Medicine Variations Guideline

National Health Regulatory Authority (NHRA)

Kingdom of Bahrain

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1. Introduction

Guideline documents are meant to provide assistance to industry and professionals on how to comply with governing statutes and regulations. Guideline documents also provide assistance to staff on how NHRA mandates and objectives should be implemented in a manner that is fair, consistent and effective.

The purpose of this guideline is to provide clear instruction on the NHRA procedure for varying a medicine license.

This guideline is adapted from the European variations legislation and associated guidance and has been developed to assist applicants in the preparation and submission of applications for variations to existing medicines licenses. Such applications should contain the data necessary to support the quality, safety and efficacy of the product as necessary. These data are reviewed by the NHRA in accordance with the procedures outlined below and a conclusion reached based upon the likely balance of the benefits versus risks associated with the variation.

2. Scope

This document applies to change(s) made on drug products that have already received a marketing authorization from the NHRA.

3. General notes

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

a) NHRA approval is a must for any variation to the approved medicine information which is not listed in this guideline.
b) NHRA will issue variation approval letter only for Type IB & II.
c) Company must implement the submitted variation within six months from the approval letter date.
d) Variation applications are accepted for products which have valid license only. However in case the re- registration of product license is scheduled, an individual variation application shall be accepted.
e) It is important to note that NHRA 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. NHRA is committed to ensure that such requests are justifiable and decisions are clearly documented.

f) Applicants should be aware that deficient documentation can lead to rejection of the application. In addition, submitting redundant or irrelevant information may hamper approval procedures.

g) All days mentioned throughout this document are expressed as working days (subjected to change).

h) Some parts in the appendixes are changed and specific for NHRA accordingly the applicant must read it and be aware of the differences between this document and other authority's similar guidance.

i) According to NHRA's eCTD implementation plan, the variation submission in eCTD format is mandatory from the 2nd of May 2017. This applies only to human medicine applications. The details are mentioned in **appendix 4.**

j) Response to information requested via an information request form (IRF) should be got within 3 months of date of issued. Otherwise the application can be rejected.

k) Variation applications that have GCC-DR approval will be considered for fast track assessment. A complete variation application along with GCC-DR approval should be submitted for assessment.

4. Submission procedure and requirements

4.1. Before submission

Applicants must prepare the variation application according to the requirements, and assure all the documents are available before submission.

Country of origin approval/proof of approval for the proposed variation is a must for all relevant variations.

4.2. Submission procedure

In order to submit a variation application the applicant must request an appointment with the PPR Department at NHRA on the designated day and time. Applicants must take appointment by email and confirmation of the date and time of the appointment will be emailed to the applicant. Appointments are assigned on a first-come basis.

4.3. Submission requirements

Other than the documents mentioned in the appendix **I** applicant must submit the following requirements**:**

a) Cover letter from the local agent clearly mentioning: product name & description, proposed variation & type and implementation date.

b) Cover letter and a duly filled variation application form signed and stamped from the MAH Company clearly mentioning: product name & description, proposed variation & type and 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.

c) Declaration from the MAH Company with the implementation date for the proposed variation and a letter of justification for the proposed variation if applicable.

d) Country of origin approval for the change or proof of the change in country of origin (where applicable).

e) Mandatory hardcopy requirements for an eCTD submission (Appendix 4)

   I. Cover letter from the agent and MAH.
   II. All relevant original document if applicable.
   III. Validation report.
   IV. Application form.

5. Classification of variation application

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

Minor variation:

• Type IA: Such minor variations do not require prior approval before implementation ("Do and Tell" procedure) but require notification submitted by the marketing authorization holder (MAH) within 60 working days after implementation (***NHRA will accept notification Type IA variation application every week on the appointed time***). 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. Type IA variation will be rejected when not all of the conditions for the Type IA variation are met, the MAH shall immediately cease to apply the rejected changes.

• Type IB: Such minor variations must be notified to NHRA by the Marketing Authorization Holder (MAH) before implementation through official application on the assigned day the MAH must wait a period of 180 working days to ensure decision from NHRA before implementing the change ("Tell, Wait and Do" procedure).

Major variation:

• 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, the appendices explicitly define the various types of changes:

• **Appendix 1** lists some major changes and most minor changes which are classified by the type of change and the conditions which frame the type of change. When the conditions are not met, the change may either classify as a major change or may make a new application necessary.

• **Appendix 2** lists examples for major changes.

• **Appendix 3** lists the types of changes that make a new application is necessary.

Appendix 1: Examples for some major changes and most minor changes

I. Administrative Changes

1.Change in the name and/or address of 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 5**	**IA**
b) Transfer the product to new marketing authorization holder.	**2**	**1,2,3,4**	**IB**
Conditions			
1) The marketing authorization holder (MAH) shall remain the same legal entity.			
2) The marketing authorization holder (MAH) is a different 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) Legalized certificate of pharmaceutical product (CPP).			
5) Declaration letter from the MAH for no change in legal entity.			

2.Change in the (invented) name of the medicinal product.	**Condition to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IB**
Conditions			
1) No confusion with the International Nonproprietary Name (INN).			
2) No confusion with other marketed trade name in Bahrain.			
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.			

3.Change in name of the active substance.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA
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.			

4.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".			

5.Change in the name/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
b) All other.			
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.

6. Change in ATC 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.			
Documentation			
1) Proof of acceptance (by WHO).			
2) Replacement of the relevant pages of the dossier that are affected by the variation.			

7.Deletion of a manufacturing sites (including for an active Substance, intermediate or finished product, packaging 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

8. 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.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The proposed manufacturer is part of the same organization as the currently approved manufacturer.	**1, 2, 3**	**1, 2, 3, 4, 5, 6,7 ,8**	**IB**
b) Submission of a new drug master file (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/immunological product.			**II**
Conditions			
1) The specifications (including in-process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.			
2) The active substance is not a biological/immunological substance or sterile.			
3) Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment of viral safety or TSE risk is required.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			
2) Legalized valid GMP certificate of the site.			
3) 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.
4) 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.
5) 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.
6) The submitted documents should clearly outline the "present" and "proposed" manufacturers.
7) 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.
8) 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 NHRA only in case of any out of specification results (OOS) along with the proposed action.

9.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**	**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 medicine 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**	**IB**
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 medicines, 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.
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) Declaration that there are 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.

10. Change in batch size of active substance or intermediate.	**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**	**1, 2**	**IA**
b) Downscaling.	**1, 2, 3, 4, 5**	**1, 2**	**IA**
c) The change relates to a biological/immunological active substance.			**II**
d) More than 10-fold increase compared to the currently approved batch size.		**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.
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).

11. 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 test and limits.	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**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, 5, 7**	**IB**
f) Deletion of a non-significant in-process test.		**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.
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 biological, unless otherwise justified) of the active 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 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 for the new in-process test and limits.

b) Control of active substance

12. 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**
b) Addition of a new specification parameter to the specification.	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 6, 8**	**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 replacement of a specification parameter as a result of a safety or quality issue.		**1, 2, 3, 4, 5, 6, 8**	**IB**

g) Deletion of a non-significant specification parameter (e. g deletion of an obsolete test e.g. organoleptic test).		**1, 2, 7**	**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.			
7) The change does not concern a genotoxic impurity.			
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 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.			

13. 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, 5**	**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. e.g. peptide map, glyco- map, etc.			**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, 6, 7**	**1, 2**	**IB**
e) Deletion of a test procedure for the active substance or a starting material/intermediate, if an alternative test procedure is already authorized.		**1**	**IA**
f) Deletion of a test procedure for reagents, if an alternative test procedure is already authorized.	**8**	**1**	**IA**

Conditions

1) The test procedure is demonstrated to be at least equivalent to the former test procedure.
2) Appropriate validation studies have been performed in accordance with the ICH guidelines and show that the updated test procedure is at least equivalent to the former.
3) There have been no changes of the total impurity limits; no new unqualified impurities are detected
4) 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).
5) The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent.
6) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
7) The active substance is not biological/immunological.
8) There is still a test procedure registered for the specification parameter.

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 showing that the current test and the proposed one are equivalent.

c) Container closure system

14. 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, 4**	**1, 2, 3, 4, 5, 6**	**IB**
b) Change in the container type for:			
1. Sterile and biological/immunological active substances.			**II**
2. All other active substances.		**1, 2, 3, 4, 5, 6**	**IB**
Conditions			
1) The change only concerns the same packaging/container type.			
2) The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
3) Relevant stability studies have been started according to the GCC stability guidelines published on the NHRA website and relevant stability parameters have been assessed in at least two pilot scale or production scale batches for at least three months.			
4) 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 NHRA only in case of any out-of-specifications (OOS) results along with the proposed action.			
6) Comparative table of the current and proposed specifications, if applicable.			

15. 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.	**1, 2, 5**	**1, 2, 3, 4**	**IA**
c) Addition or replacement of a specification parameter as a result of a safety or quality issue.		**1, 2, 3, 4**	**IB**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete test).		**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.			
6) Justification of the new specification parameter and the limits.			

16. 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, 4**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition).	**1, 2, 4, 5**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorized.	**6**	**1**	**IA**
Conditions			
1) The test procedure is demonstrated to be at least equivalent to the former test procedure.			

2) Appropriate validation studies have been performed in accordance with the ICH guidelines and show that the updated test procedure is at least equivalent to the former.
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) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
5) The active substance/ finished product is not biological/immunological.
6) There is still a test procedure registered for the specification parameter.
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 showing that the current test and the proposed one are equivalent.

d) Stability

17. 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) Reduction in the re-test period/storage period of the active substance.	**1**	**1, 2, 3**	**IB**
b) Extension or introduction of a re-test period/storage period of active substances.		**1, 2, 3**	**II**
c) Change in storage conditions of the active substance.		**1, 2, 3**	**IB**
d) 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**
Conditions			
1) The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
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 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.

II.2 *Finished product*

a) Description and composition

18. 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**	**1, 2, 4**	**IB**
b) Changes in scoring/break lines intended to divide into equal doses.		**1, 2, 3, 4**	**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.			
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.			
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)*.			
4) Updated version of the specification sheet.			

19. 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**	**IB**
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets.		**1, 2, 3, 4, 5**	**IB**
Conditions			
1) If appropriate, the dissolution profile of the reformulated product is comparable to the old one. For herbal medicine, 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.

20. 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**	**1, 2,3, 4, 5, 6**	**IB**
2) Increase or reduction.	**1, 2, 4, 5, 6**	**1, 2,3, 4**	**IB**
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, 3, 4, 5, 6, 7, 8, 9**	**IB**
c) Any minor adjustment of the quantitative composition of the finished product with respect to excipients.	**1, 2, 4, 8, 9, 10**	**1, 2, 7**	**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 specification has only been updated in respect of appearance/odor/taste and if relevant, deletion or addition of identification tests.
4) 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.
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 dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicine where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
9) The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between strengths.
10) The 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 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, 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 NHRA only in case of any out-of-specifications (OOS) results 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.

21. 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**	**1, 2,3**	**IB**
b) Gastro-resistant modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism.			**II**
Conditions			
1) The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicine where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.			
2) The coating is not a critical factor for the release mechanism.			
3) The finished product specification has only been updated in respect of weight and dimensions, if applicable.			
4) 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.			
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 published on NHRA website, 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 NHRA only in case of any out-of-specifications (OOS) results along with the proposed action.			

22. Deletion of the solvent/diluent container from the pack.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB
Conditions			
None.			
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

23. 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, 2,6**	**1, 2, 3, 4, 5, 6, 7, 9, 12**	**IB**
b) Primary packaging site.	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5, 6, 7, 9 , 12 , 16**	**IB**
c) Site where any manufacturing operation(s) take place, except batch release and secondary packaging, for sterile medicinal products, and biological/immunological medicinal products.			**II**
d) Site where any manufacturing operation(s) take place, except batch-release, primary and secondary packaging, for non-sterile medicinal products.	**1, 2, 4**	**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,16, 17**	**IB**
Conditions			
1) Satisfactory inspection in the last three 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.			

6)	The secondary packaging does not affect the product stability (e.g. Protect from light and/or moisture).
Documentation	
1)	Replacement of the relevant pages of the dossier that are affected by the variation.
2)	Justification for changing the manufacturing site.
3)	Proof that the proposed site is appropriately authorized for the pharmaceutical form or product concerned.
4)	A certificate of GMP compliance.
5)	The submitted documents should clearly outline the “present” and “proposed” finished product manufacturers.
6)	A statement defining the primary steps of manufacturing process and the site at which each step takes place.
7)	A declaration by the company that the manufacturing process will remain the same. In addition, the API(s), excipient(s) and their source(s), dosage form, concentration, the primary and secondary packaging, labeling, and all specifications for the product must remain the same as previously approved in the old site. A clarification of any proposed change(s) to the manufacturing of the product at the new manufacturing site should be provided and justified.
8)	If the new manufacturing site uses the active substance as a starting material – A declaration by the Qualified Person (QP) 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.
9)	The specifications, composition and source of the raw materials used in the manufacturing for the product concerned.
10)	Copy of approved release and end of shelf-life specifications for the product if relevant.
11)	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).
12)	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.
13)	A letter of commitment to finalize the stability studies and the data must be submitted immediately to the NHRA only in case of any out-of-specifications (OOS) results along with the proposed action.
14)	Where relevant, the batch numbers of batches (3) used in the validation study should be indicated and validation protocol (scheme) to be submitted.
15)	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.

16) 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.
17) Validation of the analytical methods needed for batch release (according to the release specifications) from the proposed secondary packaging site and/or validation for transportation process from manufacturing site to secondary packaging site along with release certificate from secondary packaging site covering all processes from receiving the semi-finished product to final pack.

24. 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**	**IB**
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and one of the test methods performed at that site is not a physico- chemical method.			**II**
c) Replacement of a manufacturer responsible for batch release:			
1) Not including batch control/testing.		**1,2,3,4,5,6,7**	**II**
2) Including batch control/testing.		**1,2,3,4,5,6,7**	**II**
3) Including batch control/testing for a biological/immunological product and one of the test methods performed at that site is not a physicochemical method.			**II**
Conditions			
1) The site is appropriately authorized by NHRA.			
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 (registration certificate) issued by NHRA.			
2) The submitted documents should clearly outline the “present” and “proposed” finished product manufacturers.			
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			

5) New Price form available on NHRA website
6) Legalized valid GMP certificate
7) Legalized certificate of pharmaceutical product (CPP).

25. 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) 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, 3, 4, 5, 6, 7, 8, 9**	**IB**
f) Minor change in the manufacturing process of an immediate release solid oral dosage form.	**1, 2, 3, 4, 5, 6,7, 8**	**1, 3, 4, 6, 7, 8, 9**	**IB**

Conditions
1) No change in qualitative and quantitative impurity profile or in physicochemical properties.
2) The product concerned is not a biological/immunological or herbal product.
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 are required to these controls.
5) The specifications of the finished product or intermediates are unchanged.
6) The product concerned is an immediate release solid oral dosage form.
7) The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
8) 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.

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 medicines, comparative disintegration data may be acceptable.
4) Justification for not submitting a new bioequivalence study.
5) Copy of approved release and end of shelf-life specifications.
6) In case of a change to the sterilization process, validation data should be provided.
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, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.
9) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the NHRA only in case of any out-of-specifications (OOS) results along with the proposed action.

26.Change in the batch size 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**	**1, 4**	**IB**
b) Downscaling down to 10-fold.	**1, 2, 3, 4, 5, 6**	**1, 4**	**IB**
c) The change relates to a biological/immunological medicinal product.			**II**
d) The change relates to all other pharmaceutical forms except standard immediate release oral and non-sterile liquids.			**II**
e) More than 10-fold increase compared to the currently approved batch size for immediate release.	**7**	**1, 2, 3, 4, 5,6**	**IB**

f) Product that was exempted from the biobatch requirement (1/10 of production scale or 100,000 units whichever is greater) because of small production.			**II**
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) 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.			
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) The batch numbers (3) used in the validation study should be indicated or validation protocol (scheme) be submitted.			
5) The results of stability studies that have been carried out according to the GCC stability, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.			
6) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the NHRA only in case of any out-of-specifications (OOS) results along with the proposed action.			

27. 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, 6**	**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 new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.

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 biological, 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 medicines 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

28. 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, 5, 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 of a specification parameter 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, 7**	**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.
7) The change does not concern a genotoxic impurity.
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 medicines, 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.

29.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, 5**	**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.	**6**	**1**	**IA**

Conditions	
1)	The test procedure is demonstrated to be at least equivalent to the former test procedure.
2)	Appropriate validation studies have been performed in accordance with the ICH guidelines and show that the updated test procedure is at least equivalent to the former.
3)	There have been no changes of the total impurity limits; no new unqualified impurities are detected.
4)	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).
5)	The test method is not a biological/immunological/immunochemical method or a method using a biological reagent.
6)	There is still a test procedure registered for the specification parameter.
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 showing that the current test and the proposed one are equivalent.

30. 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 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.			

31. Change in synthesis or recovery of a non-pharmacopeial excipient (when described in the dossier).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change in synthesis or recovery of a non-pharmacopeial excipient.	**1, 2**	**1, 2, 3, 4**	**IB**
b) The specifications are affected or there is a change in physicochemical properties.			**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 (V) ICH 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 medicine, comparative disintegration data may be acceptable.
4) Copy of approved and new (if applicable) specifications of the excipient.

d) Control of finished product

32. 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.	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 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 of a specification parameter 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, 7**	**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 a genotoxic impurity.
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, 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 medicines, 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 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, 5**	**1, 2**	**IB**
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.		**1**	**IB**
Conditions			
1) The test procedure is demonstrated to be at least equivalent to the former test procedure.			

2) Appropriate validation studies have been performed in accordance with the ICH guidelines and show that the updated test procedure is at least equivalent to the former.
3) There have been no changes of the total impurity limits; no new unqualified impurities are detected.
4) 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).
5) The test method is not a biological/immunological/immunochemical method or a method using a biological reagent.
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 showing that the current test and the proposed one are equivalent.

e) Container closure system

34. 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**	**IB**
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 for:			
1) Solid, semi-solid and non-sterile liquid pharmaceutical forms.		**1, 2, 3,4, 5, 6**	**IB**
2) Sterile medicinal products and biological/ immunological medicinal products.			**II**
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) 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.
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).
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, 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 NHRA only in case of any out-of-specifications (OOS) results along with the proposed action.
6) Comparative table of the current and proposed specifications, if applicable.

35. 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, 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.
6) Justification of the new specification parameter and the limits.

36. 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, 4**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition).	**1, 2, 4, 5**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorized.	**6**	**1**	**IA**
Conditions			
1) The test procedure is demonstrated to be at least equivalent to the former test procedure			
2) Appropriate validation studies have been performed in accordance with the ICH guidelines and show that the updated test procedure is at least equivalent to the former.			
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) Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
5) The active substance/finished product is not biological/immunological.			
6) There is still a test procedure registered for the specification parameter			
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 showing that the current test and the proposed one are equivalent.			

37. Change in shape or dimensions of the container or closure.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**

a) Non-sterile medicinal products.	**1, 2, 3**	**1, 2, 4**	**IB**
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, stability studies have been started according to the GCC stability guidelines published on NHRA website, 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, 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 NHRA only in case of any out-of-specifications (OOS) results along with the proposed action.

38.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) Change within the range of the currently approved pack sizes	**1, 2 3,4**	**1, 3, 4, 5, 6, 7, 8, 9**	**IB**

2) Change outside the range of the currently approved pack sizes.	**1, 2 ,4**	**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
b) Deletion of a pack size(s.)	**3**	**1, 2, 5**	**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.	4		**II**
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products.	**1, 2 ,4**	**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
Conditions			
1) New pack size should be consistent with the posology and treatment duration as approved in the summary of product characteristics.			
2) The primary packaging material remains the same.			
3) The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.			
4) Not as an addition to the existing pack size range			
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) A declaration that container closure system (CCS) has not been changed from the previously approved one.			
5) Updated version of the Product Information, including the SPC, labeling, PIL, and Artwork (Mock-up).			
6) The results of stability studies that have been carried out according to the GCC stability, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.			
7) A letter of commitment to finalize and submit the stability study after completion of the study and to report any out-of specification results immediately to the NHRA.			
8) A recent and official price form available on NHRA website.			
9) Samples of the finished product.			

39. 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**
	1, 2	**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.			
2) The registered information on the pack should not change.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			

40. 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**	**IB**
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) Comparative table of current and proposed specifications, if applicable.			

41. 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**
a) Change in the packaging design.	**1,2**	**1,2,3**	**IA**

b) Change in logo.		**1,3**	**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.			
2) The proposed changes should comply with the Guidelines on Container Closure System (Graphic Design section) and the GCC guidelines for Presenting the SPC, PIL and Labeling Information			
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

42. 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, 5, 6**	**IB**
2) After first opening.			
3) After dilution or reconstitution			
b) Extension of the shelf-life of the finished product.			
1) As packaged for sale		**1, 4, 5, 6**	**IB**
2) After first opening			
3) After dilution or reconstitution			
c) Change in storage conditions of the finished product or the diluted/reconstituted product		**1, 4, 5, 6**	**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**
Conditions			
1) The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
Documentation			
1) Replacement of the relevant pages of the dossier that are affected by the variation.			

2) Justification for the reduction in the shelf-life.
3) Stability studies that trigged the proposed change.
4) Recent real time stability studies (covering the entire shelf-life) conducted according to GCC stability guidelines and relevant stability parameters have been assessed on at least three production 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.
5) Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met and no extrapolation is used.
6) Copy of approved end of shelf-life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.

II.3 *CEP/TSE/Monograph*

43. Submission of a new or updated 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**	**1, 2, 3, 4**	**IA**
2) Updated certificate from an already approved Manufacturer.	**1, 2, 3, 4**	**1, 2, 4**	**IA**
3) New certificate from a new manufacturer (replacement or addition).	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA**
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, 6**	**1, 2, 3, 4**	**IA**
2) New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer.	**3, 6**	**1, 2, 3, 4**	**IA**
3) Updated certificate from an already approved manufacturer.		**1, 2, 3, 4**	**IA**
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 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.			
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) For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.			

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.

44. 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, 5**	**IA**
2) Excipient/active substance starting material.	**1, 2, 4**	**1, 2, 3, 4, 5**	**IA**
b) Change to comply with an update of the relevant monograph of the reference pharmacopeia.	**1, 2, 4, 5**	**1, 2**	**IA**
c) Change in specifications from a reference pharmacopeia to another reference pharmacopeia.	**1, 4, 5**	**1**	**IA**
Conditions			
1) The change is made exclusively to comply with the pharmacopoeia.			
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) The substance is not a biological, an immunological or an adjuvant.			
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 on two production batches of the relevant substance for all tests in the new specification.
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.
5) Where appropriate, batch analysis data (in a comparative tabulated format) on two production batches of the finished product containing the substance complying with the current and proposed specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicines, comparative disintegration data may be acceptable.

II.4 PMF*/VAMF*

45. 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**	**IB**
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 for the authorized product, • PMF holder has submitted the PMF certificate, evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder), • The PMF certificate, evaluation report and PMF dossier replace the previous PMF documentation for this Marketing Authorization.			
2) 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 products.			
4) The submitted documents should clearly outline the “present” and “proposed” PMF certificate.			

46. 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**	**IB**
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 for the authorized product, • VAMF holder has submitted the VAMF certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to 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 Drugs containing medical device

47. 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) Space device for metered dose inhaler			**II**
b) Deletion of a device	**1,**	**1**	**IB**
c) Addition or replacement of a device which is an integrated part of the primary packaging			**II**
Conditions			
1) The medicinal product can still be accurately delivered.			
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).			

III. Safety, Efficacy Changes (*Human medicinal products)*

48. Change in the summary of product characteristics, labeling and package leaflet of a generic 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**	1		**II**
Conditions			
1) The change should be approved by the reference product competent authority.			
Documentation			
1) Attached to the cover letter of the variation application: the competent authority request, if available.			
2) Revised product information (Updated and approved Summary of Product Characteristic, labeling and leaflet) and current product information.			
3) Comparison table showing the current state/situation versus the proposed state/situation			

49. Change(s) in the summary of product characteristics, labeling and package 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 NHRA/ competent authority 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.			**IB**
b) Change(s) proposed by the MAH with submission of a periodic safety update report, risk management plan, follow up measures/specific obligations.			**IB**
Conditions			
None.			

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.

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

51. Change in the legal status of a medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) For generic/hybrid medicinal products following an approved legal status change of the reference medicinal product.		**1, 2**	**IB**
b) All other legal status changes.			**II**
Conditions			
None.			
Documentation			
1) Attached to the cover letter of the variation application: proof of authorization of the legal status change.			
2) Revised product information.			

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

53.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**

Conditions
None.
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.

6. Appendix 2: Examples for major changes

Major changes (Type II) exceed the scope of the minor changes (Type I) listed in Appendix 1, e.g. they exceed or do not comply with the conditions to be fulfilled along with the change, but are not covered by the changes listed in Appendix 3.

Examples for major changes include but are not limited to the following:

- Changes in the manufacturing process of the API.
- Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human
- Changes in the composition of the finished product.
- 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.
- Changes to the immediate (primary) packaging of the product.
- Changes in the finished product manufacture:
    - Modification of an approved or introduction of a new design space.
- Changes in the control of finished product:
    - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product
- Safety, efficacy changes:
    - Variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical.
    - Change(s) to therapeutic indication(s):
    - Addition of a new therapeutic indication or modification of an approved one
    - Deletion of a therapeutic indication

PMF/VAMF- specific changes:

- Changes in the plasma pool preparation (e.g. manufacturing method, pool size, storage)
- Change in the steps that would be taken if it is found retrospectively that donation(s)
- Should have been excluded from processing (“look-back” procedure).
- Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment or to fulfill pharmacopeial requirements.
    - Removal of inventory hold period or reduction in its length.
    - Change of kit/method used to test pools (antibody or antigen or NAT test).
- Addition or change of a site testing the donations and/or plasma pool within an organization not already included in the PMF.

- Addition of a new organization in the blood/plasma collection establishments and/or addition of establishments for an organization not included in the PMF

It remains the applicant's responsibility to provide the relevant documentation (relevant parts of the dossier) intended to prove that the intended major change will not have an impact on the quality of the product that has been authorized.

7. Appendix 3: Changes that make a new application is necessary

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

1. **Changes to the API, for example:**
    I. Change of the API to a different API;
    II. Inclusion of an additional API in a multi-component product;
    III. Removal of one API from a multi-component product;
    IV. Change in the dose of one or more APIs.
2. **Changes to the pharmaceutical form/dosage form, for example**:
    I. Change from an immediate-release product to a slow- or delayed-release dosage form and vice versa;
    II. Change from a liquid to a powder for reconstitution, or vice versa.
    III. A change from multi-dose to single-dose or vice-versa (both for addition or replacement).
3. **Changes to the strength.**
4. **Change or addition of route of administration.**
5. **Addition of pack size.**
6. **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.**

8. Abbreviations

API	Active Pharmaceutical Ingredient.
ATC	Anatomical Therapeutic Chemical (ATC) Classification.
CEP	Certificate of Suitability.
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.
NHRA	National Health Regulatory Authority.
TSE	Transmissible Spongiform Encephalopathy.
VAMF	Vaccine Antigen Master File.
WHO	World Health Organization.
NAT	Nucleic Acid Testing.
MA	Marketing Authorization.
GMP	Good Manufacturing Practice.
SOPs	Standard Operating Procedures.

9. Appendix 4. Electronic Common Technical Document (eCTD)

I. Introduction

According to NHRA's eCTD implementation plan, the variation submission in eCTD format is mandatory from the 2nd of May 2017. This applies only to human medicine applications.

The ICH M4 Expert Working Group (EWG) has defined the Common Technical Document (CTD). The ICH M2 EWG has defined, in the current document, the specification for the Electronic Common Technical Document (eCTD). The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission.

The CTD as defined by the M4 EWG does not cover the full submission that is to be made in a region. It describes only modules 2 to 5, which are common across all regions. The regional Administrative Information and Prescribing Information is described in Module 1. The CTD does not describe the content of module 1 because it is regional specific, nor does it describe documents that can be submitted as amendments or variations to the initial application. Module 1 Specifications of the electronic Common Technical Document (eCTD) for Gulf Cooperation Council (GCC) are described in "GCC module 1 specifications."

This document should be read together with ICH eCTD specifications and with GCC module 1 specifications to prepare a valid eCTD submission to NHRA. The latest version of the ICH eCTD Specification can be found at: http://estri.ich.org and of GCC module 1 specification can be found at: http://www.sfda.gov.sa

NHRA will show all the cases and scenarios of eCTD submissions especially the baseline eCTD submissions.

II. Technical Baseline Application

A baseline submission is a compiled submission of the current status of the dossier, i.e. resubmission of currently valid documents that have already been provided to NHRA but in another format. Where an eCTD application is being used for the first time as variation or renewal application, applicants are obliged to submit a technical baseline for the product as this will greatly facilitate the review process. It should be clearly stated in the cover letter of the "baseline eCTD sequence" that the content of the previously submitted dossier has not been changed, only the format. There is no need for the NHRA to assess baseline submissions and hyperlinks between documents are not necessary. The submission

unit ‘reformat’ should be used in the envelope for the baseline sequence and submission type should be “none”.

III. Baseline eCTD Submission

One of the principles of eCTD is that with the use of the operation attributes, it is possible to manage the lifecycle of a product and generate a view of the “current dossier”.

To convert from CTD format to eCTD, a baseline needs to be submitted. A baseline submission is the resubmission of currently valid documents to start the eCTD life cycle.

An eCTD baseline should not contain any new information as it will not be subject to review by NHRA.

Submission of a baseline shall be after the end of a regulatory activity, i.e. the company will follow the same original submission for products under assessment until the end of the regulatory activity.

IV. Baseline Starting as Sequence 0000

For product files that are submitted as CTD, the baseline submission should be submitted as sequence (0000).

V. Baseline Cases

For products submitted as CTD:

If the product was submitted as CTD and has no regulatory activity or complete regulatory activity, a baseline shall be submitted as sequence 0000. The first regulatory activity after baseline (for example a variation request) shall be submitted as sequence 0001. For the next submissions, the sequence number will advance, 0002, 0003, etc. See table below:

Sequence No.	Submission description	Submission type	Submission Unit	Related sequence
0000	Baseline submission	None	Reformat	-
0001	Variation	Var-Type2		- -
0002	Response to Questions	Var-Type2	Response	0001

Table 1: Example for starting an eCTD with a baseline sequence.

VI. Components of an eCTD Baseline Submission:

It is composed of the currently valid documents in an eCTD format.

The cover letter should include declaration that indicates there is no new information, only the format dossier has changed.

Notes:

1. NHRA encourage applicants to move to a full eCTD (M1 to M5) at least full M1 and M3 should be submitted.

2. The applicant can submit the eCTD dossier for currently registered product in which it requires the submission of a baseline. However, once eCTD is submitted going back to other format will not be accepted.

10. References

1. European Union variations regulations and guidance

2. GCC guidelines

3. SFDA variations guidelines

4. ICH quality, safety & efficacy guidelines