

**TANZANIA FOOD AND DRUGS AUTHORITY**



***APPLICATION GUIDELINES FOR  
VARIATION OF REGISTERED HUMAN  
MEDICINAL PRODUCTS***

*(Made under the Guideline on Submission of Documentation for Registration of  
Human Medicinal Products)*

**First Edition**

**November 2008**

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## **Acknowledgements**

These Variation Guidelines have been prepared in order to define a more systematic and easy way of handling variations to registered medicinal products frequently received by the Authority.

The Guidelines were not present before, making this document to be the very first edition. The first draft of the document was prepared by a team of TFDA staff – Mr. L. R. Mhangwa, Dr. N.B. Chukilizo, Mr. M. A. Fimbo, Mr. Y. Hebron, Ms. G. Mpanda, Ms. A. Msussa, Mr. F. Apolnary and Ms. J. Komba. The team essentially reviewed the World Health Organization (WHO) Guidance Document on Variations to a Prequalified Product Dossier and subsequently recommended it for adoption and use by the TFDA.

The Authority would therefore wish to thank the above-mentioned TFDA staff for their dedication, time and commitment during preparation of the Guidelines.

The Authority is likewise highly indebted to the WHO for making their guidelines available for adoption by Member States. Special thanks are extended to TFDA stakeholders and members of expert committees for their valuable comments during development of the guidelines.

Last but not the least, contribution of TFDA Management team is greatly acknowledged during development and approval of the final draft.

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## **Abbreviations**

<b>API</b>	-	Active Pharmaceutical Ingredient
<b>BP</b>	-	British Pharmacopoeia
<b>BSE</b>	-	Bovine Spongiform Encephalopathy
<b>CE</b>	-	“Conformite Europeene”
<b>CEP</b>	-	European Certificate of Suitability
<b>CPP</b>	-	Certificate of a Pharmaceutical Product
<b>DMF</b>	-	Drug Master File
<b>DRA</b>	-	Drug Regulatory Authority
<b>FPP</b>	-	Finished Pharmaceutical Product
<b>GMP</b>	-	Good Manufacturing Practice
<b>ICH</b>	-	International Conference on Harmonization of Technical Requirements for Registration of Human Medicines
<b>INN</b>	-	International Non-proprietary Name
<b>JP</b>	-	Japanese Pharmacopoeia
<b>‘N’</b>	-	Notification
<b>NDRA</b>	-	National Drug Regulatory Authority
<b>PhEur</b>	-	European Pharmacopoeia
<b>PhInt</b>	-	International Pharmacopoeia
<b>OoS</b>	-	Out of Specification (Outside Specification)
<b>SPC</b>	-	Summary of Product Characteristics
<b>TFDA</b>	-	Tanzania Food and Drugs Authority
<b>TFDCA</b>	-	Tanzania Food, Drugs and Cosmetics Act
<b>TSE</b>	-	Transmissible Spongiform Encephalopathy
<b>USP</b>	-	United States Pharmacopoeia

## **Foreword**

This is the first edition of the Guidelines for handling variations to registered human medicinal products prepared by the Tanzania Food and Drugs Authority (TFDA). The requirements specified on the Guidelines have been adapted from the WHO Guidance Document on Variations to a Prequalified Product Dossier (WHO Technical Report Series 943; WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2007).

The Guidelines are intended to provide guidance to applicants on the conditions to be fulfilled and the type of documentation to be submitted before a variation can be approved by the Authority. Four categories of changes that require application for variations have been provided in the guidelines. These include minor changes, major changes, changes that make a new application or an extension application necessary and stability requirements for variations and changes to registered Finished Pharmaceutical Products (FPPs).

It should be noted that the guidelines are applicable only to active pharmaceutical ingredients (APIs) and excipients manufactured by chemical synthesis or semi-synthetic processes and FPPs containing such APIs and excipients. It is further elaborated that minor changes denoted by a letter **'N'** are considered as **"Notifications"**. Applications for such notifications must fulfil the conditions and documentation requirements listed in the Guidelines. The notifications will be evaluated within 3 months and can be considered approved if no correspondence from TFDA is received by the applicant within the specified timeframe. All other changes must get TFDA approval before they can be implemented.

Submission of documentation in accordance with the requirements of each type of change will significantly facilitate both assessment and approval process. It is therefore critical that the Guidelines are construed, comprehended and followed by all Marketing Authorization Holders who intend to make changes to their registered human medicinal products.

Marketing Authorization Holders as well as other stakeholders are encouraged to provide comments for improvement based on their experience on the use of the Guidelines.

**M. Ndomondo-Sigonda**  
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## Introduction

Marketing authorization or registration of medicinal products is a dynamic process. It involves pre-marketing assessment of drug dossiers to verify quality, safety and efficacy based on the existing evidence and thereafter a change depending on emerging issues that arise during the lifetime of the product.

The Marketing Authorization Holder is therefore required to take into account technical and scientific progress of a registered product throughout its lifetime. The holder is required to make any amendment that may be required to enable the registered product be manufactured and checked by means of generally accepted scientific methods.

Any changes to registered products (variations) may involve administrative and/or more substantial changes and are subject to approval by TFDA. Procedures for the implementation of the different types of variations need to be set out in order to facilitate the task of both Marketing Authorization Holders and TFDA and to guarantee that variations to the medicinal product do not give rise to public health concerns.

The Guidelines henceforth outlines conditions to be fulfilled by applicants and the type of documentation required before a variation can be approved by TFDA. Four schedules which define the various types of changes are delineated:

- Schedule I:** Lists minor changes. These are classified by the type of change as such and the conditions which frame this type of change. Whenever the conditions are not kept, the change may either become a major change or may even make a new application necessary.
- Schedule II:** Lists examples of major changes.
- Schedule III:** Lists types of changes which make a new application necessary.
- Schedule IV:** Lists stability requirements for variations and changes to registered finished pharmaceutical products (FPPs)

Before approval could granted any application for variations to a registered product shall be accompanied with the following:

- Dully filled in application forms (**Annex I**) as prescribed in these guidelines.
- Re-submission of all parts of the dossier that are affected by variation according to the structure of the Guideline on Submission of Documentation for Registration of Human Medicinal Products.
- A non-refundable variation fees as prescribed in the TFDA Fees and Charges Regulations in force.

- A detailed documentation for each category of variation as stipulated in respective Schedules along with sufficient samples whenever required
- Notification **'N'**  
Among minor changes as listed in schedule I of this document, some are classified by the letter N and can be considered as notifications. Applications for minor changes that are classified notifications (N) must provide evidence to fulfil the conditions and documentation requirements as listed in the Guidelines. Within a period of three months these notifications will be evaluated by TFDA and can be considered approved if no correspondence by TFDA with the applicant has been initiated within that time.
- For all other change applications that are not considered as notifications i.e. If the validity of the notification cannot be acknowledged by TFDA, prior approval is always necessary before the changes can be implemented. In this case, correspondence with the applicant will be started and a new period of three months must be awaited by the applicant upon submission of his response documents, accordingly.
- Certain changes are so fundamental that they alter the terms of the registered dossier and consequently cannot be considered as a change. For these cases a new dossier must be submitted (Schedule III).

## **Definition of Terms**

In the context of these guidelines the following words/phrases are defined as follows.

### *Active Pharmaceutical Ingredient (API)*

Means a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

### *Applicant*

The person or company who submits an application for a variation to an existing marketing authorization.

### *Authority*

Means the Tanzania Food and Drugs Authority, or its acronym “TFDA” established under Section 4 of the Tanzania Food, Drugs and Cosmetics Act, (TFDCA) 2003.

### *Biological API*

A substance that is produced by or extracted from a biological source and for which a combination of physico-chemical-biological testing and the production process and its control is needed for its characterization and the determination of its quality.

### *Biological Pharmaceutical Product*

A product, the API of which is a biological substance.

### *Drug Master File*

A drug master file (DMF) is a master file that provides a full set of data on an API. In some countries, the term may also comprise data on an excipient or a component of a product such as a container.

### *Excipient*

Means any component of a finished dosage form which has no therapeutic value.

### *Finished Pharmaceutical Product (FPP)*

Means a product that has undergone all stages of production, including packaging in its final container and labelling

### *Formulation*

Means the composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

### *Major Change*

Is a change to the documentation which can neither be deemed to be a minor variation within the meaning of preceding definition (see below) nor to be a change for which the submission of a new dossier would be necessary (Schedule II).



*Minor Change*

Is a variation which can be found listed in Schedule I of the Guidelines.

*Pharmacopoeia*

Means a current edition of the British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia and Japanese Pharmacopoeia.

*Pilot Scale Batch*

The pilot scale batch size corresponds to at least 10% of the production scale batch size, i.e. such that the multiplication factor for the scale-up does not exceed 10. For oral solid dosage forms this size should generally be 10% of production scale or 100,000 units whichever is the greater.

*Specifications – expiry check or shelf life*

Means the combination of physical, chemical, biological and microbiological test requirements that an active ingredient must meet up to its retest date or a drug product must meet during its shelf life.

*Specifications - release*

Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

*Stable APIs*

An API is considered as stable if it is within the initial specifications when stored at 30°C/60% RH or 65%RH, respectively, for two years and at 40°C/75%RH for 6 months and such data are available from the API manufacturer that applies for change in the manufacturing process.

*Starting material*

Means any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

*Variation*

Means a change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

## **SCHEDULE I: DOSSIER REQUIREMENTS FOR MINOR CHANGES TO REGISTERED MEDICINAL PRODUCTS**

This guide has been prepared in order to clarify what documentation should be submitted with each type of minor change. In case the change also implies a change in the pharmaceutical particulars in the Summary of Product Characteristics (SPC), labeling and/or package leaflet/insert, this also forms part of the change. The titles of the changes are numbered and subcategories depicted by letters and numbers.

The conditions necessary for a given change are outlined for each subcategory and listed below each change. In principle, all parts of the dossier that are affected by a variation are to be resubmitted according to the structure of the Guideline on Submission of Documentation for Registration of Human Medicinal Products. Moreover, any further documentation required along with the change is identified.

Applicants should present a summary of the intended change in tabulated format in which the current state/situation and the situation after the intended change are compared in order to outline the scope of the change in a transparent manner. A justification should always follow why the change needs to be introduced.

Applicants should be aware that submitting redundant or irrelevant information does not facilitate rapid procedures. Deficient documentation can lead to non-validation/rejection of the change.

<b>1</b>	<b>Change in the name and/or address of the applicant</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1	1	<b>N</b>

### **Conditions**

1. The Marketing Authorization holder of the registered product shall remain the same legal entity.

### **Documentation**

1. A formal document from a relevant official body (e.g. the national drug regulatory authority (NDRA)) in which the new name and/or address is mentioned.

<b>2</b>	<b>Change in the name of the Finished Pharmaceutical Product (FPP)</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>
		1	1,2

**Conditions**

1. No confusion with the International Nonproprietary Name (INN).

**Documentation**

1. A formal document from the National Drug Regulatory Authority (NDRA) in which the new name is approved.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.

<b>3</b>	<b>Change in the name and/or address of the manufacturer of the active pharmaceutical ingredient (API) where no European Pharmacopoeia certificate of suitability (CEP) is available</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1	1,2	<b>N</b>

**Conditions**

1. The manufacturing site shall remain the same.

**Documentation**

1. A formal document from a relevant official body (e.g. NDRA) in which the new name and/or address is mentioned.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.

<b>4</b>	<b>Change in the name and/or address of the manufacturer of the Finished Pharmaceutical Product (FPP)</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1	1,2	<b>N</b>

**Conditions**

1. The manufacturing site shall remain the same.

## Documentation

1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NDRA) in which the new name and/or address is mentioned.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.

<b>5</b>	<b>Replacement or addition of a packaging site of the FPP</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
	a) Secondary packaging for all types of pharmaceutical forms	1	1,2,5	<b>N</b>
	b) Primary packaging site			
	1. Solid pharmaceutical forms e.g. tablets and capsules	1,2,3	1,2,5	<b>N</b>
	2. Semisolid or pharmaceutical forms	1,2,3	1,2,5	<b>N</b>
	3. Liquid pharmaceutical forms (suspensions, emulsions)	1,2,3,4	1,2,4,5	

## Conditions

1. Satisfactory inspection in the last five years by TFDA, WHO or a drug regulatory authority (DRA) in the International Conference on Harmonization (ICH) region and associated countries.
2. Site appropriately authorized by a NDRA (to manufacture the pharmaceutical form and the product concerned).
3. Product concerned is not a sterile product.
4. Validation protocol 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.

## Documentation

1. Proof that the proposed site is appropriately authorized for the pharmaceutical form and the product concerned:

- a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the NDRA.
  - a GMP statement or equivalent issued by WHO or a Drug Regulatory Authority (DRA) in the International Conference on Harmonization (ICH) region and associated countries.
2. The date of the last satisfactory inspection concerning the packaging facilities by WHO or drug regulatory authority (DRA) in the International Conference on Harmonization (ICH) region and associated countries, in the last three years.
  3. Date and scope (indicate if product specific, if related to a specific pharmaceutical form, etc.) of the last satisfactory inspection.
  4. The batch numbers of batches ( $\geq 3$ ) used in the validation study should be indicated and validation protocol (scheme) to be submitted.
  5. The variation application should clearly outline the “registered” and “proposed” finished product manufacturers.
  6. Copy of registered release and end-of-shelf-life specifications.
  7. Batch analysis data of three production batches and comparative data on the last three batches from the previous site;
  8. For semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
  9. For solid dosage forms data of comparative dissolution tests [refer the Guideline on Submission of Documentation for Registration of Human Medicinal Products] with demonstration of dissolution profile similarity, performed on the last three batches from the previous site and the first three batches of the new site should be submitted.

6	Replacement or addition of a site where batch control/testing takes place	Conditions to be fulfilled	Documentation to be submitted	
		1, 2	1, 2, 3	<b>N</b>

**Conditions**

1. The site is appropriately authorized by the NDRA.
2. Method transfer from the old to the new site or new test laboratory has been successfully completed.

**Documentation**

1. The corresponding letter should clearly outline the “registered” and “proposed” quality control sites.
2. Documented evidence that the site is appropriately authorized by the NDRA.
3. Documented evidence that the Method transfer from the old to the new site or new test laboratory has been successfully completed.

7	<b>Withdrawal of any manufacturing site (including for an API, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place)</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		None	1	<b>N</b>

**Conditions**

None

**Documentation**

1. The corresponding letter should clearly name the manufacturer to be deleted.

8	<b>Minor change in the manufacturing process of the API</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1, 2	1, 2, 3	

**Conditions**

1. No change in qualitative and quantitative impurity profile or in physicochemical properties.
2. The route of synthesis remains the same, i.e. intermediates remain the same.

**Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part and of the

registered Drug Master File (where applicable), including a direct comparison of the registered 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 registered and the proposed process.
3. Copy of registered specifications of the API.

<b>9</b>	<b>Change in batch size of API or intermediate</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Up to 10 fold compared to a registered batch size	1, 2, 3	1, 2	<b>N</b>
(b)	Downscaling	1, 2, 3, 4	1, 2	<b>N</b>
(c)	More than 10 – fold compared to a registered batch size	1, 2, 3	1, 3, 4	

#### **Conditions**

1. Any changes to the manufacturing methods are only those necessitated by scale-up, 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 change does not affect the reproducibility of the process.
4. 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 according to the structure as listed in the Application Form: Quality Part.
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 registered and the proposed size. Batch data on the next two full production batches should be available on request and reported immediately to TFDA if outside specifications (OOS) with proposed action.
4. Copy of registered specifications of the API (and of the intermediate, if applicable).

10	Change in the specification of an API, a starting chemical material/intermediate/reagent used in the manufacturing process of the API	Conditions to be fulfilled	Documentation to be submitted	
(a)	Tightening of specification limits	1, 2, 3	1, 2	<b>N</b>
		2, 3	1, 2	
(b)	Addition of a new test parameter to the specification of			
	1. an API	2, 4	1, 2, 3, 4, 5, 6	
	2. a starting chemical material/intermediate/reagent	2, 4	1, 2, 3, 4	

### Conditions

- The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration or a major change procedure after registration).
- The change should not be the result of unexpected events arising during manufacture.
- Any change should be within the range of registered limits.
- Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

### Documentation

- Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
- Comparative table of registered and proposed specifications.
- Details of any new analytical method and validation data.
- Batch analysis data (in a comparative tabular format) on a minimum of two production batches of the relevant substance for all tests in the new specification manufactured to both the registered and the proposed specifications. (Batch data on the next two full production batches should be available on request or reported if outside specification (OOS) with proposed action.)
- Where appropriate comparative dissolution profile data for the finished product on at least one batch containing the API complying with the registered and the proposed specification.



6. Justification for not submitting a new bioequivalence study according to the current WHO guideline, in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and Good Clinical Practices.

<b>11</b>	<b>Change in test procedure for API or starting chemical material, intermediate, or reagent used in the manufacturing process of the API</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Minor changes to a registered test procedure	1, 2, 3	1	<b>N</b>
(b)	Other changes to a test procedure, including replacement or addition of a test procedure	2, 3, 4	1, 2	

### **Conditions**

1. 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); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. 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 according to the structure as listed in the Application Form: Quality Part 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 registered test and the proposed one are equivalent (please refer to guideline ICH Q2 (R1)).

<b>12</b>	<b>Change in the manufacturer of the API or final (ultimate) key intermediate in the manufacturing process of the</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	

	<b>API</b>			
(a)	Change in site of the already registered manufacturer (replacement or addition)	1,2	1,2,3,4,5	<b>N</b>
(b)	New manufacturer (replacement or addition)	1,2	1,2,3,4,5	

### **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 registered.
2. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products<sup>1</sup> or 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.

### **Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
2. A declaration from the marketing authorization holder of the registered FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already registered.
3. Either a TSE European Pharmacopoeia 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 the competent authority and shown to comply with the current WHO guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products<sup>1</sup> or 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.
4. Batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the registered and proposed manufacturers/sites.
5. The application should clearly outline the “registered” and “proposed” manufacturers.

13	<b>Submission of a new or updated European pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/intermediate in the manufacturing process of the API</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	From a registered manufacturer	1,2,4	1,2,3,4	<b>N</b>
(b)	From a new manufacturer (replacement or addition)			
	1. Sterile substance	1,2,3,4	1,2,3,4	
	2. Other substances	1,2,3,4	1,2,3,4	<b>N</b>

### Conditions

1. The finished product release and end-of-shelf-life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for impurities and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The API will be tested immediately prior to use if no retest period is included in the European Pharmacopoeia certificate of suitability or if data to support a retest period is not provided.
4. The manufacturing process of the API, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

### Documentation

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
3. Where applicable a document providing information of any materials falling within the scope of the WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products or 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 manufacture 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.

4. The variation application should clearly outline the “registered” and “proposed” manufacturers.

**Note**

The reference to unchanged specifications for impurities, if applicable, in condition no. 2 should refer to new additional impurities. In change No. 8: minor change in the manufacturing process of the API, condition No. 1 stipulates that there is no change in the qualitative and quantitative impurity profile or in the physiochemical properties. In change No. 10: change in specifications of API, tightening of specification limits or addition of new test parameters are allowed. One of the conditions for these changes to qualify as a minor change is that the change should not be the result of unexpected events during manufacture. The conditions of these changes should be borne in mind in the fulfilment of the conditions of change No. 13.

<b>14</b>	<b>Submission of a new or updated TSE European pharmacopoeia certificate of suitability for an API or starting chemical material/reagent/intermediate in the manufacturing process of the API for a registered manufacturer and registered manufacturing process</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		None	1,2,3	<b>N</b>

**Conditions**

None

**Documentation**

1. Copy of the current (updated) European Pharmacopoeia TSE certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
3. 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 including those which are used in the manufacture 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.

<b>15</b>	<b>Change in:</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	the re-test period of the API	1,2	1,2	
(b)	the storage conditions for the API	1,2	1,2	

### **Conditions**

1. Stability studies have been done according to the protocol used for the registered product (Guideline on Submission of Documentation for Registration of Human Medicinal Products, Section 3.7.2). The studies must show that the agreed relevant specifications are still met.
2. 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 according to the structure as listed in the Application Form: Quality Part. These must contain results of appropriate real time stability studies; conducted in accordance with the relevant stability guidelines on at least two pilot or production scale batches of the API in the registered packaging material and covering the duration of the requested re-test period or requested storage conditions.
2. Copy of approved specifications of the API.

<b>16</b>	<b>Replacement of an excipient with a comparable excipient</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1,2,3,4	1,2,3,4,5,6,7	

### **Conditions**

1. Same functional characteristics of the excipient.
2. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability according to the WHO guidelines on registration requirements to establish interchangeability - *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and Good Clinical Practices
3. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data.
4. Stability studies in accordance with the stability guidelines have been started with at least two pilot scale or production scale batches and at

least three months (accelerated and real time) satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalized. Data will be provided immediately to TFDA if outside specifications or potentially outside specification at the end of the registered shelf-life (with proposed action).

**Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part (as applicable).
2. Justification for the change/choice of excipients, etc. must be given by appropriate development pharmaceuticals (including stability aspects and antimicrobial preservation where appropriate).
3. 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.
4. Justification for not submitting a new bioequivalence study according to the WHO guidelines on registration requirements to establish interchangeability - *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and Good Clinical Practices.
5. Either a European Pharmacopoeia certificate of suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA of the ICH region and associated countries and shown to comply with the scope of the current WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products or the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products or an equivalent guide 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 evidence of its previous acceptance.
6. Data to demonstrate that the new excipient does not interfere with the finished product specification test method (if appropriate).
7. The batch numbers of the batches used in the stability studies should be given.

17	Change in specification of an excipient	Conditions to be fulfilled	Documentation to be submitted	
(a)	Tightening of specification limits	1,2,3	1,2	N

	2,3	1,2	
(b) Addition of a new test parameter to the specification	2,4	1,2,3,4,5,6	

### Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to registration of the product or a major change procedure after registration).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of registered limits.
4. 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 according to the structure as listed in the Application Form: Quality Part.
2. Comparative table of registered and proposed specifications.
3. Details of any new analytical method and summary of validation data (please refer to guideline ICH Q2 (R1)).
4. Batch analysis data on two production batches for all tests in the new specification.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot scale batch containing the excipient complying with the registered and proposed specification.
6. Justification for not submitting a new bioequivalence study according to the current WHO guidelines on registration requirements to establish interchangeability - *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and Good Clinical Practices.

18	Change in test procedure for an excipient	Conditions to be fulfilled	Documentation to be submitted	
(a)	Minor changes to an approved test	1,2,3	1	<b>N</b>

	procedure			
(b)	Other changes to a test procedure, including replacement of an approved test procedure by a new test procedure	2,3,4	1,2	

### Conditions

1. 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); no new impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. 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 according to the structure as listed in the Application Form: Quality Part 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 (please refer to guideline ICH Q2 (R1)).

<b>19</b>	<b>Submission of a new or updated European pharmacopoeia certificate of suitability for an excipient</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	From an approved manufacturer	1,2,3	1,2,3	<b>N</b>
(b)	From a new manufacturer (replacement or addition)			
	1. Sterile substance	1,2,3	1,2,3	
	2. Other substances	1,2,3	1,2,3	<b>N</b>

### Conditions

1. The finished product release and end-of-shelf-life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.



3. The manufacturing process of the excipient does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

**Documentation**

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
3. Where applicable, a document providing information of any materials falling within the scope of the WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products or 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 manufacture of the excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

20	<b>Submission of a new or updated TSE European pharmacopoeia certificate of suitability for an excipient</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
	From an approved manufacturer or a new manufacturer (replacement or addition)	None	1,2,3	<b>N</b>

**Conditions**

None

**Documentation**

1. Copy of the current (updated) TSE European Pharmacopoeia certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
3. 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 including those which are used in the manufacture of the excipient. The following information should be included for each such

material: name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

21	<b>Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1	1,2	<b>N</b>

### 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 pharmaceutical product.

22	<b>Change to comply with a major international pharmacopoeia (BP, PhInt, JP, PhEur, USP)</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
	Change of specifications of a former non-major pharmacopoeial substance to comply with a monograph of a major international pharmacopoeia			
(a)	API	1,2	1,2,3,4,5	
(b)	Excipient	1,2	1,2,3,4,5	

### Conditions

1. The change is made exclusively to comply with a major international pharmacopoeia.
2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form), if applicable.

### Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
2. Comparative table of registered and proposed specifications.

3. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.
4. Analysis of the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities.
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 registered and proposed specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch.

<b>23</b>	<b>Change in the specifications of the immediate packaging of the finished product</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Tightening of specification limits	1,2,3	1,2	<b>N</b>
		2,3	1,2	
(b)	Addition of a new test parameter	2,4	1,2,3,4	

#### **Conditions**

1. The change is not a consequence of any commitments from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration of the product or a major change procedure after registration).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of registered limits.
4. 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 according to the structure as listed in the Application Form: Quality Part.
2. Comparative table of registered and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).
4. Batch analysis data on two batches for all tests in the new specification.

<b>24</b>	<b>Change in the specifications of the immediate packaging of the finished product</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	

(a) Minor change to an approved test procedure	1,2,3	1	<b>N</b>
(b) Other changes to a test procedure, including replacement or addition of a test procedure	2,3,4	1,2	

### Conditions

1. 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).
2. Appropriate (re-)validation studies were performed in accordance with relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. 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 according to the structure as listed in the Application Form: Quality Part, which includes a description of the analytical methodology and a summary of validation data.
2. Comparative validation results showing that the registered test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).

<b>25</b>	<b>Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1	1	<b>N</b>

### Conditions

1. The change does not concern a fundamental 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 according to the structure as listed in the Application Form: Quality Part.

<b>26</b>	<b>Change in the qualitative and/or quantitative composition of the immediate packaging material</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Semisolid and liquid pharmaceutical forms	1,2,3,4	1,2,3,4,5	
(b)	All other pharmaceutical forms	1,2,3,4	1,4,5	<b>N</b>
		1,3,4	1,2,3,4,5	

### **Conditions**

1. The product concerned is not a sterile product.
2. The packaging type and material remain the same (e.g. blister to blister).
3. The proposed packaging material must be at least equivalent to the registered material in respect of its relevant properties.
4. Relevant stability studies in accordance with the stability guidelines have been started with at least two pilot scale or production scale batches and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to TFDA if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

### **Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for O<sub>2</sub>, CO<sub>2</sub> and 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 batch numbers of batches used in the stability studies should be indicated.
5. Comparison of the registered and proposed specifications, if applicable.

<b>27</b>	<b>Change (replacement, addition or deletion) in supplier of</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
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	<b>packaging components or devices (when mentioned in the dossier), spacer devices for metered dose inhalers are exclude</b>			
(a)	Deletion of a supplier	1	1	<b>N</b>
(b)	Replacement or addition of a supplier	1,2,3,4	1,2,3	

**Conditions**

1. No deletion of packaging component or device.
2. The qualitative and quantitative composition of the packaging components/device remains 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 according to the structure as listed in the Application Form: Quality Part.
2. Data to demonstrate accuracy, precision and compatibility of the device or certification to this extent.
3. Comparative table of registered and proposed specifications, if applicable.

<b>28</b>	<b>Change to in-process tests or limits applied during the manufacture of the product</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Tightening of in-process limits	1,2,3 2,3	1,2 1,2	<b>N</b>
(b)	Addition of new tests and limits	2,4	1,2,3,4,5	

**Conditions**

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to registration of the product or a major change procedure after registration).
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. Any change should be within the range of registered limits.

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

### Documentation

- Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
- Comparative table of registered and proposed specifications.
- Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).
- Batch analysis data on two production batches of the finished product for all tests in the new specification.
- Justification for addition of new tests and limits.

<b>29</b>	<b>Change in the batch size of the finished product</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Up to 10 fold compared to an approved batch size	1,2,3,4	1,4	<b>N</b>
(b)	Downscaling to 10 fold	1,2,3,4,5	1,4	<b>N</b>
(c)	Other situations	1,2,3,4,5,6	1,2,3,4,5,6	

### Conditions

- The change does not affect reproducibility and/or consistency of the product.
- The change relates only to standard immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
- 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.
- Validation protocol 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 WHO guideline on validation of manufacturing processes (Supplementary guideline on good manufacturing practices for Pharmaceutical Products: validation. Annex 4, WHO Technical Report Series, No. 937, 2006).
- The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

6. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or production scale batch and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to TFDA if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

**Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the registered and the proposed sizes. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the registered product if outside specifications (with proposed action).
3. Copy of registered release and end-of-shelf life specifications.
4. The batch numbers ( $\geq 3$ ) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5. The batch numbers of batches used in the stability studies should be indicated.
6. For solid dosage forms: dissolution profile data on a minimum 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 dissolution profile similarity requirements.

30	Minor change in the manufacture of the finished product	Conditions to be fulfilled	Documentation to be submitted	
		1,2,3,4	1,2,3,4,5,6,7,8	

**Conditions**

1. The overall manufacturing principle remains the same.
2. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
3. In case of a change in the sterilization process, the change is to a standard pharmacopoeial cycle only.



4. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or production scale batch and at least three months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to TFDA if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

**Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
2. For semisolid and liquid products in which the API 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. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the registered product if outside specifications (with proposed action).
4. Justification for not submitting a new bioequivalence study according to the WHO guidelines on registration requirements to establish interchangeability - *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7* (WHO Technical Report Series, No. 937) and Good Clinical Practices.
5. In case of a change to the sterilization process, validation data should be provided.
6. Copy of registered 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 registered and the proposed process. Batch data on the next two full production batches should be made available upon request and reported immediately by the supplier of the registered product if outside specification (with propose action).
8. The batch numbers of batches used in the stability studies should be indicated.

<b>31</b>	<b>Change in the colouring system or the flavouring system currently used in the finished</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
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	<b>product</b>			
(a)	Reduction or deletion of one or more components of the			
	1. Colouring system	1,2,3,4	1,2,3	<b>N</b>
	2. Flavouring system	1,2,3,4	1,2,3	<b>N</b>
(b)	Increase, addition or replacement of one or more components of the			
	1. Colouring system	1,2,3,4,5,6	1,2,3,4,5	
	2. Flavouring system	1,2,3,4,5,6	1,2,3,4,5	

### 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/odour/taste and if relevant, deletion or addition of an identification test.
4. Stability studies (long-term and accelerated) in accordance with relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalized. Data shall be provided immediately to TFDA if outside specifications or potentially outside specification at the end of the registered shelf life (with proposed action). In addition, where relevant, photostability testing should be performed.
5. Any new proposed components must comply with section 4.8 of the Guideline on Submission of Documentation for Registration of Human Medicinal Products.
6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products or the Guideline on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products or an equivalent guide of the ICH region and associated countries.

### Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part (if appropriate, where the end-of-shelf-life specifications have been updated).
2. The batch numbers of the batches used in the stability studies should be indicated.
3. Sample of the new product.
4. Either a European Pharmacopoeia certificate of suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA in the ICH region or associated countries and shown to comply with the scope of the current guideline in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
5. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.

<b>32</b>	<b>Change in coating weight of tablets or change in weight of capsule shells</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Immediate-release oral pharmaceutical forms	1,3,4	1,4	<b>N</b>
(b)	Gastro-resistant, modified or prolonged release pharmaceutical forms	1,2,3,4	1,2,3,4	

### **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. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and assurance that these studies will be finalized.  
Data will be provided immediately to TFDA if outside specifications or potentially outside specifications at the end of the registered shelf life (with proposed action).

### **Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
2. Comparative dissolution profile data of at least two pilot scale batches of the new formulation and two production batches of the registered formulation (no significant differences regarding comparability to WHO guidelines on registration requirements to establish interchangeability – *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7 (WHO Technical Report Series, No. 937)* and Good Clinical Practices.
3. Justification for not submitting a new bioequivalence study according to the current WHO Guideline on Bioequivalence.
4. The batch numbers of the batches used in the stability studies should be indicated.

<b>33</b>	<b>Change in shape or dimensions of the container or closure</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Sterile pharmaceutical forms	1,2,3	1,2,3	
(b)	Other pharmaceutical forms	1,2,3	1,2,3	<b>N</b>

#### **Conditions**

1. No change in the qualitative or quantitative composition of the container and/or closure.
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 in accordance with the relevant guidelines have been started with at least two pilot scale or production scale batches and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that data will be provided immediately to TFDA if outside specifications or potentially outside specifications at the end of the registered shelf-life (with proposed action).

#### **Documentation**

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part (including description, detailed drawing and composition of the container or closure material).
2. The batch numbers of the batches used in the stability studies should be indicated, where applicable.

3. Samples of the new container/closure.

<b>34</b>	<b>Change in the specification of the finished product</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Tightening of specification limits	1,2,3	1,2	<b>N</b>
		2,3	1,2	
(b)	Addition of a new test parameter	2,4	1,2,3,4	

#### **Conditions**

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration of the product or a major change procedure after registration).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of limits of registered product.
4. 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 according to the structure as listed in the Application Form: Quality Part.
2. Comparative table of specifications of registered and proposed product.
3. Details of any new analytical method and validation data (please refer to guidelines ICH Q2 (R1))
4. Batch analysis data on two production batches of the finished product for all tests in the new specification.

<b>35</b>	<b>Change in test procedure of the finished product</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
(a)	Minor change to an approved test procedure	1,2,3,4	1	<b>N</b>
(b)	Other changes to a test procedure, including replacement or addition of a test procedure	2,3,4	1,2	

#### **Conditions**

1. 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).
2. Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines.
3. Results of method validation show new test procedure to be at least equivalent to the former procedure.
4. 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 according to the structure in the Application Form: Quality Part 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 registered test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).

36	<b>Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
		1,2	1,2	<b>N</b>

### 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 section 4.8 excipients of the Guideline on Submission of Documentation for Registration of Human Medicinal Products.

### Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part (including a detailed drawing or written description of the current and new appearance).
2. Submit a sample of the product.

37	<b>Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
	(a) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets	1,2	1,2,3,4,5	
	(b) All other tablets, capsules, suppositories and pessaries	1,2	1,4	<b>N</b>

### Conditions

1. 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).

### Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part. (Including a detailed drawing of the current and proposed situation).
2. Comparative dissolution data on at least one pilot scale batch of the current and proposed dimensions (no significant differences regarding comparability according to the WHO guidelines on registration requirements to establish interchangeability- *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, 2006, Annex 7 (WHO Technical Report Series, No. 937)* and Good Clinical Practices.
3. Justification for not submitting a new bioequivalence study according to the current WHO Guideline on Bioequivalence.
4. Samples of the finished product.
5. Where applicable, data on breakability test of tablets at release must be given and Commitment to submit data on breakability at the end of shelf-life.

38	<b>Change in pack size of the FPP</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
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	(a) Change in the number of units (e.g. tablets, ampoules, etc) in a pack			
	1. Change within the range of the approved pack sizes	1,2	1,3	<b>N</b>
	2. Change outside the range of the approved pack sizes	1,2	1,2,3	
	(b) Change in the fill weight/fill volume of non parenteral multi-dose products	1,2	1,2,3	

### Conditions

1. New pack size should be consistent with the posology and treatment duration as registered in the SPC.
2. The primary packaging material remains the same.

### Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part.
2. Justification for the new pack-size, showing that the new size is consistent with the dosage regimen and duration of use as registered in the SPC.
3. Written commitment that stability studies will be conducted in accordance with the TFDA guidelines for products where stability parameters could be affected. Data to be reported immediately if outside specifications (with proposed action).

<b>39</b>	<b>Change in:</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
	(a) the shelf-life of the finished product			
	1. As packaged for sale	1,2,3	1,2	
	2. After first opening	1,2	1,2	
	3. After dilution or reconstitution	1,2	1,2	
	(b) The storage conditions of the finished product or the diluted/reconstituted product	1,2	1,2	



### Conditions

1. Stability studies have been done according to stability protocol of the registered product. The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
3. The shelf-life does not exceed five years.

### Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part. Replaced pages must contain results of appropriate real-time stability studies conducted in accordance with the relevant stability guidelines on at least two production scale batches of the finished product in the registered packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included.
2. Copy of registered end-of-shelf-life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.

<b>40</b>	<b>Addition or replacement or deletion of a measuring or administration device not being an integrated part of the primary packaging (spacer devices for metered dose inhalers are excluded)</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
	(a) Addition or replacement	1,2	1,2,3	<b>N</b>
	(b) Deletion	3		

### Conditions

1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the registered posology and results of such studies should be available.
2. The new device is compatible with the FPP.
3. The FPP can still be accurately delivered.

### Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Application Form: Quality Part (including

description, detailed drawing and composition of the device material and supplier where appropriate).

2. Reference to CE marking for device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device.
3. Samples of the new device.

<b>41</b>	<b>Change in the Summary of Product Characteristics (Clinical part)</b>	<b>Conditions to be fulfilled</b>	<b>Documentation to be submitted</b>	
	(a) New indication	1,2	1, 2, 3, 4	
	(b) New side effect(s)	1, 2	2, 3	

**Conditions**

1. Potential benefits of the product, when used to treat the identified disease or condition, outweigh the known and potential risks of the product.

**Documentation**

1. Data on safety and effectiveness for recommended indication under the recommended conditions of use such as dosage and dosage, status and age of patients eg pregnancy paediatric, liver or kidney insufficiency or other co-morbidities.
2. A discussion of risks and benefits.
3. A description of the information for health care providers or authorized dispensers and recipients of the product.
4. Safety information in humans from clinical trials and individual patient experience be provided, if available

## **SCHEDULE II: MAJOR CHANGES (EXAMPLES)**

Major changes exceed the scope of minor changes as listed in Schedule I, e.g. they exceed/do not comply with the conditions to be fulfilled along with the change, but still do not cover the changes listed in Schedule III.

They most likely consist of:

- 1. Change or addition of a manufacturing site of finished product**
- 2. Change in the manufacturing process of the API**
- 3. Change in the composition of the finished product**
- 4. Change of immediate packaging of the product**

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

## **SCHEDULE III: CHANGES THAT MAKE A NEW APPLICATION/ EXTENSION APPLICATION NECESSARY**

Changes that make a new application necessary consist of:

- 1. Change or addition of a manufacturing site of finished product**

Changes of all manufacturing operations except packaging and batch release

- 2. Changes to the API**

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

- 3. Changes to the pharmaceutical form/dosage form**

- a. Change from an immediate-release product to a slow- or delayed-release dosage form and vice versa.
- b. Change from a liquid to a powder for reconstitution, or vice versa.

- 4. Changes in the route of administration**

## **SCHEDULE IV: STABILITY REQUIREMENTS FOR VARIATIONS AND CHANGES TO REGISTERED FINISHED PHARMACEUTICAL PRODUCTS (FPPs)**

This Schedule outlines the stability data which have to be generated in case of changes. The scope and design of stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs.

The available information must be taken into account such as:

### **For APIs:**

1. The stability profile including the results on stress testing.
2. The supportive data.
3. The primary data of accelerated and long-term testing.

### **For FPPs:**

1. The supportive data.
2. The primary data of accelerated and long-term testing.

In all cases of variations and changes the registered supplier has to investigate whether or not the intended change will have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability.

When stability data are required, the choice of test conditions defined in this Schedule refers to the Guideline on the Submission of Documentation for Registration of Human Medicinal Products.

In all cases of variations which require generation of stability data on the FPP, the stability studies required, including commitment batches, should always be continued up to the approved shelf-life and TFDA should be informed immediately if any problems with the stability appear during storage, e.g. if outside specification or potentially outside specification.

### **A. Minor changes**

In cases of minor changes as listed in Schedule I of this variation guide which require generation of stability data on the FPP, the minimum set of data to be submitted with the variation application is defined in Schedule I. The results of these studies covering the requested time period as defined in Schedule I, using accelerated and long-term testing conditions, should be compared to the results of studies performed on the unchanged API/FPP in order to ensure that the change does not negatively impact the stability profile, i.e. that the specification limits of the API/FPP are still met at the end of the proposed retest period/shelf-life. The comparison data may come from earlier studies and need not necessarily be collected in combination with the study on the unchanged product.

## **B. Major changes**

In cases of major changes the following are widely encountered examples:

1. Change in the manufacturing process of the API
2. Change in composition of the FPP
3. Change of immediate packaging of the FPP.

### **1. Change in the manufacturing process of the API**

If the quality characteristics (e.g. physical characteristics, impurity profile) of the API are changed in such a way, that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the API before and after the change:

APIs known to be stable: three months on one batch of at least pilot scale

APIs known to be unstable: six months on three batches of at least pilot scale

If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, additional stability data on the FPP, in accelerated and long term testing conditions, three months on two batches on at least pilot scale, may be required.

Physical quality characteristics: crystallinity and/or polymorphic state, if applicable, and characteristics derived from crystallinity such as solubility, hygroscopicity, etc.

Chemical quality characteristics: impurity profile, degradation products.

### **2. Change in composition of the finished product**

For conventional dosage forms (e.g. conventional release solid dosage forms, solutions) and when the API is known to be stable, comparative stability data, six months duration, long-term and accelerated testing conditions on two pilot scale batches are required.

For critical dosage forms (e.g. prolonged release form) or when the API is known to be unstable, comparative stability data, six months duration long-term and accelerated stability testing conditions on three pilot scale batches are required.

### **3. Change on immediate packaging of the finished product**

In the case of less protective packaging or when a risk of interaction occurs, mainly for semisolid or liquid dosage forms, comparative stability

data are required using accelerated and long-term testing conditions of six months duration on three pilot scale batches of the finished product.

## **COMMITMENT BATCHES**

### **A. Minor changes**

For all minor changes that require the generation of stability data on the FPP, adequate follow-up studies on commitment batches need to be performed.

### **B. Major changes**

For all major changes that require the generation of stability data on the FPP, at least the first production scale batch manufactured according to the registered variation should be placed on long-term stability testing using the same stability testing protocol as described above unless it has already been submitted as part of the variation application.

Stability studies need to be continued to cover the entire shelf-life. The results of these stability studies should be made available on request and TFDA should be informed immediately if any problems appear with the stability studies.

**Annex I:**

**TANZANIA FOOD AND DRUGS AUTHORITY**



For Official Use Date..... Application No.....
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**APPLICATION FORM**

**For variation of a registered human medicinal product in Tanzania**

<b>1. Proprietary name</b>	
<b>1.1 Name of the active ingredient(s) (International Non-proprietary Name in English)</b>	
<b>1.2 Pharmacotherapeutic classification (Anatomic-Therapeutic Classification system)</b>	
<b>2. Pharmaceutical Dosage form</b>	
<b>2.2 Type of change(s)</b> ( <i>State which type of Variation</i> )	
<b>2.3 Other Application(s)</b> ( <i>Please provide brief information on any ongoing variation or other variation(s) submitted in parallel, or renewal application(s), or line-extension(s)</i> )	
<b>2.4. Scope</b> ( <i>Please specify scope of the change(s) in a concise way</i> )	
<b>2.5 Background for change &amp; Justification for Consequential change(s) (If applicable)</b> ( <i>Please give brief background explanation for the proposed change(s) to your marketing authorization as well as a justification in case of consequential change(s)</i> )	

2.6 <b>Present</b> <i>(Please specify precise present wording or specification)</i>	<b>Proposed</b> <i>(Please specify precise proposed wording or specification)</i>

In the case of changes to the Summary of Product Characteristics and/or package leaflet, applicants should always enclose a working model clearly showing the differences (new text and deleted text) between the proposed new version and the current text, previous version or reference text.

3. Details of applicant (Must be the holder of the marketing authorization/registration certificate)		
Name:		
Business Address:		
Postal Address:		
Country:		
Phone:	Fax:	Email:

<b>Declaration of the Applicant:</b>	
I hereby submit an application for the above Marketing Authorization to be varied in accordance with the proposals given above.	
I declare that <i>(Please tick the appropriate declarations)</i> :	
<ul style="list-style-type: none"> <li>✓ There are no other changes than those identified in this application (except for those addressed in other variations submitted in parallel; such parallel variations have to be specified under 'Other Application(s)');</li> <li>✓ Where applicable, Variation fees have been paid;</li> <li>✓ Change will be implemented from: Next production run/next printing</li> </ul>	
<b>Name:</b>	
<b>Qualification:</b>	
<b>Position in the company:</b>	
<b>Signature:</b>	
<b>Date:</b>	<b>Official stamp:</b>