مجلس الصحة
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Gulf Health Council

The GCC Guidelines for Variation Requirements

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What is New in the GCC Guidelines for variation requirements version 6.0?

- 12 variations have been changed from type **IA** to **IA$_{IN}$**.

No.	Change Position	No.	Change Position
1	1 - A	7	43 – A
2	4	8	47 – A – 1
3	6 – A	9	67 - A
4	14 - A	10	69
5	29 – A	11	70
6	38 – a – 1	12	71

- 13 variations have been changed from type IB to **IA$_{IN}$**.

No.	Change Position	No.	Change Position
1	20 – A	8	47 – B – 1
2	21 – A	9	48 – A – 1
3	22 – A – 1	10	51 – B
4	26 – A	11	59 – A
5	26 – B	12	59 – B
6	46 – A (1 & 2 & 3)	13	59 – D –1
7	47 – A – 3		

- 53 variations have been changed from type IB to IA.

No.	Change Position	No.	Change Position
1	10 - A	28	36 – D
2	11 - A	29	38 - A - 1
3	11 - B	30	39 - D
4	12 - B	31	40 - B
5	12 - F	32	40 - C
6	14 - B	33	41 - A
7	14 - G	34	44 - B
8	15 - A	35	47 - B - 2
9	15 - D	36	47 - B - 3
10	15 - E	37	48 - A – 2
11	16 - A	38	48 - B
12	17 - D	39	48 - C
13	18 -A	40	49 - D
14	18 - B	41	50 - C
15	18 - C	42	52 - B
16	19 – A - 1	43	52 - F
17	22 – A - 2	44	53 - A
18	28 - F	45	53 - B
19	29 - A	46	53 - C
20	29 - B	47	59 - C
21	30 - B &F	48	59 -D - 2
22	31 - F	49	59 - F
23	32 – D	50	59 - G
24	34 - A	51	59 - H
25	35 - B	52	59 - I
26	35 - F	53	59 - J
27	36 - A		

- 35 variations have been added with various types.

No.	Change Position	No.	Change Position	No.	Change Position
1	9 - F	13	24	25	46 - E
2	9 - G	14	26 - F	26	47 – (A – 4) & (A – 5)
3	9 - H	15	29 - F	27	47 – (B – 4) & (B – 5)
4	9 - I	16	31 - G	28	51 – A – 2
5	9 - J	17	35 - G	29	51 – A – 3
6	9 - K	18	36 - E	30	60
7	11 - E	19	37	31	66 A & B
8	13 - A	20	38 – B - 3	32	67 A & B
9	14 - H	21	42 - A	33	68
10	19 – A - 2 & 3	22	43 – A & B	34	69
11	19 - B (1) & C	23	45	35	70
12	21 - C	24	46 - B (4)		

- Two variations have been changed from type II to IB.

No.	Change Position	No.	Change Position
1	19 - A - 3	2	46 - B - 1 & 2 & 3

Table of Contents

1. Introduction

These guidelines are adopted from the EMA Guidelines on the details of the various categories of variations, Regulation (EC).

This document has been developed to assist applicants in the preparation and submission of drug applications for variations.

2. General Notes

The following notes should be taken into consideration when submitting any variation application:

- An application for Variation to a Marketing Authorization should always be submitted (please refer to latest edition of the framework).
- Applicants should present a summary of the intended change in tabular form in which the current state/situation and the situation after the intended change are compared to outline the scope of the change in a transparent manner.
- A justification for the introduction of the change should always follow.
- Some documents such as certificate of analysis (COA), specification sheet, and approval letters from the country of origin …etc should be submitted when relevant.
- It is important to note that the authority reserves the right to request any additional information and data not specifically described in this document, in order to assess adequately the safety, efficacy and quality of drug products. Authority is committed to ensuring that such requests are justifiable and decisions are clearly documented.
- Applicants should be aware that deficient documentation can lead to rejection of the application. In addition, submitting redundant or irrelevant information may delay approval procedures.

3. Scope

This document applies to change(s) made to drug products that have already received a marketing authorization by GCC or any local authority within GCC.

4. Objectives

To classify variations and to provide applicants with recommendations on the data required for each type of variation; which may impact the safety, efficacy and quality of drug products.

5. Types of Variations

The variation or post-marketing changes can be classified into two categories:

A. Minor variations:

– Type IA: Such minor variations do not require prior approval before implementation ("Do and Tell" procedure). Type IA_{IN} variations should be submitted immediately, within 14 days following implementation. Other type IA variations, however, can be compiled in a single variation application, to be submitted to the SFDA no later than January 31st of each year. The variation application for every product should clearly indicate:

- All IA variations that have been implemented during the previous year.
- Date of implementation of each variation.
- Code of each variation, based on this guideline, and a proof that the conditions of such variations have been met.
- All the corresponding documentation listed in this guideline for each variation.

When one or more conditions established in this guideline for minor change of Type IA are not met, the concerned change may be submitted as Type IB variation unless the change is specifically classified as a major change variation of type II. While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately upon the request of the authority, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected

with the consequence that the holder must immediately cease to apply already implemented variations concerned. Editorial changes and typos are to be treated as Type IA changes unless otherwise stated.

- Type IB: Such minor variations must be sumbitted to the authority by the Marketing Authorization Holder (MAH) before implementation, but do not require a formal approval. However, the MAH must wait a period of time (please refer to latest edition of the framework) to ensure that the application is deemed acceptable before implementing the change ("Tell, Wait and Do" procedure).

B. Major variations:

- Type II: Such major variations, which may have a significant impact on the Quality, Safety or Efficacy of a medicinal product and require prior approval before implementation.

In order to facilitate the classification of variation or post-market changes, examples and appendices listed below are explicitly define the various types of changes:

- Appendix 1; example of some major changes and most minor changes; which are classified by the type of change. When the conditions are not met, the change may classified as either a major change or may make a new application is necessary.
- Appendix 2 list the types of changes that make a new application necessary.
- Appendix 3 Requirements for addition/change to an API suppliers.

6. Appendix 1 Examples for some major changes and most common minor changes

I. Administrative Changes

1. Change in the marketing authorization holder	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change in the name and/or address of the marketing authorization holder	**1**	**1, 2, 4**	**IA$_{IN}$**
b) Transfer the product to new marketing authorization holder (different legal entity)		**1, 2 , 3 ,4 , 5**	**IB**
Conditions			
1) The marketing authorization holder (MAH) shall remain the same legal entity.			
Documentation			
1) A formal document from a relevant official body (e.g. chamber of commerce, national drug regulatory authority…etc) in which the new name or new address is mentioned.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			
3) Copy of the agreement			
4) Certificate of a Pharmaceutical Product (CPP)			
5) A recent and official price certificate by the company and legalized by the Saudi Embassy in the country of origin.			

2. Remove agent name from the artwork (Mock-up)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA**
Conditions			
1) The proposed artwork should comply with the GCC guidelines for Presenting the SPC, PIL and Labeling Information.			
Documentation			
1) Samples of the artwork.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

3. Change in the (invented) name of the medicinal product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	**IB**
Documentation			
1) A formal document from the national drug regulatory authority in which the new name is approved, if applicable.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

4. Change in name of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1, 2**	**IA_{IN}**
Conditions			
1) The active substance shall remain the same.			
Documentation			
1) Proof of acceptance by WHO or copy of the INN list.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

5. Change in the name and/or address of a manufacturer or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Certificate of Suitability is available	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1, 2, 3**	**IA**
Conditions			
1) The manufacturing site and all manufacturing operations shall remain the same.			
Documentation			

1) A formal document from a relevant official body (e.g. chamber of commerce, national drug regulatory authority…etc) in which the new name and/or address is mentioned.
2) Replacement of the relevant pages of the dossier that are affected by the variation.
3) In case of a drug master file (DMF), an updated "letter of access".

6. Change in the name and/or address of a manufacturer of the finished product, including quality control sites	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Manufacturer responsible for batch release	**1**	**1, 2**	**IA$_{IN}$**
b) All other	**1**	**1, 2**	**IA**
Conditions			
1) The manufacturing site and all manufacturing operations shall remain the same.			
Documentation			
1) Copy of the modified manufacturing authorization, if available; or a formal document from a relevant official body (e.g. chamber of commerce, national drug regulatory authority… etc) in which the new name and/or address is mentioned.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

7. Change in ATC Code /ATC Vet Code	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA**
Conditions			
1) Change following granting of or amendment to ATC Code by WHO/ATC Vet Code.			
Documentation			
1) Proof of acceptance (by WHO) or copy of the ATC (Vet) Code list.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

8. Deletion of a manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient, when mentioned in the dossier).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1, 2**	**IA**
Conditions			
1) There should at least remain one site/manufacturer, as previously authorized, performing the same function as the one(s) concerned by the deletion.			
2) The deletion should not be due to critical deficiencies concerning manufacturing.			
Documentation			
1) The submitted documents should clearly outline the "present" and "proposed" manufacturers.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

II. Quality Changes

II.1 Active substance

a) Manufacture

	Conditions to be fulfilled	Documentation to be supplied	Procedure type
9. Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer of the active substance, where no Certificate of Suitability is available			
a) The proposed manufacturer is part of the same organization as the currently approved manufacturer.		**1, 2, 3, 4, 5, 6, 7**	**I**B
b) Introduction of a manufacturer of the active substance supported by an DMF.			**II**
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.			**II**
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			**II**
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product			**II**
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	**1, 2**	**1, 5**	**IA**
g) Addition of an alternative sterilisation site for the active substance using a pharmacopeial method		**1, 2, 4, 5, 8**	**IB**
h) Introduction of a new manufacturer of the active substance that is not supported by an DMF and requires significant update to the relevant active substance section of the dossier			**II**

i) Introduction of a new site of micronisation	**1, 3**	**1, 4, 5, 6**	**IA**
j) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological/immunological/immunochemical method takes place			**II**
k) New storage site of Master Cell Bank and/or Working Cell Banks		**1, 5**	**IB**

Conditions

1) The active substance is not a biological/immunological substance or sterile.

2) Method transfer from the old to the new site has been successfully completed.

3) The particle size specification of the active substance and the corresponding analytical method remain the same.

Documentation

1) Replacement of the relevant pages of the dossier that are affected by the variation.

2) A declaration from the marketing authorization holder that the synthetic route (or in case of herbal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.

3) Either a TSE Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by a national drug regulatory authority of the ICH region and associated countries and shown to comply with the current Note for Guidance on FMinimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products or an equivalent guideline of the ICH region and associated countries. The information should include the following: 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 (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.

5) The submitted documents should clearly outline the “present” and “proposed” manufacturers.

6) A declaration by the Qualified Person (QP) at the site responsible for batch release that starting material/reagent/intermediate used in the manufacturing of the active substance and the active substance are manufactured in accordance with the good manufacturing practice (GMP) guidelines.

7)	Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance.
8)	Proof that the proposed site is appropriately authorized for the pharmaceutical form or product or manufacturing operation concerned.

10. Changes in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change in the manufacturing process of the active substance.	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.			**II**
c) The substance is a biological/immunological substance.			**II**
d) The change relates to a herbal product and there is a change to any of the following: geographical source, manufacturing route or production.			**II**
e) Minor change to the restricted part of drug master file (DMF).		**1, 2, 3, 4**	**I**B

Conditions	
1)	No change in qualitative and quantitative impurity profile or in physicochemical properties.
2)	The product concerned is not a biological /immunological medicinal product.
3)	The synthetic route remains the same, i.e. intermediates remain the same and there are no changes to the reagents, catalysts or solvents used in the process. In the case of herbal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.
4)	The specifications of the active substance or intermediates are unchanged.
5)	The change is fully described in the open ("applicant's") part of drug master file (DMF), if applicable.
6)	The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product.
7)	The change does not refer to the restricted part of an Active Substance Master File.
Documentation	

1) Replacement of the relevant pages of the finished product dossier and drug master file (DMF) (where applicable), including a direct comparison of the present process and the new process.
2) Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process.
3) Copy of approved specifications of the active substance.
4) A declaration from the marketing authorisation holder or the DMF 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 active substance or intermediates are unchanged.
Note: for 10.b), for chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.

11. Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Up to 10-fold increase compared to the currently approved batch size	**1, 2, 3, 4, 6, 7, 8**	**1, 2 , 5**	**IA**
b) Downscaling down to 10-fold	**1, 2, 3, 4, 5**	**1, 2 , 5**	**IA**
c) The change requires assessment of the comparability of a biological/immunological active substance			**II**
d) More than 10-fold increase compared to the currently approved batch size		**1, 2, 3, 4**	**IB**
e) The scale for a biological/immunological active substance is increased/decreased without process change (e.g. duplication of line)		**1, 2, 3, 4**	**IB**
Conditions			
1) Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.			
2) Test results of at least two batches according to the specifications should be available for the proposed batch size.			
3) The product concerned is not a biological/immunological medicinal product.			
4) The change does not affect the reproducibility of the process.			
5) The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
6) The specifications of the active substance/intermediates remain the same.			
7) The active substance is not sterile.			
8) The currently approved batch size was not approved via a Type IA variation.			

Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) The batch numbers of the tested batches having the proposed batch size.
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. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action).
4) Copy of approved specifications of the active substance (and of the intermediate, if applicable).
5) A declaration from the marketing authorisation holder or the DMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.

12. Change to in-process tests or limits applied during the manufacture of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of in-process limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new in-process test and limits	**1, 2, 5, 6**	**1, 2, 3, 4, 6**	**IA**
c) Widening of the approved in-process control (IPC) limits, which may have a significant effect on the overall quality of the active substance			**II**
d) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance			**II**
e) Addition or replacement of an in-process test as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**
f) Deletion of a non-significant in-process test	**1, 2, 7**	**1, 2, 5**	**IA**
Conditions			
1) The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).			
2) The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.			
3) Any change should be within the range of currently approved limits.			
4) The test procedure remains the same.			
5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel 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 (does not include standard pharmacopoeial microbiological methods).			

Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Comparative table of current and proposed in-process tests.
3) Details of any new Non pharmacopoeial analytical method and validation data.
4) Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters
5) Justification/risk-assessment showing that the parameter is non-significant.
6) Justification for the new in-process test and limits.

13. Changes to the active substance of a seasonal, prepandemic or pandemic vaccine against human influenza	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Replacement of the strain(s) in a seasonal, prepandemic or a pandemic vaccine against human influenza			**II**

b) Control of active substance

14.	Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Tightening of specification limits**	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**
b)	**Addition of a new specification parameter to the specification with its corresponding test method**	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
c)	**Change outside the approved specifications limits range for the active substance**			**II**
d)	**Widening of the approved specifications limits for starting materials/reagents/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product**			**II**
e)	**Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product**			**II**
f)	**Addition or replacementt (excluding biological or immunological substance) of a specification parameter as a result of a safety or quality issue**		**1, 2, 3, 4, 5, 7**	**IB**
g)	**Deletion of a non-significant specification parameter (e. g deletion of an obsolete test e.g. organoleptic test)**	**1, 2, 8**	**1, 2, 6**	**IA**
h)	**a change in specification from in-house to a non-official Pharmacopoeia**		**1, 2, 3, 4, 5, 7**	**IB**
Conditions				
1)	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).			
2)	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.			
3)	Any change should be within the range of currently approved limits.			
4)	The test procedure remains the same.			
5)	Any new test method does not concern a novel non-standard technique or a standard technique			

used in a novel way.
6) The test method is not a biological/immunological/immunochemical method or a method using a biological reagent.
7) For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with ICH/VICH limits, any new impurity control should be in line with the official Pharmacopoeia
8) The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Comparative table of current and proposed specifications.
3) Details of any new analytical method and validation data.
4) Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.
5) Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal products, comparative disintegration data may be acceptable.
6) Justification/ risk-assessment showing that the parameter is non-significant.
7) Justification of the new specification parameter and the limits.

15. Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Change (including replacement or addition) to a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance.			**II**
c) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate		**1, 2**	**IB**

d) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	**1, 2, 3, 5, 6**	**1, 2**	**IA**
e) Deletion of a test procedure for the active substance or a starting material/intermediate, if an alternative test procedure is already authorized	**7**	**1**	**IA**
Conditions			
1) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former.			
2) There have been no changes of the total impurity limits; no new unqualified impurities are detected			
3) The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
4) The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent.			
5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
6) The active substance is not biological/immunological.			
7) An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA variation.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation, which includes a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).			
2) Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.			

c) Container closure system

16. Change in immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change in the qualitative and quantitative composition.	**1, 2, 3**	**1, 2, 3, 4, 5, 6**	**IA**
b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances			**II**
c) Liquid active substances (non-sterile)		**1, 2, 3, 4, 5, 6**	**IB**
Conditions			
1) The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
2) Satisfactory results of the Relevant stability studies that have been started according to the GCC stability guidelines and relevant stability parameters have been assessed in at least two pilot scale or production scale batches for at least three months.			
3) Sterile and biological/immunological active substances are excluded.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) Appropriate data on the new packaging (comparative data on permeability e.g. for O2, CO2 moisture), including a confirmation that the material complies with relevant pharmacopeial requirements.			
3) Proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack).			
4) The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.			
5) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the authority only in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf life along with the proposed action(s).			
6) Comparative table of the current and proposed specifications, if applicable.			

17. Change in the specification parameters and/or limits of the immediate packaging of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4 , 6**	**IA**
c) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4 , 6**	**IB**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete test)	**1, 2**	**1, 2, 5**	**IA**
Conditions			
1) The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.			
2) The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.			
3) Any change should be within the range of currently approved limits.			
4) The test procedure remains the same.			
5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) Comparative table of current and proposed specifications.			
3) Details of any new analytical method and validation data.			
4) Batch analysis data on two batches of the immediate packaging for all specification parameters.			
5) Justification/risk-assessment showing that the parameter is non-significant.			
6) Justification of the new specification parameter and the limits.			

18.	Change in test procedure for the immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**
	b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
	c) Deletion of a test procedure if an alternative test procedure is already authorized	**5**	**1**	**IA**
	Conditions			
	1) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former.			
	2) The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
	3) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
	4) The active substance/ finished product is not biological/immunological.			
	5) There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA variation.			
	Documentation			
	1) Replacement of the relevant pages of the dossier that are affected by the variation, which includes a description of the analytical methodology, a summary of validation data.			
	2) Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure			

d) Stability

19.	Change in the re-test period/storage period or storage conditions of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	a) Retest period/storage period			
	1. Reduction	**1**	**1, 2, 3**	**IA**
	2. Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol			**II**
	3. Extension or introduction of a re-test period/storage period supported by real time data		**1, 2, 3**	**IB**
	b) Storage conditions			
	1. Change to more restrictive storage conditions of the active substance	**1**	**1, 2, 3**	**IA**
	2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			**II**
	3. Change in storage conditions of the active Substance		**1, 2, 3**	**IB**
	c) Change to an approved stability protocol	**1, 2**	**1, 4**	**IA**
	Conditions			
	1) The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
	2) The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
	Documentation			
	1) Replacement of the relevant pages of the dossier that are affected by the variation. These must contain results of appropriate recent real time stability studies; conducted in accordance with the GCC stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorized packaging material and covering the duration of the requested re-test period or requested storage conditions.			
	2) Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.			
	3) Copy of approved specifications of the active substance.			
	4) Justification for the proposed changes			

e) Design space:

20.	**Introduction of a new design space or extension of an approved design space for the active substance, concerning:**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	a) One unit operation in the manufacturing process of the active substance including the resulting in- process controls and/or test procedures		**1, 2, 3**	**II**
	b) Test procedures for starting materials/reagents/intermediates and/or the active substance		**1, 2, 3**	**II**
	Documentation			
	1) The design space has been developed in accordance with the relevant scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.			
	2) Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
	3) Replacement of the relevant pages of the dossier that are affected by the variation.			

II.2 Finished product

a) Description and composition

21.	**Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	a) Changes in imprints, bossing or other markings	**1, 2, 3,4**	**1, 2**	**IA_{IN}**
	b) Changes in scoring/break lines intended to divide into equal doses		**1, 2, 3**	**IB**
	Conditions			
	1) Finished product release and end of shelf-life specifications have not been changed (except for appearance).			
	2) Any ink must comply with the relevant pharmaceutical legislation.			
	3) The scoring/break lines are not intended to divide into equal doses.			
	4) Any product markings used to differentiate strengths should not be completely deleted.			

Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation including a detailed drawing or written description of the current and new appearance and including revised product information as appropriate.
2) Samples of the finished product where applicable.
3) Results of the appropriate compendial tests demonstrating equivalence in characteristics/correct dosing (i.e. results demonstrating that the proposed tablet breaks evenly).

22. Change in the shape or dimensions of the pharmaceutical form	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Immediate release tablets, capsules, suppositories and pessaries	**1, 2, 3, 4**	**1, 4**	**IA_{IN}**
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets		**1, 2, 3, 4, 5**	**IB**
c) Addition of a new kit for a radiopharmaceutical preparation with another fill volume			**II**
Conditions			
1) If appropriate, the dissolution profile of the reformulated product is comparable to the old one. For herbal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one.			
2) Release and end of shelf-life specifications of the product have not been changed (except for dimensions).			
3) The qualitative or quantitative composition and mean mass remain unchanged.			
4) The change does not relate to a scored tablet.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation including a detailed drawing of the current and proposed situation.			
2) Comparative dissolution data on at least one pilot batch of the current and proposed dimensions. For herbal product comparative disintegration data may be acceptable.			
3) Justification for not submitting a new bioequivalence study.			
4) Samples of the finished product where applicable.			
5) Results of the appropriate compendial tests demonstrating equivalence in characteristics/correct dosing.			

23. Changes in the composition (excipients) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Changes in components of the flavoring or coloring system			
1. Addition , deletion or replacement	**1, 2, 3, 4, 5, 6, 7, 8, 9**	**1, 3, 4, 5, 6**	**IA_{IN}**
2. Increase or reduction	**1, 2, 3, 4, 9**	**1, 3, 4**	**IA**

3. Biological veterinary medicinal products for oral use for which the coloring or flavoring agent is important for the uptake by target animal species.			**II**
b) Other excipients			
1. The change relates to a biological/immunological product			**II**
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product.			**II**
3. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk.			**II**
4. Change that is supported by a bioequivalence study.			**II**
5. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		**1, 2, 4, 5, 6, 7, 8, 9, 10**	**IB**
6. Any minor adjustment of the quantitative composition of the finished product with respect to excipients		**1, 3, 4, 7, 8,**	**IB**
Conditions			
1) No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.			
2) Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.			
3) The finished product specifications have only been updated in respect of appearance/odor/taste and if relevant, deletion or addition of an identification test.			
4) Stability studies have been started according to the GCC stability guidelines and relevant stability parameters have been assessed in at least two pilot scale or production scale batches for at least three months. In addition, where relevant, photo-stability testing should be performed.			
5) Any new proposed components must comply with the relevant guidelines for flavors or colors.			
6) The new excipient does not include the use of materials of human or animal origin for which assessment of viral safety or TSE risk is required.			
7) Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for pediatric formulations.			
8) The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between strengths.			

9) For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species.
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation including identification method for any new colorant and if appropriate updated end of shelf-life specifications.
2) The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months and a letter of commitment to finalize the stability studies and to submit the data must immediately to the authority in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf life along with the proposed action.
3) A declaration letter that stability studies will be finalized and that data will submitted immediately to the authority in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf life along with the proposed action.
4) Sample of the new product, where applicable.
5) Either a TSE Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by a national drug regulatory authority of the ICH region and associated countries and shown to comply with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* or an equivalent guideline of the ICH region and associated countries. The information should include the following: 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.
6) Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.
7) Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics(including stability aspects and antimicrobial preservation where appropriate).
8) For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal products, comparative disintegration data may be acceptable.
9) Justification for not submitting a new bioequivalence study.
10) For veterinary medicines intended for use in food producing, justification that the excipient does not have pharmacological activity at the dose at which it is administered to the target animal.

24. Change in coating weight of oral dosage forms or change in weight of capsule shells	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Solid oral pharmaceutical forms.		**1, 2,3, 4**	**IB**

b) Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism.			**II**
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.			
3) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the authority only in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf lif along with the proposed action.			
4) Comparative dissolution profile of at least two pilot scale batches of the finished product in the new and old composition . For herbal products, comparative disintegration time may be acceptable.			

25. 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	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

26. Deletion of the solvent/diluent container from the pack	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2	**IB**
Documentation			
1) Justification for the deletion, including a statement regarding alternative means to obtain the solvent/ diluent as required for the safe and effective use of the medicinal product.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

b) Manufacture

27. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**

a) Secondary packaging site	**1, 2**	**1, 2, 3, 4, 5, 6**	**IA_{IN}**
b) Primary packaging site	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5, 6, 8, 12, 15, 16**	**IA_{IN}**
c) Site where any manufacturing operation(s) take place, except batch release, batch control and secondary packaging, for biological/immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			**II**
d) Site where any manufacturing operation(s) take place, except batch-release, batch control primary and secondary packaging, for non-sterile medicinal products.		**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16**	**IB**
e) Site, which requires an inspection by SFDA.			**II**
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products		**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15**	**IB**
Conditions			
1) Satisfactory inspection in the last five years.			
2) Site appropriately authorized (to manufacture the pharmaceutical form or product concerned).			
3) Product concerned is not a sterile product.			
4) Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.			
5) Product concerned is not a biological/immunological medicinal product.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) Proof that the proposed site is appropriately authorized for the pharmaceutical form or product concerned.			
3) A certificate of GMP compliance issued from the SFDA or GCC, *if available*.			
4) Registration of the new manufacturing site at the SFDA, if not registered.			

5) Certificate of a Pharmaceutical Product (CPP) or Electronic CPP (eCPP) stating the new manufacturing site. When the manufacturer is not mentioned on the CPP, the approval of the corresponding variation granted in the reference country can be provided instead.
6) The submitted documents should clearly outline the "present" and "proposed" finished product manufacturers.
7) If the new manufacturing site uses the active substance as a starting material – A declaration by the Qualified Person (QP) or qualified key person at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.
8) Copy of approved release and end of shelf-life specifications for the product if relevant.
9) Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).
10) Relevant stability studies have been started according to the GCC stability and relevant stability parameters have been assessed in at least two pilot scale or production scale batches for at least three months.
11) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the authority only in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf lif along with the proposed action.
12) Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
13) For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
14) For solid dosage forms, data from comparative dissolution tests with demonstration of similarity of dissolution profile, performed on the last three batches from the previous site and the first three batches from the new site should be submitted.
15) A recent and official price certificate by the company and legalized by the Saudi Embassy in the country of origin.
16) If the manufacturing site and the primary and/or secondary packaging site are different, conditions of transport and bulk storage should be specified and validated.

28. Change to batch release arrangements and quality control testing of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Replacement or addition of a site where batch control/testing takes place	**1, 2, 3**	**1, 2, 4**	**IA_{IN}**

b)	**Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method**			**II**
c)	**Replacement or addition of a manufacturer responsible for batch release**			
	1. Not including batch control/testing	**1**	**1, 2, 3, 4**	**IA_{IN}**
	2. Including batch control/testing	**1, 2, 3**	**1, 2, 3, 4**	**IA_{IN}**
	3. Including batch control/testing for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method			**II**
	Conditions			
	1) The site is appropriately authorized.			
	2) The product is not a biological/immunological medicinal product.			
	3) Method transfer from the old to the new site or new test laboratory has been successfully completed.			
	Documentation			
	1) Attach copy of manufacturing authorization(s) or where no manufacturing authorization exists a certificate of GMP compliance issued within the last 3 years by the relevant competent authority.			
	2) The submitted documents should clearly outline the "present" and "proposed" finished product manufacturers batch control/testing and batch release sites.			
	3) A declaration by the Qualified Person (QP) responsible for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorization operate in compliance with the detailed guidelines on good manufacturing practice for starting materials.			
	4) Replacement of the relevant pages of the dossier that are affected by the variation.			

29.	**Change in the manufacturing process of the finished product**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a)	**Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product.**			**II**
b)	**The change relates to a biological/immunological medicinal product.**			**II**

c) Introduction of a non-standard terminal sterilization method.			**II**
d) Introduction or increase in the overage that is used for the active substance.			**II**
e) Minor change in the manufacturing process of an aqueous oral suspension.		**1, 2, 4, 6, 7, 8, 9**	**IB**
f) Minor change in the manufacturing process	**1, 2, 3, 4, 5, 6,7**	**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IA**
Conditions			
1) No change in qualitative and quantitative impurity profile or in physicochemical properties.			
2) Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product concerned is not a biological/immunological or herbal medicinal product; Or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form).			
3) The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.			
4) The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits)are required to these controls.			
5) The specifications of the finished product or intermediates are unchanged.			
6) The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.			
7) Relevant stability studies have been started according to the GCC stability guidelines and relevant stability parameters have been assessed in at least one pilot scale or production scale batches for at least three months. Assurance is given that these studies will be finalised and that the data will be provided immediately to the authority if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation, including a direct comparison of the present process and the new process.			
2) For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.			
3) For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal products, comparative disintegration data may be acceptable.			

4) Justification for not submitting a new bioequivalence study.
5) For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.
6) Copy of approved release and end of shelf-life specifications.
7) Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action).
8) The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least one pilot or production scale batches for at least three months.
9) A letter of commitment to finalize the stability studies with indication of the batch concerned and the data must be submitted immediately to the authority only in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf life along with the proposed action.

30. Change in the batch size (including batch size ranges) of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Up to 10-fold compared to the currently approved batch size.	**1, 2, 3, 4, 5, 7**	**1, 4**	**IA_{IN}**
b) Downscaling down to 10-fold.	**1, 2, 3, 4, 5, 6**	**1, 4**	**IA**
c) The change relates to a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study.			**II**
d) The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes			**II**
e) More than 10-fold increase compared to the currently approved batch size for immediate release (oral) pharmaceutical forms.		**1, 2, 3, 4, 5,6, 7**	**IB**
f) The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)		**1, 2, 3, 4, 5, 6, 7**	**IB**
Conditions			

1) The change does not affect reproducibility and/or consistency of the product.
2) The change relates to standard immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms.
3) Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment.
4) Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the ICH guidelines.
5) The product concerned is not a biological/immunological medicinal product.
6) The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
7) The currently approved batch size was not approved via a Type IA variation.
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specifications (with proposed action).
3) Copy of approved release and end of shelf-life specifications.
4) Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5) The validation results should be provided
6) The results of stability studies that have been carried out according to the GCC stability guidelines , on the relevant stability parameters, on at least one pilot or production scale batches for at least three months.
7) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the authority only in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf life along with the proposed action. For biologicals/immunologicals: a declaration that an assessment of comparability is not required.

31.	Change to in-process tests or limits applied during the manufacture of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	**Tightening of in-process limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new tests and limits**	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**IA**
c)	**Widening of the approved IPC limits, which may have a significant effect on the overall quality of the finished product**			**II**
d)	**Deletion of an in-process test which may have a significant effect on the overall quality of the finished product**			**II**
e)	**Addition or replacement of an in-process test as a result of a safety or quality issue**		**1, 2, 3, 4, 5, 7**	**IB**
f)	**Deletion of a non-significant in-process test**	**1, 2, 7**	**1, 2, 6**	**IA**

Conditions

1) The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).

2) The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.

3) Any change should be within the range of currently approved limits.

4) The test procedure remains the same.

5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel 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.

7) The in-process test does not concern the control of a critical parameter, e.g.: assay, impurities (unless a particular solvent is definitely not used in the manufacture) any critical physical characteristics (particle size, bulk, tapped density, etc.) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)

Documentation

1) Replacement of the relevant pages of the dossier that are affected by the variation.

2) Comparative table of current and proposed in-process tests.

3) Details of any new analytical method and validation data.

4) Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.

5) Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests. For herbal products, comparative disintegration data may be acceptable.
6) Justification/ risk-assessment showing that the parameter is non-significant.
7) Justification of the new in-process test and limits.

c) Control of excipients

32. Change in the specification parameters and/or limits of an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 6, 8**	**IA**
c) Change outside the approved specifications limits range			**II**
d) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
e) Addition or replacement (excluding biological or immunological product) of a specification parameter parameter with its corresponding test method, as a result of a safety or quality issue		**1, 2, 3, 4, 5, 6, 8**	**IB**
f) Deletion of a non-significant specification parameter (e. g deletion of an obsolete test e.g. organoleptic test)	**1, 2, 8**	**1, 2, 7**	**IA**
g) a change in specification from in-house to a non-official Pharmacopoeia		**1, 2, 3, 4, 5, 6, 8**	**IB**

Conditions

1) The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).

2) The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.

3) Any change should be within the range of currently approved limits.

4) The test procedure remains the same.

5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6) The test method is not a biological/immunological/immunochemical method.

7) The change does not concern a genotoxic impurity.

8) The specification parameter does not concern the control of a critical parameter, e.g.:

impurities (unless a particular solvent is definitely not used in the manufacture of the excipient)

any critical physical characteristics (particle size, bulk, tapped density, etc.) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Comparative table of current and proposed specifications.
3) Details of any new analytical method and validation data.
4) Batch analysis data on two production batches (3 production batches for biological excipients,) of the excipient for all specification parameters.
5) Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal products, comparative disintegration data may be acceptable.
6) Justification for not submitting a new bioequivalence study, if appropriate.
7) Justification/ risk-assessment showing that the parameter is non-significant.
8) Justification of the new specification parameter and the limits.

33. Change in test procedure for an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Change (including replacement or addition) to a biological/immunological/immunochemical test method or a method using a biological reagent			**II**
c) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**
d) Deletion of a test procedure if an alternative test procedure is already authorized	**5**	**1**	**IA**
Conditions			
1) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former.			

2) There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3) The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4) The test method is not a biological/immunological/immunochemical method or a method using a biological reagent.
5) . An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA variation.
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation, which includes a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2) Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

34. Change in source of an excipient or reagent with TSE risk	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change from TSE risk material to vegetable or synthetic origin:			
1. For excipients or reagents used in the manufacture of biological active substance or a finished product containing a biological active substance		**1, 2**	**IB**
2. For excipients or reagents not used in the manufacture of biological active substance or a finished product containing a biological active substance	**1**	**1**	**IA**
b) Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability			**II**
Conditions			
1) Excipient and finished product release and end of shelf-life specifications remain the same.			
Documentation			
1) Declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin.			

2) Study of equivalence of the materials and the impact on production of the final material and impact on behavior (e.g. dissolution characteristics) of the finished product.

35. Change in synthesis or recovery of a non-pharmacopeial excipient (when described in the dossier) or a novel excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change in synthesis or recovery of a non-pharmacopeial excipient or a novel excipient	**1, 2**	**1, 2, 3, 4**	**IA**
b) The specifications are affected or there is a change in physicochemical properties of the excipient which may affect the quality of the finished product.			**II**
c) The excipient is a biological/immunological substance			**II**
Conditions			
1) The synthesis and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with ICH / VICH limits), or in physicochemical properties.			
2) Adjuvants are excluded.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.			
3) Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal products, comparative disintegration data may be acceptable.			
4) Copy of approved and new (if applicable) specifications of the excipient.			

d) Control of finished product

36. Change in the specification parameters and/or limits of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
c) Change outside the approved specifications limits range			**II**
d) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
e) Addition or replacement(excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
f) Deletion of a non-significant specification parameter (e. g deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	**1, 2, 8**	**1, 2, 6**	**IA**
g) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product	**1, 2, 3, 4, 7, 8**	**1, 2**	**IA**

Conditions

1) The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).

2) The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.

3) Any change should be within the range of currently approved limits.

4) The test procedure remains the same.

5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6) The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.

7) The change does not concern any impurities (including genotoxic) or dissolution.

8) The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the finished product) any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.) a test that is required for the particular dosage form in accordance with the general monograph in an official pharmacopeia; any request for skip testing.
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Comparative table of current and proposed specifications.
3) Details of any new analytical method and validation data.
4) Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.
5) Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal products, comparative disintegration data may be acceptable.
6) Justification/ risk-assessment showing that the parameter is non-significant.
7) Justification of the new specification parameter and the limits.

37. Change in test procedure for the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure.	**1, 2, 3, 4**	**1, 2**	**IA**
b) Change (including replacement or addition) to a biological/immunological/immunochemical test method or a method using a biological reagent.			**II**
c) Other changes to a test procedure (including replacement or addition).		**1, 2**	**IB**
d) Deletion of a test procedure if an alternative method is already authorized.	**4**	**1**	**IA**
e) Update of the test procedure to comply with the updated general monograph in an official pharmacopeia.	**2, 3, 4, 5**	**1**	**IA**
Conditions			

1) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2) There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3) The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4) The test method is not a biological/immunological/immunochemical method or a method using a biological reagent. (does not include standard pharmacopoeial microbiological methods). -
5) The registered test procedure already refers to the general monograph of an official pharmacopeia and any changes are minor in nature and require update of the technical dossier.
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation, which includes a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2) Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.; This requirement is not applicable in case of an addition of a new test procedure.

38. Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

e) Container closure system

39. Change in immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change in qualitative and quantitative composition			
1. Solid pharmaceutical forms.	**1, 2, 3**	**1, 2, 3, 4,5, 6**	**IA$_{IN}$**
2. Semi-solid and non-sterile liquid pharmaceutical forms.		**1, 2, 3,4, 5, 6**	**IB**
3. Sterile medicinal products and biological/ immunological medicinal products.			**II**
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			**II**
b) Change in the container type or addition of a new container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms.		**1, 2, 3,4, 5, 6 , 7**	**IB**
2. Sterile medicinal products and biological/ immunological medicinal products.			**II**
3. Deletion of an immediate packaging that does not lead to the complete deletion of a strength or pharmaceutical form	**4**	**1,8**	**IA**
Conditions			
1) The change only concerns the same packaging/container type (e.g. blister to blister).			
2) The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
3) Satisfactory results of the relevant stability studies have been started according to the GCC stability guidelines and relevant stability parameters have been assessed in at least two pilot scale or production scale batches for at least three months.			
4) The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			

2)	Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture).
3)	Proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). including confirmation that the material complies with relevant pharmacopoeial requirements.
4)	The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.
5)	A letter of commitment to finalize the stability studies and the data must be submitted immediately to the authority only in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf life with the proposed action.
6)	Comparative table of the current and proposed immediate packaging specifications, if applicable.
7)	Samples of the new container/closure where applicable
8)	Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics.

40.	**Change in the specification parameters and/or limits of the immediate packaging of the finished product**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a)	**Tightening of specification limits.**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new specification parameter to the specification.**	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c)	**Addition or replacement of a specification parameter as a result of a safety or quality issue.**		**1, 2, 3, 4, 6**	**IB**
d)	**Deletion of a non-significant specification parameter (e. g deletion of an obsolete test).**	**1, 2**	**1, 2, 5**	**IA**

	Conditions
1)	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).
2)	The change does not result from unexpected events arising during manufacture.
3)	Any change should be within the range of currently approved limits.
4)	The test procedure remains the same.

5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Comparative table of current and proposed specifications.
3) Details of any new analytical method and validation data.
4) Batch analysis data on two batches of the immediate packaging for all specification parameters.
5) Justification/risk-assessment showing that the parameter is non-significant or that it is obsolete.
6) Justification of the new specification parameter and the limits.

41. Change in test procedure for the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorized	**5**	**1**	**IA**
Conditions			
1) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former.			
2) The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
3) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
4) The active substance/finished product is not biological/immunological.			
5) An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA variation.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation, which includes a description of the analytical methodology and a summary of validation data.			

2) Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure .

42. Change in shape or dimensions of the container or closure (immediate packaging)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Non-sterile medicinal products	**1, 2, 3**	**1, 2, 4**	**IA**
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product			**II**
c) Sterile medicinal products		**1, 2, 3, 4**	**IB**

Conditions
1) No change in the qualitative or quantitative composition of the container.
2) The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
3) In case of a change in the headspace or a change in the surface/volume ratio, a satisfactory results of the stability studies that have been started according to the GCC stability guidelines, and relevant stability parameters have been assessed in at least two pilot scale or production scale batches (three for biological/ immunological medicinal product) and at least three months (six months for biological/immunological medicinal product).
Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation (including description, detailed drawing and composition of the container or closure material).
2) Samples of the current and new container/closure where applicable .
3) Re-validation studies have been performed in case of sterile products terminally sterilized and the summary of validation data is required.
4) In case of a change in the headspace or a change in the surface/volume ratio, the following should be submitted: • The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches (three batches for biological/immunological medicinal product) for at least three months (six months for biological/immunological medicinal product). • A letter of commitment to finalize the stability studies and the data must be submitted immediately to the authority only in case of any out-of-specifications (OOS) results or potentially outside specifications at the end of the approved shelf life with the proposed action.

43. Change in pack size of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack		**1, 2, 3, 4, 5, 6, 7**	**IB**
b) Deletion of a pack size(s)	**1**	**1, 2**	**IA**
c) Change in the fill weight/fill volume of sterile multi-dose (or single-dose, partial use) medicinal products, and biological/ immunological multi-dose medicinal products.			**II**
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		**1, 2, 3, 4, 5, 6, 7**	**IB**
Conditions			
1) The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation, including revised product information as appropriate.			
2) Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of use as approved in the summary of product characteristics.			
3) Certificate of a Pharmaceutical Product (CPP) stating the new pack size.			
4) The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.			
5) A letter of commitment to finalize the stability study and to report any out-of-specification results immediately to the authority.			
6) A recent and official price certificate by the company and legalized by the Saudi Embassy in the country of origin (indicating the new pack size).			
7) Samples of the finished product.			
Note: for 40.a), New pack size should be consistent with the posology and treatment duration as approved in the summary of product characteristics, and the primary packaging material remains the same.			

44. Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as color of flip-off caps, color code rings on ampoules, change of needle shield (different plastic used)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change that affects the product information	**1**	**1**	**IA$_{IN}$**
b) Change that does not affect the product information	**1**	**1**	**IA**
Conditions			
1) The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			

45. Change in supplier of packaging components or devices (when mentioned in the dossier)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Deletion of a supplier	**1**	**1**	**IA**
b) Replacement or addition of a supplier	**1, 2, 3, 4**	**1, 2, 3**	**IA**
c) Any change to suppliers of spacer devices for metered dose inhalers			**II**
Conditions			
1) No deletion of packaging component or device.			
2) The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.			
3) The specifications and quality control method are at least equivalent.			
4) The sterilization method and conditions remain the same, if applicable.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) For devices for medicinal products for human use, proof of CE marking.			
3) Comparative table of current and proposed specifications, if applicable.			

46. Change in the packaging design of the primary and/or Secondary packaging not in contact with the finished product formulation	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1,2,3	**IB**
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) The submitted documents should clearly outline the “present” and “proposed” mock-up.			
3) Sample of the artwork			

f) Stability

47. Change in the shelf-life or storage conditions of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Reduction of the shelf-life of the finished product			
1. As packaged for sale	**1**	**1, 2, 3**	**IA$_{IN}$**
2. After first opening			
3. After dilution or reconstitution			
b) Extension of the shelf-life of the finished product			
1. As packaged for sale (supported by real time data)		**1, 2, 3**	**IB**
2. After first opening (supported by real time data)			
3. After dilution or reconstitution (supported by real time data)			
4. Extension of the shelf-life of a biological/immunological medicinal product in accordance with an approved stability protocol		**1, 2, 3**	**IB**
c) Change in storage conditions of the finished product or the diluted/reconstituted product		**1, 2, 3**	**IB**
d) Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol			**II**
e) Change to an approved stability protocol	**1, 2**	**1, 2, 4**	**IA**
Conditions			
1) The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
2) The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			

2)	Recent real time stability studies (covering the entire shelf-life) conducted according to the GCC stability guidelines and relevant stability parameters have been assessed on at least two pilot scale batches* of the finished product in the authorized packaging material and/or after first opening or reconstitution (in-use stability), as appropriate; where applicable, results of appropriate microbiological testing should be included.
3)	Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.
4)	Justification for the proposed change(s).
Note: for Documentation 2) Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches	

g) Design Space:

48.	**Introduction of a new design space or extension of an approved design space for the finished product, concerning:**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
c)	**One unit operation in the manufacturing process of the finished product including the resulting in- process controls and/or test procedures**		**1, 2, 3**	**II**
d)	**Test procedures for excipients/intermediates and/or the finished product**		**1, 2, 3**	**II**
Documentation				
4)	The design space has been developed in accordance with the relevant scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.			
5)	Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
6)	Replacement of the relevant pages of the dossier that are affected by the variation.			

II.3 CEP/TSE/Monograph

49. Submission of a new or updated certificate of suitability or deletion of certificate of suitability: • **For an active substance.** • **For a starting material/reagent/intermediate used in the manufacturing process of the active substance.** • **For an excipient.**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Certificate of Suitability			
1. New certificate from an already approved manufacturer.	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
2. Updated certificate from an already approved Manufacturer.	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition).	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
4. Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
5. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**
b) TSE Certificate of suitability for an active substance/starting material/reagent/intermediate/or excipient.			
1. New certificate for an active substance from a new or an already approved manufacturer.	**3, 5, 6, 11**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
2. New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer.	**3, 6, 9**	**1, 2, 3, 4, 5**	**IA**
3. Updated certificate from an already approved manufacturer.	**7, 9**	**1, 2, 3, 4, 5**	**IA**
4. Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
5. New/updated certificate from an already approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect			**II**

to potential contamination with adventitious agents is required			

Conditions

1) The finished product release and end of shelf-life specifications remain the same.
2) Unchanged (excluding tightening) additional specifications 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 active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4) For active substance only, it will be tested immediately prior to use if no retest period is included in the Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5) The active substance/starting material/reagent/intermediate/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 medicinal products: there has been no change in the source of material.
8) For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
9) If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should only be manufactured in compliance with the relevant country requirements.
10) At least one manufacturer for the same substance remains in the dossier.
11) If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Documentation

1) Copy of the current (updated) Certificate of Suitability.
2) The submitted documents should clearly outline the “present” and “proposed” manufacturers.
3) Replacement of the relevant pages of the dossier that are affected by the variation.
4) Where applicable, a document providing information of any materials falling within the scope of the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products or an equivalent guideline of the ICH region and associated countries including those which are used in the manufacturer of the API. 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) Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance 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. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. The manufacture of intermediates also require a QP declaration, while 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) Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

50. Change to comply with reference pharmacopeia	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change of specification(s) of a former non-pharmacopeial substance to comply with reference pharmacopeia			
1. Active substance	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA_{IN}**
2. Excipient/active substance starting material	**1, 2, 4**	**1, 2, 3, 4**	**IA**
b) Change to comply with an update of the relevant monograph of the reference pharmacopeia, or changing specifications from in-house to reference pharmacopeia.	**1, 2, 4, 5**	**1, 2 , 3, 4**	**IA**
c) Change in specifications from a reference pharmacopeia to another reference pharmacopeia.	**1, 4, 5**	**1 , 2, 3, 4**	**IA**
Conditions			
1) The change is made exclusively to comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.			
2) Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form).			
3) No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened.			
4) Additional validation of a new or changed pharmacopoeial method is not required.			
5) For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.			

Documentation
1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Comparative table of current and proposed specifications.
3) Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable.
4) Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.

II.4 PMF/VAMF

51. Inclusion of a new, updated or amended Plasma Master File in the marketing authorization dossier of a medicinal product.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) First-time inclusion Plasma Master File affecting the properties of the finished product			**II**
b) First-time inclusion of a new Plasma Master File not affecting the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA**
Conditions			
1) The new, update or amended Plasma Master File has been granted a certificate of compliance from the competent authority			
Documentation			
1) Letter declaring that: • The PMF certificate, evaluation report and PMF are fully applicable to the authorized product, • PMF holder has submitted the PMF certificate, evaluation report and PMF dossier to the MAH (where the MAH is different from the PMF holder), • The PMF certificate, evaluation report and PMF dossier replace the previous PMF documentation for this Marketing Authorization.			
2) Plasma Master File (PMF) certificate, evaluation report and PMF dossier (or amended parts).			
3) An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished product.			
4) The submitted documents should clearly outline the "present" and "proposed" PMF certificate.			

52. Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorization dossier of a medicinal product.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) First-time inclusion Vaccine Antigen Master File affecting the properties of the finished product			**II**
b) Inclusion of an updated/amended Vaccine Antigen Master File when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Vaccine Antigen Master when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA**

Conditions

1) The new, update or amended Vaccine Antigen Master File has been granted a certificate of compliance from the competent authority.

Documentation

1) Letter declaring that:
   - The VAMF certificate, evaluation report and VAMF are fully applicable to the authorized product,
   - VAMF holder has submitted the VAMF certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different from the VAMF holder),
   - The VAMF certificate, evaluation report and VAMF dossier replace the previous VAMF documentation for this Marketing Authorization.
2) VAMF certificate, evaluation report and VAMF dossier (or amended parts).
3) An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products.
4) The submitted document should clearly outline the “present” and “proposed” VAMF certificate.

II.5 Drug containing medical device

53. Change of a measuring or administration device	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Spacer device for metered dose inhalers			**II**
2. Certified Device (for example with CE marking)	**1, 2, 3, 6, 7**	**1, 2**	**IA_{IN}**
3. Non certified Device for veterinary products only		**1, 3**	**IB**
b) Deletion of a device	**4, 5**	**1, 4**	**IA_{IN}**
c) Addition or replacement of a device which is an integrated part of the primary packaging			**II**
Conditions			
1) The proposed measuring or administration device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.			
2) The new device is compatible with the medicinal product.			
3) The change should not lead to substantial amendments of the product information.			
4) The medicinal product can still be accurately delivered.			
5) For veterinary medicinal products, the device is not crucial for the safety of the person administering the product.			
6) The medical device is not used as a solvent of the medicinal product.			
7) If a measuring function is intended the certification should cover the measuring function.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation (including description, detailed drawing and composition of the device material and supplier where appropriate).			
2) Proof of certification.			
3) Data to demonstrate accuracy, precision and compatibility of the device.			
4) Justification for the deletion of the device.			

54. Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Widening of the approved specifications limits, which has a significant effect on the overall quality of the device			**II**
d) Deletion of a specification parameter that has a significant effect on the overall quality of the device			**II**
e) Addition of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**
f) Deletion of a non-significant specification parameter (e. g deletion of an obsolete test)	**1, 2**	**1, 2, 5**	**IA**
Conditions			
1) The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).			
2) The change should not be the result of unexpected events arising during manufacture.			
3) Any change should be within the range of currently approved limits.			
4) The test procedure remains the same.			
5) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) Comparative table of current and proposed specifications.			
3) Details of any new analytical method and summary of validation data.			
4) Batch analysis data on two production batches for all tests in the new specification.			
5) Justification/risk-assessment showing that the parameter is non-significant.			
6) Justification for the new specification parameter and the limits.			

55. Change in test procedure of a measuring or administration device for veterinary medicinal products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change to an approved test procedure	**1, 2,**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorized	**4**	**1**	**IA**

Conditions

1) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former.

2) The method of analysis should remain the same.

3) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

4) An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1) Replacement of the relevant pages of the dossier that are affected by the variation which includes a description of the analytical methodology and a summary of validation data.

2) Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

III. Safety, Efficacy, Pharmacovigilance Changes

III. 1 Human and veterinary medicinal products

56. Change in the summary of product characteristics, labeling and patient information leaflet of a generic/hybrid/biosimilar medicinal product following assessment of the same change for the reference product.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Implementation of change(s) for which no new additional data are submitted by the MAH		**1, 2**	**IB**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH, or the change has not been approved for the reference product by the competent authority.			**II**
Documentation			
1) Attached to the cover letter of the variation application: the competent authority request, if available.			
2) Revised product information.			

57. Change(s) in the summary of product characteristics, labeling and patient information leaflet related to an urgent safety restriction, class labeling, a periodic safety update report, risk management plan, or follow up measure/specific obligation.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Implementation of change(s) requested by GCC or any local authority within GCC following the assessment of an urgent safety restriction, class labeling, a periodic safety update report, risk management plan, or follow up measure/specific obligation.			
1. Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH		**1, 2**	**IB**
2. Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			**II**
b) Change(s) proposed by the MAH with submission of a periodic safety update report, risk management plan, follow up measures/specific obligations.			**II**

Documentation
1) Attached to the cover letter of the variation application: the competent authority request with attached relevant assessment report, if available.
2) Revised product information.
Note: MAHs are reminded that once new information becomes available (e.g. new study data) which might entail the variation of the MA, this should be submitted as a variation.

58. Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

59. Change(s) to therapeutic indication(s)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Addition of a new therapeutic indication or modification of an approved one			**II**
b) Deletion of a therapeutic indication			**II**

60. Deletion of:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) a pharmaceutical form		**1, 2**	**IB**
b) a strength		**1, 2**	**IB**
Documentation			
1) Declaration that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.			
2) Revised product information.			

61. Change(s) to a PSMF following the assessment of the same change(s) to the same DDPS in relation to another medicinal product of the same MAH.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1**	**IA**
Conditions			
1) The same changes to the PSMF are introduced for all medicinal products of the same MAH (same final PSMF version)			
Documentation			
1) Latest approved version of the PSMF.			

III. 2 Veterinary medicinal product - Specific Changes

62. Variations concerning a change to or addition of a non-food producing target species.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

63 Deletion of a food producing or non-food producing target species.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Deletion as a result of a safety issue			**II**
b) Deletion not resulting from a safety issue		**1, 2**	**IB**
Documentation			
1) Justification for the deletion of the target species.			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

64. Changes to the withdrawal period for a veterinary medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

65. Variations concerning the 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.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

66. Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

67. Changes to the labeling or the package leaflet which are not connected with the summary of product characteristics.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) **Administrative information concerning the holder's representative**		**1**	**IA$_{IN}$**
b) **Other changes.**		**1**	**IB**
Conditions			
None			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			

68. Introduction of a new Pharmacovigilance system	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Which has not been assessed by the relevant national competent authority for another product of the same MAH			**II**
b) Which has been assessed by the relevant national competent authority for another product of the same MAH		**1, 2**	**IB**
Documentation			
1) The new Detailed Description of the Pharmacovigilance System(DDPS)			
2) Reference to the application/procedure and product in which the DDPS was assessed previously			

IV. PMF/VAMF

69. Change in the name and/or address of the VAMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1**	**IA_{IN}**
Conditions			
1) The VAMF certificate holder must remain the same legal entity.			
Documentation			
1) A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

70. Change in the name and/or address of the PMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1**	**IA_{IN}**
Conditions			
1) The PMF certificate holder must remain the same legal entity.			
Documentation			
1) A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

71. Change or transfer of the current PMF certificate holder to a new PMF certificate holder, i.e. different legal entity	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3, 4, 5, 6	**IA_{IN}**
Documentation			
1) A document including the identification (name and address) of the current PMF Holder (transferor) and the identification (name and address) of the person to whom the transfer is to be granted (transferee) together with the proposed implementation date — signed by both companies.			
2) Copy of the latest PMF Certificate page 'EMA Plasma Master File (PMF) Certificate of compliance with Community legislation'.			

3) Proof of establishment of the new holder (Excerpt of the commercial register and the English translation of it) — signed by both companies.
4) Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee — signed by both companies.
5) Letter of Authorisation including contact details of the person responsible for communication between the competent authority and the PMF holder — signed by the transferee.
6) Letter of Undertaking to fulfil all open and remaining commitments (if any) — signed by the transferee.

72. Change in the name and/or address of a blood establishment including blood/plasma collection centers	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1, 2, 3,**	**IA**
Conditions			
1) The blood establishment shall remain the same legal entity.			
2) The change shall be administrative (e.g. merger, take over); change in the name of the blood establishment/ collection centre provided the blood establishment shall remain the same.			
Documentation			
1) Signed declaration that the change does not involve a change of the quality system within the blood establishment.			
2) Signed declaration that there is no change in the list of the collection centers.			
3) Updated relevant sections and annexes of the PMF dossier.			

73. Replacement or addition of a blood/plasma collection establishment within a blood establishment already included in the PMF.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2, 3	**IB**
Documentation			
1) Epidemiological data for viral markers related to the blood/plasma collection centre covering the last 3 years. For newly opened centre(s) or in case no data are yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s).			
2) Statement that the centre is working under the same conditions as the other centers belonging to the blood establishment, as specified in the standard contract between blood establishment and PMF holder.			
3) Updated relevant sections and annexes of the PMF dossier.			

74. Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the for testing donations and plasma pools.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	**1**	**IA**
Conditions			
1) The reason for deletion or change of status should not be related to a GMP issue.			
2) The establishments(s)/centre(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.			
Documentation			
1) Updated relevant sections and annexes of the PMF dossier.			

75. Addition of a new blood establishment for the collection of blood/plasma not included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

76. Replacement or addition of a blood centre for testing donations and/or plasma pools within an establishment already included in the PMF.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	**IB**
Documentation			
1) Statement that the testing site is performed following the same SOPs and/or test methods as the already accepted.			
2) Updated relevant sections and annexes of the PMF dossier.			

77. Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

78. Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	**IB**
Documentation			
1) Statement that the storage centre is working following the same SOPs as the already accepted establishment.			
2) Updated relevant sections and annexes of the PMF dossier.			

79. Deletion of a blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1**	**IA**
Conditions			
1) The reason for deletion should not be related to a GMP issues.			
Documentation			
1) Updated relevant sections and annexes of the PMF dossier.			

80. Replacement or addition of an organization involved in the transport of plasma.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	**IB**
Documentation			
1) Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organization, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.			

81. Deletion of an organization involved in the transport of plasma	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1**	**IA**
Conditions			
1) The reason for deletion should not be related to GMP issues.			
Documentation			
1) Updated relevant sections and annexes of the PMF dossier.			

82. Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1, 2**	**IA**
Conditions			
1) The new test kit is CE-marked.			
Documentation			
1) List of testing site(s) where the kit is used.			
2) Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".			

83. Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new test kit has not previously been approved in the PMF for any blood centre for testing of donations			**II**
b) The new test kit has been approved in the PMF for other blood centre(s) for testing of donations		**1, 2**	**IA**
Documentation			
1) List of testing centre(s) where the kit is currently used and a list of testing centre(s) where the kit will be used.			
2) Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".			

84. Change of kit/method used to test pools (antibody or antigen or NAT test).	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

85. Introduction or extension of inventory hold procedure.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	**1**	**IA**
Conditions			
1) The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).			
Documentation			
1) Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.			

86. Removal of inventory hold period or reduction in its length.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	**IB**
Documentation			
1) Updated relevant sections of the PMF dossier.			

87. Replacement or addition of blood containers (e.g. bags, bottles)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new blood containers are CE-marked	**1, 2**	**1**	**IA**
b) The new blood containers are not CE-marked		**1**	**II**
Conditions			
1) The container is CE-marked.			
2) The quality criteria of the blood in the container remain unchanged.			

Documentation
1) Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.

88. Change in storage / transport	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) storage and/or transport conditions	**1**	**1**	**IA**
b) maximum storage time for the plasma	**1, 2**	**1**	**IA**
Conditions			
1) The change should tighten the conditions and be in compliance with Ph. Eur. requirements for Human Plasma for Fractionation.			
2) The maximum storage time is shorter than previously.			
Documentation			
1) Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).			

89. Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

90. Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1	**IB**
Documentation			
1) Updated relevant sections of the PMF dossier.			

91. Change in the steps that would be taken if it is found retrospectively that donation(s) should have been	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**

excluded from processing (“look-back” procedure).			
			II

7. Appendix 2: Changes that make a new application necessary

Examples for changes that make a new application necessary include but are not limited to the following:

1. Changes to the API, for example:

    - Change of the API to a different API;
    - Inclusion of an additional API in a multi-component product;
    - Removal of one API from a multi-component product;
    - Change in the dose of one or more APIs.

2. Changes to the pharmaceutical form/dosage form, for example:

    - Change from an immediate-release product to a slow- or delayed-release dosage form and vice versa;
    - Change from a liquid to a powder for reconstitution, or vice versa.
    - A change from multi-dose to single-dose or vice-versa (both for addition or replacement).

3. Changes to the strength.

4. A change or addition of route of administration.

5. The addition or replacement of measuring or administration device being an integrated part of the primary packaging that results in a change to the strength, pharmaceutical form or route of administration of the product.

6. Other changes specific to veterinary medicinal products to be administered to food-producing animals; change or addition of target species.

8. Appendix 3: Requirements for addition/change to API suppliers:

1. Addition/change to an API supplier that has already been submitted:

Requirements:

1. A declaration letter indicating that the DMF of the new API supplier has been evaluated by SFDA during the last five years and no changes have been made since that time.
2. Section (3.2.P) :

   A letter of commitment to immediately initiate accelerated and long term (covering shelf life) stability studies on at least one production batch of the finished product according to the GCC guidelines using API from the new supplier and submit stability data immediately to the authority only in case of any out of specification results (OOS) or potentially outside specifications at the end of the approved shelf life along with the proposed action.

   Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance from both the current and proposed sites. For herbal products, comparative disintegration data may be acceptable.

2. Addition/change to an API supplier where a Certificate of Suitability (CEP) is available:

Requirements:

1. Section (3.2.S):

   The applicant should submit:

   - A valid Certificate of Suitability (CEP) (including any annexes) where the declaration of access for the CEP should be duly filled out by the CEP holder.
   - written assurance that no significant changes in the manufacturing method have taken place following the granting of certificate or its last revision.
   - 3.2.S.1.3 General properties.
   - 3.2.S.3.1 Elucidation of structure and other characteristics.
   - 3.2.S.4.1 Specification from both API manufacturer and the finished product manufacturer.

- 3.2.S.4.4 Batch analysis from both API manufacturer and the finished product manufacturer.
- 3.2.S.7 Stability.

2. Section (3.2.P):

   A letter of commitment to immediately initiate accelerated and long term (covering shelf life) stability studies on at least one production batch of the finished product according to the GCC guidelines using API from the new supplier and submit stability data immediately to the authority only in case of any out of specification results (OOS) or potentially outside specifications at the end of the approved shelf life along with the proposed action.

   Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance from both the current and proposed sites. For herbal products, comparative disintegration data may be acceptable.

3. Addition/change to an API supplier where no Certificate of Suitability (CEP) is available:

Requirements:

1. Section (3.2.S):

   Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the drug substance may be submitted as DMF.

2. Section (3.2.P):

   A letter of commitment to immediately initiate accelerated and long term (covering shelf life) stability studies on at least one production batch of the finished product according to the GCC guidelines using API from the new supplier and submit stability data immediately to the authority only in case of any out of specification results (OOS) or potentially outside specifications at the end of the approved shelf life along with the proposed action.

   Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance from both the current and proposed sites. For herbal products, comparative disintegration data may be acceptable.

– Abbreviations

API	Active Pharmaceutical Ingredient.
ATC	Anatomical Therapeutic Chemical (ATC) Classification.
CEP	Certificate of Suitability.
DDPS	Detailed Description of Pharmacovigilance System.
DER	Drug Extract Ratio.
DMF	Drug Master File.
ICH	International Conference on Harmonization.
INN	International Nonproprietary Name.
IPC	In-Process Control.
MAH	Marketing Authorization Holder.
PMF	Plasma Master File.
QP	Qualified Person.
SFDA	Saudi Food and Drug Authority.
TSE	Transmissible Spongiform Encephalopathy.
VAMF	Vaccine Antigen Master File.
WHO	World Health Organization.
NAT	Nucleic Acid Testing.
Vet	Veterinary.
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products.
MA	Marketing Authorization.
QPPV	Qualified Person for Pharmacovigilance.
PSURs	Periodic Safety Update Reports.
ICSRs	Individual Case Safety Reports.
CV	Curriculum Vitae.
GMP	Good Manufacturing Practice.
SOPs	Standard Operating Procedures.

– References

- Guidelines on the details of the various categories of variations, Regulation (EC) No 1234/2008 article 4(1)(a).