion of a specification parameter which could impact significantly on the quality of the API and/or the FPP	1,2	1,2,6	Mj
F	Addition or replacement of a specification parameter due to safety or quality concern (excludes biological/ immunological substance)	1,2	1,2,6	Mj
G	Change in the standard claimed for the FPP from an in-house to an officially recognized standard	8-10	8-13	AN
H	Update to the specifications to comply with an officially recognized pharmacopoeia monographs as a result of an update to this monograph to which the FPP is controlled	None	8, 10, 13	AN

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during manufacture e.g. changes in impurity profile, or total impurities.
3. The change should be within currently approved limits
4. The test procedure remains the same (or with insignificant changes)
5. The test procedure is not a novel method or an old method used in a non-standardard way
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biologically active

substance (Standard pharmacopoeial microbiological methods are exempt)

7. The change does not concern a genotoxic impurity
8. The change is made exclusively to comply with the officially recognized pharmacopeia.
9. No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test).
10. No deletion of or relaxation of any of the tests, analytical procedures, or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 37a or 37d and should follow the corresponding reporting types.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
2. Comparative current and proposed specifications in tabular format
3. Details of the new non-pharmacopeia method with validation protocol and data
4. Batch analysis data on two production batches (three for biologicals) of the API for all specifications parameters
5. Comparative dissolution profile, where applicable, of the FPP of at least one pilot batch with the current and proposed API specifications.
6. For herbal products, comparative disintegration data is to be provided.
7. Justification through risk assessment showing that the test parameter is insignificant
8. Justification from MAH/APIMF holder for the new IPQC tests and/or limits
9. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
10. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial

11. pharmacopoeial methods.
12. (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented.
13. (P.5.6) Justification for the proposed FPP specifications.

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B2.d.ii	**Change in test procedure for FPP**			
A	Minor changes to already approved test Procedure	1 to 4	1,2	Mn
B	Deletion of a test procedure when an alternative test procedure is approved	4	1	AN
D	Change to a biological/immunological/ immunochemical test or a method using a biological test reagent	4	1	Mj
E	Other changes to a test procedure (including replacement of an analytical procedure)	4	1,2	Mn
F	Updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph	None	1-2	AN
G	Change from an in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeial monograph or from one officially recognized pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph	1-2	1-2	IN

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and the currently approved method.

2. There are no changes in total impurities and no new (unqualified) impurities
3. The analytical method should essentially remain the same with minor changes, such as changes in column length and not column type for HPLC methods.
4. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biologically active substance (Standard pharmacopeia microbiological methods are exempt)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data between the current and proposed test methods in a tabular format (this is not a requirement in case of the addition of a test method)

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.d.iii	**Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving**			
A	Changes in imprints, embossing or other markings	1 to 3	1,2, 5-6	IN
B	Deletion of a scoreline	2-5	1, 5-6	IN
D	Addition of a scoreline	2-4	1,3, 5-6	Mn
E	Addition of Ink	None	1,2, 4-6	Mj

Conditions

1. Any ink complies with section 3.2.P.4 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.

2. The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP.
3. Changes to the FPP specifications are those necessitated only by the change to the appearance or the scoring.
4. The addition or deletion of a score line from a generic product is consistent with a similar change in the comparator product or was requested by PPB
5. The scoring is not intended to divide the FPP into equal doses

Documentation required

1. Sample of the FPP.
2. (P.1.) Qualitative composition of the ink, if purchased as a mixture.
3. (P.2) Demonstration of the uniformity of the dosage units of the tablet portions, where the scoring is intended to divide the FPP into equal doses
4. (P.2.) Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified, or prolonged release products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

B2.e Container closure system

VarT No.	Description of change	Condition (s)	Documentation	Variation type
B2.e.i	**Change in the primary packaging of the FPP**			
A	Composition (qualitative and quantitative)			
	1. Solid dosage forms	1,2,3	1,2,3,4,6	IN
	2. Liquid & semi-solid	1,2,3	1,2,3,5,6	Mn
	3. Sterile and Biological/immunological products	1,2,3	1,2,3,5,6	Mj

	4. Change to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	1,2,3	1,2,3,5,6	Mj
B	Type of container			
	1. Solid dosage, Liquid & semi-solid formulations	1,2,3	1,2,3,5,6,7	Mn
	2. Sterile/Biological/immunological products	1,2,3	1,2,3,5,6,7	Mj

Conditions

1. The change concerns the same packaging
2. The proposed packaging material is equivalent to the currently approved material
3. Relevant stability studies under ICH conditions, evaluating all relevant test parameters (on at least three production scale batches).

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data (e.g. permeability data on O2, CO2, moisture) between the current and proposed packaging in a tabular format
3. Where appropriate, provide proof of no interaction between the packaging and the FPP
4. A declaration that the stability studies have been appropriately carried out
5. Stability data
6. Comparison (in tabular format) of the current and proposed packaging specifications
7. Samples of the new container closure system, where applicable.

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**

B2.e.ii	**Change in the specification parameters and/or limits of the primary packaging of the FPP**			
A	Tightening of specification limits	1,2,3,4	1,2	AN
B	Addition of specification parameters with accompanying test method(s)	1,2,5	1,2,3,4,6	AN
C	Deletion of a non-significant specification parameter	1,2	1,2,5	AN
D	Addition/Replacement of a test parameter due to safety or quality concern	1,2	1,2,3,4,6	Mn

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during the manufacture of the packaging or storage of the API.
3. Any change should be within the currently approved packaging specification limits
4. The test procedure is unchanged (minor changes to the procedure could be exempted but need approval in addition)
5. The test procedure is not a novel method or an old method used in a non-standard way

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
2. Comparison of the currently approved and the proposed specifications in tabular format
3. New analytical method details and validation data

4. Batch analysis data (of three batches) between the currently approved and proposed primary packaging for all specification parameters
5. Justification (through risk assessment) from MAH or APIMF holder that a specification parameter is not significant
6. Justification of the new specification parameter(s) and/or limits

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.e.iii	**Change in test procedure for the Primary packaging of the FPP**			
A	Minor changes to already approved test procedure	1 to 3	1,2	AN
B	Other changes to a test procedure (including Addition/deletion)	1,3,4	1,2	AN
C	Deletion of a test procedure (if there is an already approved test method)	5	1	AN

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and the currently approved method.
2. The analytical method should essentially remain the same with minor changes, such as a change in column length and not column type for HPLC methods.
3. The test procedure is not a novel method or an old method used in a non-standard way
4. The active substance is not biological or immunological
5. An alternative test procedure is already approved (should not have been approved through a minor variation)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative validation data between the current and proposed test methods in a tabular format (this is not a requirement in case of the addition of a test method)

VarT No.	**Description of change**	**Condition (s)**	**Documentation**	**Variation type**
B2.e.iv	**Change in shape or dimensions of the Primary packaging**			
A	Non-sterile products	1 to 3	1,2,4	AN
B	The change in shape/dimensions concerns a critical part of the packaging material which may significantly affect the delivery, use, safety or stability of the FPP	1 to 3	1,2,4	Mn
C	Sterile products	1 to 3	1 to 4	Mn

Conditions

1. There is no change in the qualitative or quantitative composition of the packaging
2. The change does not affect a critical part of the packaging material which may significantly impact the delivery, use, safety, or stability of the FPP
3. Stability studies as per ICH in case of change of head space or change in the surface-volume ratio of the packaging

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Samples
3. Revalidation data for terminally sterilized products

4. Stability data as per ICH in case of a change of head space or change in the surface-volume ratio of the packaging.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.e.v	**Change in pack size of the finished product**			
A	Change in the number of units (e.g. tablets, ampoules, etc.) in a pack	1,2	1,3	IN
	1. Change within the range of the currently approved pack sizes	1,2	1,2,3	IN
	2. Change outside the range of the currently approved pack sizes	3	1,2	IN
B	Deletion of a pack size	3	1,2	AN
C	Change in the fill weight/volume of sterile (multidose/single-dose, partial use) parenteral and biological/ immunological multidose parenteral FPPs. ***NB: any changes to the 'strength' of the FPP would require the submission as a new CTD application.***	3	1,2	Mj
D	Change in the fill weight/volume of non-parenteral multi-dose, single-dose, partial use FPPs ***NB: any changes to the 'strength' of the FPP would require the submission as a new CTD application.***	3	1,2,3	Mn

Conditions

1. The proposed pack size should be consistent with the posology and treatment duration as stated in SmPC
2. The primary packaging material remains the same
3. The remaining product presentation(s)/pack sizes must be adequate for the dosing instructions and treatment duration as mentioned in the SmPC

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Justification of the proposed pack sizes in relation to treatment instructions and treatment duration
3. Stability data as per ICH in case of change of head space or change in the surface-volume ratio of the packaging
4. Process validation

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.e.vi	**Change in any part of the (primary) packaging material not in contact with the FPP formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)**			
A	Change that affects product information	1,2	1,2	Mn
B	Change that doesn't affect product information	1	1,2	Mn

Conditions

1. The change doesn't affect a part concerned with product delivery, stability, or safety
2. That critical product information is not omitted because of the proposed change

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM
2. Samples or colored artworks

VarT No.	Description of change	Condition (s)	Documentation	Variation type

B2.e.vii	**Change in the primary packaging of the FPP**			
A	Composition (qualitative and quantitative)			
	1. Solid dosage forms	2,3	1,2,3,4,6	Mn
	2. Liquid & semi-solid formulations	2,3	1,2,3,5,6	Mn
	3. Sterile and Biological/immunological products	1,2,3	1,2,3,5,6	Mj
	4. Change to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	2,3	1,2,3,5,6	Mj
B	Type of container			
	1. Solid dosage, Liquid & semi-solid formulations	2,3	1,2,3,5,6,7	Mn
	2. Sterile/Biological/ Immunological products	2,3	1,2,3,5,6,7	Mj

Conditions

1. The change concerns the same packaging
2. The proposed packaging material is equivalent to the currently approved material
3. Relevant stability studies under ICH conditions, evaluating all relevant test parameters (on at least three production scale batches)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative data (e.g. permeability data on O2, CO2, moisture) between the current and proposed packaging in a tabular format
3. Where appropriate, provide proof of no interaction between the packaging and the FPP
4. A declaration that the stability studies have been appropriately carried out

5. Stability data
6. Comparison (in tabular format) of the current and proposed packaging specifications
7. Samples of the new container closure system, where applicable.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.e. viii	**Change in any part of the (secondary pack) packaging material of the FPP (including dimensions, colour, manufacturing address etc)**			
A	Change that affects product information	1,2	1,2,3	Mn
B	Change that doesn't affect product information	1	1,2,3	Mn/IN

Condition

That critical product information is not omitted because of the proposed change

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC. COMPENDIUM format
2. Samples or colored artworks
3. Information in a tabular format indicating the current and proposed.

VarT No.	Description of change	Condition (s)	Documentation	Variation type
B2.e. xi	**Additional primary packaging of the FPP**			
A	Composition (qualitative and quantitative)			
	1. Solid dosage forms	2,3	1,2,3,4,6	Mn
	2. Liquid & semi-solid formulations	2,3	1,2,3,5,6	Mn
	3. Sterile and Biological/immunological products	1,2,3	1,2,3,5,6	Mj

	4. Change to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	1,2,3	1,2,3,5,6	Mj
B	Type of container			
	1. Solid dosage, Liquid & semi-solid formulations	2,3	1,2,3,5,6,7	Mn
	2. Sterile/Biological/immunological products	1,2,3	1,2,3,5,6,7	Mj
C	**Deletion/withdrawal of a primary packaging of the FPP**		1,2,3	**IN**

Conditions

1. The change concerns the same packaging
2. The proposed packaging material is equivalent to the currently approved material
3. Relevant stability studies under ICH conditions, evaluating all relevant test parameters (on at least three production scale batches)

Documentation

1. Application for deletion/withdrawal of the product with the particular container closure system
2. Comparison (in tabular format) of the current and proposed container closure systems
3. Justification for deletion/withdrawal

B2.f FPP Stability

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.f.i	**Change in shelf life or storage conditions of the FPP**			
A	**Shelf life Reduction**			
	1. As packaged for sale	1	1 to 4	IN
	2. After first opening	1	1 to 4	IN

	3. After dilution/reconstitution	1	1 to 4	IN
B	**Increase in Shelf life**			
	1. As packaged for sale	1	1 to 4	Mn
	2. After first opening	1	1 to 4	Mn
	3. After dilution/reconstitution	1	1 to 4	Mn
	4. Increase in storage period of a biological/ immunological medicinal product	1	1 to 4	Mj
C	**Storage Conditions**			
	1. Change in storage conditions of biological/ immunological active when the stability studies have not been performed according to a currently approved stability protocol	1	1 to 4	Mn
	2. Change in storage conditions of the FPP as packaged for sale or a diluted/reconstituted product	1	1 to 4	Mn

Condition

The change is not due to unexpected events during manufacture or stability concerns.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Stability data showing stability studies were done according to the approved protocol meeting all the test specifications
3. Revised product information
4. A copy of the approved (signed and dated) specifications

B2.g FPP design space/facilities

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.g.i	**Introduction of a new design space or extension of an approved design space for the finished product, excluding biologicals**			
A	Description of the design space in tabular format		1,2	Mj

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM Format
2. Provision of cGMP from PPB

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.g.ii	**Introduction of a new design space or extension of an approved design space for sterile finished product (biologicals)**			
A	Site where any manufacturing operation(s) take place, EXCEPT batch release, batch control, and secondary packaging	1 to 2	1 to 7	Mj
B	Site where batch release, batch control, and secondary packaging	1 to 2	1, 3 to 5	Mn
C	Change in design space that is not critical		1, 6	IN

Conditions

1. Satisfactory GMP inspection as evidenced by a PPB cGMP certificate
2. Manufacturing license from the relevant drug regulatory authority.
3. Validation by the relevant validation protocol(s) for the new line

Documentation

1. A cGMP from PPB for the manufacturing site
2. Validation protocol and validation report that has at least three validation batches for the new line
3. The variation application form should clearly outline the "present" and "proposed" FPP manufacturing lines (s)
4. A copy/copies of approved (signed and dated) release and shelf-life specifications
5. Batch analysis data (in a comparative tabular format) for at least two pilot batches and one production batch from the new line and three production batches from the currently approved manufacturing line(s).
6. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
7. Media fill simulation studies (study protocol/s and reports).

B2.h FPP Contract Manufacturing

VarT No.	Description of change	Condition (s)	Documentation	Variation type
B2.h.i	**Change in the contract manufacturer**			
A	Change in the name of the contract manufacturer but physical address of the manufacturing site(s) remains the same		1,2	Mn
B	Deletion/Replacement of a contract manufacturer		1,2	Mn
	NB: All other rules in this guideline apply, particularly B2.b			

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Legal (Notarized) contractual agreement between the contract giver (MAH) and the Contract acceptor (manufacturer).

B2.i FPP Change in equipment

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B2.i.i	**Change in equipment**			
A	Change in equipment model		1,2	Mj
B	Change in equipment size		1	mj

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM Format
2. Provision of manufacturing process validation and equipment qualification
3. Provision of revised master BMR and at least three executed BMRs

B3.a Updates to monographs

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B3.a.i	**Change to comply with PPB recognized Pharmacopoeias**			
A	Change of specification(s) of a former non Pharmacopeial substance to comply with a PPB recognized pharmacopoeia			Mn
	1. API	1 to 5	1 to 5	Mn
	2. Excipient	1,2,4	1 to 5	Mn
B	Monograph update	1,2,4,5	1 to 4	Mn
C	Change in specifications from In-house to pharmacopoeia	1,4,5	1 to 4	Mn

Conditions

1. The change is made only to comply with a pharmacopeia

2. Product-specific parameters e.g. particle size, and polymorphic form (additional to Pharmacopeia specifications) are unchanged and are as per the application dossier
3. The impurities profile (qualitative and quantitative) remains the same unless tightening of the limits of the specifications
4. Additional Validation may be required
5. For herbal active substances, the manufacturing route, physical form, extraction solvent, and drug extract ratio should remain unchanged.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative current and proposed specifications in tabular format
3. Batch analysis data on two production batches (three for biologicals) of the FPP for all specifications parameters
4. Data evidencing the suitability of the monograph in controlling API impurities (potential impurities)

B3.b CEP and TSE

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B3.b.i	**New or updated Ph. Eur. Certificate of suitability (CEP) submission for: An active ingredient/substance A starting material/reagent/ intermediate used in the manufacture of the active ingredient/substance An excipient**			
A	**CEP to the relevant Ph. Eur. Monograph**			
	1. New CEP from an already approved manufacturer	1 to 5, 8	1 to 6	Mn
	2. Updated CEP from already approved manufacturer	1 to 4, 8	1 to 6	IN

	3. New CEP from a new manufacturer (Addition or replacement)	1 to 5, 8	1 to 6	Mn
B	**Ph. Eur. TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient**			
	New TSE cert. for an active substance from a new or an already approved manufacturer	3, 6	1 to 6	Mn
	New TSE cert. for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	3, 6	1 to 6	Mn
	Updated TSE cert. from an already approved manufacturer	7	1 to 6	IN

Conditions

1. The finished product release and end-of-shelf life specifications remain the same.
2. Additional specifications (to Ph. Eur.) for impurities (excluding residual solvents, provided they comply with ICH/VICH) and product-specific requirements e.g. Particle size profiles, polymorphic form, if applicable.
3. The manufacturing process of the API (active substance), starting material, reagent, or intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. The API or active substance will be tested immediately before use if no retest period is included in the CEP or if data to support a retest period is not already provided in the dossier.
5. The active substance, starting material, reagent, intermediate, or excipient is not sterile.
6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE.

7. For veterinary medicines: there has been no change in the source of material
8. For herbal active substances: the manufacturing route, physical form, extraction solvent, and drug extract ratio should remain the same.

Documentation

1. A copy of the updated CEP
2. In case of an addition of a manufacturing site, the variation application form should clearly outline the “present” and “proposed” manufacturers in a tabular format.
3. Amendment of the dossier's relevant section(s) is presented in the EAC COMPENDIUM Format.
4. Where applicable, provide information on materials with a risk of TSE/BSE including those used in the manufacture of API (active substance) or excipient. The following information should be included for each such material: Name of manufacturer, species, and tissues from which the material is a derivative, country of origin of the source animals, and its use.
5. Declaration by the Qualified Person (QP) for the active substance batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with good manufacturing practices for starting materials. The manufacture of intermediates also requires a QP declaration. As far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the currently listed manufacturing sites.
6. Comparative current and proposed specifications in tabular format

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B3.b.ii	**New or updated WHO APICPQ submission for an active ingredient/substance**			

A	**New Confirmation of WHO API**			
	1. Updated WHO APICPQ from an already approved manufacturer	1 to 3	1-3, 5	AN
	2. New WHO APICPQ from an already approved manufacturer	1 to 2	1-5	Mn
B	New WHO APICPQ from a new manufacturer	1 to 3	1-3, 5	IN
	New WHO APICPQ from a new manufacturer (Addition or replacement)	1 to 2	1 -3, 5, 6	Mn

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. For low solubility APIs, the API polymorph is the same, and whenever particle size is distributed, compared to the API lot used in the preparation of the bio batch. Including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied.
3. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications

Documentation required

1. Copy of the current (updated) confirmation of the API-PQ document. The API manufacturer should duly fill out the authorization box with the name of the applicant or FPP manufacturer seeking to use the document.
2. A written commitment that the applicant will inform PPB if the APICPQ is withdrawn or canceled.
3. Replacement of the relevant pages of the dossier with the revised information

4. For sterile APIs, data on the sterilization process of the API, including validation data.
5. Copy of FPP manufacturer's revised API specifications.
6. If the quality of the API is changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of the FPP of at least pilot-scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to PPB.

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B3.b.iii	**New or updated EAC APIMF submission for an active ingredient/substance**			
A	**New Confirmation of EAC APIMF**			
	1. New EAC APIMF from an already approved manufacturer	1 to 3	1-3, 5	IN
	2. New EAC APIMF from an already approved manufacturer	1 to 2	1-5	Mn
	3. Updated EAC APIMF from already approved manufacturer	1 to 3	1-3, 5	AN
B	New EAC APIMF from a new manufacturer (Addition or replacement)	1 to 2	1 -3, 5, 6	Mn

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. For low solubility APIs, the API polymorph is the same, and whenever particle size is distributed, compared to the API lot used in the preparation of the bio batch. Including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied.
3. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications

Documentation required

1. Copy of the current (updated) confirmation of the EAC APIMF document. The API manufacturer should duly fill out the authorization box with the name of the applicant or FPP manufacturer seeking to use the document.
2. A written commitment that the applicant will inform PPB if the EAC APIMF is withdrawn or canceled.
3. Replacement of the relevant pages of the dossier with the revised information
4. For sterile APIs, data on the sterilization process of the API, including validation data.
5. Copy of FPP manufacturer's revised API specifications.
6. If the quality of the API is changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of the FPP of at least pilot-scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to PPB.

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B3.C.i	**Variation to a WHO prequalified product**	None		

Documentation required

1. Cover letter with a summary of the changes
2. WHO PQ approval letter
3. Copy of FPP manufacturer's FPP release and shelf-life specifications.
4. Replacement of all the relevant pages of the dossier with the revised information

B4.a Measuring/Administration devices

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B4.a.i	**Change of a measuring or administration device**			
A	**Addition or replacement of a device which is not an integrated part of the primary packaging**			
	1. Device with CE marking	1,2,3	1,2,4	Mn
	2. Device without CE marking (**VET only**)	1,2,3	1,3,4	Mn
	3. Spacer for Metered dose inhalers	1,2,3	1,3,4	Mj
B	**Deletion of a device**	4,5	1,5	Mn
C	**Addition or replacement of a device which is an integrated part of the primary packaging NB:** any change which results in a "new pharmaceutical form" requires the submission of a new CTD application	4,5	1,5	Mj

Conditions

1. The proposed measuring device must accurately deliver the required dose for the product concerned as per the approved posology (the results of such studies should be provided).
2. The proposed device should be compatible with the product.
3. The change should not necessitate significant revision of product information
4. The product can be accurately delivered without the use of a device
5. The device is not crucial for the safety of the person administering the product (VET products)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Evidence of CE marking
3. Data to evidence accuracy, precision, and compatibility of the device
4. Sample
5. Justification for deletion

B.5. Changes to a marketing Authorization resulting from other regulatory procedures

B.5.a) Plasma Master File (PMF) or Technical Master File (TMF)/Vaccine Master file (VAMF)

VarT No.	Description of change	Condition(s)	Documentation	Variation type
B5.a.i	**Inclusion of a new, updated or amended PMF/TMF in the product dossier (Technical document) of a plasma derived medicinal product.**			
A	Submission of a new PMF/TMF affecting the properties of the final blood product		1 to 6	Mj
B	Submission of a new PMF/TMF not affecting the properties of the final blood product		1 to 6	Mn
C	Submission of an updated/amended PMF/TMF when changes affect the properties of the final blood product	1,2,3	1 to 6	Mn
D	Submission of an updated/amended PMF/TMF when changes do not affect the properties of the final blood product	1,2,3	1 to 6	IN

NB: Please note that the technical master file (TMF) as per PPB definition may include Active Blood Component/Derivatives i.e. Whole blood, Blood

components, and plasma derivatives. The TMF as per PPB guidelines is part of the Technical document (Product dossier).

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during manufacture.
3. The updated or amended PMF has been granted a certificate of compliance from a stringent Regulatory Authority or the Pharmacy and Poisons Board.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD format
2. Comparative information between the current and proposed changes in a tabular format
3. A declaration that the submitted PMF (TMF) is for the proposed final blood product.
4. PMF or TMF certificate and evaluation report
5. An expert statement outlining all the changes introduced with the certified PMF/TMF evaluating their potential impact on the final blood product.
6. The PMF/TMF should include related dossiers (final blood products)

VarT No.	**Description of change**	**Condition(s)**	**Documentation**	**Variation type**
B5.a.ii	**Inclusion of a new, updated or amended PMF/TMF in the product dossier (Technical document) of a plasma derived medicinal product.**			
A	Submission of a new PMF/TMF affecting the properties of the final blood product		1 to 6	Mj

B	Submission of a new PMF/TMF not affecting the properties of the final blood product		1 to 6	Mn
C	Submission of an updated/amended PMF/TMF when changes affect the properties of the final blood product	1,2,3	1 to 6	Mn
D	Submission of an updated/amended PMF/TMF when changes do not affect the properties of the final blood product	1,2,3	1 to 6	IN

NB: Please note that the technical master file (TMF) as per PPB definition may include Active Blood Component/Derivatives i.e. Whole blood, Blood components, and plasma derivatives. The TMF as per PPB guidelines is part of the Technical document (Product dossier).

Conditions

1. The change is not resulting from any commitment from previous assessments meant to review specification limits (e.g. New MAH application).
2. The change is not due to unexpected events during manufacture.
3. The updated or amended PMF has been granted a certificate of compliance from a stringent Regulatory Authority or the Pharmacy and Poisons Board.

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
2. Comparative information between the current and proposed changes in a tabular format
3. A declaration that the submitted PMF (TMF) is for the proposed final blood product.

4. PMF or TMF certificate and evaluation report
5. An expert statement outlining all the changes introduced with the certified PMF/TMF evaluating their potential impact on the final blood product.
6. The PMF/TMF should include related dossiers (final blood products)

B SAFETY/EFFICACY/PV UPDATES

Human products

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C1.a.i	**Change in the SmPC, Labelling or PIL of the innovator**			Mj

Documentation

Revised product information

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C1.a.ii	**Change in the SmPC, Labelling or PIL of a generic/hybrid/biosimilar product following assessment of the same change for the reference product.**			
A	Implementation of change(s) for which no new additional data are submitted by the MAH		1	IN
B	Implementation of change(s) for which new. additional data are submitted by the MAH	1	1,2	Mj

Conditions

Equivalence between the innovator and the proposed product

Documentation

1. Revised product information
2. Equivalence data

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C1.a.iii	**Change requested by PPB**			
A	Implementation of agreed wording for which no new additional data are submitted by the MAH		1	Mn
B	Implementation of change(s) for which new additional data are submitted by the MAH	1	1,2	Mj

Documentation

Revised product information Data

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C1.a.iv	**Variations related to significant modifications of the SmPC due to new quality, pre-clinical, clinical or pharmacovigilance data**			Mj

Documentation

Revised product information Data

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C1.a. v	**Variations related to change in drug scheduling (legal) status**			
A	For generic/hybrid/biosimilar products following an approved legal status change of the reference (innovator) product		1,2	Mn
B	Any other legal status change		1,2	Mj

Documentation

1. Proposed legal status
2. Revised product information

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C1.a.vi	**Change(s) to therapeutic indication(s)**			
A	Addition of a new therapeutic indication or modification of an approved one NB: C.I.a.i and C.I.a.ii apply, for innovator and generic products, respectively.		1,2,3	Mn
B	Deletion of a therapeutic indication		1,2,3	Mj

Documentation

1. Proposed legal status
2. Revised product information Data

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C1.a.vii	**Deletion (termination of a dosage form or strength)**			
A	Deletion of a dosage form		1,2	Mn
B	Deletion of a strength		1,2	Mj

Documentation

1. A declaration that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as mentioned in the SmPC
2. Revised product information
3.

VarT No.	Description of change	Condition(s)	Documentation	Variation type
C2.a.vi	**Periodic Safety Update Reports (PSURS)**		1,2	N

Documentation

1. Data (for review by DPER before submission to PV directorate by applicants)
2. Revised product information, if relevant.

Variation application Numbering

A variation of application numbering with the following format is to be included in all applications as part of the PRIMS system. The number shall be automatically generated once the application has been done (upon payment of the requisite regulatory fee). Introduction of Variation application Number with the following format: VAR: Year (4 digits): serial Number (5 digits) e.g. VAR-2021-00100 to allow for tracking of single variations or grouped variations.

Variations can be grouped based on the following:-

1. Application at the same time and/or
2. Affecting related dossiers (CTDs) e.g. variations on change in LTR, change in MAH, change in API specifications, change in labeling affecting many products, and change in the manufacturing site.

Contributors and Reviewers

Contributors:

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REVISION HISTORY

Change	Description of change	Date
A2	Correction of a typographical error in the Description "Change in the (invented) name of the medicinal product" by including "…name of the…" in the text "Change in the (invented) medicinal product" under variation code: Change in the (invented) name of the medicinal product.	August 2021
A4	Revision of the text of the variation code "Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the API, starting material, reagent or intermediate used in the manufacture of the API (where specified in the product dossier) where no EU CEP, WHO APICPQ or EAC APIMF is part of the approved dossier in the name of the API" by including exception of WHO APICPQ and EAC APIMF. Additionally, documentation text for No.3 has been revised to "An updated letter of access, in case of change in the name of the holder of the APIMF".	August 2021
B1.a.iii	Inclusion of documentation requirement "Stability data- Provide a commitment to place one batch per year on stability for the proposed batch size. Any OOS or atypical trend to be immediately reported to the Pharmacy and Poisons." Under variation code "B1.a.iii: Change in batch size/batch size ranges of API or intermediate"	August 2021
B2.g.ii	Inclusion of "Introduction of a new design space or extension of an approved design space for sterile finished product (biologicals)" variation code	August 2021

B3.b	Correction of a typographical error in the title “B3. b CEP/TSE & WHO APICPQ & WHO FPP CPQ” by deleting WHO FPP CPQ	August 2021
B3.b.ii	Updated “New or updated WHO APICPQ submission for an active ingredient/substance”	August 2021
B3.b.iii	Inclusion of a new code “New or updated EAC APIMF submission for an active ingredient/substance”	August 2021
B3.C.i	Variation to a WHO prequalified product	August 2021
C2.a.vi	Inclusion of “Periodic Safety Update Reports (PSURS)	August 2021
B2.b.i	Replacement or addition of a manufacturing site for part or all of the manufacturing processes of the FPP: Inclusion of additional documentation	August 2021
B2.a.iii	Changes in the Excipients Composition: Inclusion of Reference to Reference to the SUPAC-IR: Immediate-Release Solid Oral Dosage Forms guidelines with regard to change in excipients	August 2021
Variation application Numbering	Introduction of Variation application Number with the following format: VAR: Year (4 digits): serial Number (5 digits) e.g. VAR-2021-00100 to allow for tracking of single variations or grouped variations applied at one time	August 2021
Corrections of typo errors on classification of variations	A, B & C parts of the Guideline and Abbreviations section	January 2022
New variation codes introduced	Variations codes introduced A7ii-iii, B1.b.iii, B1.b.iv, B2.c.i.G, B2.d.ii.F-G and B2.d.iii	January 2022
Definitions	Further information on Immediate (IN) and Annual notification (AN), provided.	January 2022
Version no. 3	Updated from Rev. No. 2 to Revision 3	August 2022

Timelines for Evaluations of applications for Variations	Referred applicants to the service charter with respect to timelines for processing variation application	August 2022
Version 4	Updated from Rev. No. 3 to Revision 4	January 2024
Title	Change of term in the title from Human products to Medicines	January 2024
Definitions	Inclusion of requirement for prior approval in the definition of major variation	January 2024
Scope	Updated to specify that vaccines and biologicals not part of the guideline	January 2024
Payment and Mode of payment	Updated to indicate reference to service charter for fees applicable to variations.	January 2024
Timelines for evaluation.	Warning on misclassification of variations provided and notice on number of cycles of review provided.	January 2024
Reliance	Updated to include mechanisms on reliance in handling variations	January 2024

Key Reference Documents

1. World Health Organization (WHO) Guidance on variations to a prequalified product dossier.

2. EMA Guideline on dossier requirements for Type IA and IB notifications Health Canada Post-Notice of Compliance (NOC) Changes - Quality Guidance Appendix 1 for Human Pharmaceuticals.

3. SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation NOVEMBER 1995

ANNEXES

ANNEX 1: APPLICATION FOR SUBMISSION OF VARIATION

REPUBLIC OF KENYA

PHARMACY AND POISONS BOARD

APPLICATION FOR VARIATION TO A REGISTERED PHARMACEUTICAL PRODUCTS

(Please complete each section of this application form electronically as a word document AND as a scanned signed PDF file. To be submitted as one original hard copy and one electronic copy (in Ms –Word and PDF version on a CD-ROM)

CONFIDENTIAL
(Effective from January 2022)

Application Number (VAR No.)		
Date of submission of the dossier		
Name of the 1st Evaluator		Signature
Name of the 2nd Evaluator		Signature
Date of 1st evaluation		
Date of 2nd Evaluation		
Number of files received		
CONCLUSION OF THE ASSESSMENT **APPROVED** *(no outstanding issues)* **QUERY RAISED** *(Indicate the sections where query is raised)*		

REJECTED *(indicate the sec(s) that led to the rejection)* ***(Please delete which does not apply)***	

Annex 1. Applicant Form for Variation details

REPUBLIC OF KENYA

PHARMACY AND POISONS BOARD

APPLICATION FOR VARIATION TO A REGISTERED PHARMACEUTICAL PRODUCTS

(Please complete each section of this application form electronically as a word document AND as a scanned signed PDF file. To be submitted as one original hard copy and one electronic copy (in Ms –Word and PDF version on a CD-ROM)

CONFIDENTIAL
(Effective from 13th Jan 2022)

THE REGISTRAR
PPB OFFICES,
LENANA ROAD,
DRUG REGISTRATION DEPARTMENT,
P.O. BOX 27663-00506,
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info@pharmacyboardkenya.org

Application Number	

(VAR No.)		
Date of submission of the dossier		
Name of the 1st Evaluator		Signature
Name of the 2nd Evaluator		Signature
Date of 1st evaluation		
Date of 2nd Evaluation		
Number of files received		
CONCLUSION OF THE ASSESSMENT **APPROVED** *(no outstanding issues)* **QUERY RAISED** *(Indicate the sections where query is raised)* **REJECTED** *(indicate the sec(s) that led to the rejection)* ***(Please delete which does not apply)***		

1. Applicant details

Information required (Particulars of the applicant)	**Information to be filled by the Applicant**
a) Name and Business Address of the Marketing Authorization Holder(MAH)	Company) Name: Address: Country: Telephone: Telefax: E-Mail:
b)Name and complete address of the Local Technical Representative of Manufacturer(if Applicable or different from section (a) above)	Company name: Address: **PPB File Number:** Telephone: Telefax: E-Mail:

1.1 Product Details

Information required (Product Details)	**Information to be filled by the Applicant**
a) Trade Name of the product, Product registration number, Product retention number , Active pharmaceutical ingredient (s) etc Note: Product retention number is not applicable(N/A) for a product registered the same year during which the variation is applied	Trade Name of the product: Product registration number: Product retention number(N/A for products registered within the same year: Active pharmaceutical ingredient ((s) (API) : Strength of the API(s): Dosage form: e.g. Tablet Registered Shelf Life: Registered Batch Size(s): Registered Pack Size(s)

1.1 Variation type: (tick all applicable options)

☐ Notification

☐ Minor variation ☐ Major variation

1.2 Grouping of variations

☐ Single variation ☐ Grouped variations

2. Variation title and Summary of the proposed changes

2.1. Variation title(s) and Variation type Number (s):
Indicate the variation title e.g. Change of Batch size of the finished pharmaceutical product. For multiple variations (grouped variations), indicate all the titles of the variation as per the PPB Variation guideline.

2.2 Summary of the proposed changes

Provide a summary of the proposed changes as indicated in the table below. For Multiple variations(Grouped Variations), reproduce this section

Current Details	**Proposed Details (change)**

2. 3 Reason for Change(s)

Provide the reason(s) and justification for the requested changes

3. Documentation required to be provided

3.1 Mandatory documents applicable for every variation (tick all applicable options)

The following documentation ***SHALL be*** *provided for each variation requested*

Name of the Document to be Submitted	**Applicant to tick all applicable options, if the document is provided**
Copy of Pharmacy and Poisons Board Initial registration certificate of the product	☐
Copy of Pharmacy and Poisons Retention certificate of the product	☐
Copy of cGMP from PPB for the Manufacturing site/ Evidence for payment for GMP	☐

3.2 Mandatory specific documents required to fulfill the condition set for a specific variation

Provide in the table below the supportive documentation as described (listed) in the Pharmacy and Poisons Board variation Guideline. For multiple variations (grouped variations), this table

Name of the Document(s) to be Submitted	**Applicant to tick all applicable options, if the document is provided**
Refer to Pharmacy and Poisons Board Variation Guideline to indicate the specific document	☐

4. Declaration

I declare that:

1. I, the undersigned certify that all the information in this application form and accompanying documentation is correct, complete, and true to the best of my knowledge.
2. I further confirm that the information referred to in my application is available for verification during GMP inspection.
3. I also agree that the undersigned will continue to carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports by PPB requirements

4. I also agree that I am obliged to follow the requirements of the Pharmacy and Poisons Act, which are related to pharmaceutical products.
5. I also consent to process information provided by the Pharmacy and Poisons Board.
6. I hereby confirm that fees will be paid/have been paid as provided for in the Pharmacy and Poisons Board Drug Registration Guideline.

Name: ……

Position in the company (Title/ Designation):
……

Signature: ……
Date: ……..

Official stamp:

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