Guidelines for Variation Requirements

Version 1.0

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## Document Control

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author(s)</th>
<th>Comments</th>
</tr>
</thead>
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<td>Draft</td>
<td>2012</td>
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<td>Draft</td>
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1. Introduction

These guidelines are adapted from the EMEA Guidelines on the details of the various categories of variations, Regulation (EC) No 1234/2008 article4 (1) (a), Doc. Ref: EMEA/122634/2009 & from The GCC Guidelines for Variation Requirements (version 3.3).

This document has been developed to assist applicants in the preparation and submission of drug applications for variations to existing products to the "Pharmacy & Drug Control Department – MOPH, Qatar ".

2. General Notes

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

Application for Variation to a Marketing Authorization should always be submitted (please refer to website of Ministry of Public Health).

Applicants should present a summary of the intended change in tabular form in which the current state/situation and the situation after the intended change are compared to outline the scope of the change in a transparent manner.

A justification for the introduction of the change should always follow.

Some documents such as certificate of analysis (COA), specification sheet, approval letters from the country of origin …etc should be submitted when relevant.

It is important to note that "Pharmacy & Drug Control Department –MOPH, Qatar" 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. "Pharmacy & Drug Control Department " is committed to ensuring that such requests are justifiable and decisions are clearly documented.

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

This document applies to change(s) made on drug products that have already received a marketing authorization from "Pharmacy & Drug Control Department – MOPH, Qatar".

4. Objectives

- To illustrate most common variations made after the marketing authorization has been granted from the "Pharmacy & Drug Control Department – MOPH, Qatar".

- To provide applicants with recommendations on the data required for each type of variation which may impact the safety, efficacy and quality of drug products.
5. Appendix 1: Examples for some major changes and most minor changes

I. Administrative Changes

<table>
<thead>
<tr>
<th>1. Change in the name and / or address of the marketing authorization holder</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

**Conditions**

1) The marketing authorization holder (MAH) shall remain the same legal entity.

**Documentation**

1) A formal document from a relevant official body (e.g. chamber of commerce, national drug regulatory Authority…etc) in which the new name or new address is mentioned.

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

3) Legalized CPP(s) for related products.

<table>
<thead>
<tr>
<th>2. Change in the (invented) name of the medicinal product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

**Conditions**

1) No confusion with the International Non proprietary Name (INN).

**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) Legalized CPP(s) for related products.

<table>
<thead>
<tr>
<th>3. Change in name of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

**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 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1, 2, 3</td>
<td></td>
</tr>
</tbody>
</table>

**Conditions**

1) The manufacturing site and all manufacturing operation 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 and/or address of a manufacturer of the finished product, including quality control sites  | Conditions to be fulfilled | Documentation to be supplied |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Manufacturer responsible for batch release</td>
<td>1</td>
<td>1, 2</td>
</tr>
<tr>
<td>b) All other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.

3) Legalized CPP(s) for related products.

6. Change in ATC Code  | Conditions to be fulfilled | Documentation to be supplied |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1, 2</td>
<td></td>
</tr>
</tbody>
</table>

**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.
<table>
<thead>
<tr>
<th>7. Deletion of a manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release site where batch control takes place, or supplier of a starting material, reagent or excipient, when mentioned in the dossier).</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1, 2</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>8.</th>
<th>Change in the manufacture 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.</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>The proposed manufacturer is part of the same organization as the currently approved manufacturer.</td>
<td>1, 2, 3</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
</tr>
<tr>
<td></td>
<td>[ ] b) Submission of a new drug master file (DMF).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] d) New manufacturer of material for which a new assessment is required of viral safety and/or TSE risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ ] e) The change relates to a biological/immunological product.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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) A declaration from the marketing authorization holder that the synthetic route, quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.

3) Either a TSE Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by a national drug regulatory authority of the ICH region and associated countries and shown to comply with the current *Note for Guidance on 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.

4) Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.
5) The submitted documents should clearly outline the “present” and “proposed” manufacturers.

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

7) 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 Pharmacy & Drug Control Directorate –MOPH, Qatar only in case of any out of specification results (OOS) along with the proposed action.

<table>
<thead>
<tr>
<th>9.</th>
<th>Changes in the manufacturing process of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Minor change in the manufacturing process of the active substance.</td>
<td>1, 2, 3, 4, 5</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>b)</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c)</td>
<td>The substance is a biological/immunological substance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d)</td>
<td>Minor change to the restricted part of drug master file (DMF).</td>
<td></td>
<td>1, 2, 3, 4</td>
</tr>
</tbody>
</table>

**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.

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 physicochemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.
<table>
<thead>
<tr>
<th>10.</th>
<th>Change in batch size of active substance or intermediate</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Up to 10-fold increase compared to the currently approved batch size</td>
<td>1, 2, 3, 4, 6, 7</td>
<td>1, 2</td>
</tr>
<tr>
<td>b)</td>
<td>Downscaling</td>
<td>1, 2, 3, 4, 5</td>
<td>1, 2</td>
</tr>
<tr>
<td>c)</td>
<td>The change relates to a biological/immunological active substance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d)</td>
<td>More than 10-fold increase compared to the currently approved batch size</td>
<td></td>
<td>1, 2, 3, 4</td>
</tr>
</tbody>
</table>

**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).

<table>
<thead>
<tr>
<th>11.</th>
<th>Change to in-process tests or limits applied during the manufacture of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Tightening of in-process limits</td>
<td>1, 2, 3</td>
<td>1, 2</td>
</tr>
<tr>
<td>b)</td>
<td>Addition of a new test and limits</td>
<td>1, 4</td>
<td>1, 2, 3, 4, 5, 7</td>
</tr>
<tr>
<td>c)</td>
<td>Widening of the approved in-process control (IPC) limits, which may have a significant effect on the overall quality of the active substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d)</td>
<td>Deletion of an in-process test which may have a significant effect on the overall quality of the active substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e)</td>
<td>Addition or replacement of an in-process test as a result of a safety or quality issue</td>
<td></td>
<td>1, 2, 3, 4, 5, 7</td>
</tr>
<tr>
<td>f)</td>
<td>Deletion of a non-significant in-process test</td>
<td></td>
<td>1, 2, 6</td>
</tr>
</tbody>
</table>
### Conditions

1. The change does not result from unexpected events arising during manufacture e.g. new unqualified
2. Any change should be within the range of currently approved limits.
3. The test procedure remains the same.
4. 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 biologicals, 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.
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

<table>
<thead>
<tr>
<th>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</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tightening of specification limits</td>
<td>1, 2, 3</td>
<td>1, 2</td>
</tr>
<tr>
<td>b) Addition of a new specification parameter to the specification</td>
<td>1, 4, 5</td>
<td>1, 2, 3, 4, 5, 6, 8</td>
</tr>
<tr>
<td>c) Change outside the approved specifications limits range for the active substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f) Addition or replacement of a specification parameter as a result of a safety or quality issue</td>
<td>1, 2, 3, 4, 5, 6, 8</td>
<td></td>
</tr>
<tr>
<td>g) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete test e.g. organoleptic test)</td>
<td>1, 2, 7</td>
<td></td>
</tr>
</tbody>
</table>
### Conditions

1) The change does not result from unexpected events arising during manufacture e.g. new unqualified.

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

3) The test procedure remains the same.

4) The test method is not a biological/immunological/immunochemical method or a method using a biological.

5) 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.

5) Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch.

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.

<table>
<thead>
<tr>
<th>13. Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Minor changes to an approved test procedure</td>
<td>1, 2, 3, 4, 5</td>
<td>1, 2</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate</td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>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</td>
<td>1, 2, 3, 6, 7</td>
<td>1, 2</td>
</tr>
<tr>
<td>e) Deletion of a test procedure for the active substance or a starting material/intermediate, if an alternative test procedure is already authorized</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>f) Deletion of a test procedure for reagents, if an alternative test procedure is already authorized</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>
### 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

<table>
<thead>
<tr>
<th>14. Change in immediate packaging of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Change in the qualitative and quantitative composition.</td>
<td>1, 2, 3, 4</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>b) Change in the container type for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sterile and biological/immunological active substances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. All other active substances</td>
<td></td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
</tbody>
</table>

### 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 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 MOPH 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.

<table>
<thead>
<tr>
<th>15. Change in the specification parameters and/or limits of the immediate packaging of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tightening of specification limits</td>
<td>1, 2, 3</td>
<td>1, 2</td>
</tr>
<tr>
<td>b) Addition of a new specification parameter to the specification</td>
<td>1</td>
<td>1, 2, 3, 4, 6</td>
</tr>
<tr>
<td>c) Addition or replacement of a specification parameter as a result of a safety or quality issue.</td>
<td></td>
<td>1, 2, 3, 4, 6</td>
</tr>
<tr>
<td>d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete test)</td>
<td></td>
<td>1, 2, 5</td>
</tr>
</tbody>
</table>

**Conditions**

1) The change does not result from unexpected events arising during manufacture.

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

3) The test procedure remains 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) 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.
<table>
<thead>
<tr>
<th>16.</th>
<th>Change in test procedure for the immediate packaging of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Minor changes to an approved test procedure</td>
<td>1, 2, 3, 4</td>
<td>1, 2</td>
</tr>
<tr>
<td>b)</td>
<td>Other changes to a test procedure (including replacement or addition)</td>
<td>1, 2, 4, 5</td>
<td>1, 2</td>
</tr>
<tr>
<td>c)</td>
<td>Deletion of a test procedure if an alternative test procedure is already authorized</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th></th>
<th>Change in the re-test period/storage period or storage conditions of the active substance</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Reduction in the re-test period/storage period of the active substance.</td>
<td>1</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>b)</td>
<td>Extension or introduction of a re-test period/storage period of active substances.</td>
<td></td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>c)</td>
<td>Change in storage conditions of the active substance.</td>
<td></td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>d)</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorized packaging material and covering the duration of the requested re-test period or requested storage conditions.

2) Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.

3) Copy of approved specifications of the active substance.
II.2 Finished product

a) Description and composition

<table>
<thead>
<tr>
<th>18. Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Changes in imprints, bossing or other markings</td>
<td>1, 2, 3</td>
<td>1, 2, 4</td>
</tr>
<tr>
<td>b) Changes in scoring/break lines intended to divide into equal doses</td>
<td></td>
<td>1, 2, 3, 4</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>19. Change in the shape or dimensions of the pharmaceutical form</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Immediate release tablets, capsules, suppositories and pessaries.</td>
<td>1, 2, 3, 4</td>
<td>1, 4</td>
</tr>
<tr>
<td>b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets</td>
<td></td>
<td>1, 2, 3, 4, 5</td>
</tr>
</tbody>
</table>

**Conditions**
1) If appropriate, the dissolution profile of the reformulated product is comparable 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.
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.
<table>
<thead>
<tr>
<th>20. Changes in the composition (excipients) of the finished product.</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) Changes in components of the flavoring or coloring system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Addition, deletion or replacement</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>2. Increase or reduction</td>
<td>1, 2, 4, 5, 6</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td><strong>b) Other excipients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. The change relates to a biological/immunological product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Change that is supported by a bioequivalence study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level</td>
<td>1, 3, 4, 5, 6, 7, 8, 9, 10</td>
<td></td>
</tr>
<tr>
<td><strong>c) Any minor adjustment of the quantitative composition of the finished product with respect to excipients</strong></td>
<td>1, 2, 4, 8, 9, 10</td>
<td>1, 2, 7</td>
</tr>
</tbody>
</table>

**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 an identification test.

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.

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 (including approval of COO) of the dossier that are affected by the variation including identification method for any new colorant and if appropriate updated end of shelf-life specifications.

2) The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.

3) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the MOPH 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 pharmaceuticals (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.

9) Justification for not submitting a new bioequivalence study.

<table>
<thead>
<tr>
<th>21. Change in coating weight of oral dosage forms or change in weight of capsule shells</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Solid oral pharmaceutical forms.</td>
<td>1, 2, 3, 4</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>b) Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conditions**

1) The dissolution profile of the new product determined on a minimum of two pilot scale batches 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, 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 MOPH only in case of any out-of-specifications (OOS) results along with the proposed action.

4) Comparative dissolution data of at least two pilot batches of the finished products in the new and old statues.

<table>
<thead>
<tr>
<th>22. Deletion of the solvent/diluent container from the pack</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conditions</strong></td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>None.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Documentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Replacement of the relevant pages of the dossier (including a new price certificate) that are affected by the variation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**b) Manufacture**

<table>
<thead>
<tr>
<th>23. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) Secondary packaging site</strong></td>
<td>1, 2, 6</td>
<td>1, 2, 3, 4, 5, 6, 7, 9, 12, 19, 20</td>
</tr>
<tr>
<td><strong>b) Primary packaging site</strong></td>
<td>1, 2, 3, 4, 5</td>
<td>1, 2, 3, 4, 5, 6, 7, 9, 12, 16, 19</td>
</tr>
<tr>
<td><strong>c) Site where any manufacturing operation(s) take place, except batch release and secondary packaging, for sterile medicinal products, and biological/immunological medicinal products.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>d) Site where any manufacturing operation(s) take place, except batch-release, primary and secondary packaging, for non-sterile medicinal products.</strong></td>
<td>1, 2, 4</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15</td>
</tr>
<tr>
<td><strong>e) Site which requires a registration by MOPH.</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conditions**

1) Satisfactory GMP compliance in the COO 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) Legalized Manufacturing license issued from the COO.

4) Legalized certificate of GMP compliance issued from the COO.

5) Registration of the new manufacturing site at the MOPH.

6) Certificate of a Pharmaceutical Product (CPP) stating the new manufacturing site.

7) The submitted documents should clearly outline the “present” and “proposed” finished product Manufacturers.

8) A statement defining the primary steps of manufacturing process and the site at which each step takes place.

9) 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.
10) 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.

11) The specifications, composition and source of the raw materials used in the manufacturing for the product concerned.

12) Copy of approved release and end of shelf-life specifications for the product if relevant.

13) 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).

14) 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.

15) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the MOPH only in case of any out-of-specifications (OOS) results along with the proposed action.

16) Where relevant, the batch numbers of batches (≥3) used in the validation study should be indicated and validation protocol (scheme) to be submitted.

17) 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.

18) 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.

19) A recent and official price certificate by the company and legalized by the Qatari Embassy in the country of origin.

20) 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.

<table>
<thead>
<tr>
<th>24.</th>
<th>Change to batch release arrangements and quality control testing of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Replacement or addition of a site where batch control/testing takes place</td>
<td>1, 2, 3</td>
<td>1, 2, 4</td>
</tr>
<tr>
<td>b)</td>
<td>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 physicochemical method.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c)</td>
<td>Replacement or addition of a manufacturer responsible for batch release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Not including batch control/testing</td>
<td>1</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>2.</td>
<td>Including batch control/testing</td>
<td>1, 2, 3</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>3.</td>
<td>Including batch control/testing for a biological/immunological product and one of the test methods performed at that site is not a physicochemical method.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Conditions**

1) The site is appropriately authorized.

2) The product is not a biological/immunological medicinal product.

3) Method transfer from the old to the new site or new test laboratory has been successfully completed.

**Documentation**

1) A legalized manufacturing authorization(s) & A legalized certificate of GMP compliance issued within the last 3 years by the relevant competent authority.

2) The submitted documents should clearly outline the “present” and “proposed” finished product manufacturers.

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.

<table>
<thead>
<tr>
<th>25. Change in the manufacturing process of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) The change relates to a biological/immunological medicinal product.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Introduction of a non-standard terminal sterilization method.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Increase in the overage that is used for the active substance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Minor change in the manufacturing process of an aqueous oral suspension.</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
<td></td>
</tr>
<tr>
<td>f) Minor change in the manufacturing process of an immediate release solid oral dosage form</td>
<td>1, 2, 3, 4, 5, 6, 7, 8</td>
<td>1, 3, 4, 6, 7, 8, 9</td>
</tr>
</tbody>
</table>

**Conditions**

1) No change in qualitative and quantitative impurity profile or in physicochemical properties.

2) The product concerned is not a biological/immunological 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).

4) Justification for not submitting a new bioequivalence study.

5) In case of a change to the sterilization process, validation data should be provided.

6) Copy of approved release and end of shelf-life specifications.

7) Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action).

8) The results of stability studies that have been carried out according to the GCC stability guidelines, and relevant stability parameters have been assessed in at least two pilot or production scale batches for at three months.

9) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the MOPH only in case of any out-of-specifications (OOS) results along with the proposed action.

<table>
<thead>
<tr>
<th>26. Change in the batch size of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Up to 10-fold compared to the currently approved batch size.</td>
<td>1, 2, 3, 4, 5</td>
<td>1, 4</td>
</tr>
<tr>
<td>b) Downscaling down to 10-fold.</td>
<td>1, 2, 3, 4, 5, 6</td>
<td>1, 4</td>
</tr>
<tr>
<td>c) The change relates to a biological/immunological medicinal product.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) The change relates to all other pharmaceutical forms except standard immediate release oral and non-sterile liquids.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) More than 10-fold increase compared to the currently approved batch size for immediate release.</td>
<td>7</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>f) Product that was exempted from the biobatch requirements (1/10 of production scale or 100,000 units, whichever is greater) because of the small production scale.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.

1) The batch numbers (≥3) used in the validation study should be indicated or validation protocol (scheme) be submitted.

2) The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches for at least three months.

3) A letter of commitment to finalize the stability studies and the data must be submitted immediately to the MOPH only in case of any out-of-specifications (OOS) results along with the proposed action.

<table>
<thead>
<tr>
<th>27. Change to in-process tests or limits applied during the manufacture of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tightening of in-process limits</td>
<td>1, 2, 3, 4</td>
<td>1, 2</td>
</tr>
<tr>
<td>b) Addition of a new tests and limits</td>
<td>1, 2, 5, 6</td>
<td>1, 2, 3, 4, 5, 7</td>
</tr>
<tr>
<td>c) Widening of the approved IPC limits, which may have a significant effect on the overall quality of the finished product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Deletion of an in-process test which may have a significant effect on the overall quality of the finished product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Addition or replacement of an in-process test as a result of a safety or quality issue</td>
<td>1, 2, 3, 4, 5, 7</td>
<td></td>
</tr>
<tr>
<td>f) Deletion of a non-significant in-process test</td>
<td>1, 2, 6</td>
<td></td>
</tr>
</tbody>
</table>
### 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 biologicals, unless otherwise justified) of the finished product for all specification parameters.

5) Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests.

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

<table>
<thead>
<tr>
<th>28. Change in the specification parameters and/or limits of an excipient</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tightening of specification limits</td>
<td>1, 2, 3, 4</td>
<td>1, 2</td>
</tr>
<tr>
<td>b) Addition of a new specification parameter to the specification</td>
<td>1, 2, 5, 6, 7</td>
<td>1, 2, 3, 4, 5, 6, 8</td>
</tr>
<tr>
<td>c) Change outside the approved specifications limits range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Addition or replacement of a specification parameter as a result of a safety or quality issue</td>
<td>1, 2, 3, 4, 5, 6, 8</td>
<td></td>
</tr>
<tr>
<td>f) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete test e.g. organoleptic test)</td>
<td>1, 2, 7</td>
<td></td>
</tr>
</tbody>
</table>

### 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 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.

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.

<table>
<thead>
<tr>
<th>29. Change in test procedure for an excipient</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Minor changes to an approved test procedure</td>
<td>1, 2, 3, 4, 5</td>
<td>1, 2</td>
</tr>
<tr>
<td>b) Change (including replacement or addition) to a biological/immunological/immunochemical test method or a method using a biological reagent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Other changes to a test procedure (including replacement or addition)</td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>d) Deletion of a test procedure if an alternative test procedure is already authorized</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>30. Change in source of an excipient or reagent with TSE risk</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a)</strong> Change from TSE risk material to vegetable or synthetic origin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. For excipients or reagents used in the manufacture of biological active substance or a finished product containing a biological active substance</td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>2. For excipients or reagents not used the manufacture of biological active substance or a finished product containing a biological active substance</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>b)</strong> 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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.
<table>
<thead>
<tr>
<th>31. Change in synthesis or recovery of a non-pharmacopeial excipient (when described in the dossier)</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Minor change in synthesis or recovery of a non-pharmacopeial excipient</td>
<td>1, 2</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>b) The specifications are affected or there is a change in physicochemical properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) The excipient is a biological/immunological substance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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).

4) Copy of approved and new (if applicable) specifications of the excipient.
### d) Control of finished product

<table>
<thead>
<tr>
<th>Change in the specification parameters and/or limits of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tightening of specification limits</td>
<td>1, 2, 3, 4</td>
<td>1, 2, 8</td>
</tr>
<tr>
<td>b) Addition of a new specification parameter to the specification</td>
<td>1, 2, 5, 6, 7</td>
<td>1, 2, 3, 4, 5, 6, 8</td>
</tr>
<tr>
<td>c) Change outside the approved specifications limits range</td>
<td></td>
<td>1, 2, 3, 4, 5, 6, 8</td>
</tr>
<tr>
<td>d) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product</td>
<td></td>
<td>1, 2, 3, 4, 5, 6, 8</td>
</tr>
<tr>
<td>e) Addition or replacement of a specification parameter as a result of a safety or quality issue</td>
<td></td>
<td>1, 2, 3, 4, 5, 6, 8</td>
</tr>
<tr>
<td>f) Deletion of a non-significant specification parameter (e.g deletion of an obsolete test (e.g. organoleptic test)</td>
<td></td>
<td>1, 2, 7</td>
</tr>
</tbody>
</table>

#### 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 any other major 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 biologicals, unless otherwise justified) of the finished product for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification.

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 specification parameter and the limits.
<table>
<thead>
<tr>
<th></th>
<th>Change in test procedure for the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Minor changes to an approved test procedure.</td>
<td>1, 2, 3, 4, 5</td>
<td>1, 2</td>
</tr>
<tr>
<td>b)</td>
<td>Change (including replacement or addition) to a biological/immunological/immunochemical test method or a method using a biological reagent.</td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>c)</td>
<td>Other changes to a test procedure (including replacement or addition).</td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>d)</td>
<td>Deletion of a test procedure if an alternative method is already authorized.</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>34. Change in immediate packaging of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Change in qualitative and quantitative composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Solid pharmaceutical forms.</td>
<td>1, 2, 3</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
</tr>
<tr>
<td>2. Semi-solid and non-sterile liquid pharmaceutical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>forms.</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>3. Sterile medicinal products and biological/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>immunological medicinal products.</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>4. The change relates to a less protective pack where</td>
<td></td>
<td></td>
</tr>
<tr>
<td>there are associated changes in storage conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and/or reduction in shelf life.</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>b) Change in the container type for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Solid, semi-solid and non-sterile liquid pharmaceutical forms.</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>2. Sterile medicinal products and biological/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>immunological medicinal products.</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td></td>
</tr>
</tbody>
</table>

**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 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 MOHP 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.

7) Price certificate or a confirmation letter that there is no change in the approved price.
### 35. Change in the specification parameters and/or limits of the immediate packaging of the finished product

<table>
<thead>
<tr>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tightening of specification limits.</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>b) Addition of a new specification parameter to the specification.</td>
<td>1, 2, 5</td>
</tr>
<tr>
<td>c) Addition or replacement of a specification parameter as a result of a safety or quality issue.</td>
<td>1, 2, 3, 4, 6</td>
</tr>
<tr>
<td>d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete test).</td>
<td>1, 2, 5</td>
</tr>
</tbody>
</table>

#### 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

<table>
<thead>
<tr>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Minor changes to an approved test procedure</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>b) Other changes to a test procedure (including replacement or addition)</td>
<td>1, 2, 4, 5</td>
</tr>
<tr>
<td>c) Deletion of a test procedure if an alternative test procedure is already authorized</td>
<td>6</td>
</tr>
</tbody>
</table>

#### 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.

<table>
<thead>
<tr>
<th>37. Change in shape or dimensions of the container or closure</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a- Non-sterile medicinal products</td>
<td>1, 2, 3</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>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</td>
<td></td>
<td>1, 2, 3, 4, 5</td>
</tr>
<tr>
<td>c- Sterile medicinal products</td>
<td></td>
<td>1, 2, 3, 4, 5</td>
</tr>
</tbody>
</table>

**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, 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 along with artworks for inner and outer labels where applicable.
3. CPP certificate or approval issued from competent health authority at the country of origin.
4. Re-validation studies have been performed in case of sterile products terminally sterilized and the summary of validation data is required.
5. In case of a change in the headspace or a change in the surface/volume ratio, the following should be submitted:
   - The results of stability studies that have been carried out according to the GCC stability guidelines, on the relevant stability parameters, on at least two pilot or production scale batches (three batches for biological/immunological medicinal product) for at least three months (six months for biological/immunological medicinal product).
   - A letter of commitment to finalize the stability studies and the data must be submitted immediately to the MOPH only in case of any out-of-specifications (OOS) results along with the proposed action.
### 38. Change in pack size of the finished product

<table>
<thead>
<tr>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a- Change in the number of units (e.g. tablets, ampoules, etc.) in a pack</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
</tr>
<tr>
<td>1. Change within the range the currently approved pack sizes</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
</tr>
<tr>
<td>2. Change outside the range of the currently approved pack sizes</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
</tr>
<tr>
<td>b- Deletion of a pack size(s)</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
</tr>
<tr>
<td>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</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
</tr>
<tr>
<td>d- Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products</td>
<td>1, 2, 3, 4, 5, 6, 7, 8, 9</td>
</tr>
</tbody>
</table>

### 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.

### 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. Legalized 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 guidelines, 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 MOPH.

8. A recent and official price certificate by the company and legalized by the Qatari Embassy in the country of origin (indicating the new pack size).

9. Samples of the finished product.
<table>
<thead>
<tr>
<th>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))</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

**Conditions**

1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

**Documentation**

1. Replacement of the relevant pages of the dossier that are affected by the variation.
2. Samples of the new container/closure along with artworks for inner and outer labels where applicable.

<table>
<thead>
<tr>
<th>Change in outer pack &amp; label (artwork, dimension, logo, etc..) replacement or deletion of measuring administration devices on integrated part of primary pack</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

**Conditions**

1) The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

**Documentation**

1) Replacement of the relevant pages of the dossier that are affected by the variation.
2) Samples of the new container/closure along with artworks for inner and outer labels where applicable.

<table>
<thead>
<tr>
<th>Change in supplier of packaging components or devices (when mentioned in the dossier)</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>a- Deletion of a supplier</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>b- Replacement or addition of supplier</td>
<td>1, 2, 3, 4</td>
<td>1, 2</td>
</tr>
<tr>
<td>c- Any change to suppliers of spacer devices for metered dose inhalers</td>
<td>1, 2</td>
<td></td>
</tr>
</tbody>
</table>

**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.
### f) Stability

<table>
<thead>
<tr>
<th>42. Change in shelf-life or storage conditions of the finished product</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a</strong>- Reduction of the shelf-life of the finished product (As packaged for sale/ After first opening/ After dilution or reconstitution)</td>
<td>1</td>
<td>1, 2, 3, 5, 6</td>
</tr>
<tr>
<td><strong>b</strong>- Extension of the shelf-life of the finished product (As packaged for sale/ After first opening/ After dilution or reconstitution)</td>
<td></td>
<td>1, 4, 5, 6</td>
</tr>
<tr>
<td><strong>c</strong>- Change in storage conditions of the finished product or the diluted/reconstituted product</td>
<td></td>
<td>1, 4, 5, 6</td>
</tr>
<tr>
<td><strong>d</strong>- Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol</td>
<td></td>
<td>1, 4, 5, 6</td>
</tr>
</tbody>
</table>

**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 the 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.

<table>
<thead>
<tr>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a- Certificate of Suitability.</strong></td>
<td></td>
</tr>
<tr>
<td>1. New certificate from an already approved manufacturer</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>2. Updated certificate from an already approved manufacturer</td>
<td>1, 2, 3, 4, 6</td>
</tr>
<tr>
<td>3. New certificate from a new manufacturer (replacement or addition)</td>
<td>1, 2, 3, 4, 5</td>
</tr>
<tr>
<td><strong>b- TSE Certificate of suitability for an active substance/starting material/reagent/intermediate/or excipient.</strong></td>
<td></td>
</tr>
<tr>
<td>1. New certificate for an active substance from a new or an already approved manufacturer.</td>
<td>3</td>
</tr>
<tr>
<td>2. New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer.</td>
<td>3</td>
</tr>
</tbody>
</table>

#### Conditions

1. The finished product release and end of shelf-life specifications remain the same.

2. Unchanged (excluding tightening) additional specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.

3. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data.

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.
### 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 products, comparative disintegration data may be acceptable.
III. Changes related to Patient Information Leaflet “From the current guideline”

<table>
<thead>
<tr>
<th>45. Updating /Changing Patient information Leaflet</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
</tr>
</thead>
</table>
| a) Addition of new indication or modified indication and consequential changes including new dose instructions.  
- New dose regimen No change to indication.  
- Deletion of contraindications, warnings, side effects, precautions & drug interactions. | | 1,2,3,4,5,6 |
| b) Addition of (contraindications, warning, side effects, precautions & drug interaction) | 1,2 | 2,3,5,6,7,8,9 |
| c) Revised wording of the leaflet or redesign or new company logo without change in approval information. | 1,2,3 | 3,5 |

**Conditions**

1) No Change in Dose regimen, No change or modification to indications.

2) There is no deletion for any (Contraindications, Warnings, Side effects, Precautions & drug interactions).

3) No change in any information concerning any section of Patient leaflet.

**Documentation**

1) Approval of the regulatory authorities in the country of origin or CPP in WHO format with SmPC.

2) Copy of the package leaflet text (in a readable font).

3) Comparison table between the old and new leaflet.

4) Justification document for the change(s).

5) Artworks of old and new leaflets.

6) Sample of finished product with new leaflet (if applicable).

7) Clinical documents supporting the proposed changes.

8) Acceptance in other countries "if applicable".

9) Company core data sheet (CDDS) supporting the new changes.
6. Appendix 2: Examples for major changes

Major changes exceed the scope of the minor changes 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 influenza.
- 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, and pharmacovigilance changes:
  - Variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data.
  - Change(s) to therapeutic indication(s):
    - Addition of a new therapeutic indication or modification of an approved one
    - Deletion of a therapeutic indication
    Introduction of a new pharmacovigilance system for the medicinal product concerned.

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

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

3. Changes to the strength.

4. A change or addition of route of administration.

5. The addition or replacement of measuring or administration device being an integrated part of the primary packaging that results in a change to the strength, pharmaceutical form or route of administration of the product.
8. Appendix 4 addition /Change to an API supplier that has already been registered by regulatory Authority.

Requirements:

1- A declaration letter indicating that DMF of the new API supplier has been evaluated by regulatory authority during the last five years and no changes have been made since this time.

2- Section (3.2.P)
A letter of commitment to immediately initiate accelerated and long term (covering shelf life) Stability studies on at least one production batch of the finished product according to GCC guidelines using API from the new supplier and submit stability data immediately to regulatory authority only in case of any out of specification results (OOS) along with proposed action.
## 9. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient.</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical (ATC) Classification.</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability.</td>
</tr>
<tr>
<td>DER</td>
<td>Drug Extract Ratio.</td>
</tr>
<tr>
<td>DMF</td>
<td>Drug Master File.</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization.</td>
</tr>
<tr>
<td>INN</td>
<td>International Nonproprietary Name.</td>
</tr>
<tr>
<td>IPC</td>
<td>In-Process Control.</td>
</tr>
<tr>
<td>MOPH</td>
<td>Ministry of Public Health.</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorization Holder.</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy.</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization.</td>
</tr>
<tr>
<td>NAT</td>
<td>Nucleic Acid Testing.</td>
</tr>
<tr>
<td>MA</td>
<td>Marketing Authorization.</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice.</td>
</tr>
<tr>
<td>SOPs</td>
<td>Standard Operating Procedures.</td>
</tr>
</tbody>
</table>
10. References

- Requirements for Minor Changes of Registered Pharmaceutical Companies and their Products (Draft).

- The GCC Guideline for Variation requirements 3.3.
