Botswana Medicines Regulatory Authority

BOMRA
MEDICINES REGULATORY AUTHORITY

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Date of Approval (DD/MM//YY)

Revision status sheet

Page	Changes made	Issue No	Process owner's name	Date

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1 Purpose

These guidelines provide guidance to applicants intending to make administrative and quality changes to sections of the product dossier for an API or an FPP. It also provides guidance on the documentation to be submitted with each type of variation.

2 Scope

These guidelines apply to applicants intending to make changes to a registered FPP and related API. If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a variation. It should be noted that these guidelines are applicable only to APIs and excipients manufactured by chemical synthesis, classical fermentation, or semi-synthetic processes and FPPs containing such APIs and excipients.

3 Abbreviations and Definitions

3.1 Abbreviations

For the purpose of these guideline, the following abbreviations shall apply:

3.1.1 **API** - Active Pharmaceutical Ingredient

3.1.2 **APIMF** - Active Pharmaceutical Ingredient Master File

3.1.3 **AN** - Annual Notification

3.1.4 **BOMRA** - Botswana Medicines Regulatory Authority

3.1.5 **IN** - Immediate Notification

3.1.6 **CEP** - Certificate of Suitability to the monograph of European Pharmacopeia

3.1.7 **CTD** - Common Technical Document

3.1.8 **EDQM** - European Directorate for the Quality of Medicines and Healthcare

3.1.9 **EU** - European Union

3.1.10 **FPP** - Finished Pharmaceutical Product

3.1.11 **GMP** - Good Manufacturing Practice

3.1.12 **ICH** - International Council on Harmonisation for Technical Requirements of Pharmaceuticals for Human Use

3.1.13 **PI** - Product Information

3.1.14 **SADC** - Southern African Development Community

3.1.15 **SRA** - Stringent Regulatory Authority

3.1.16 **SmPC** - Summary of Product Characteristics

3.1.17 **NMRA** - National Medicines Regulatory Authority or equivalent

3.1.18 **WHO** - World Health Organization

3.2 Definitions

For the purpose of these guidelines, the following definitions shall apply:

3.2.1 **Active pharmaceutical ingredient (API) or drug substance -** Any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals. It may sometimes be referred to as Drug Substance (DS).

3.2.2 **Active pharmaceutical ingredient starting material (APISM) –** 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.

3.2.3 **Biobatch -** The Finished Pharmaceutical Product batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or bio-waiver studies, respectively.

3.2.4 **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. It may sometimes be referred to as drug product.

3.2.5 **In-process controls –** Checks performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

3.2.6 **Marketing Authorization Holder (MAH) -** Is a person or entity who holds authorization to place a finished pharmaceutical product in the market and is responsible for that product.

3.2.7 **Manufacturer-** A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

3.2.8 **Officially recognized pharmacopoeia-** Those pharmacopoeias recognized by BOMRA (i.e. The International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopeia (USP).

3.2.9 **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.

3.2.10 **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.

3.2.11 **Stringent Regulatory Authority (SRA) -** National Medicines Regulatory Authorities

which are:

a) A member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or

b) An ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or

c) A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.

4 Introduction

MAH is responsible for the registered FPP throughout its life-cycle, irrespective of the regular reviews by BOMRA. It is acknowledged that technical and scientific progress may necessitate changes to the registered product over time. Any changes to a registered FPP (variation), whether administrative or substantial, are subject to approval by the Authority. Henceforth, guidance for the implementation of the different types of variations is set out in this document to facilitate the task of both MAHs and BOMRA to guarantee that variations to the FPP do not compromise the quality, safety and efficacy of the registered product.

The BOMRA Variation Guidelines are an administrative instrument and as such, allows for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. These approaches should be discussed in advance with the Authority.

In addition, it must be noted that BOMRA reserves the right to request information or material, or define conditions not specifically described in these guidelines, in order to allow for adequate assessment of safety, efficacy or quality of the pharmaceutical product.

The requirements specified in these guidelines have been adapted from the current *SADC Variations Guideline*, *WHO Guidance on Variations to a Prequalified Product* and the *European Union Guidelines on Variations*.

4.1 Objectives

These guidelines are intended to:

a) Assist applicants with the classification of changes made to a registered FPP and related API;

b) Provide guidance on the technical and other general data requirements to support the proposed changes.

4.2 General Guidance

All variation applications will be subjected to payment as per current fees schedules of BOMRA.

When a variation leads to a revision of the Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling, 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.

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

Further to the requirements of these guidelines, BOMRA may prescribe additional requirements.

4.3 Guidance for implementation

4.3.1 Reporting Types

The reporting types are intended to provide guidance with respect to the classification of administrative, quality, safety and efficacy-related changes. Specific change examples are provided in these guidelines. However, it is to be noted that a change not cited in these guidelines, should be decided on a case-by-case basis. Whenever the applicant is unclear about the classification of a particular change, the Authority should be contacted. 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, safety and efficacy of the product.

Each application should be for one product. Grouped variations for a product will be charged individually.

4.3.2 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 approval but must be notified to BOMRA immediately after implementation (immediate notification (IN), or within 12 months following implementation annual notification (AN) of the change. Notifications can be considered accepted if an objection is not issued by BOMRA within 2 months.

It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant ceases to apply the already implemented variation.

4.3.3 Minor variation (Vmin)

Minor variations are changes that may have minimal 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 3 months. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from BOMRA.

4.3.4 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 must be submitted. Prior approval by BOMRA is required before the changes can be implemented.

A change that is not specified in these guidelines should be considered as a major variation by default. However, if the applicant believes that the change is unlikely to have major effects on the overall quality, safety and efficacy of the product, the Authority should be consulted for classification of the changes.

4.3.5 New applications

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

5.0 Labelling, Safety and Efficacy related changes

Any changes to labelling information (SmPC, PIL, labels) that are due to safety updates should be submitted to BOMRA Pharmacovigilance and Clinical Trials department.

6.0 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 the conditions stipulated for these specific circumstances may be considered to be a major variation.

7.0 Documentation required

For each variation, the required documentation to be submitted have been identified. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support each variation.

8.0 Fees

Applicants should consult the current BOMRA fees schedule.

9.0 Administrative changes

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
1.Change of the Marketing Authorization Holder (MAH) of the FPP				
1a	Change in the name and/or corporate address of the (MAH).	1,2	1,3, 4	Vmin
1b	Change of MAH from one company to another.	2	1-4	Vmin
Conditions to be fulfilled				
1) Confirmation that the MAH of the FPP remains the same legal entity. 2) No change in the location of manufacturing site and in the manufacturing operations.				
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 (signed and dated) transfer of ownership documents. 3) Revised product information, where applicable.				

Description of change	Conditions to be fulfilled	Documentation required	Report-ing type
2. Change in the name and/or address of a manufacturer of an API	I	I	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.			

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	I	I-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. Revised product information, where applicable.			

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
4. Deletion of a manufacturing site or manufacturer involving:				
4a	Production of the API starting material.	I	I	AN

4b	Production or testing of the API intermediate or API.	1–2	I	IN
4c	Production, packaging or testing of the FPP intermediate or FPP.	1–2	I	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 the 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.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
5. Change in the name of Finished Pharmaceutical Product (FPP)	1-4	1-2	Vmin

Conditions to be fulfilled

1) The brand name should not have been accepted for another product in the country of submission of the variation.
2) No confusion with another drug product either when spoken or written.
3) The new name does not (i) imply superiority over another similar product and (ii) imply the presence of substance(s) not present in the product.
4) The new name should not contain a stem of an already established INN.

Documentation required

1) Revised product information.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
6. Change of the layout/artwork without altering meaning.	1	1 - 3	IN
Conditions to be fulfilled			
1) There are no changes made to the contents or meaning of the contents in the Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips.			
Documentation required			
1) Copy of currently approved product labelling. 2) Proposed product labelling, a clean and annotated version highlighting the changes made.			

10.0 Changes to a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) or to a Confirmation of API-prequalification document (CPQ).

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
7. Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API:				
7a.1	From a currently accepted manufacturer.	1–5	1–5	AN
7a.2		1–4	1–6	IN
7a.3		1, 3–4	1–6	Vmin
7b.1	From a new manufacturer.	1–4	1–6	IN
7b.2		1, 3– 4	1–6	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 biobatch.
5. No revision of the FPP manufacturer's API specifications is required.

Documentation required

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.
2. A written commitment that the applicant will inform BOMRA, 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 the BOMRA Registration Quality Guidelines.
4. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation data.
5. (P.8.2) 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 BOMRA who refer to the CEP.
6. (S.4.1) Copy of FPP manufacturer's revised API specifications.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
8. Submission of a new or updated CPQ				
8a.1	From a currently accepted manufacturer.	1–3	1–3, 5	AN
8a.2		1–2	1–5	Vmin
8b.1	From a new manufacturer.	1–3	1–3, 5	IN
8b.2		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, compared to that of the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.
Documentation required
1. Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box with 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 (*Option 1: confirmation of API Prequalification document*) stipulated under section 3.2.S. of the BOMRA Registration Quality Guidelines. 3. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation. 4. (S.4.1) Copy of FPP manufacturer's revised API specifications. 5. (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 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 BOMRA.

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

11.0 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:				
10a.1	Production of API starting material.	3–4	1–2, 11	Vmin
10a.2		None	1,2,5, 6–7,11, 12	Vmaj
10b.1	Production of API.	1, 8–10	1–2, 4, 7–8	Vmin
10b.2		None	1, 2, 4, 5, 6–7, 9–10, 12	Vmaj
10c	Addition of an alternative sterilization site for the API.	Conditions are not applicable None	1,2,4,5,8	Vmaj
10d	Introduction of a new site of micronization.	1,11	1,4,5	AN
Conditions to be fulfilled				
1. The API is non-sterile.				

2. The transfer of analytical methods has been successfully undertaken.

3. No change in the FPP manufacturer's API specifications.

4. 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.

5. 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.

6. No change in the FPP release and end-of-shelf-life specifications.

7. 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.

8. 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.

9. 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 a new contract manufacturing site with evidence of an acceptable and similar quality system to that of the main manufacturer).

10. 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 equivalent guidelines of the ICH region and associated countries.

11. The particle size specification of the API and the corresponding analytical methods remains the same.

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 and a tabulated summary of the differences.

3. (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalence 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 and/or sites.

5. Relevant sections of (3.2.S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the BOMRA Registration Quality Guidelines.

6. (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 BOMRA.

7. (S.4.1) A copy of the FPP manufacturer's API specifications.

8. (S.2) A declaration from the supplier of the prequalified 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.

9. A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.

10. 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.

11. Certificates of analysis for at least one batch of API starting material or intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material or intermediate (as applicable) from the new source and from a previously accepted source. For an alternative source of plant-derived starting material, control of pesticide residues must be established. This can either be in the form of an attestation from the starting material supplier that no pesticides are used during the growth of the plant material, or by providing the results of pesticide screening from one batch of the starting material.

12. 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 type
11. Change in the manufacturing process of the API				
11a		1–3, 9	1-2,7	AN
11b.1		1–4, 6–9	2–3, 10–11	IN
11b.2		1–4, 6–8, 10	2–3, 10–11	Vmin
11c		1–4,7	2–3, 10–11	Vmin
11d		None	1–13	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 that of the API lot used in the preparation of the biobatch.

3. The API manufacturing site is currently accepted.

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.

10. The change does not require revision of the API specifications.

Documentation required

1. (P.8.2) If the quality characteristics of the API are changed in a way that 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 BOMRA.

2. (S.2.2) A side-by-side comparison of the current process and the new process.

3. (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).

4. (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.

5. (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 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 equivalent guidelines of the ICH region and associated countries.

6. (S.2.4) Information on controls of critical steps and intermediates, where applicable.

7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.

8. (S.3.1) Evidence for elucidation of structure, where applicable.

9. (S.3.2) Information on impurities.

10. (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).

11. (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.

12. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.

13. 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 required	Reporting type
12. Change in the in-process tests or limits applied during the manufacture of the API				
12a	Tightening of in-process limits	1–3	1	AN
12b	Addition of a new in-process test and limit	1,4	1–5	AN
12c	Addition or replacement of an in-process test as a result of a safety or quality issue	None	1–5, 7, 8–10	Vmin
12d.1	Deletion of an in-process test	1, 5–6	1–3, 6	AN
12d.2		None	1–3, 7–10	Vmaj
12e	Relaxation of the in-process test limits	None	1–3, 5, 7–10	Vmaj
Conditions to be fulfilled				
1. The change is not necessitated by unexpected events arising during manufacture e.g. a new unqualified impurity or a change in total impurity limits. 2. The change is within the range of currently accepted limits. 3. The analytical procedure remains the same, or changes to the analytical procedure are minor. 4. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way. 5. The affected parameter is non-significant. 6. The change does not affect the sterilization procedures of a sterile API.				
Documentation required				

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 and/or 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**
13. Change in batch size of the API or intermediate involving:				
13a	Up to 10-fold compared to the currently accepted batch size.	1–2, 4, 5	1, 3–4	AN
13b.1	Downscaling.	1–4	1, 3–4	AN
13b.2		1–3	1–4	IN
13c	More than 10-fold increase compared to the currently accepted batch size.	1–2, 4, 5	1, 3–4	Vmin
Conditions to be fulfilled				

1. No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of a 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. 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.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
14. 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:				
14a	Tightening of the specification limits	1–3	1–3	AN
14b	Minor change to an analytical procedure	4–6	2–3	AN
14c	Addition of a new specification parameter and a corresponding analytical procedure where necessary	1, 6–8	1–3	AN

14d	Deletion of a specification parameter or deletion of an analytical procedure	1, 9	1–4	AN
14e	Addition or replacement of a specification parameter as a result of a safety or quality issue	None	1–3, 5	Vmin
14f	Relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	1, 6, 8–9	1, 3–4	IN
14g	Relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1–3, 5	Vmaj

Conditions to be fulfilled

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

2. Any change is within the range of currently accepted limits.

3. The analytical procedure remains the same.

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 and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).

5. 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.

6. No change to the total impurity limits; no new impurities are detected.

7. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.

8. The change does not concern a genotoxic impurity.

9. The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

Documentation required

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 and/or risk assessment showing that the parameter is non-significant. 5. (S.3.2) Information on impurities, where applicable.

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

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
15. 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.	1	1–4	IN

Conditions to be fulfilled
1. 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 required
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 type
16. Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:				
16a	Updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopeial monograph as a result of an update to this monograph to which the API is controlled.	10	1–5	AN
16b.1	Deletion of a test parameter.	1–2	1, 6	AN
16b.2		None	1, 6	IN
16c.1	Addition of a test parameter.	1, 4–8	1–6	AN
16c.2		1, 5–6	1–6	Vmin
16c.3		None	1–7	Vmaj
16d.1	Replacement of a test parameter	1, 5–8	1–6	IN
16d.2		5, 7	1–6	Vmin
16d.3		None	1–7	Vmaj
16e.1	Tightening of an acceptance criterion	1, 3, 9	1, 6	AN
16f.1	Relaxation of an acceptance criterion	1, 5–9	1, 6	IN
16f.2		5, 7	1, 6	Vmin
16f.3		None	1, 6–7	Vmaj

Conditions to be fulfilled
1. The change is not necessitated by failure to meet specifications resulting from unexpected events 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. No change is required in FPP release and shelf-life specifications.
Documentation required

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 or 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 equivalence 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 one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batch used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact NMRA for advice. For changes to the polymorph of an insoluble API the applicant should contact NMRA for advice before embarking upon any investigation.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
17. Change to the analytical procedures used to control the API by the FPP manufacturer involving:				
17a	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
17b	Change from a currently accepted in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another official recognized pharmacopoeia.	None	1–4	IN
17c.1	Addition of an analytical procedure.	1–3	1–3	AN
17c.2		3,8	1–3	AN
17c.3		None	1–3	Vmaj
17d.1	Modification or replacement of an analytical procedure.	1–6	1–4	AN
17d.2		2–3, 5–6,8	1–4	AN
17d.3		1–3, 5–6	1–4	Vmin
17d.4		5–6,8	1–4	Vmin

17d.5		None	1–4	Vmaj
17e.1	Deletion of an analytical procedure.	6–7	1, 5	AN
17e.2		6,8	1, 5	IN
17e.3		None	1, 5	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 failure to meet specifications resulting from unexpected events 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 and other parameters, 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 alternative 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.

Documentation required

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 or 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. (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
18. Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API.				
18a1	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API.	1–2, 3	2–3	IN
18a2		3	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, and moisture permeability among others).

2. The change does not concern a sterile API.

3. 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 and specifications) and data in fulfillment of condition 1.

3. (S.7.1) Results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing of the API in the proposed primary packaging type.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
19. Change in the specifications of the immediate packaging for the storage and shipment of the API involving:				
19a	tightening of specification limits.	1–2	1	AN
19b	addition of a test parameter.	2–3	1–3	AN
19c	deletion of a non-critical parameter.	2	1, 4	AN
Conditions to be fulfilled				
1. The change is within the range of currently accepted limits. 2. The change is not necessitated by failure to meet specifications resulting from unexpected events 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. (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 one batch. 4. Justification to demonstrate that the parameter is not critical.				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
20. Change to an analytical procedure on the immediate packaging of the API involving:				
20a	Minor change to an analytical procedure.	1–3	1	AN

20b	Other changes to an analytical procedure including addition or replacement of an analytical procedure.	2–4	1	AN
20c	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 and other parameters, 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 currently accepted 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 alternative method and is equivalent to a currently accepted method.				
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**
21. Change in the retest period or shelf-life of the API involving:				
21a	Reduction.	3	1–2	IN
21b	Extension.	1–2	1–3	Vmin
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 were 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. (S.7.1) Proposed retest period or 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.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
22. Change in the labelled storage conditions of the API involving:				
22a	Any change in the storage conditions.	I	I	Vmin
Conditions to be fulfilled				
1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.				
Documentation required				
1. (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**
23. Change in the composition of a solution dosage form.				
23a	Change in the composition of a solution dosage form.	1–6	2, 4, 7, 9–10	IN
23b		None	1–10	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 prequalified product.				
Documentation required				

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current *WHO Guideline on INVIVO Bioequivalence Studies*.

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, 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 NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.

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 2 months of accelerated (and intermediate, as appropriate) and 2 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 are no changes to the production documents other than those highlighted.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type

24. Change in the colouring system or the flavouring system currently used in the FPP involving:				
24a	Reduction or increase of one or more components of the colouring or the flavouring system.	1–3, 6-7	1, 4, 6–8	AN
24b	Deletion, addition or replacement of one or more components of the colouring or the flavouring system.	1–7	1–8	IN

Conditions to be fulfilled

1. No change in the functional characteristics of the pharmaceutical form e.g. disintegration time or dissolution profile.

2. Any minor adjustment to the formulation to maintain the total weight is made using 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 and/or taste or if relevant, deletion or addition of a test for identification.

4. Any new component must comply with section 3.2.P.4 of the *BOMRA Registration Quality Guidelines.*

5. Any new component does not include the use of materials of human or animal origin for which assessment of viral safety data is required, or is in 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 guide from the ICH region and associated countries.

6. For paediatric 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. Sample of the FPP.

2. (P.2) Discussion on the components of the FPP (e.g. compatibility of API and qualitative composition of the colouring or flavouring 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 NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.

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 2 months of accelerated (and intermediate, as appropriate) and 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.

8. Revised product information, where applicable.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
25. Change in weight of tablet coatings or capsule shells involving:				
25a	Immediate-release oral FPPs.	1–3	2–5	AN
25b	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 routine release medium on at least two batches of pilot- or production-scale), are similar to the dissolution profiles of the Biobatch. 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 *WHO Guideline on INVIVO Bioequivalence Studies.* 2. (P.2) Comparative multipoint in vitro dissolution profiles in the routine 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 one pilot- or production-scale batch with a minimum of 2 months of accelerated (and intermediate, as appropriate) and 2 months of long-term testing. 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**
26. Change in the composition of an immediate-release solid oral dosage form including:				
26a.1	Replacement of a single excipient with a comparable excipient at a similar concentration.	1–5	1–11	Vmin
26a.2		None	1–11	Vmaj
26b.1	Quantitative changes in excipients.	1–4	1–4, 7–11	Vmin
26b.2		None	1–4, 7–11	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 using an excipient which currently makes up a major part of the FPP formulation. 3. Stability studies have been started under conditions according to *BOMRA Registration Quality Guidelines* (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot- or production-scale batches, satisfactory stability data covering at least 2 months are at the disposal of the applicant, and the stability profile is similar to that of 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 biobatch. 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 *WHO Guideline on INVIVO Bioequivalence Studies SADC.*

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 obtained on at least two batches of pilot- or production-scale of the proposed product and the biobatch (depending on the solubility and permeability of the drug, dissolution in the routine 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 an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is 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 2 months of accelerated (and intermediate, as appropriate) and 2 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.

11. Revised product information, where applicable.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
27. 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:				
27a	Changes in imprints, embossing or other markings.	1–3	1–2, 5–7	IN
27b	Deletion of a scoreline.	2–5	1, 5–7	IN
27c.1	Addition of a scoreline.	2–4	1, 3, 5–7	Vmin
27c.2		None	1, 3–7	Vmaj

Conditions to be fulfilled

1. Any ink complies with section 3.2.P.4 of the *BOMRA Registration Quality Guidelines*.

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 from a generic product is consistent with a similar change in the comparator product or was requested by the Authority.

5. The scoring is not intended to divide the FPP into equal doses.

Documentation required

1. Sample of the FPP.

2. (P.1.) Qualitative composition of the ink, if purchased as a mixture.

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.

7. Revised product information, where applicable.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
28. Change in dimensions without change in qualitative or quantitative composition and mean mass of:				
28a	Tablets, capsules, suppositories and pessaries other than those stated in change no. 29b.	1–2	2–6	IN
28b	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 routine 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 *WHO Guideline on INVIVO Bioequivalence Studies*. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions.

2. Sample of the FPP.

3. (P.2) Discussion on the differences in manufacturing process(es) between the currently accepted and proposed products and the potential impact on product performance.

4. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium, on at least one batch of pilot- or production-scale of the current and proposed 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 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**
29. Addition/deletion of a solvent/diluent container from the pack.				
29a	Deletion of the solvent/diluent container from the pack.	None	1-2	Vmin
29b	Addition of solvent/diluent container in the pack.	None	2-5	Vmaj
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) samples of the proposed product
4) Replacement of the relevant pages of the dossier as per the *BOMRA Registration Quality Guidelines.*
5) Evidence that the site responsible for the manufacture of the solvent/diluent is authorized by the competent Authority in the country of origin and satisfactorily inspected by the relevant SADC member states, SRA or Authorities recognised by BOMRA.

3.2. P.3 Manufacture

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
30. Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving (Manufacturer remains the same entity as the currently approved manufacturer)				
30a	Secondary packaging of all types of FPPs.	2–3	1	Vmaj
30b	Primary packaging site of:			
30b.1	Solid FPPs (e.g. tablets, capsules), semi-solid FPPs (e.g. ointments, creams) and solution liquid FPPs.	2–4	1, 8	Vmaj
30b.2	Other liquid FPPs (suspensions, emulsions).	2–5	1, 5, 8	Vmaj
30c	Site where any manufacturing operation(s) take place, except batch release, batch control and/or release testing.	1-3,5	1-10	Vmaj
30d	Site where batch release, batch control and/or release testing take place.	1,3,5-6	1-11	Vmaj

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 inspection by the relevant SADC member states, an SRA and/or authorities recognised by BOMRA. 3. Evidence that the site is authorized by the competent Authority in the country of origin. 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. 6. Transfer of methods from the current testing site to the proposed testing site has been successfully completed.
Documentation required

1. Evidence that the site responsible for the manufacture of the FPP is authorized by the competent Authority in the country of origin and satisfactorily inspected by the relevant SADC member states, SRA and/or authorities recognised by BOMRA.

2. Date and scope (with indication as to whether scope was e.g. product-specific or related to a specific pharmaceutical form) 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 production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches.

5. (P.3.5) Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f2 calculation as necessary.

6. (P.5.1) Copies of release and shelf-life specifications.

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.

10. Revised product information.

11. (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
31. Change in the batch size of the FPP involving:				
31a	Up to and including a factor of 10 compared to the biobatch.	1–7	2, 5–6	IN
31b	Downscaling.	1–5	2, 6	AN
31c	More than 10 folds compared to the biobatch.	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-sized equipment.
4. A validation protocol is available or validation of the manufacture of two 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 size was at least 100 000 units in the case of solid oral dosage forms.

Documentation required

1. (P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next two full production-scale batches should be available on request and should be reported if they do not meet 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 two 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 full production-scale batches should be available on request and should be reported immediately by the supplier of the product, 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) (above) 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 *WHO Guideline on INVIVO Bioequivalence Studies*.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
32. Change in the manufacturing process of FPP				
32a	Change in the manufacturing process of the FPP.	1–9	1–4, 6–7	AN
32b		1–3, 5–9	1–7	Vmin

32c	Introduction or increase in the overage that is used for the API.	I-9	I-8	Vmin

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 physicochemical properties; dissolution profiles are similar to those of the biobatch.

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 or dry granulation or vice versa would be considered a change in manufacturing principle), the 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 (with 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 failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns, or for the sole purpose of extending the shelf life.

7. The change does not involve packaging or labelling 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 Guideline on INVIVO Bioequivalence Studies SADC.*

2. (P.2) Discussion on the development of the manufacturing process; where applicable:

- comparative in vitro testing, e.g. multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch 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 on one batch from the previous process and the biobatch 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) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the proposed process.

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 2 months of accelerated (and intermediate, as appropriate) and 2 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. Justification and supporting documentation for the introduction or increasing of an overage.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
33. Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:				
33a	Tightening of in-process limits.	1–2, 5	1	AN
33b	Deletion of a test.	2, 4	1, 6	AN
33c	Addition of new tests and limits.	2–3	1–6	AN
33d	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 failure to meet specifications resulting from unexpected events 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. colour) 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 equivalence 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 or deletion of the tests and limits.

3.2. P.4 Control of excipients

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
34. Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin.	1	1	AN
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.			

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
35. Change in the specifications or analytical procedures for an excipient involving:				
35a	Deletion of a non-significant in-house parameter.	2	1–3	AN

35b	Addition of a new test parameter or analytical procedure.	2–3	1–2	AN
35c	Tightening of specification limits.	1–2, 4	1–2	AN
35d	Change or replacement of an analytical procedure.	2–3	1–2	Vmin

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events 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**	**Documentation required**	**Reporting type**
36. 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. no 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**
37. Change to comply to an officially recognized pharmacopoeial standard/monograph				
37a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard.	1–3	1–5	AN
37b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the FPP is controlled.	None	1, 3, 5	AN
Conditions to be fulfilled				
1. The change is made exclusively to comply with the officially recognized pharmacopoeia. 2. No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test). 3. No deletion of or relaxation of any of the tests, analytical procedures or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 39a or 39d and should follow the corresponding reporting types.				
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 equivalence 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**
38. Change in the specifications of the FPP involving test parameters and acceptance criteria:				
38a	Deletion of a test parameter.	5	1, 6	AN
38b	Addition of a test parameter.	2–4, 7	1–6	AN
38c	Tightening of an acceptance criterion.	1–2	1, 6	AN
38d	Relaxation of an acceptance criterion.	2, 4, 6–7	1, 5–6	IN
38e	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 failure to meet specifications resulting from unexpected events arising during manufacture e.g new unqualified impurity; change in total impurity limits, 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 equivalence 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**
39. Change in the analytical procedures for the FPP involving:				
39a	Deletion of an analytical procedure.	5	1, 6	AN

39b	Addition of an analytical procedure.	3–4, 6–7	1–5	AN
39c.1	Modification or replacement of an analytical procedure.	1–4, 6–7	1–5	AN
39c.2		2–4, 6–7	1–5	Vmin
39d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph.	None	1–5	AN
39e	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 and other parameters, 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 alternative method and is equivalent to a currently accepted analytical procedure.

6. The change is not necessitated by failure to meet specifications resulting from unexpected events 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 equivalence 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**
40. Change in primary packaging type of FPP				
40a	Replacement or addition of a primary packaging type.	1	1–2, 4–6	Vmin
40b		None	1–6	Vmaj
Conditions to be fulfilled				
1. The change does not concern a sterile FPP.				
Documentation required				

1. Samples of the product as packaged in the new container-closure system to be provided post approval from the first marketed batch.

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, and results of transportation studies, if appropriate).

5. (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 2 months of accelerated (and intermediate, as appropriate) and 2 months of long-term testing and where applicable, results of photostability 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 were provided in documentation 5.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
41. Change in the package size involving:				
41a	Change in the number of units (e.g. tablets, ampoules, etc.) in a package.	1–2	1–3	Vmin
41b.1	Change in the fill weight or fill volume of non-parenteral multidose products.	1–3	1–3	IN
41b.2		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. 3. No increase in the headspace or surface/volume ratio.				

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 the SADC guidelines for products where stability parameters could be affected. 3. Revised product information.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
42. Change in the shape or dimensions of the container or closure for:				
42a	Non-sterile FPPs.	1–2	1–3	AN
42b	Sterile FPPs.	1–2	1–4	Vmin

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. Samples of the product packaged in the new container-closure system, where applicable. 2. (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications). 3. (P.8.1) In the case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 2 months of accelerated (and intermediate, as appropriate) and 2 months of long-term testing and, where applicable, results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above 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
43. Change in qualitative and/or quantitative composition of the immediate packaging material for:				
43a	Solid FPPs.	I–3	I–3	IN
43b	Semisolid and liquid FPPs.	I–3	I–3	Vmin

Conditions to be fulfilled

1. The change does not concern a sterile FPP.

2. No change in the packaging type and material (an example of an allowable change is blister to blister).

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, and moisture).

2. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).

3. (P.8.1) Stability summary and conclusions, results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of two batches of pilot- or production-scale, of 2 months of accelerated (and intermediate, as appropriate) and 2 months of long-term testing and, where applicable, results of photostability studies.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
44. Change in the specifications of the immediate packaging involving:				
44a	Tightening of specification limits.	1–2	1	AN
44b	Addition of a test parameter.	2–3	1–2	AN
44c	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 failure to meet specifications resulting from unexpected events 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
45. Change to an analytical procedure on the immediate packaging involving:				
45a	Minor change to an analytical procedure.	1–3	1	AN
45b	Other changes to an analytical procedure including addition or replacement of an analytical procedure.	2–4	1	AN

45c	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 and other parameters, 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 alternative 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 to demonstrate the equivalence of the deleted method and a currently accepted method.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
46. 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, or change of needle shield).	1	1–2	IN

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.

Documentation required
1. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications). 2. Sample of the FPP.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
47. Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers) involving:				
47a	Addition or replacement.	1, 2	1–2	IN
47b	Deletion.	3	3	IN
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. Sample of the device. 3. Justification for the deletion of the device.				

3.2. P.8 Stability

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

48. Change in the shelf-life of the FPP (as packaged for sale) involving:				
48a	Reduction.	3	1–3	IN
48b	Extension.	1–2	1–3	Vmin
Conditions to be fulfilled				
1. No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage. 2. Stability data were 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 for a period sufficient to support the proposed shelf-life. 3. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change. 4. Revised product information.				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
49. Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):				
49a	Reduction.	1	1, 3	IN
49b	Extension.	None	1–3	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. (P 5.1) Copy of currently accepted end of shelf-life FPP specifications and, where applicable, specifications after dilution or reconstitution. 3. Revised product information.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
50. 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 failure to meet specifications resulting from unexpected events 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. Revised product information			

12. Appendix I

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 in a multicomponent product. 3. Removal of one API from a multicomponent product. 4. Change in the dose and/or 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 from a liquid to a powder for reconstitution or vice versa. 7. Changes in the route of administration. 8. Change or addition of the manufacturing site of the FPP (Proposed manufacturer is different from the currently approved manufacturer)	None	1	New application
Conditions to be fulfilled			
None			
Documentation required			
1. Documents in fulfilment of the requirements outlined in the *BOMRA Registration Quality Guidelines.*			

13.0 Appendix 2

Permissible quantitative changes to excipients

Excipient	Percentage excipient (w/w) out of total target dosage form core weight
Filler	± 5.0
Disintegrant	
• starch	± 3.0
• other	± 1.0
Binder	± 0.5
Lubricant	
• Ca or Mg Stearate	± 0.25
• other	± 1.0
Glidant	
• talc	± 1.0
• 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.

14.0 References

- 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).

- 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.

- SADC Variation Guidelines, 3rd Draft, 2020.