RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR VARIATION OF REGISTERED HUMAN PHARMACEUTICAL PRODUCTS

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FORWARD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of Rwanda FDA is to regulate matters related to quality, safety and efficacy of human pharmaceutical products in order to protect public health by increasing access and availability of essential medicines.

Considering the provisions of the technical Regulations Governing the registration of human medicinal products 20, the authority has issued *Guidelines for Variation of registered human pharmaceutical products.*

These guidelines have been developed to provide guidance to the applicants and the Authority in managing applications for variation of registered human Pharmaceutical products. They were developed in reference to the existing Ministry of Health (MOH) Guidelines on Variations to a Registered Pharmaceutical Product, World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for variation of Registered Medicines for Human Use (ICH) and other available literature.

The Authority acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

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GUIDELINES DEVELOPMENT HISTORY

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ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
AN	Annual notification
IN	Immediate notification
CEP	Certificate of Suitability to the monograph of European Pharmacopeia
CTD	Common Technical Document
EAC	East African Community
EAC-MRH	East African Community Medicines Registration Harmonization
EAC-NMRAs	East African Community Partner States' National Medicines Regulatory Authorities
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
ICH	International Council on Harmonization
PI	Product Information
SDRA	Stringent Drug Regulatory Authority
SmPC	Summary of Product Characteristics
Rwanda FDA	Rwanda Food and Drugs authority

DEFINITIONS

The definitions provided below apply to the terms used in these guidelines. They may have different meanings in other contexts and documents.

Active pharmaceutical ingredient (API) or drug substance

A substance used in the FPP, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

Active Pharmaceutical Ingredient (API) Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting

material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

Applicant

An applicant is a person who applies for registration of a human pharmaceutical product to Rwanda FDA, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured. After the product is registered, the applicant shall be the Marketing Authorisation Holder.

Authority:

The authority means the Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under the article 2 of the Law No. 003/2018 of 09/02/2018.

Biobatch

The batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or biowaiver studies, respectively.

Final Intermediate

The last reaction intermediate in the synthetic pathway that undergoes synthetic transformation to the API or the crude API. Purification is not considered to be a synthetic transformation.

Finished Pharmaceutical Product (Fpp)

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labelling.

In-Process Control

Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

Manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.

Officially Recognized Pharmacopoeia (Or Compendium)

Those pharmacopoeias recognized by Rwanda FDA i.e. *The International Pharmacopoeia* (Ph. Int.), the *European Pharmacopoeia* (Ph. Eur.), the *British Pharmacopoeia* (BP), the *Japanese Pharmacopoeia* (JP), the *United States Pharmacopeia* (USP) or any other pharmacopoeia as recommended by the Rwanda FDA.

Pilot-Scale Batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

Production Batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

Stringent Regulatory Authority (SRA) is(a) The medicines regulatory authority in a country which is: (a) a member of the International Council on Harmonisation (ICH) (European Union (EU), Japan and the United States of America); or

(b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);

(c) Only in relation to good manufacturing practices (GMP) inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at http://www.picscheme.org

1. INTRODUCTION

1.1 Background

The *"Guidelines for Variation of Registered human pharmaceutical product, is* a Rwanda Food and Drugs Authority publication which sets out procedures and requirements for documentation to support the variation of registered human Pharmaceutical product. They are issued in pursuance of Articles 3 and 9 of Law No. 003/2018 of 09/02/2018 establishing Rwanda FDA. These guidelines have been developed in order to maintain safety, efficacy and quality human medicinal product that have been issued Marketing Authorizations.

Rwanda FDA adopted the Common Technical Document (CTD) Guidelines on Submission of Documentation for Registration of Human Pharmaceutical product. Post approval changes to a registered Pharmaceutical product form part of the product life cycle. An applicant is responsible for the safety, efficacy and quality of a product throughout its life-cycle. Therefore, the applicant is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the registered product. Such changes, whether administrative or substantive, are referred to as variations and may be subject to acceptance by Rwanda FDA prior to implementation. These Guidelines are intended to provide supportive information on how to present an application to implement a change to a registered human Pharmaceutical product. Applicants are encouraged to refer to these Guidelines as they prepare documentation to support variations to registered human ~~medicinal~~ pharmaceutical products.

These Guidelines have been developed technically and structurally in line with the WHO Technical Report Series (TRS) 981 Guideline on Post Approval Changes that provides the various categories of variations to the terms of marketing authorizations for pharmaceutical products for human use. They include the classification of post-approval changes and establishes the level of risk inherent to each change. These Guidelines are developed to help the applicant to classify changes that may occur related to all the major sections of a quality dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

The change categories are organized according to the structure of the Common Technical Document (CTD). The specific CTD sections associated with individual data requirements have been identified in order to assist in the filing of documentation (reproduced with corresponding numbers in bold). Presentation corresponds to section 1.4 in Annex 4 of WHO Technical Report Series, No. 970.

Changes are classified as major variation (Vmaj) only in those instances where the level of risk is considered to be high and it is deemed necessary to provide Rwanda FDA with adequate time for an assessment of the supporting documentation. Particular circumstances are identified where lower reporting requirements (annual notification (AN), immediate notification (IN) or minor variation (Vmin)) are possible. In all cases where notification to Rwanda FDA or acceptance by Rwanda FDA is required prior to implementation, assessment timelines will be published in order to provide predictable and reasonable timeframes.

In addition, the guidelines assist in understanding the possible consequences of the listed changes and may be useful as a risk management tool to promote or enhance best practices within organizations.

Technical requirements for the different types of variations are set out in these guidelines in order to facilitate the submission of appropriate documentation by applicants and their assessment by Rwanda FDA and to ensure that variations to the pharmaceutical product do not result in health concerns.

The Variation guidelines are not exhaustive; applicants are encouraged to contact Rwanda FDA for advice for variations not covered under these guidelines.

1.2 Objectives

These guidelines are intended to:

- Assist applicants with the classification of changes made to a registered finished pharmaceutical product (FPP);
- Provide guidance on the technical and other general data requirements to support changes to the quality, safety, efficacy and administrative attributes of the Finished Pharmaceutical Products (FPPs),its APIs and excipients.

1.3 Scope

These guidelines apply to applicants intending to make changes to the different sections of product dossiers for a registered human medicinal product. These guidelines should be read in conjunction with the Rwanda FDA Guidelines for registration of human pharmaceutical products as well as other related applicable guidelines.

The FPPs whose APIs are produced by fermentation and APIs of biological, biotechnological or herbal origin are treated as special cases. The applicant is requested to contact Rwanda FDA regarding planned variations to such products.

The notification requirements for API-related changes differ depending on the manner in which information on the API was submitted in the FPP application, namely, use of an active pharmaceutical ingredient master file (APIMF), WHO Prequalification of API or use of a European Pharmacopoeia Certificate of Suitability (CEP).

The conditions and documentation stipulated in these guidelines for API related variations focus primarily on those FPPs that relied upon the provision of full APIMF for API information within the FPP dossier. When an FPP relies upon a CEP, WHO-APIMF or EAC APIMF, FPP applicants are required to notify Rwanda FDA only when the associated CEP, WHO-APIMF and EAC APIMF have been revised.

When a variation leads to a revision of the summary of product characteristics (SmPC), the patient information leaflet (PIL), labelling and packaging leaflet, updated product information should be submitted as part of the application.

For variations that require generation of stability data on the API or FPP, the stability studies required, including commitment batches, should always be continued to cover the currently accepted retest or shelf-life period. Rwanda FDA should be informed immediately if any problems with the stability of APIs or FPPs occur during storage, e.g. if found to be outside specifications or potentially outside specifications.

Applicants should be aware that some variations may require the submission of additional consequential variations. Therefore, for any given change the applicant should consider whether one or more variations may be required to be submitted.

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation, but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

All variations with the exception of annual notifications should be approved by Rwanda FDA prior to their implementation.

1.4 Fees

Applicable fees are defined in the regulation determining regulatory services tariffs/ fees and fines. Note that Rwanda FDA reserves the right to determine the correct interpretation of the fee payable based on the published schedule. Please note that relevant variation application fees apply to all variations. Any application not accompanied by the relevant proof of payment will not be considered.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of changes. Specific examples of changes are provided in these guidelines. Whenever the applicant is unclear about the classification of a particular change, Rwanda FDA should be contacted for guidance prior to any change/modification. However, it should be noted that a change not covered by these guidelines, should be considered as a major change by default. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product.

Whenever FPPs have been registered on the basis of approval by a stringent regulatory authority (SRA) (innovator products or generic products) or WHO prequalification, subsequent applications for variations should also be approved by the same SRA and WHO PQP, respectively, and the Authority shall be notified of the approval of the changes and the applicant shall submit proof of approval of such changes from the respective authority, if applicable.

For the products registered under collaborative procedures, the changes may be submitted as an IN.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only under the following circumstances:

a. when variations are consequential to each other, e.g. introduction of a new impurity
b. specification that requires a new analytical procedure;

c. when all the changes are annual notification.

For the purposes of classification, an application involving two or more types of variations will be considered as the highest risk type and charged as such as per Rwanda FDA's Regulations governing tariff/fees and charges on services, e.g. a variation grouping both a minor change and a major change will be classified as a major change.

Applicants are also advised to exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified as a particular reporting type, classification within a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact Rwanda FDA prior to submission of the variation application to obtain guidance on classifying such changes.

2.2 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance, but must be notified to Authority immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change. It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

2.3 Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to Rwanda FDA within 12 months of implementation of the changes.

Annual notifications submitted at once in one calendar year will be considered as one minor variation and will be charged as such as per Rwanda FDA's Regulations governing tariff/fees and charges on services.

2.4 Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by the Authority within 60 calender days of the date of acknowledgement of receipt of the application. Submitted immediate notification will be considered as one minor variation and will be charged as such as per Rwanda FDA's Regulations governing tariff/fees and charges on services

2.5 Minor variation

Minor variations are changes that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.
Such variations can be implemented if no objection letter has been issued within 90 calender days from the date of acknowledgement of the application. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of approval from Rwanda FDA.

2.6 Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by Rwanda FDA is required before the changes can be implemented. Such variations will be handled within 6 months from the date of acknowledgement of the application. A letter of approval will be issued for all major variations if and when the variation is considered acceptable.

2.7 New applications and extension applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. In these cases, a new dossier must be submitted. Examples of such changes are listed in Appendix 1.

2.8 Labelling information

For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, Rwanda FDA must be notified and submission of the revised labelling information is expected as per *Rwanda FDA Guidelines for registration of human Pharmaceutical products*

2.9 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN or Vmin) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a Vmaj.

In some circumstances Vmaj categories have been specifically stated for a given variation. This has been done to indicate to applicants what documents should be provided. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy or quality of the FPP.

2.10 Documentation required

For each variation, certain documents have been identified as supporting data and are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation. The application consists of electronic copies, that are submitted through online submission portal

Where applicable, the following should be included in the application:

- a variation application form (a template can be downloaded from the web site). All sections of this form should be completed and the document signed.,
- an updated quality information summary (QIS) (if applicable);
- replacement of the relevant sections of the dossier as per CTD format;
- copies of SmPC, PIL and labels, if relevant.

- Product sample (if applicable). However, if a commercial sample is not available, a mock-

up is acceptable, with commitment letter that the sample will be submitted prior to distribution.

- Payment of relevant fees according to Rwanda FDA Regulations governing tariff/fees and charges on services

It should be noted that Rwanda FDA reserves the right to request further information not explicitly described in these guidelines.

The QIS provides a summary of the key quality information from the product dossier. For FPPs that have an agreed-upon QIS, the QIS should be revised and its tracked and clean versions submitted (in Word format only) with every variation application. Any revised sections within the QIS should be highlighted. If there is no change to the QIS as a result of the variation, a statement should be made in the cover letter to this effect.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that Rwanda FDA may request information or material, or define conditions not specifically described in these guidelines, in order to adequately assess the safety, efficacy and quality of an FPP.

3.1 ADMINISTRATIVE CHANGES

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1	Change of the of the Marketing Authorization Holder (MAH) of the FPP			
a	Change in the name and/or corporate address of the (MAH)	1	1, 3	IN
b	Change of MAH from one company to another	2	2-3	IN
	Conditions to be fulfilled			
1)	Confirmation that the MAH of the product remains the same legal entity			
2)	All legal requirements for change of MAH have been met & Legal transfer of change has been completed			
	Documentation required			
1)	A formal document from a relevant official body (e.g. the national medicines regulatory authority (NMRA)) in which the new name and/or address is mentioned.			
2)	Notarized transfer documents			
3)	Company registration certificate from the relevant jurisdiction			

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2	Change in the name or address of a manufacturer of an API	1	1-2	IN
Conditions to be fulfilled				
1)	No change in the location of the manufacturing site and in the manufacturing operations.			
Documentation required				
1)	A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.			
2)	An updated Letter of Access in the case of a change in the name of the APIMF Holder, CEP, WHO APIMF and EAC APIMF as applicable.			

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3	Change in the name and/or address of a manufacturer of the FPP	1	1-2	IN
Conditions to be fulfilled				
1)	No change in the location of the manufacturing site and in the manufacturing operations.			
Documentation required				

1) Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned. 2) Two (2) commercial samples of the product. However, if a commercial sample is not available, a mock- up is acceptable, with commitment letter that the samples will be submitted prior to distribution.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
4	Deletion of a manufacturing site or manufacturer involving:			
a	production of the API starting material	1	1,3	AN
b	production or testing of the API intermediate or API	1-2	1,3	IN
c	production, packaging or testing of the intermediate or FPP	1-2	1-3	IN
	Conditions to be fulfilled			
1)	At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.			
2)	The deletion of site is not a result of critical deficiencies in manufacturing.			
	Documentation required			
1)	Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.			
2)	Two (2) commercial samples of the product required or mock-ups with commitment letter that the sample will be submitted prior to distribution.			
3)	Updated manufacturers information and their roles			

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
5	Change of Local Technical Representative (LTR)	1	1-4	IN
	Conditions to be fulfilled			
1)	Proposed LTR should be licensed (or equivalent).			
	Documentation required			

1) Letter of appointment from the product Marketing Authorization Holder 2) Letter of acceptance from the proposed LTR and a copy of termination notice of previous LTR. 3) List of affected products, including registration numbers. Affected products should appear on the current Drug Register. 4) A copy of authorization issued by Rwanda FDA to the LTR

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
6	Change of Proprietary/Product name	None	1-2	Vmin
	Conditions to be fulfilled			
	1) The brand name should not have been accepted for another product.			
	Documentation required			
	1) Revised product information 2) Two (2) commercial samples of the product or mock-ups with commitment letter that the sample will be submitted prior to distribution. 3) A copy of trademark certificate from relevant competent authority in Rwanda (if applicable)			

CHANGES TO A CEP OR TO A CONFIRMATION OF API PREQUALIFICATION DOCUMENT

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
7	Submission of a new or updated European Pharmacopoeia Certificate of Suitability for an API or starting material or intermediate used in the manufacturing process of the API:			
7a	Updated CEP	1-5	1-7	IN
7b	from a new manufacturer	1, 3-5	1-7	Vmin
	Conditions to be fulfilled			

1) No change in the FPP release and shelf-life specifications.
2) Unchanged (excluding tightening) additional (to Ph.Eur.) specifications for any impurities including organic, inorganic and genotoxic impurities and residual solvents, with the exception of residual solvents when the limits stipulated comply with ICH requirements.
3) The manufacturing process of the API, starting material or intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4) For low solubility APIs the polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the bio batch.
5) The site must be GMP compliant

Documentation to be supplied

1) Copy of the current (updated) CEP, including any annexes and a declaration of access for the CEP to be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to Rwanda FDA who refers to the CEP.
2) A written commitment that the applicant will inform Rwanda FDA in the event that the CEP is withdrawn and an acknowledgement that withdrawal of the CEP will require additional consideration of the API data requirements to support the product dossier.
3) Replacement of the relevant pages of the dossier with the revised information for the CEP submission option stipulated under section 3.2.S of Rwanda FDA *Guidelines on Submission of Documentation for registration of Human Medicinal products*
4) For sterile APIs, data on the sterilization process of the API, including validation data.
5) In the case of the submission of a CEP for an API, if the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of the FPP of at least pilot scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to Rwanda FDA.
6) Copy of FPP manufacturer's revised API specifications and standard test procedure.
7) Proof of GMP compliance

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
8	Submission of a new or updated WHO Confirmation of API -Prequalification Document (CPQ)			
8a	Updated CPQ	1-3	1-3, 5	IN
8b	from a new manufacturer	1-2	1-5	Vmin

Conditions to be fulfilled

1) No change in the FPP release and shelf-life specifications.
2) For low solubility APIs the API polymorph is the same, and whenever particle size is critical

(including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch. 3) There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic, genotoxic impurities and residual solvents, to the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.
Documentation to be supplied
1) Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box on the name of the applicant or FPP manufacturer seeking to use the document. 2) Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option 3) For sterile APIs, data on the sterilization process of the API, including validation. 4) Copy of FPP manufacturer's revised API specifications and standard test procedure. 5) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of at least pilot scale of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to Rwanda FDA.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
9	Submission of a new or updated transmissible spongiform encephalopathy European Pharmacopoeia Certificate of Suitability for an excipient or API (addition or replacement)	None	1	AN
	Conditions to be fulfilled			
	None			
	Documentation required			
1)	1. Copy of the current (updated) TSE CEP.			

3.2. QUALITY CHANGES

3.2. S DRUG SUBSTANCE (OR API)

3.2. S.2 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
10	Replacement or addition of a new manufacturing site or manufacturer of an API involving:			
a	API testing only	1, 2,4	1, 3-4	IN
b.1	production of API starting material	3-4	No variation is required. Such changes are handled as amendments to the APIMF by the APIMF holder as part of the EAC or WHO APIMF procedure.	
b.2		4-5	1-2, 12	IN
b.3		None	1,2,5, 7-8,12, 13	Vmaj
c.1	production of API intermediate	3-4	No variation is required such changes are handled as amendments to the APIMF by the APIMF holder as part of the EAC or WHO APIMF procedure	
c.2		4, 6	1-2, 12	IN
c.3		None	1,2,5, 7-8,12	Vmaj
d.1	production of API	1, 7-11	1-2, 4, 8-9	IN
d.2		None	1,2,4,6,5,7-8, 10-11, 13	Vmaj

Conditions to be fulfilled

1) The API is non-sterile.
2) The transfer of analytical methods has been successfully undertaken.
3) The new site is supported by an APIMF that has been currently accepted through the EAC Partner States' or WHO APIMF procedure and the FPP manufacturer holds a valid Letter of Access.
4) No change in the FPP manufacturer's API specifications.
5) The impurity profile of the API starting material is essentially the same as other accepted sources. The introduction of the new supplier does not require the revision of the API manufacturer's API starting material specifications. The route of synthesis is verified as identical to that already accepted.
6) Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require the revision of the API manufacturer's API intermediate specifications.
7) No change in the FPP release and end-of-shelf-life specifications.
8) No difference in impurity profile of the proposed API to be supplied, including organic, inorganic and genotoxic impurities and residual solvents. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.
9) For low solubility APIs the API polymorph is the same, and whenever particle size is critical

(including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.

10) Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or new contract manufacturing site with evidence of an acceptable and similar quality system to the main manufacturer).
11) 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 Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products or EMA's 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 required

1) (S.2.1) Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s). A valid testing authorization or a certificate of GMP compliance, if applicable.
2) (S.2.2) A side-by-side comparison of the manufacturing flowcharts for production of the API, intermediate, or API starting material (as applicable) at the parent and proposed sites.
3) (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalency of analytical procedures to be used at the proposed testing site.
4) (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and proposed manufacturers/sites.
5) Relevant sections of (S) documentation in fulfilment of requirements for full information provided in the dossier
6) The open part of the new APIMF (with a Letter of Access provided in Module 1)
7) (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to Rwanda FDA.
8) (S.4.1) A copy of the FPP manufacturer's API specifications.
9) (S.2) A declaration from the supplier of the registered FPP that the route of synthesis, materials, 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 accepted.
10) A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.
11) For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low solubility APIs) where there is a significant difference in particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and

bioavailability of the FPP.

12) Certificates of analysis for at least one batch of API starting material/intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material/intermediate (as applicable) from the new source and from a previously accepted source.

13) An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting
11a	change or addition of a manufacturing block/unit at a currently accepted site of API manufacture	1-5	1-4	IN
11b		1,3-5		

Conditions to be fulfilled

1) The API is non-sterile.
2) API manufacturing block/unit is currently accepted by Rwanda FDA and EAC/WHO if applicable.
3) The same quality system covers currently accepted and proposed units/blocks.
4) For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API lot used in the preparation of the biobatch.
5) No change in 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).

Documentation required

1) (S.2) A declaration from the supplier of the 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 accepted.
2) (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s). A valid manufacturing and/or testing authorization and a certificate of GMP compliance, if available.
3) (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from the currently accepted and proposed units/blocks.
4) (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units/blocks

	Description of change	Conditions to be fulfilled	Documentation to be supplied	Reporting type
12a	change in the manufacturing process	1-3, 9	1-2, 8	AN

12b	of the API	1-2, 4, 6-9	3-4, 11-12	IN
12c		1-2, 4-7	3-4, 11-12	Vmin
12d		None	2-14	Vmaj

Conditions to be fulfilled

1) No change in the physical state (e.g. crystalline, amorphous) of the API.
2) For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change in the particle size distribution compared to the API lot used in the preparation of the biobatch.
3) API manufacturing site is currently accepted by Rwanda FDA and EAC or WHO
4) Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5) No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process.
6) No change in qualitative and quantitative impurity profile or in physicochemical properties of the API.
7) The change does not affect the sterilization procedures of a sterile API.
8) The change involves only steps before the final intermediate.
9) The change does not require revision of the starting material, intermediate or API specifications

Documentation to be supplied

1) A copy of the EAC or WHO letter of acceptance for APIMF amendment
2) (P.8.2) if the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to Rwanda FDA.
3) (S.2.2) A side-by-side comparison of the current process and the new process.
4) (S.2.2) A flow diagram of the proposed synthetic process (es) and a brief narrative description of the proposed manufacturing process (es).
5) (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
6) (S.2.3)Either a TSE CEP for any new source of material or, where applicable, documented evidence that the specific source of the material that carries a risk of TSE 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* or EMA's *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.
7) (S.2.4) Information on controls of critical steps and intermediates, where applicable.

8) (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.
9) (S.3.1) Evidence for elucidation of structure, where applicable.
10) (S.3.2) Information on impurities.
11) (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
12) (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot scale) manufactured according to the current and proposed processes.
13) (S.7.1) Results of two batches of at least pilot scale with a minimum of three (3) months of accelerated (and intermediate as appropriate) and three (3) months of long-term testing of the proposed API.
14) For low solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low solubility APIs) where there is dissimilar particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP

Description of change		**Conditions to be fulfilled**	**Documentation to be supplied**	**Reporting type**
13	Change in the in-process tests or limits applied during the manufacture of the API:			
13a	any change in the manufacturing process controls	1	No variation is required. Such changes are handled as amendments to the APIMF by the APIMF holder as part of the EAC or WHO APIMF procedure.	
13b	tightening of in-process limits	2-4	1	AN
13c	addition of a new in-process test and limit	2, 5	1-5	AN
13d	addition or replacement of an in-process test as a result of safety or quality issue	None	1-5,7, 8-10	Vmin
13e.1	deletion of an in-process test	2,6-7	1-3, 6	AN
13e.2		None	1-3, 7-10	Vmaj
13f	relaxation of the in-process test limits	None	1-3, 5,7-10	Vmaj
Conditions to be fulfilled				

1) API manufacturing site is currently accepted by Rwanda FDA and EAC or WHO.
2) The change is not necessitated by unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3) The change is within the range of currently accepted limits.
4) The analytical procedure remains the same, or changes to the analytical procedure are minor.
5) Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6) The affected parameter is non-significant. (*"The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.")*
7) The change does not affect the sterilization procedures of a sterile API.

Documentation to be supplied

1) A comparison of the currently accepted and the proposed in-process tests.
2) (S.2.2) Flow diagram of the proposed synthetic process (es) and a brief narrative description of the proposed manufacturing process (es).
3) (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.
4) Details of any new non-pharmacopoeial analytical method and validation data where relevant.
5) Justification for the new in-process test and/or limits.
6) Justification/risk-assessment showing that the parameter is non-significant.
7) (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, where applicable.
8) (S.3.2) Information on impurities, if applicable.
9) (S.4.1) Copy of currently accepted specifications of API (and intermediates, if applicable).
10) (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot scale) for all specification parameters.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
14	Change in batch size of the API involving:			
14a	up to 10-fold compared to the currently accepted batch size	1-2,4,6	1,3-4	AN
14b	Downscaling (to at least pilot batch size)	1-4	1,3-4	AN
14c	more than 10-fold increase compared to the currently accepted batch size	1-2,4,6	1,3-4	Vmin
14d	Any other change in scale	5	1-2, 4-5	AN

Conditions to be fulfilled
1) No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of different size of equipment). 2) The change does not affect the reproducibility of the process. 3) The change is not necessitated by unexpected events arising during manufacture or due to stability concerns. 4) The change does not concern a sterile API. 5) API manufacturing site and batch size is currently accepted by Rwanda FDA and EAC or WHO. 6) The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation.
Documentation required
1) (S2.2) A brief narrative description of the manufacturing process. 2) (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization. 3) (S.4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable). 4) (S.4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size. 5) A copy of the EAC or WHO letter of acceptance for APIMF amendment.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
15	Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts) involving:			
15a	any change	1	No variation is required. Such changes are handled as amendments to the APIMF by the APIMF holder as part of the EAC or WHO APIMF procedure.	
15b	tightening of the specification limits	2-4	1-3	AN
15c	minor change to an analytical procedure	5-7	2-3	AN
15d	addition of a new specification parameter and a corresponding analytical procedure where necessary.	2,7-9	1-3	AN
15e	deletion of a specification parameter or deletion of an analytical procedure	2,10	1-4	AN

15f	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1-7	Vmin
15g	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	4,7,9-10	1,3-4	IN
15h	relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1-3,5,6,7	Vmaj

Conditions to be fulfilled

1) API manufacturing site is currently accepted by Rwanda FDA and EAC or WHO.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any change is within the range of currently accepted limits.
4) The analytical procedure remains the same.
5) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method).
6) Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7) No change to the total impurity limits; no new impurities are detected.
8) Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
9) The change does not concern a genotoxic impurity.
10) The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

Documentation to be supplied

1) Comparative table of currently accepted and proposed specifications.
2) (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
3) (S.2.4) Information on intermediates, where applicable.
4) Justification/risk-assessment showing that the parameter is non-significant.
5) (S.3.2) Information on impurities, where applicable.
6) Batch analysis data on two production batches
7) Where appropriate, comparative dissolution profile data for the FPP on at least one pilot batch containing the API complying with current and proposed specifications.

3.2. S.4 Control of the API by the API manufacturer

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
16	Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturer's API specifications involving:			
16a	API supported through the EAC Partner State's and WHO APIMF procedure.	1-2	No variation is required, such changes are handled as amendments to the associated APIMF	
16b	API not supported through the EAC Partner State's APIMF procedure.	2	1-4	IN

Conditions to be fulfilled

1) The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APIMF (EAC and WHO APIMF procedure) and accepted.
2) The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer's API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API is maintained.

Documentation to be supplied

1) (S.4.1) Copy of the current and proposed API specifications dated and signed by the API manufacturer.
2) (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
4) Justification as to why the change does not affect the FPP manufacturer's specifications.

3.2. S.4 Control of the API by the FPP manufacturer

	Description of change	Conditions to be fulfilled	Documentation required	Reporting
17	Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:			
17a	updating a test parameter or acceptance criterion controlled in	11	1-5	AN

	compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.			
17b.1	deletion of a test parameter	1-2	1,6	AN
17b.2		10	1, 6, 8	IN
17b.3		None	1, 6	Vmaj
17c.1	addition of a test parameter	1, 4-8	1-6	AN
17c.2		1, 5-7, 10	1-6,8	IN
17c.3		1,5-7	1-6	Vmin
17c.4		None	1-7	Vmaj
17d.1	replacement of a test parameter	1, 5-8	1-6	IN
17d.2		5, 7, 10	1-6,8	Vmin
17d.3		None	1-7	Vmaj
17e.1	tightening of an acceptance criterion	1, 3, 9	1,6	AN
17f.1	relaxation of an acceptance criterion	1, 5-9	1,6	IN
17f.2		5, 7, 10	1, 6,8	Vmin
17f.3		None	1,6-7	Vmaj

Conditions to be fulfilled

1) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
2) The deleted test has been demonstrated to be redundant with respect to the remaining tests.
3) The change is within the range of currently accepted acceptance criteria.
4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5) For insoluble APIs there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no change in particle size distribution acceptance criteria.
6) No additional impurity found over the ICH identification threshold.
7) The change does not concern sterility testing.
8) The change does not involve the control of a genotoxic impurity.
9) The associated analytical procedure remains the same.
10) The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF amendment.
11) No change is required in FPP release and shelf-life specifications.

Documentation to be supplied

1) (S.4.1)A copy of the proposed API specifications (of the FPP manufacturer) dated and signed by

authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.

2) (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (S.4.3) Copies or summaries of validation/verification reports issued by the FPP manufacturer, if new analytical procedures are used.
4) (S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.
5) (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.
6) (S.4.5) Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
7) (P.2) Where changes have occurred to the particle size criteria of an insoluble API or wherever particle size is critical, evidence is provided that the changes do not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for 2 batches. of FPP manufactured using API controlled to the proposed criteria; 2 batches of FPP manufactured using API controlled to the currently accepted criteria; and data on the FPP 2 batches. used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact Rwanda FDA for advice. For changes to the polymorph of an insoluble API the applicant should contact Rwanda FDA for advice before embarking upon any investigation.
8) A copy of the EAC or WHO letter of acceptance for APIMF amendment.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
18	Change to the analytical procedures used to control the API by the FPP manufacturer involving:			
18a	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.	None	1-3	AN
18b	change from a currently accepted house analytical procedure to an analytical procedure in a officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical	None	1-4	IN

	procedure in another officially recognized pharmacopoeia			
18c.1	addition of an analytical procedure	1-3	1-3	AN
18c.2		3, 8	1-3, 5	AN
18c.3		8	1-3, 5	Vmin
18c.4		None	1-3	Vmaj
18d.1	modification or replacement of an analytical procedure	1-6	1-4	AN
18d.2		2-3, 5-6, 8	1-5	AN
18d.3		1-3, 5-6	1-4	Vmin
18d.4		5-6, 8	1-5	Vmin
18d.5		None	1-4	Vmaj
18e.1	deletion of an analytical procedure	6-7	1,6	AN
18e.2		6, 8	1, 5-6	IN
18e.3		None	1, 6	Vmaj

Conditions to be fulfilled

1) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) No new impurities have been detected as a result of the use of the new analytical method.
4) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
5) Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
6) The change does not concern sterility testing.
7) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method.
8) The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF.

Documentation to be supplied

1) (S.4.1) Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (S.4.2) Copies or summaries of analytical procedures, if new or significantly modified analytical procedures are used.
3) S.4.3) Copies or summaries of validation/verification reports issued by the FPP manufacturer, if new or significantly modified analytical procedures are used.
4) (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures.
5) A copy of the EAC or WHO letter of acceptance for APIMF amendment
6) (S.4.5) Justification for the deletion of the analytical procedure, with supporting data.

3.2. S.6 Container-closure system

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
19a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	3-4	1-2,4	AN
19b		1-2, 4	2-3	IN
19c		4	1-3	Vmin

Conditions to be fulfilled

1) Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, moisture permeability etc.).
2) The change does not concern a sterile API.
3) The change has previously been accepted by Rwanda FDA and EAC or WHO.
4) The change is not the result of stability issues.

Documentation required

1) (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process.
2) (S.6) Information on the proposed primary packaging (e.g. description, specifications etc.) and data in fulfillment of condition 1.
3) (S.7.1) Results of a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing of the API in the proposed primary packaging type.
4) A copy of the EAC or WHO letter of acceptance for APIMF amendment.

Description of change	Conditions to	Documentation	Reporting

		be fulfilled	required	type
20	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
20a	tightening of specification limits	1-2	1	AN
20b	addition of a test parameter	2-3	1-3	AN
20c	deletion of a non-critical parameter	2	1,4	AN
20d	addition or replacement of a specification parameter as the result of a safety or quality issue	1,3	1-4	Vmin
20e	any other change of EAC or WHO APIMF procedure	4	No variation is required, such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1) The change is within the range of currently accepted limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) The change has previously been accepted through the EAC or WHO APIMF procedure.

Documentation required

1) (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2) (S.4.2) Details of method and summary of validation of new analytical procedure.
3) (S.6) Certificate of analysis for two batches.
4) Justification to demonstrate that the parameter is not critical.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporti ng type**
21	Change to an analytical procedure on the immediate packaging of the API involving:			
a	minor change to an analytical procedure	1-3	1	AN
b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2-4	1	AN
c	deletion of an analytical procedure	5	2	AN

d	any change (EAC or WHO APIMF procedure)	6	No variation is required, such changes are handled as amendments to the associated APIMF
Conditions to be fulfilled			
1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method). 2) Appropriate (re)validation studies have been performed in accordance with the relevant guidelines. 3) Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure. 4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 5) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method. 6) The change has previously been accepted through the EAC or WHO APIMF procedure.			
Documentation required			
1) (S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent. 2) Justification for deletion of the analytical procedure.			

3.2. S.7 Stability

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
22	Change in the retest period/shelf-life of the API involving:			
a	reduction	3	1-2	IN
b	extension	1-2	1-3	Vmin
c	any other change of EAC or WH APIMF procedure	4	4	IN
Conditions to be fulfilled				

1) No change to the primary packaging in direct contact with the API or to the recommended condition of storage. 2) Stability data was generated in accordance with the currently accepted stability protocol. 3) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns. 4) The revised retest period has previously been accepted through the EAC or WHO APIMF
Documentation required
1) (S.7.1) Proposed retest period/shelf-life, summary of stability testing according to currently accepted protocol and test results. 2) (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable. 3) (S.7.3) Stability data to support the change 4) A copy of the EAC or WHO letter of acceptance for APIMF amendment.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
23	Change in the labelled storage conditions of the API involving:			
a	any change in storage conditions EAC or WHO APIMF procedure	1	1	IN
b	any other change in storage conditions	2	2	Vmin
	Conditions to be fulfilled			
1) The revised storage conditions have previously been accepted through the EAC or WHO APIMF procedure. 2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.				
	Documentation required			
1) A copy of the EAC or WHO letter of acceptance for APIMF amendment. 2) (S.7.1)Stability and/or compatibility test results to support the change to the storage conditions.				

3.2. P Drug product (or FPP)

3.2. P.1 Description and composition of the FPP

Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**

24a	Change in the composition of a solution dosage form	1-6	2,4,7,9-10	IN
24b		None	1-11	Vmaj

Conditions to be fulfilled

1) The affected excipient(s) does/do not function to affect the solubility and/or the absorption of the API.
2) The affected excipient(s) does/do not function as a preservative or preservative enhancer.
3) No change in the specifications of the affected excipient(s) or the FPP.
4) No change in the physical characteristics of the FPP (e.g. viscosity, osmolality, pH).
5) The change does not concern a sterile FPP.
6) The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within ±10% of the amount (or concentration) of each excipient in the originally

Documentation required

1) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current Authority Guidelines on Bioequivalence.
2) (P.1) Description and composition of the FPP.
3) (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, preservative effectiveness, suitability studies on the packaging system for the changed product).
4) (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5) (P.4) Control of excipients, if new excipients are proposed.
6) (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an SRA and shown to comply with the scope of the current guideline in the SRA. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals and its use.
7) (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot or production scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8) (P.8.1) Results of stability testing generated on at least two pilot or production scale batches with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing.
9) (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10) (R.1)Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there

up is acceptable, with commitment letter that the samples will be submitted prior to distribution.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
25	Change in the coloring system or the flavoring system currently used in the FPP involving			
a	Reduction or increase of one or more components of the coloring or the flavoring system	1-3,6	1,4,6-7	AN
b	Deletion, addition or replacement of one on more components of the coloring or flavoring system	1-7	1-7	IN

Conditions to be fulfilled

1) No change in the functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile etc.
2) Any minor adjustment to the formulation to maintain the total weight is made by an excipient which currently makes up a major part of the FPP formulation.
3) Specifications for the FPP are updated only with respect to appearance/odour /taste or if relevant, deletion or addition of a test for identification.
4) Any new component must comply with the relevant section of Rwanda FDA "*Guidelines on Submission of Documentation for registration of Human Pharmaceutical products*
5) 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 is in compliance with the current *WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products* or EMA's *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.
6) For pediatric products, the change does not require submission of results of palatability studies.
7) *The change is not the result of stability issues and/or should not result in potential safety concerns, i.e. differentiation between strengths*

Documentation required

1) Two (2) commercial samples of the product
2) (P.2) Discussion on the components of the FPP (e.g. compatibility of API and qualitative composition of the coloring or flavoring system if purchased as a mixture, with specifications, if relevant).
3) (P.4.5) Either a CEP for any new component of animal origin susceptible to TSE risk or where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an SRA and shown to comply with the scope of the current guideline of the SRA. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals and its use.
4) (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot or production scale batches.
5) (P.5.3) If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
6) (P.8.1) Results of stability testing generated on at least two pilot or production scale batches with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing.
7) (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
26	Change in weight of tablet coatings or capsule shells involving			
a	immediate-release oral FPPs	1-3	2-5	AN
b	gastro-resistant, modified or prolonged release FPPs	None	1-5	Vmaj

Conditions to be fulfilled

1) Multipoint in vitro dissolution profiles of the proposed version of the product (determined in the release medium on at least two batches of pilot or production scale), are similar to the dissolution profiles of the bio batch.
2) Coating is not a critical factor for the release mechanism.
3) Specifications for the FPP are updated only with respect to weight and dimensions, if applicable.

Documentation required

1) Justification for not submitting a new bioequivalence study according to the current *Rwanda FDA Guidance on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*.
2) (P.2) Comparative multipoint in vitro dissolution profiles in the release medium (or media), on at least two batches of pilot or production scale of the proposed product versus the biobatch.
3) (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot or production scale batch.
4) (P.8.1) Results of stability testing generated on at least two pilot or production scale batches with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing. In addition, a written commitment, that the stability studies will be finalized should be provided
5) (R.1)Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
27	Change in the composition of an immediate-release solid oral dosage form including			
a.1	replacement of a single excipient with a comparable excipient at a similar level	1-5	1-10	Vmin
a.2		None	1-10	Vmaj
b.1	quantitative changes in excipients	1-4	1-4, 7-10	Vmin
b.2		None	1-4, 7-10	Vmaj

Conditions to be fulfilled

1) No change in functional characteristics of the pharmaceutical form.
2) Only minor adjustments (see appendix 2) are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made by an excipient which currently makes up a major part of the FPP formulation.
3) Stability studies have been started under conditions according to *Rwanda FDA Guidelines on Stability Testing for Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)* (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot or production scale batches and at least three months' satisfactory stability data are at the disposal of the applicant and the stability profile is similar to the currently accepted product.
4) The dissolution profile of the proposed product determined on a minimum of two pilot scale batches is similar to the dissolution profile of the bio batch.
5) The change is not the result of stability issues and/or does not result in potential safety concerns i.e. differentiation between strengths.

Documentation required

1) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current *Rwanda FDA Guidelines on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*.
2) (P.1) Description and composition of the FPP.
3) (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles on at least two batches of pilot or production scale of the proposed product and the bio batch (depending on the solubility and permeability of the drug, dissolution in the release medium or in multiple media covering the physiological pH range).
4) (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5) (P.4) Control of excipients, if new excipients are proposed.
6) (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by World Health Organization Listed Authorities (WLAs) and shown to comply

with the scope of the current guideline of the World Health Organization Listed Authorities (WLAs). The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals and its use.

7) (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot or production scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8) (P.8.1) Results of stability testing generated on at least two pilot or production scale batches with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing.
9) (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10) (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch, and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
28	Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving:			
a	changes in imprints, embossing or other markings	1-3	1-2, 5-6	IN
b	deletion of a score line	2-5	1,5-6	IN
c.1	addition of a score line	2-4	1, 3, 5-6	Vmin
c.2		None	1, 3-6	Vmaj

Conditions to be fulfilled

1) Any ink must comply with the pharmacopoeial requirements of EU, Japan, US or any other recognised pharmacopeia and must be food grade
2) The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP.
3) Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring.
4) Addition or deletion of a score line to a generic product is consistent with a similar change in the comparator product.
5) The scoring is not intended to divide the FPP into equal doses.

Documentation required

1) Two (2) commercial samples of the Product. However, if commercial samples are not available, a

mock-up is acceptable, with commitment letter that the samples will be submitted prior to distribution.

2) (P.1.) Qualitative composition of the ink.
3) (P.2) Demonstration of the uniformity of the dosage units of the tablet portions, where the scoring is intended to divide the FPP into equal doses.
4) (P.2) Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified or prolonged release products.
5) (P.5) Copies of revised FPP release and shelf-life specifications.
6) (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions t	Documentation required	Reporting type
29	Change in dimensions without change in qualitative or quantitative composition and mean mass of;			
a	tablets, capsules, suppositories and pessaries other than those stated in change #b	1-2	2-6	IN
b	gastro-resistant, modified or prolonged release FPPs and scored tablets	1-2	1-6	Vmin

Conditions to be fulfilled

1) Specifications for the FPP are updated only with respect to dimensions of the FPP.
2) Multipoint in vitro dissolution profiles of the current and proposed versions of the product (determined in the release medium, on at least one batch of pilot or production scale), are comparable.

Documentation required

1) For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according to the current *Rwanda FDA Guidance on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions.
1) Two (2) commercial samples of the Product. However, if commercial samples are not available, a mock-up is acceptable, with commitment letter that the samples will be submitted prior to distribution.
2) (P.2) Discussion on the differences in manufacturing process (es) between the currently accepted and proposed products and the potential impact on product performance.
3) (P.2) Comparative multipoint in vitro dissolution profiles in the release medium, on at least one batch of pilot or production scale of the current and proposed products.
4) (P.5) Copies of revised FPP release and shelf-life specifications.
5) (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
30	Deletion of the solvent/diluent container from the pack	None	1-3	Vmin
	addition of solvent/diluent container in the pack"		2-5	Vmajor
	Documentation required			
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 pharmaceutical product. 2) Revised product information 3) Two (2) commercial samples of the product. However, if commercial samples are not available, a mock-up is acceptable, with commitment letter that the samples will be submitted prior to distribution. 4) Necessary information required for a new application (refer to Rwanda FDA guidelines on Submission of documentation for registration of human medicinal products *N^{o} DHT/GDL/001*) 5) Documented evidence that the site is appropriately authorized by NMRA in the country of origin and satisfactorily inspected by Rwanda FDA.				

3.2.P.3 Manufacture

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
31	Addition or replacement of a manufacturing site for part or all of the manufacturing g process for a FPP involving			
a	secondary packaging of all types of FPPs	2-3	1	IN
b	primary packaging site of:			
b.1	solid FPPs (e.g. tablets, capsules) ,	2-4	1,8	IN

	semisolid (e.g. ointments, creams) and solution liquid FPPs			
b.2	other liquid FPPs (suspensions, emulsions)	2-5	1,5,8	IN
c	all other manufacturing operations except batch control/release testing	1-3,5	1-9	Vmin

Conditions to be fulfilled

1) No change in the batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, or FPP specifications.
2) Satisfactory GMP inspection by Rwanda FDA or joint inspection by EAC Partner States in the last three years.
3) Site appropriately authorized by an NMRA in the country of origin (to manufacture the pharmaceutical form and the product concerned).
4) The change does not concern a sterile FPP.
5) Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production scale batches in accordance with the current protocol.

Documentation required

1) Evidence that the proposed site is appropriately authorized in the last 3 years, for the pharmaceutical form and the product concerned:

a. a copy of the current manufacturing authorization, a GMP certificate or equivalent issued by the NMRA.
b. a GMP certificate issued by Rwanda FDA.
c. date of the last satisfactory inspection concerning the packaging facilities by Authority

2) Date and scope of the last satisfactory inspection.
3) (P.2) Where applicable, 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.
4) (P.2) For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one (1) production scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two (2) more production scale batches.
5) (P.3.5) Process validation reports or validation protocol (scheme) for three (3) batches of the proposed batch size that includes comparative dissolution against the biobatch results with f2 calculation as necessary.
6) (P.5.1) Copies of FPP release and shelf-life specifications from the proposed manufacturing site.
7) (P.5.4)Batch analysis data on one production scale batch from the proposed site and comparative data on the last three batches from the previous site.

8) (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the FPP produced at the new site, into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
9) (R.1) Executed production documents for one batch of the FPP manufactured at the new site. Commitment letter to submit batch records of two more commercial batches at the new manufacturing site.
7) **Note:** Two (2) commercial samples of the product should be submitted where the manufacturing site appears on the product label. However, if commercial samples are not available, a mock-up is acceptable, with commitment letter that the samples will be submitted prior to distribution.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
32	Replacement or addition of a site involving batch control testing	1-2	1-3	AN
	Conditions to be fulfilled			
1)	Site is appropriately authorized by Rwanda FDA and should be GMP compliant			
2)	Transfer of analytical methods from the current testing site to the proposed testing site has been successfully completed.			
	Documentation required			
1)	Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application.			
2)	Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected by Rwanda FDA.			
3)	(P.5.3) Documented evidence of successful transfer of analytical procedures from the current to the proposed site.			

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
33	Change in the batch size of the FPP involving			
a	up to and including a factor of ten (10 compared to the bio batch	1-7	2, 5-6	IN
b	downscaling (to at least pilot batch size)	1-5	2,6	AN
c	Any other change in scale	1-7	1-7	Vmin
	Conditions to be fulfilled			
1)	The change does not affect the reproducibility and/or consistency of the product.			

2)	The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3)	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 size equipment.
4)	A validation protocol is available or validation of the manufacture of three production scale batches has been successfully undertaken in accordance with the current validation protocol.
5)	The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6)	The change does not require supporting *in vivo* data.
7)	The biobatch was at least of 100,000 units in case of solid oral dosage forms.
	Documentation required
1)	(P.2) For solid dosage forms: dissolution profile data on a minimum of one representative production scale batch performed in routine release medium and comparison of the data with the biobatch results and one production scale batch from the previous batch size. Data on the next two (2) full production scale batches should be available on request and should be reported if outside dissolution profile similarity (f2) requirements. For semi-solid dosage forms (e.g. lotions, gels, creams and ointments), containing the API in the dissolved or non-dissolved form, comparative in vitro data on membrane diffusion (membrane release testing) should be submitted or be available on request.
2)	(P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
3)	(P.5.1) Copies of release and shelf-life specifications.
4)	(P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two (2) full production scale batches should be available on request and should be reported immediately if outside specifications (with proposed remedial action).
5)	(P.8.2) Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6)	(R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch (if manufactured as required by documentation 4) and confirmation that there are no changes to the production documents other than those highlighted.
7)	Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current *Rwanda FDA Guidance on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data*..

Description of change	**Conditions to be**	**Documentation**	**Reporting**

		fulfilled	**required**	**type**
34a	Change in the manufacturing process of the FPP	*1-9*	*1-4, 6-7*	*AN*
b		1-3, 5-9	1-7	Vmin
	Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of a medicinal product	none	1-8	Vmajor

Conditions to be fulfilled

1) The change does not require supporting in vivo data.
2) No change in qualitative and quantitative impurity profile or in physico-chemical properties; dissolution profiles are similar with those of the bio batch.
3) The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet/dry granulation or vice versa would be considered a change in manufacturing principle), same processing intermediates and there are no changes to any manufacturing solvent used in the process.
4) The same classes of equipment, operating procedures, in-process controls (no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters.
5) No change in the specifications of the intermediates or the FPP.
6) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
7) The change does not involve packaging or labeling where the primary packaging provides a metering and/or delivery function.
8) The change does not concern a gastro-resistant, modified or prolonged release FPP.
9) The change does not affect the sterilization parameters of a sterile FPP.

Documentation required

1) Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO Guidelines on Bioequivalence.
2) (P.2) Discussion on the development of the manufacturing process; where applicable:

- comparative in vitro testing, e.g. multipoint dissolution profiles in the release medium for solid dosage units (one production batch and comparative data of one batch from the previous process and the bio batch results, data on the next two production batches should be available on request or reported if outside specification);
- comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data of one batch from the previous process and the bio batch results, data on the next two production batches) should be submitted or be available on request;
- microscopic imaging of particles to check for visible changes in morphology and comparative size

distribution data for liquid products in which the API is present in non-dissolved form.

3) (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
4) (P.5) Specification(s), certificate of analysis for one production scale batch each manufactured according to the currently accepted and the proposed processes.
5) P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products one pilot batch, the other one can be smaller) with a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing.
6) P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the proposed product into the long-term stability programme.
7) (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.
8) Updated quality, safety and efficacy data

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
35	Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:			
a	tightening of in-process limits	1-2,5	1	AN
b	deletion of a test	2,4	1, 6	AN
c	addition of new tests and limits	2-3	1-6	AN
d	revision or replacement of a test	2-3	1-6	IN

Conditions to be fulfilled

1) The change is within the range of acceptance limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way.
4) The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. color) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).
5) No change in the analytical procedure.

Documentation required

1) (P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2) (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.

4) (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.
5) (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented.
6) (P.5.6) Justification for the addition/deletion of the tests and limits.

3.2.P.4 Control of excipients

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
36 a	Change in source of an excipient from a transmissible spongiform encephalopathy risk to a material of vegetable or synthetic origin.	1	1	AN
b	Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material	None	1-2	Vmajor
Conditions to be fulfilled				
1) No change in the excipient and FPP release and shelf-life specifications.				
Documentation required				
1) Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin. 2) A TSE/BSE certificate of suitability				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
37	Change in the specifications or analytical procedures of an excipient involving:			
a	deletion of a non-significant in-house parameter	2	1-3	AN
b	addition of a new test parameter or analytical procedure	2-3	1-2	AN
c	tightening of specification limits	1-2,4	1-2	AN
d	change or replacement of an analytical procedure	2-3	1-2	Vmin

1) The change is within the range of currently accepted limits. 2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 4) No change in the analytical procedure.
Documentation required
1) Justification for the change. 2) (P.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable). 3) Justification to demonstrate that the parameter is not critical.

	Description of change	**Conditions to be fulfilled**	**Documentationrequired**	**Reporting type**
38	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	1	1	AN
	Conditions to be fulfilled			
1)	No change to the specifications other than those required to comply with the pharmacopoeia (e.g. n o change in particle size distribution).			
	Documentation required			
1)	Comparative table of currently accepted and proposed specifications for the excipient.			

3.2. P.5 Control of FPP

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
39a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard.	1-3	1-5	AN
3b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the	1	1, 3, 5	AN

	FPP is controlled			
	Conditions to be fulfilled			
1)	The change is made exclusively to comply with the officially recognized pharmacopoeia.			
2)	No change to the specifications that result in a potential impact on the performance of the FPP (e.g. dissolution test).			
3)	No deletion of or relaxation to any of the tests, analytical procedures or acceptance criteria of the specifications.			
	Documentation required			
1)	(P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.			
2)	(P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.			
3)	(P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented.			
4)	(P.5.6) Justification for the proposed FPP specifications.			
5)	(P.5.3) Demonstration of the suitability of the monograph to control the FPP.			

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
40	Change in the specifications of the FPP involving test parameters and acceptance criteria:			
a	deletion of a test parameter	5	1,6	AN
b	addition of a test parameter	2-4, 7	1-6	AN
c	tightening of an acceptance criterion	1-2	1,6	AN
d	relaxation of an acceptance criterion	2,4,6-7	1,5-6	IN
e	replacement of a test parameter	2-4,6-7	1-6	IN
	Conditions to be fulfilled			
1)	The change is within the range of currently accepted limits.			
2)	The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.			
3)	Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.			
4)	No additional impurity found over the ICH identification threshold.			
5)	The deleted test has been demonstrated to be redundant with respect to the remaining tests.			
6)	The change to the specifications does not affect the stability and the performance of the product.			
7)	The change does not concern sterility testing.			
	Documentation required			
1)	(P.5.1)Copy of the proposed FPP specifications dated and signed by authorized personnel and a			

comparative table of currently accepted and proposed specifications.

2) (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3) (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4) (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.
5) (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed procedures, if new analytical procedures are implemented.
6) (P.5.6) Justification for the proposed FPP specifications.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
41	Change in the analytical procedures for the FPP involving:			
a	deletion of an analytical procedure	5	1,6	AN
b	addition of an analytical procedure	3-4,6-7	1-5	AN
c.1	modification or replacement of an analytical procedure	1-4, 6-7	1-5	AN
c.2		2-4, 6-7	1-5	Vmin
d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to this monograph	None	1-5	AN
e	change from an in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeial monograph or from the analytical procedure in one officially recognized pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph	2,7	1-3, 5	IN

Conditions to be fulfilled

1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
2) Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

4) The change does not concern sterility testing. 5) The deleted analytical procedure is an alternate method and is equivalent to another currently accepted analytical procedure. 6) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 7) No new impurities have been detected.
Documentation required
1) (P.5.1) A copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. 2) (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used. 3) (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods if new analytical procedures are used. 4) (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods. 5) (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed analytical procedures. 6) Justification for the deletion of the analytical procedure, with supporting data.

3.2.P.7 Container-closure system

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
42a	Replacement or addition of a primary packaging type	1	1-2,4-6	Vmin
b		None	1-6	Vmaj
	Conditions to be fulfilled			
1)	The change does not concern a sterile FPP.			
	Documentation required			
1)	Two (2) commercial samples of the product as packaged in the new container-closure system. However, if commercial samples are not available, a mock- up is acceptable, with commitment letter that the sample will be submitted prior to distribution.			
2)	(P.2) Data on the suitability of the container closure system (e.g. extractable/leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging.			

3) (P.3.5) For sterile FPPs, process validation and/or evaluation studies.
4) (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, results of transportation studies, if appropriate).
5) (P.8.1) Stability summary and conclusions, results for a minimum of two (2) batches of pilot or production scale, of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing and where applicable, results of photo stability studies.
6) (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production scale batch of the proposed product into the long-term stability programme, unless data was provided in documentation 5.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
43	Change in the package size involving:			
a	change in the number of units (e.g. tablets ampoules etc.) in a package	1-2	1-3	IN
b	change in the fill weight/fill volume of non-parenteral multidose products	1-2	1-3	Vmin

Conditions to be fulfilled

1) The change is consistent with the posology and treatment duration accepted in the SmPC.
2) No change in the primary packaging material.

Documentation required

1) Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SmPC.
2) (P.8.2) A written commitment that stability studies will be conducted in accordance with *Rwanda FDA Guidelines on stability testing for Active Pharmaceutical Ingredients and FPP* for products where stability parameters could be affected.
3) Two (2) commercial samples of the product. However, if a commercial sample is not available, a mock-up is acceptable, with commitment letter that the sample will be submitted prior to distribution.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
44	Change in the shape or dimensions of the container or closure for:			
a	non-sterile FPPs	1-2	1-3	IN
b	sterile FPPs	1-2	1-4	Vmin

c	The change does concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP			Vmajor
Conditions to be fulfilled				
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 could affect the delivery, use, safety or stability of the FPP.				
Documentation required				
1) Two (2) commercial samples of the product. However, if a commercial sample is not available, a mock-up is acceptable, with commitment letter that the sample will be submitted prior to distribution. 2) (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, specifications etc.). 3) (P.8.1) In the case of a change in the headspace, a change in the surface/volume ratio or a change in the thickness of a packaging component: stability summary and conclusions, results for a minimum of two batches of pilot or production scale, of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing and where applicable, results of photo stability studies. 4) (P.3.5) Evidence of revalidation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
45	Change in qualitative and/or quantitative composition of the immediate packaging material for:			
a	solid FPPs	1-3	1-3	IN
b	semisolid and non-sterile liquid FPPs	1-3	1-3	Vmin
c	Sterile medicinal products and biological/immunological medicinal products	None		Vmajor
Conditions to be fulfilled				
1) The change does not concern a sterile FPP. 2) No change in the packaging type and material (e.g. a different blister, but same type). 3) The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material.				
Documentation required				

1) (P.2) Data demonstrating the suitability of the proposed packaging material (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, moisture etc.).
2) (P.7) Information on the proposed packaging material (e.g. description, materials of construction, specifications etc.).
3) (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot or production scale, of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing and where applicable, results of photo stability studies.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
46	Change in the specifications of the immediate packaging involving:			
a	tightening of specification limits	1-2	1	AN
b	addition of a test parameter	2-3	1-2	AN
c	deletion of a non-critical parameter	2	1,3	AN

Conditions to be fulfilled

1) The change is within the range of currently accepted limits.
2) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.
3) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

Documentation required

1) (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2) (P.7) Description of the analytical procedure and summary of validation of the new analytical procedure.
3) Documentation to demonstrate that the parameter is not critical.

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
47	Change to an analytical procedure on the immediate packaging involving:			
a	minor change to an analytical procedure	1-3	1	AN
b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2-4	1	AN
c	deletion of an analytical procedure	5	2	AN

Conditions to be fulfilled

1) The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length, etc., but do not include variations beyond the acceptable ranges or a different type of column and method). 2) Appropriate (re)validation studies have been performed in accordance with the relevant guidelines. 3) Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure. 4) Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 5) The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method.	
Documentation required	
1) (P.7) Description of the method and comparative validation results demonstrating that the currently accepted and proposed methods are at least equivalent. 2) Documentation demonstrating that condition #5 is met.	

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
48	Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, change of needle shield), and change of secondary pack			
a	Change in any part of the (primary) packaging material not in contact with the finished pharmaceutical product formulation (e.g. colour of flip-off caps, colour code rings on ampoules, change of needle shield)	1	1-2	IN
b.1	Change of secondary packaging components	2	2-3	IN
b.2		None	1-4	Vmin
Conditions to be fulfilled				
1) The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the FPP. 2) The registered and proposed secondary packaging components are non-functional				
Documentation required				

1) (P.7) Information on the proposed packaging material (e.g. description, materials of construction, specifications etc.).
2) Two (2) commercial samples of the product. However, if a commercial sample is not available, a mock- up is acceptable, with commitment letter that the sample will be submitted prior to distribution.
3) Brief description of the secondary packaging components
4) Discussion on suitability with respect to, for example, protection from moisture and light, and provide supportive data e.g. moisture permeability, photo-degradation, stability studies

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
49	Change to an administration or measuring device			
a	addition or replacement of a device which is not an integral part of the primary packaging	1-2	1-2	IN
b	deletion of a device	3	3	IN
c	Change to an administration or measuring device that is an integral part of the primary packaging	1-2	1-3	Vmajor
d	addition or replacement of spacer devices for metered dose inhalers	1-2	1-2,4	Vmajor

Conditions to be fulfilled

1) The proposed measuring device is designed to accurately deliver the required dose for the product concerned, in line with the posology and results of such studies are available.
2) The proposed device is compatible with the FPP.
3) The FPP can be accurately delivered in the absence of the device.

Documentation required

1) (P.2) Data to demonstrate accuracy, precision and compatibility of the device.
2) Two (2) samples of the device.
3) Justification for the deletion, addition or replacement of the device.
4) Justification for the addition or replacement of spacer devices for metered dose inhalers

3.2.P.8 Stability

Description of change	**Conditions to b**	**Documentation**	**Reporting type**

		fulfilled	**required**	
50	Change in the shelf-life of the FPP (as packaged for sale) involving:			
a	reduction	3	1-4	IN
b	extension	1-2	1-4	Vmin
Conditions to be fulfilled				
1) No change to the primary packaging type in direct contact with the FPP and to the recommended condition of storage. 2) Stability data was generated in accordance with the currently accepted stability protocol. 3) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.				
Documentation required				
1) (P.5.1) Copy of the currently accepted shelf-life specifications. 2) (P 8.1) Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two pilot or production scale batches. 3) (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change. 4) Two (2) commercial samples of the product. However, if a commercial sample is not available, a mock- up is acceptable, with commitment letter that the sample will be submitted prior to distribution.				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
51	Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):			
	Reduction	1	1, 3-4	IN
	Extension	None	1-4	Vmin
Conditions to be fulfilled				
1) The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.				
Documentation required				

1) (P 8) Proposed in-use period, test results and justification of change.
2) (P5.1) Copy of currently accepted end of shelf-life FPP specifications and where applicable, specifications after dilution/reconstitution.
3) The revised label information
4) Two (2) commercial samples of the product. However, if a commercial sample is not available, a mock- up is acceptable, with commitment letter that the sample will be submitted prior to distribution.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
52	Change in the labelled storage conditions of the FPP (as packaged for sale), the product during the in-use period or the product after reconstitution or dilution	1	1-3	Vmin

Conditions to be fulfilled

1) The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.

Documentation required

1) (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage conditions.
2) (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.
3) Two (2) commercial samples of the product. However, if a commercial sample is not available, a mock-up is acceptable, with commitment letter that the sample will be submitted prior to distribution.

4. SAFETY AND EFFICACY CHANGES

Description of change	Conditions	Documentation	Reporting

		to be fulfilled	required	type
53	Change in the Summary of product Characteristics, Labelling or Package Leaflet of a generic pharmaceutical product following assessment of the same change for the reference (innovator) product			
a	Implementation of change(s) for which no new additional data are submitted by the MAH		1	Vmin
b	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)		1-2	Vmaj
c	• Change of the layout/artwork without altering meaning. • Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts that do not imply an unapproved indication.		3-6	Vmin
Documentation required				
1) Revised product information 2) Applicable additional data 3) Current approved product labeling. 4) Proposed product labeling, a clean and annotated version highlighting the changes made. 5) Letter of declaration from the marketing authorization holder stating that no other changes on the label except for the intended change. 6) Relevant document/reference to support the changes (where applicable).				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
54	Implementation of change(s) requested by Rwanda FDA following assessment of an Urgent safety restriction, class labelling or periodic safety update report			
a	Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH		1-2	Vmin
b	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			Vmaj
Documentation required				

1) Rwanda FDA request with attached relevant assessment report 2) Revised product information

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
55	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			
			1-2	Vmaj

Conditions to be fulfilled				
None				
Documentation required				
1) The proposed SmPC 2) Supporting data for the proposed change				
	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
56	Change(s) to therapeutic indication(s)			
a	Addition of a new therapeutic indication or modification of an approved one			Vmaj
b	Deletion of a therapeutic indication			Vmin
Note: Where the addition or modification of a therapeutic indication takes place in the context of the implementation of changes to the product information of a generic product following assessment of the same change for the reference (innovator) product, variations 54 and 55 apply respectively.				

- **Other**	**±0.1**

- These percentages are based on the assumption that the active pharmaceutical ingredient (API) in the finished pharmaceutical product (FPP) is formulated to 100.0% of label/potency declaration. The total additive effect of all changes to excipients should be not more than 5.0% relative to the target dosage form weight (e.g. in a product consisting of API, lactose, microcrystalline cellulose and magnesium stearate, the lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%).
- If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (e.g. ± 1.0% for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification and supporting data should be provided to demonstrate that the wider range will not affect the other function of the excipient.

Appendix 1: Examples of changes that make a new application necessary

Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
1. Change of the API to a different API 2. Inclusion of an additional API to a multicomponent product	None	1	New application
3. Removal of one API from a multicomponent product 4. Change in the dose/strength of one or more APIs 5. Change from an immediate-release product to an extended or delayed-release dosage form or vice versa 6. Change in dosage form 7. Changes in the route of administration			
Conditions to be fulfilled			
None			
Documentation required			
3) Documents in fulfillment of the requirements outlined in *Rwanda FDA Guidelines on Submission of Documentation for Registration of Human Medicinal products*			

Appendix 2: Changes to excipients

Excipient	**Percentage Excipient (w/w) out of total target dosage form core weight**
Filler	**±5.0**

Disintegrate - **Starch** - **Other**	 **± 3.0** **±1.0**
Binder	**±5.0**
Lubricant - **Ca or Mg Stearate** - **Other**	 **±0.25** **±1.0**
Glident - **Talc**	 **±1.0**

5. REFERENCES:

1. EU Guidelines on the details of the various categories of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products, 12 December 2008.
2. Guidelines on variations to a prequalified product, In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty seventh report. Geneva, World Health Organization, 2013, Annex 3 (WHO Technical Report Series, No. 981).
3. Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 943), Annex 6.
4. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 4.

6. ENDORSEMENT OF THE GUIDELINES

	Prepared by	**Checked by**		**Approved by**
Title	**Division manager**	**Head of Department**	**Quality Assurance Analyst**	**Director General**
Names	Clarisse IRASABWA	Dr Vedaste HABYALIMANA	Theogene NDAYAMBAJE	Dr Emile BIENVENU
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