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Prepared by Quality Assurance Officer

Sign.....

Date.....

Director, Product Evaluation and Registration

Sign.....

Date.....

Checked by Head, Quality Management

Sign.....

Date.....

Authorized by Registrar

Sign.....

Date.....

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

VARIATION GUIDELINES

OCTOBER 2018

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OBJECTIVE OF THE GUIDELINE

This guideline is a document meant to assist pharmaceutical manufacturers in filing various variations of registered human products as per Cap 244 laws of Kenya submitted to the Pharmacy and Poisons Board. This document will simplify and streamline the process for submitting post-approval changes

SCOPE OF THE GUIDELINES

This guideline primarily covers the conditions to be fulfilled, documentation required and the format of submission of a variation.

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

Key Reference Documents

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

APPLICATION FOR VARIATION OF A REGISTERED MEDICINAL PRODUCT

All applications for variation to a registered product shall be made according to requirements stipulated in this Guideline and clearly outlined in the Variation application form.

PAYMENT OF FEES

Every application shall be accompanied by requisite fees at the time of application. Any application that will not be accompanied by requisite fees will not be accepted (PSURs are exempted).

Mode of Payment: Payments by crossed or bankers cheque shall be made payable to **PHARMACY AND POISONS BOARD**.

For variations to an already registered product, an application fee of USD 200 must be paid except for periodic safety updates.

SUBMISSION OF APPLICATION

The application should be submitted to the following address:

The Registrar,

Pharmacy and Poisons

Board Lenana Road,

P. O. Box 27663-00506,

NAIROBI.

ABBREVIATIONS

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

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DEFINITIONS

A variation is a post-approval amendment that details the proposed change(s) to information appertaining to approved documentation for the purpose of updating of the details of the Marketing authorization licence 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.
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 adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance, but must be notified to PPB immediately after implementation or within 12 months following implementation of the change. e.g Periodic Safety Update Reports.

Active substance may mean 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 make reference to the WHO Variation guidelines (latest Technical Reference Series).

A 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	Mn

Conditions

1. 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) medicinal product**	1	1,2	Mn

Conditions

1. 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**

Conditions

1. 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 is part of the approved dossier in the name of the API**	1	1,2,3	Mn

Conditions

1. 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. In case of change in the name of the holder of the APIMF, updated "letter of access by PPB".

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	Mn
II	Manufacturer involved in any other activity	1	1,2	Mn

Conditions

1. 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/ATC VET code**	1	1,2,3	Mn

Conditions

1. Approval of change by WHO or VET ATC code

Documentation

1. Proof of approval of the ATC code change by WHO or ATC VET 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 control site, or supplier of a starting material, reagent or excipient (stated in the dossier).**	1,2	1,2,3	Mn

Conditions

1. It should be evidenced that at least one site or manufacturer, as previously authorized, remains performing 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

1. A letter of no objection from the currently approved LTR
2. A legal (notarized) contractual agreement between the proposed LTR and 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

Conditions

1. 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
3. Regulatory authority f r o m t h e country o f origin o r official body dealing with registration of business names) in which the new name or new address is mentioned.
4. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
5. 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

Conditions

1. There is transfer of legal entity.

Documentation

1. A letter or any formal document from a relevant official institution (e.g. a regulatory authority from country of origin and official body dealing with registration 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.

B 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, methods of analysis) are as 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 as currently approved.
3. The API is not a biological/immunological substance or sterile
4. In case manufacturing involves 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 successfully 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 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 of 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 authorisation 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 change to the manufacturing process of the API which could impact significantly on 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 on 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 or in physico-chemical properties.
2. The synthetic route remains the same including starting materials, catalysts, reagents.
3. In case of herbal products, the geographical source, production of the herbal substance and the manufacturing route of herbal product remains 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 in physico-chemical 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	Mn
B	Reduction in batch size	1 to 5	1 ,2,5	Mn
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	Mj
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 BMR (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 provide batch data on the next two production batches.
5. A copy of the approved (dated and signed) API/intermediates specifications

6. 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	Mn
B	Addition of IPQC tests or limits	1,2,5,6	1,2,3,4,6	Mn
C	Deletion of non significant IPQC tests	1,2	1 ,2,5	Mn
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, 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 biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (Standard pharmacopoeial microbiological methods are exempt)

Documentation

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

showing that the test parameter is insignificant

7. 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	Mn
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	Mn
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/Mj

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, 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 biological 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-pharmacopoeia 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 is no change in total impurities and no new (unqualified) impurities
3. The analytical method should essentially remain the same with minor changes, such as, 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 biological active substance (Standard pharmacopoeia microbiological methods are exempt)
5. The test procedure is not a novel method or an old method used in a non standard 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 addition of a test method)

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	Mn
B	Addition of specification parameters with accompanying test method(s)	1,2,5	1,2,3,4,6	Mn
C	Deletion of a non significant specification parameter	1,2	1,2,5	Mn
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 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	Mn
B	Other changes to a test procedure (including Addition/deletion)	1,3,4	1,2	Mn
C	Deletion of a test procedure (if there is an already approved test method)	5	1	Mn

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, 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 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	Mn
	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	Mj
B	**Storage Conditions**			
	1. Change to more restrictive conditions	1	1 to 3	Mn
	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			Mj

Conditions

1. 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

1. 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 in relation to 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

Conditions

1. FPP release and shelf life specifications remain unchanged except in relation to 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 equivalence of doses

VarT No.	Description of change	Condition (s)	Documentation	Variation type
B2.a.ii	**Change in the shape or dimensions of the pharmaceutical form**			
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 case of herbal products, the disintegration time compares between the old and new pharmaceutical form.
3. Release and shelf life specifications remain the same except for

dimensions

4. The qualitative and quantitative composition remain 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 where 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 flavours/colours**			
	1. Addition/deletion/replacement	1 to 7, 9	1 to 6	Mn
	2. Increase/reduction	1 to 4	1,2,4	Mn
	3. Biological VET products for oral use where the colouring or flavouring 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
2. formulation
3. 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.
4. The FPP specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an

identification test.

5. Stability studies as per ICH conditions (on at least two pilot batches and one production batch)
6. The proposed component must comply with international guidelines on safety
7. 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
8. The change does not affect strength differentiation and palatability especially in paediatric medicines
9. The dissolution is comparable between the currently approved and the proposed formulations while for herbal products, disintegration is comparable.
10. The change is not a consequence of stability problems and there is no strength differentiation issue that could impact on safety
11. 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 were 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

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 were carried out in accordance to 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 initial inspection	1 to 5	1 to 4, 7, 8	Mj
E	Site where any manufacturing operation(s) take place, EXCEPT batch-release, batch control, primary and secondary packaging for **non-sterile** FPPs.	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 licence from the relevant drug regulatory authority.
3. The product is not a sterile product
4. Validation in accordance with 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. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM format
8. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated

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 of 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 successfully 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 authorisation operate 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 requires **an assessment of comparability.**	1 to 7	1, 3, 4,6, 7, 8	Mj
D	Introduction of a non-standard terminal sterilisation 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
2. profile or in physico-chemical properties.
3. The active substance is not a biological / immunological/herbal medicinal product
4. The manufacturing process remains unchanged
5. The currently registered manufacturing process is well controlled through IPQC tests without widening the IPQC test parameters
6. The FPP or intermediate specifications remain unchanged
7. The new process leads to an identical product in regard to quality, efficacy and safety
8. 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 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 forms manufactured by 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 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
2. format
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 provide batch data on the next two

production batches.

5. A copy of the approved (dated and signed) release and shelf life specifications of the FPP
6. Batch numbers (of tested batches) of the proposed batch sizes
7. Validation results (at least three batches)
8. 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 during the manufacture of the FPP**			
A	Tightening of IPQC limits	1 to 4	1 ,2	Mn
B	Addition of IPQC tests or limits	1,2,5,6	1 to 5,7	Mn
C	Deletion of non significant IPQC tests	1,2	1 ,2,6	Mn
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
2. to review specification limits (e.g. New MAH application).
3. The change is not due to unexpected events during manufacture e.g. change in impurity profile, total impurities.
4. The change should be within currently approved limits
5. The test procedure remains the same (or with insignificant changes)
6. The test procedure is not a novel method or an old method used in a non standard way
7. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (Standard pharmacopoeial microbiological methods are exempt)

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD
2. format
3. Comparative data between the current and proposed test methods in a tabular format
4. Details of the new non-pharmacopoeia method with validation protocol and data

5. Batch analysis data on three production batches of the FPP for all specifications parameters
6. 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.
7. Justification through risk assessment from MAH/Manufacturer showing that the test parameter is insignificant
8. 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	Mn
B	Addition of specification parameters with accompanying test method(s)	1,2,5,6,7	1, 2, 3, 4, 6, 8	Mn
C	Deletion of a non significant specification parameter	1,2	1,2,7	Mn
D	Change outside the approved specification limits	1,2	1,2,7	Mj
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

Conditions

1. The change is not resulting from any commitment from previous assessments meant
2. to review specification limits (e.g. New MAH application).
3. The change is not due to unexpected events during manufacture of the packaging or storage of the API.
4. Any change should be within the currently approved packaging specification limits
5. The test procedure is unchanged (minor changes to the procedure could be exempted but need approval in addition)
6. The test procedure is not a novel method or an old method used in a non standard way
7. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent (standard pharmacopoeial microbiological methods are exempt)
8. The change does not involve a genotoxic impurity

Documentation

1. Amendment of the relevant section(s) of the dossier presented in the PPB-CTD
2. format
3. Comparison of the currently approved and the proposed specifications in tabular format
4. New analytical method details and validation data
5. Batch analysis data (of three batches) of the formulation containing the excipient on all specification parameters
6. 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.

7. Justification for not providing BE studies data
8. Justification (through risk assessment) that a specification parameter is not significant
9. 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 an	5	1,2	Mns

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and
2. the currently approved method.
3. There is no change in total impurities and no new (unqualified) impurities
4. The analytical method should essentially remain the same with minor changes, such as, change in column length and not column type for HPLC methods.
5. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (Standard pharmacopoeia microbiological methods are exempt)
6. 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

Conditions

1. The FPP release and shelf life specifications remain unchanged

Documentation

2. Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.
3. 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 is no change 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 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	Mn
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	Mn
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	Mj
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

Conditions

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

Documentation

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

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

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	Mn
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	4	1,2	Mn

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and the currently approved method.
2. There is no change in total impurities and no new (unqualified) impurities
3. The analytical method should essentially remain the same with minor changes, such as, 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 biological active substance (Standard pharmacopoeia 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 addition of a test method)

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 API**			
A	Composition (qualitative and quantitative)			
	1. Solid dosage forms	1,2,3	1,2,3,4,6	Mn
	2. Liquid & semi-solid formulations	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	Mn
B	Addition of specification parameters with accompanying test method(s)	1,2,5	1,2,3,4,6	Mn

C	Deletion of a non significant specification parameter	1,2	1,2,5	Mn
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
2. to review specification limits (e.g. New MAH application).
3. The change is not due to unexpected events during manufacture of the packaging or storage of the API.
4. Any change should be within the currently approved packaging specification limits
5. The test procedure is unchanged (minor changes to the procedure could be exempted but need approval in addition)
6. 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
2. format
3. Comparison of the currently approved and the proposed specifications in tabular format
4. New analytical method details and validation data
5. Batch analysis data (of three batches) between the currently approved and proposed primary packaging for all specification parameters
6. Justification (through risk assessment) from MAH or APIMF holder that a specification parameter is not significant
7. 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	Mn
B	Other changes to a test procedure (including Addition/deletion)	1,3,4	1,2	Mn
C	Deletion of a test procedure (if there is an already approved test method)	5	1	Mn

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and
2. the currently approved method.
3. The analytical method should essentially remain the same with minor changes, such as, change in column length and not column type for HPLC methods.
4. The test procedure is not a novel method or an old method used in a non standard way
5. The active substance is not biological or immunological
6. 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 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	Mn
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 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 change of head space or change in 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	Mn
	1. Change within the range of the currently approved pack sizes	1,2	1,2,3	Mn
	2. Change outside the range of the currently approved pack sizes	3	1,2	Mn
B	Deletion of a pack size	3	1,2	Mn
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
2. duration as stated in SmPC
3. The primary packaging material remains the same
4. 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 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 format
2. Samples or coloured 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

Conditions

1. 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 coloured artworks
3. Information in 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	Mn
	2. After first opening	1	1 to 4	Mn
	3. After dilution/reconstitution	1	1 to 4	Mn
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

Conditions

1. 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. 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

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) remain 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

3. Amendment of the relevant section(s) of the dossier presented in the EAC COMPENDIUM Format
4. Provision of manufacturing process validation and equipment qualification
5. 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 Pharmacopoeial substance to comply with a PPB recognized pharmacopoiea			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 Pharmacopoeial	1,4,5	1 to 4	Mn

Conditions

1. The change is made only for the purposes of complying with a pharmacopoiea
2. Product specific parameters e.g. particle size, polymorphic form (additional to Pharmacopoiea specifications) are unchanged and are as per application dossier
3. The impurities profile (qualitative and quantitative) remain the same unless tightening of the specifications limits
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/TSE & WHO APICPQ & WHO FPP CPQ

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	Mn
	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	Mn

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 are in compliance 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 prior to 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 from, 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 relevant section(s) of the dossier 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 practice 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 actual 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**			
	1. New WHO APICPQ from an already approved manufacturer	1 to 4	1 to 4	Mn
	2. Updated WHO APICPQ from already approved manufacturer	1 to 4	1 to 4	Mn

Conditions

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 critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
3. There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications

Documentation

1. Copy of the current (updated) confirmation of 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. Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option
3. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation.
4. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of at least pilot-scale of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO-PQP.

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
2. product concerned as per the approved posology (the results of such studies should be provided).
3. The proposed device should be compatible with the product.
4. The change should not necessitate significant revision of product information
5. The product can be accurately delivered without the use of a device
6. 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

VarT No.	Description of change	Condition (s)	Documentation	Variation type
B4.a.ii	**Change in specification parameters and/or limits of a measuring or administration device for VET products**			
A	Tightening of specification limits	1 to 4	1 ,2	Mn
B	Addition of new specification parameters with accompanying test method	1,2,5	1,2,3,4,6	Mn
C	Widening of the approved specifications limits, which may have a significant effect on the quality of the device	1,2,5	1,2,3,4,6	Mj
D	Deletion of the approved specifications parameter which may have a significant effect on the quality of the device	1,2,5	1,2,3,4,6	Mj
E	Addition or replacement/deletion of a specification parameter due to safety or quality concern	1,2,5	1,2,3,4,6	Mn
F	Deletion of the approved specifications parameter which may not have a significant effect on the quality of the device	1,2,5	1,2,5	Mn

Conditions

1. The change is not resulting from any commitment from previous assessments meant
2. to review specification limits (e.g. New MAH application).
3. The change is not due to unexpected events during manufacture e.g. change in impurity profile, total impurities.
4. The change should be within currently approved limits
5. The test procedure remains the same (or with insignificant changes)
6. 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. Comparative information between the current and proposed test specifications in a tabular format
3. Details of the new analytical method with validation protocol and data
4. Batch analysis data on two production batches for all specifications parameters
5. Justification through risk assessment showing that the test parameter is not significant
6. Justification for the new specification parameters and/or limits

VarT No.	Description of change	Condition (s)	Documentation	Variation type
B4.a.iii	**Change in test procedure of a measuring or administration device for VET products**			
A	Minor changes to an already approved test procedure	1,2	1,2	Mn
B	Deletion of a test procedure when an alternative test procedure is approved	4	1	Mn
C	Other changes to a test procedure (addition/replacement)	1,3	1,2	Mn

Conditions

1. Validation studies to demonstrate equivalence between the proposed test method and
2. the currently approved method.
3. The analytical method should essentially remain the same
4. The test procedure is not a novel method or an old method used in a non standard way
5. The active substance is not biological or immunological
6. 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 of the proposed to the current test methods in a tabular format (this is not a requirement in case of addition of a test method)

B.5. Changes to a marketing authorisation 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
2. format
3. Comparative information between the current and proposed changes in a tabular format
4. Declaration that the submitted PMF (TMF) is for the proposed final blood product.
5. PMF or TMF certificate and evaluation report
6. An expert statement outlining all the changes introduced with the certified PMF/TMF evaluating

their potential impact on the final blood product.

7. 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. 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)

C SAFETY/EFFICACY/PV UPDATES

Human & VET products

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

Documentation

1. 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 products 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	Mn
B	Implementation of change(s) for which new additional data are submitted by the MAH	1	1,2	Mj

Conditions

1. 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

1. 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

1. 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. 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

Specific VET products

VarT No.	Description of change	Condition (s)	Documentation	Variation type
C2.a.i	**Changes to target species.**			
A	Changes to or addition of a non-food producing target species.		(1), 2	Mj
B	Deletion of a food producing or non-food producing target species.			
	1. Deletion as a result of a safety concern		2	Mj
	2. Deletion which is not due to safety concern		1,2	Mn

Documentation

1. Justification
2. Revised product information

VarT No.	Description of change	Condition (s)	Documentation	Variation type
C2.a.ii	**Changes to the withdrawal period for a VET product**		1,2	Mj

Documentation

1. Data for justification
2. Revised product information

VarT No.	Description of change	Condition (s)	Documentation	Variation type
C2.a.iii	**Replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.**		1,2	Mj
C.2.a.iv	**Replacement of a strain for a VET vaccine against equine influenza.**		1,2	Mj
C2.a.v	**Changes to the labelling or the package leaflet which are not connected with the SmPC of VET products**		1,2	Mn

Documentation

1. Data for justification
2. Revised product information

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 prior to submission to PV directorate by applicants)
2. Revised product information, if relevant

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