Medicines Control Authority of Zimbabwe

MCAZ/EVR/GL-03

GUIDELINE FOR SUBMITTING APPLICATIONS FOR VARIATIONS TO REGISTERED MEDICINES

EFFECTIVE DATE: ....30 July 2021.....

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ABBREVIATIONS AND ACRONYMS

API:	Active Pharmaceutical Ingredient
BP:	British Pharmacopoeia
CEP:	European Pharmacopoeia Certificate of suitability
DRA:	Drug Regulatory Authority
FPP:	Finished Pharmaceutical Product. (The acronym FPP always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release)
ICH:	International Conference on Harmonization International
JP:	Japanese Pharmacopoeia
NDRA:	National Drug Regulatory Authority
OOS:	Out of specification (outside specification)
Ph Eur:	Pharmacopoeia Europa (European Pharmacopoeia)
Ph Int:	International Pharmacopeia
USP:	United States Pharmacopoeia

1.0 APPLICATION

This guideline applies to all applicants who wish to submit applications to variations to products registered by the Medicines Control Authority of Zimbabwe (MCAZ) when making an application for variations to a registered medicine.

2.0 PURPOSE

This guideline provides the necessary information that must be submitted by all applicants to the Medicines Control Authority of Zimbabwe (MCAZ) when making an application for variations to a registered medicine.

The better part of this guideline was derived from the World Health Organization (WHO) "Guidance on variations in a dossier submitted within the prequalification program" , the European Union (EU) "Guideline on dossier requirements for type IA and IB notifications"[1], Food and Drug Administration (FDA) "Guidance for Industry: Changes to an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA)", and Scale-up and Post-Approval Changes (SUPAC). guidelines.

3.0 BACKGROUND / INTRODUCTION

Once a medicine is registered by the MCAZ for sale in Zimbabwe, any variations to the original information submitted with the application or set as conditions for registration must be submitted for approval. Variations to details of a medicine may be made to alter or to improve the medicinal product, to introduce an additional safeguard due to new scientific knowledge or to meet market demands.

The conditions of registration of a medicine are therefore considered dynamic taking into account that variations to the original registered dossier may become necessary during the lifetime of the medicine.

Applicants should be aware that the guidelines retain the basic structure and function of the previous variation guidelines, and have been expanded to include the classification of additional post-approval/post-prequalification changes and to establish the level of risk inherent to each change. Although the general requirements have not significantly changed, the additional details help the reader to classify changes that may occur related to all the major sections of a quality dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

Apart from revisions in the general structure for submission and information required the guideline has been revised to also include information required for variations for

sterile products including the conditions to be fulfilled and the documentation required.

Procedures for the implementation of the different variations are presented here to assist applicants and MCAZ evaluators.

3.1 Objectives:

This guideline is intended to:

3.1.1 Assist applicants on the preparation of applications for variations to registered medicines by providing clear general guidance on type of variation, required documentation and the format of the variation application submission;

3.1.2 Fully adopt the modular format of the Common Technical Document - Quality (M4Q) as developed by ICH; and

3.1.3 Provide guidance on the technical and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of applications for variations for registered products by applicants and the subsequent assessment submissions by MCAZ.

3.2 Scope

This guidance document is applicable only to active pharmaceutical ingredients (APIs) and excipients manufactured by chemical synthesis or semisynthetic processes and finished pharmaceutical products (FPPs) containing such APIs and excipients. Variations to a biological API and/or biological excipient, or biological finished products are assessed as major changes. In this case the applicant should refer to guidance documents that specifically address biological APIs, excipients and finished products (e.g. ICH Q5A (R1), Q5B, Q5C, Q5D, Q5E, and Q6B).

This guideline applies to all variations whether from the applicant's initiative or requested by the Authority. This guideline does not apply to medicines whose application is still under consideration by the MCAZ.

3.3 General Principles:

The guidance document has similar classification of the reporting types for various variation applications as per WHO guidelines on variations to a prequalified product. Furthermore the guideline structure has been made to follow the Common Technical Document structure for ease of reference and assist in the compilation and submission of required documents in the relevant sections, whose requirement previously stated, "Replacement of the relevant pages of the dossier according to the structure as listed in the MC8 FORM". Also included in the guideline are the following appendices:
Appendix I–Guidance on minor adjustments to excipient quantities i.e. "Percentage excipient (w/w) out of total target dosage form core weight".

i. Appendix II– Variations that make a new application necessary.

ii. Appendix III- Examples of changes which are not described in the variation guideline that should be submitted as major, or be reclassified as minor variations or as notifications
iii. Appendix IV– Examples of changes that do not need to be filed as variation applications but should be implemented as per GMP change control
iv. Appendix V–Additional web-links from which additional information may be accessed to best assist with further information and guidance on particular subject matters.
v. Appendix VI– Requirements for submission of applications for registration, reinstatements, responses to queries (additional data) and applications for variation(s) to registered medicines

4.0 DEFINITIONS

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines.

4.1 **Active pharmaceutical ingredient (API):** Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have a direct effect in restoring, correcting or modifying physiological functions in human beings.

4.2 **API starting material:** A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce; a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (ref. ICH Q7). See also starting materials for synthesis.

4.3 **Applicant:** Means the person or entity by, or on whose behalf, an application for registration is made.

4.4 **Biological pharmaceutical product:** A product, the API of which is a biological substance.

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

4.6 **Commitment batches:** Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application (ref. WHO Technical Report Series, No. 953, Annex 2, 2009).

4.7 **Existing API:** An API that is not considered a new active substance that has been previously approved through a finished product by a stringent regulatory authority, MCAZ or WHO, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

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

4.9 **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.

4.10 **In-process control:** Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

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

4.12 **Multisource (generic) pharmaceutical products:** Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable (WHO Technical Report Series, No. 937, Annex 7, 2006).

4.13 **Officially recognized pharmacopoeia (or compendium):** Those pharmacopoeias recognized by the MCAZ (i.e. The International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP) and the United States Pharmacopeia (USP)).

4.14 **Ongoing stability study:** The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

4.15 **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.

4.16 **Primary batch:** A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. Primary batch requirements are outlined in 3.2.S.7.1 and 3.2.P.8.1 for the API and FPP, respectively.

4.17 **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,

4.18 **Starting materials for synthesis:** Materials that mark the beginning of the manufacturing process as described in an application or in an APIMF. A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API. See also API starting material.

4.19 Stringent regulatory authority (SRA) is:

4.19.1 the medicines regulatory authority in a country which is: (a) a member of the International Conference on Harmonisation (ICH) (European Union (EU), Japan and the United States of America); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);

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

5.0 GUIDELINES

5.1 Guidance on format

MCAZ adopted the CTD guidelines for submissions of applications for registration of medicines in March 2013. Applicants are encouraged to refer to the MCAZ Guideline on Submission of Documentation for Registration of a Multi-source (Generic) Finished Pharmaceutical Product (FPP): Quality Part of the Common Technical Document (CTD) Format" when compiling submissions for applications for variations. The relevant sections of the CTD document as outlined under documents to be submitted for each variation should be adhered to.

5.2 Guidance on presentation

Applicants are required to submit electronic copies of the variation application in the format recommended in ***Appendix IV: Format for saving documents in the USB flash drives or CDs***. Notwithstanding the above requirement hard copies of the documents of affected sections in Module 1 e.g. variation application form, proof of payment of appropriate fees, revised MC8 form and the original MCAZ registration certificate, should be submitted. Scanning the entire submission into one pdf file will result in the submission being deemed not acceptable for assessment. Applicants are reminded that a text selectable pdf format should be used for all documents submitted.

5.2.1 Variations and Responses to Queries (Additional Data)

All quality related variations and responses to queries must be provided with the following;

i. The applicable variation application form (either EVRF55 or EVRF56) for all quality related amendments/variations and a cover letter for responses to queries (additional data)
ii. An updated MC8 form and the MS Word Quality Information Summary (QIS) where the proposed amendments/variations or responses to queries result in a change in the information on the original MC8 form or Quality Information Summary (QIS)
iii. Only the modules and subsections affected by the variation(s) or responses to queries should be provided as a soft copy and documentation should be presented following the format described above in the section on applications for registration and reinstatements.

5.2.2 Grouping of Variations

The applicant may also consider grouping of variations as part of the application submission. Grouping of variations is acceptable only under the following circumstances:

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

ii. When the same change affects multiple FPPs, e.g. addition of a new API manufacturing site for multiple FPPs;
iii. When all the changes are annual notification.

A grouped variation should be filed in one application form, and will be reviewed as one application. For the purposes of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change. For example, additional manufacturing site for an FPP for all the manufacturing processes (the new site has been satisfactorily inspected by WHO) with scale up of batch size at the new site (up to 10 times to the bio-batch) should be submitted as a grouped variation of variation no.30c (Vmin) and variation no. 32a(IN). The overall variation type is a minor variation, and the implementation and assessment timelines will therefore be those for a minor variation. The conditions and documentation for both changes should be considered and submitted in the application.

5.3 Guidance for Implementation

5.3.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of quality-related changes. Specific examples of changes are provided in these guidelines. However, it should be noted that a change not covered by these guidelines, should be considered as a major change by default. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product. Individual changes normally require the submission of separate variations.

Applicants are also advised to exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified as a particular reporting type, classification within a higher risk category may be warranted as a result of the composite effect of these changes.

5.3.2 Notifications

i. Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. An annual notification should be submitted with a completed annual notification form, including a summary of the change(s) and the date(s) of implementation. The summary should be sufficiently detailed to enable the assessor to easily determine whether the appropriate reporting category has been used. A

summary of studies performed to assess the impact of each change on product quality should be provided in the application form, if applicable.

When an annual notification involves a change in specifications or standard test procedures (STP) for an API or FPP, the signed and dated version of the revised specification and STP including the change history should be attached to the notification application form.

Additional associated documentation is not required to be submitted. However, the information used to support the change must be generated prior to distributing the product manufactured with the change, and should be available on request, or to inspectors during an inspection. ANs should be submitted to MCAZ within 12 months of implementation of the changes. For convenience applicants may group several "AN" changes as a single submission.

ii. Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application.

For both types of notifications, applicants are advised that an "IN" or "AN" may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

Note to applicants: Where an application is submitted as a notification by the applicant, but on evaluation the MCAZ reclassifies the variation, it no longer will be deemed as a notification. Furthermore should more information be requested by the MCAZ during evaluation of the notification, new period of three months begins upon submission of the new information.

i. **Minor Variation (Vmin)** – this is a variation that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

ii. **Major Variation (Vmaj)** - is a variation to the documentation which can neither be deemed to be a minor variation nor to be a variation for which the submission of a new dossier would be necessary (Appendix III). Such major variations require approval of MCAZ before implementation.

iii. **New applications and extension applications** -Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. In these cases a new dossier must be submitted. Examples of such changes are listed in Appendix II.

iv. **Labelling information** -For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, *MCAZ* must be notified and guidance on the submission documents required can be sought by email addressed to mcaz@mcaz.co.zw carbon copy (Cc) adminevr@mcaz.co.zw. The

email should contain sufficient details of the proposed change to enable MCAZ to provide advice.

5.3.3 Changes where change category is not captured in the guideline

A change that is not addressed in the MCAZ variation guidelines (variation guideline) should be considered as a major change by default as per the guideline. This is to give MCAZ enough time to review the unclassified change. However, if the applicant believes that the change is unlikely to have major effects on the overall safety, efficacy and quality of the product, MCAZ can be consulted for classification of the particular change, by email addressed to mcaz@mcaz.co.zw carbon copy (Cc) adminevr@mcaz.co.zw. The email should contain sufficient details of the proposed change to enable MCAZ to provide advice. Examples of changes which are not described in the Variation guideline that should be submitted as major, or be reclassified as minor or notification, are given in appendix III.

5.3.4 Conditions to be fulfilled

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

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

The applicant must provide evidence to fulfill the conditions (or sufficient justification for the lack thereof) and documentation requirements as listed for each respective variation.

5.3.5 Documentation Required

Examples of variations are organized according to the structure of the CTD. For each variation, certain documents have been identified as supporting data and are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation.

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

i. A variation application form (applicable template(s) can be downloaded from the web site). All sections of this form should be completed and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF, should be provided in addition to the printed version;
ii. Proof of payment of appropriate fees;
iii. Replacement of the relevant sections of the dossier as per CTD format;
iv. Revised MC8 form;
v. Copies of SmPC, PIL and labels, if relevant.
vi. The original MCAZ registration certificate.

If variations to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier. In such cases the changes should be clearly identified in the application form as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation submitted should be provided. It should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

Applications for variations that are classified as annual notifications (ANs) must include evidence to fulfill the conditions and documentation requirements as listed for each respective variation. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted (except when the variations result in revision of specifications and/or test procedures). However applicants are reminded that documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to MCAZ within 12 months of implementation of the changes.

5.3.7 Fees

Applicants should consult the current fee schedule for the correct and appropriate fee. Note that MCAZ reserves to determine the correct interpretation of the fee payable based on the published schedule. Please note that relevant variation application fees also apply to notifications. All applicants are advised that a duly completed quotation confirmation form (available on the MCAZ website) signed by the Evaluation and Registration division should be presented to MCAZ cash office together with the proof of payment when applications for variations (dossiers) are submitted. MCAZ

will not accept applications for variations prior to full payment of fees applicable to the applications made.

5.4 Dossier Requirements for Variations to Registered Products

Although this guideline was prepared in order to clarify what documentation should be submitted with each type of variation, the applicant is advised to ensure compliance with other MCAZ guidelines e.g. MCAZ CTD guidelines, MCAZ guidelines on biowaivers, SADC guidelines on bioavailability and bioequivalence, Data requirements for applications for registration of biosimilar medicines and other relevant guidelines as advised by MCAZ.

The titles of the variations are numbered and subcategories depicted by letters and numbers. The conditions necessary for a given variation are outlined for each subcategory and listed below each variation.

In principle, all parts of the dossier that are affected by a variation should be resubmitted according to the structure of the MC8 Form (Application for registration of a medicine) and CTD format. Moreover, any further documentation required along with the variation is identified.

Applicants should present a summary of the intended variation in tabulated format in the applicable variation application form, in which the current state/situation and the situation after the intended variation are compared in order to outline the scope of the variation in a transparent manner. Each variation application should be accompanied by a justification.

5.5 Requirements for Variations to Products Registered Through the WHO Collaborative Registration Procedure

Applicants with products registered through the WHO Collaborative Registration Procedure must inform MCAZ of any post-approval changes (variations) made to the prequalified product as soon as the variation has been approved by WHO. To ensure that consistency between the prequalified product and the MCAZ-registered product is maintained, all post-approval changes must follow those approved by WHO.

In submitting such variation applications, applicants must submit copies of the WHO approval letters for the variations. Applicants will receive an email acknowledgment of notification of the variation within 45 calendar days of receipt. Be advised that, further information regarding the variation may be requested by the Authority.

Note to applicants: Some changes (deviations) are however acceptable without prior approval by WHO e.g. changes in labelling or product information but changes relating to quality aspects will mean that the MCAZ-registered product is no longer considered to be the same as the prequalified product.

5.6 Variations to Innovator or Multisource (Generic) FPPs Approved by Stringent Regulatory Authorities (SRAs)

For variation applications for innovator FPP or multisource (generic) FPP, that received approval from a stringent regulatory authority (SRA), applicants may submit copies of the SRA approval letters for the variations as part of the application so as to expedite review of such variation applications. In addition, updated Quality Information Summary of the FPP, product information (Summary of Product Characteristics, Patient Information Leaflet, Labelling), FPP specifications and/or test procedures should be submitted if affected by the variation. Be advised that, further information regarding the variation may be requested by the Authority.

5.7 Administrative changes

1. Variation in the name and/or address of the applicant or principal

1	Variation in the name and/or address of the applicant or principal	Conditions to be fulfilled	Required documentation	Reporting type
		1, 2	1,2,3,4	AN

Conditions to be fulfilled:

1. The applicant shall remain the same legal entity.
2. Application fee as indicated on the fee schedule accompanies the application

Documentation submitted:

1. A formal document from a relevant official body in which the name and or the new address is mentioned. Where applicable, information on legal status e.g. evidence of merger, sale of formulation, variation of name etc. must be submitted.
2. Completed page 1 of the MC8 Form
3. Written declaration confirming correctness of information submitted and that no other administrative variations have been made to those already approved by the MCAZ
4. A copy of the current medicine registration certificate

2. Variation in the name of the Medicine or Finished Pharmaceutical Product (FPP)

2	Variation in the name of the Finished Pharmaceutical Product (FPP)	Conditions to be fulfilled	Required documentation
		1	1, 2,3,4

Conditions to be fulfilled:

No confusion with the names of existing registered products or with the international nonproprietary name (INN).

Documentation submitted:

1. A formal document from the National Drug Regulatory Authority (NDRA) in which the new name is approved.
2. Replacement of the relevant pages of the dossier according to the structure of the MC8 form

3. Revised label(s), SmPC and package insert reflecting the proposed name of the FPP
4. A copy of the current medicine registration certificate

3 Variation in the name and/or address of a manufacturer of the active pharmaceutical ingredient (API) where no European Pharmacopoeia certificate of suitability (CEP) is available

3	Variation in the name and/or address of a manufacturer of the active pharmaceutical ingredient (API) where no European Pharmacopoeia certificate of suitability (CEP) is Available	Conditions to be fulfilled	Required documentation to	Reporting type
		1	1, 2,	IN

Conditions

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation

1. A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.
2. Replacement of the relevant pages of the dossier according to the structure as listed Form MC8 or MCAZ CTD Guideline
3. An updated Letter of Access in case of change in the name of the holder of the APIMF.

4 Variation in the name and/or address of a manufacturer of the finished pharmaceutical product (FPP)

4	Variation in the name and/or address of a manufacturer of the finished pharmaceutical product (FPP)	Conditions to be fulfilled	Required Documentation	Reporting type
		1	1, 2,3,4	IN

Conditions to be fulfilled:

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation to be submitted:

1 Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. N DRA) in which the new name and/or address is mentioned.
2. Replacement of the relevant pages of the dossier according to the structure as listed in the MC8 form.
3. Revised label and package insert reflecting the proposed name of the FPP
4. A copy of the current medicine registration certificate

5 Deletion of a manufacturing site or manufacturer involving production of the API starting material or production or testing of the API intermediate or API or production, packaging or testing of the intermediate or FPP

5. Deletion of a manufacturing site or manufacturer involving	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
5a. Production of the API starting material	1	1	AN
5b. Production or testing of the API intermediate or API	1-2	1	IN
5c. production, packaging or testing of the intermediate or FPP	1-2	1	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 to be submitted:
1. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.

6 Changes to a CEP or to a confirmation of API-prequalification document

Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API

6. Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API		Conditions to be fulfilled	Required Documentation	Reporting type
6a.1	from a currently accepted manufacturer	1-5	1-5	AN
6a.2		1-4	1-6	IN
6a.3		1, 3-4	1-6	Vmin
6b.1	from a new manufacturer	1-4	1-6	IN
6b.2		1, 3-4	1-6	Vmin

Conditions

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 with the exception of residual solvents when the limits stipulated comply
3. The manufacturing process of the API, starting material or intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. For low solubility APIs the polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the bio-batch.
5. No revision of the FPP manufacturer's API specifications required.

Documentation

1. Documentation of the current (updated) CEP, including any annexes and a declaration of access for the CEP to be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to MCAZ who refers to the CEP.
2. A written commitment that the applicant will inform MCAZ in the event that the CEP is withdrawn and an acknowledgment that the 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 MCAZ Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part in the CTD format.

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 WHO/PQP.
6. (S.4.1) Copy of FPP manufacturer's revised API specifications.

7 Submission of a new or updated confirmation of API-prequalification document

7. Submission of a new or updated confirmation of API-prequalification document		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
7a.1	from a currently accepted manufacturer	1-3	1-3, 5	AN
7a.2		1-2	1-5	Vmin
7b.1	from a new manufacturer	1-3	1-3, 5	IN
7b.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 bio-batch.
3. There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic and 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

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 MCAZ

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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 MCAZ.

8 Submission of a new or updated BSE/TSE European Pharmacopoeia certificate of suitability for and excipient or API (addition or replacement) manufacturing process

8. Submission of a new or updated BSE/TSE European Pharmacopoeia certificate of suitability for and excipient or API (addition or replacement) manufacturing process		Conditions to be fulfilled	Required Documentation	Reporting type
8		None	1	AN

Conditions to be fulfilled:
None

Documentation to be submitted:

1. Copy of the current (updated) European Pharmacopoeia TSE certificate of suitability.

5.8 Quality changes

3.2. S Drug substance (or API)

3.2. S.2 Manufacture

9 Replacement or addition of a new manufacturing site or manufacturer of an API or biological/immunological product:

9. Replacement or addition of a new manufacturing site or manufacturer of an Active substance		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
9a.1	API testing only	1, 2, 4	1, 3-4	**IN**
9a.2		2, 4	1, 3-4	Vmin
9b.1	production of API starting material	3-4	No variation is required, such changes are handled as variations to the A PIMF by the APIMF holder.	
9b.2		4-5	1-2, 12	**IN**
9b.3		None	1, 2, 5, 7-8, 12, 13	Vmaj
9c.1	Production of API intermediate	3-4	No variation is required, such changes are handled as variations to the A PIMF by the APIMF holder.	
9c.2		4-6	1-2, 12	**IN**
9c.3		None	1, 2, 5, 7-8, 12, 13	Vmaj
9d.1	production of API (full dossier)	1, 9-11	1-2, 4, 8-9	IN
9d.2		None	1, 2, 4, 5, 7-8, 10-11, 13	Vmaj
9e	The change relates to production of a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological or immunological product	None	1, 2, 4, 5, 7-8, 10-11, 13	Vmaj

9f	Addition of an alternative sterilization site for the active substance	None	2, 4, 5, 9, 14	Vmin
9g	Introduction of a new site of micronisation	1, 12	4, 5,11,12,14	AN
9h	Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological or immunological or immunochemical method takes place	None	1, 3, 4, 5, 8, 15	Vmaj
9i	New storage site of Master Cell Bank and/or Working Cell Banks	None	5, 14	(IN)

Conditions to be fulfilled:

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

manufacture's specifications do not require the revision of the FPP manufacturer's API specifications.

9. For low-solubility APIs the API polymorph is the same, and whenever particle size is critical (including low-solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the bio-batch.
10. Specifications (including in-process controls, methods of analysis of all materials), method 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).
11. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (www.who.int/biologicals) or EMA's Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (www.emea.europa.eu/ema) or equivalent guidelines of the ICH region and associated countries.
12. The particle size specification of the active substance and the corresponding analytical method remain the same.

Documentation to be submitted:

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 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 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 batches, copies of certificates of analysis data 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 (S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the MCAZ Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part.[7]
6. The open part of the new APIMF (with a Letter of Access provided in Module 1) and documentation in fulfilment of requirements for the API section 3.2.S of the MCAZ Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product.[8]

7. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO/PQP.
8. (S.4.1) A copy of the FPP manufacturer's API specifications.
9. (S.2) A declaration from the supplier of the FPP that the route of synthesis, materials, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
10. A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.
11. For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low-solubility solubility APIs) where there is a significant difference in particle size distribution compared to the lot used in the bio-batch, evidence that the difference do not impact the quality and bioavailability of the FPP.
12. 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.
13. An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary.
14. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 3.2.S.2.
15. (S.4.2) Documented evidence of successful transfer of analytical procedures from the current to the proposed site.

10 Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture

10. change or addition of a manufacturing block or unit at a currently accepted site of API manufacture		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
10a	Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	1-5	No variation is required, such changes are handled as variations to the APIMF by the APIMF h older.	
10b		1, 3-5	1-4	IN

Conditions to be fulfilled:

1. The API is non-sterile.
2. The API manufacturing block or unit is currently accepted through the APIMF procedure.
3. The same quality system covers currently accepted and proposed units or blocks.
4. For low-solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API lot used in the preparation of the bio-batch.
5. No change in the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable). Minor changes in the equipment is acceptable.

Documentation to be submitted:

1. (S.2) A declaration from the supplier of the FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
2. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s)). A valid manufacturing and/or testing authorization and certificate of GMP compliance, if available.
3. (S.4.4)Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed units or blocks.
4. (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

11. Change in the manufacturing process of the API

11. Change in the manufacturing process of the Active substance		Conditions to be fulfilled	Required Documentation	Reporting type
11a	change in the manufacturing process of the API	1-3, 9	1-2, 8	AN
11b.1		1-2, 4, 6-9	3-4, 11-12	IN
11b.2	change in the manufacturing process of the API	1-2, 4, 6-8, 10	3-4, 11-12	Vmin
11c		1-2, 4-7	3-4, 11-12	Vmin
11d		None	2-14	Vmaj
11e	The change refers to a biological or immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol	None	Relevant sections of the dossier	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 bio-batch.
3. The API manufacturing site is currently accepted through the APIMF procedure.
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 to submitted:

1. A copy of the APIMF variation acceptance letter.
2. (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 MCAZ.
3. (S.2.2) A side-by-side comparison of the current process and the new process.
4. (S.2.2) A flow diagram of the proposed synthetic process (es) and a brief narrative description of the proposed manufacturing process (es).
5. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
6. (S.2.3) Either a TSE CEP for any new source of material or, where applicable, documented evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent authority and shown to comply with the current WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (www.who.int/biologicals) or EMA's note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (www.emea.europa.eu/ema) or equivalent guidelines of the ICH region and associated countries.
7. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
8. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable
9. (S.3.1) Evidence for elucidation of structure, where applicable.
10. (S.3.2) Information on impurities.
11. S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
12. (S4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) manufactured according to the current and proposed processes.
13. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.
14. For low-solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low-solubility APIs) where there is dissimilar particle size distribution compared to the lot used in the bio-batch, evidence that the lot used in the bio-batch, evidence that the differences do not impact the quality and bioavailability of the FPP.

12 Change in the in-process tests or limits applied during the manufacture of

12. Change in the in-process tests or limits applied during the manufacture of the API:		Conditions to be fulfilled	Required Documentation	Reporting type
12a. any change in the manufacturing process controls		1	No variation is required; such changes are handled as variations to the APIMF by the APIMF holder	
12b tightening of in-process limits		2-4	1	AN
12c addition of a new in-process test and limit		2, 5	1-5	AN
12d	addition or replacement of an in-process test as a result of a safety or quality issue	None	1-5, 7, 8-10	Vmin
12e.1	Deletion of an in-process test	2, 6-7	1-3, 6	AN
12e.2		None	1-3, 7-10	Vmaj
12f	Relaxation of the in-process test limits	None	1-3, 5, 7-10	Vmaj

Conditions to be fulfilled:

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by unexpected events arising during manufacture e.g. a new unqualified impurity or a change in total impurity limits.
3. The change is within the range of currently accepted limits.
4. The analytical procedure remains the same, or changes to the analytical procedure are minor.
5. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The affected parameter is non-significant.
7. The change does not affect the sterilization procedures of a sterile API.

Documentation to be submitted:

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 fir 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.

13 Change in batch size of the API or intermediate:

13. Change in batch size of the API or intermediate involving:		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
13a.	up to 10-fold compared to the currently accepted batch size	1-2, 4, 6	1, 3-4	AN
13b.1	Downscaling	1-4	1, 3-4	AN
13b.2		1-3	1-4	IN
13c	Any change in scale (APIMF procedure)	5	1-2, 4-5	AN
13d	More than 10-fold increase compared to the currently accepted batch size	1-2, 4, 6	1, 3-4	Vmin
13e	The change requires assessment of the comparability of a biological/immunological active substance	None	Relevant sections of the dossier	Vmaj
13f	The scale for a biological/immunological active substance is increased/decreased without process change (e.g. duplication of line)	1,2,3,6	1, 2, 3, 4	Vmin

Conditions to be fulfilled:

1. Any variations to the manufacturing methods are only those necessitated by scale-up, e.g. use of different sized equipment.
2. The variation does not affect the reproducibility of the process.

3. The variation should not necessitated by unexpected events arising during manufacture or because of stability concerns.
4. The change does not concern a sterile API.
5. The API manufacturing site and batch size is currently accepted through the APIMF procedure.
6. The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation.

Documentation

1. S2.2) A brief narrative description of the manufacturing process.
2. S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.
3. S.4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable).
4. S.4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.
5. A copy of the APIMF variation acceptance letter.

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

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:**	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
14a)	Any change	1	No variation is required; such changes are handled as variations to the APIMF by the APIMF holder	
14b)	Tightening of the specification limits	2-4	1-3	AN
14c	Minor change to an analytical procedure	5-7	2-3	AN
14d	Addition of a new specification parameter and corresponding analytical procedure where necessary	2, 7-9	1-3	AN
14e	Deletion of a specification parameter or deletion of an analytical procedure	2, 10	1-4	AN
14f	Addition or replacement of a specification parameter as a result of a safety or quality issue	None	1-3, 5	Vmin
14g	Relaxation of the currently accepted specification limits for solvents, reagents, catalysts an raw materials	4, 7, 9-10	1, 3-4	IN
14h	Relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1-3, 5	Vmaj

Conditions

1. API manufacturing site is currently accepted through the APIMF procedure.
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 change is within the range of currently accepted limits.
4. The analytical procedure remains the same.
5. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments, to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).

6. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7. No change to the total impurity limits; no new impurities are detected.
8. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
9. The change does not concern a genotoxic impurity.
10. The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

Documentation

1. Comparative table of registered 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

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 specifications

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 specifications involving:**	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
15a)	API supported through the APIMF procedure.	1-2	No variation is r equired; such changes are handled as variations to t he APIMF by the A PIMF holder	
15b)	API not supported through the APIMF procedure.	2	1-4	IN

Conditions to be fulfilled:

1. The revised test parameters, acceptance criteria, or analytical procedures have been submitted as variations to the associated APIMF and accepted.

2. The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer's API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API is maintained.
3.

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 manufacture's specifications.

16. Change to the test parameters or acceptance criteria of the API specifications of the FPP

16	**Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:**	Conditions to be fulfilled	Required Documentation	Reporting type
16a)	Updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.	1-2	No variation is required; such changes are handled as variations to t he APIMF by the A PIMF holder	
16b.1	Deletion of a test parameter (other than that in 16f)	1-2	1, 6	AN
16b.2		10	1, 6, 8	IN
16b.3		None	1, 6	Vmaj
16c.1	Addition of a test parameter	1, 4-8	1-6	AN
16c.2		1, 5-6, 10	1-6, 8	IN
16c.3		1, 5-6	1-6	Vmin
16c.4		None	1-7	Vmaj
16d.1	Replacement of test parameter	1, 5-8	1-6	IN
16d.2		5, 7, 10	1-6, 8	Vmin
16d.3		None	1-7	Vmaj
16e.1	Tightening of 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, 10	1, 6, 8	Vmin
16f.3		None	1, 6-7	Vmaj
16g	Deletion of a test for heavy metals	12, 13	1	AN

16h	Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue	None	1, 2, 3, 5, 6	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. The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF variation.
11. No change is required in FPP release and shelf-life specifications.
12. Information about the elemental impurities in API or excipients should be available to the FPP manufacturer.
13. The FPP manufacturer should conduct associated risk assessment on elemental impurities which should be available in case requested by assessors or for verification by the MCAZ inspection team.

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. 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 stud. However, if the routine dissolution medium contains a surfactant, the applicant should contact MCAZ for advice. For changes to the polymorph of an insoluble API the applicant should contact MCAZ for advice before embarking upon any investigation.
8. Copy of the APIMF variation acceptance letter.

17. Change to the analytical procedures used to control the API by the FPP manufacturer involving:		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
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		None	1-4	IN
17c.1	addition of an analytical procedure	1-3	1-3	AN
17c.2		3, 8	1-3, 5	AN
17c.3		8	1-3, 5	Vmin
17c.4		None	1-3	Vmaj

		, 2,		
17d.1	modification or replacement of an analytical procedure	1-6	1-4	AN
17d.2		2-3, 5-6	1-5	AN
17d.3		1-3, 5-6	1-4	Vmin
17d.4		5-6, 8	1-5	Vmin
17d.5		None	1-4	Vmaj
17e.1	deletion of an analytical procedure	6-7	1, 6	AN
17e.2		6, 8	1, 5, 6	IN
17e.3		None	1, 6	Vmaj
17f	Substantial change to or replacement of a biological/immunological/immune-chemical test method or a method using a biological reagent for a biological active substance	None	Relevant sections of the dossier	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 method 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 and has been accepted as part of an variation to the associated APIMF.

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. A copy of the APIMF acceptance letter
6. (S.4.5) Justification for the deletion of the analytical procedure, with supporting data.

3.2. S.6 Container-closure system

18 Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API

18. Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
18a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	3, 4	1-2, 4	AN
18b		1-2, 4	2-3	IN
18c		4	1-3	Vmin
18d	Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances	None	Relevant sections of the dossier	Vmaj

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 has previously been accepted through the APIMF procedure.
4. The change is not the result of stability issues.

Documentation Required:

1. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process.
2. (S.6) Information on the proposed primary packaging (e.g. description 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.
4. A copy of the APIMF variation acceptance letter.

19 Change in the specifications of the immediate packaging for the storage and shipment of the API:

19. Change in the specifications of the immediate packaging for the storage and shipment of the API involving:	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
19a tightening of specification	1-2	1	AN
li**19**itsb addition of a test	2-3	1-3	AN
parameter**19c** deletion of a non - critical parameter	2	1, 4	AN
19d any change (APIMF procedure)	4	No variation is required; such changes are handled as variations to the APIMF by the APIMF holder	

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. The change has previously been accepted through the APIMF procedure.

Documentation Required:

1. S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2. (S4.2) Details of method and summary of validation of new analytical procedure.
3. (S.6) Certificate of analysis of one batch
4. Justification to demonstrate that the parameter is not critical

20 Change to an analytical procedure on the immediate packaging of the API:

20. Change to an analytical procedure on the immediate packaging of the API involving:	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
20a minor change to an analytical procedure	1-3	1	AN
I20**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
20d any change (APIMF procedure)	6	No variation is required; such changes are handled as variations to the APIMF by the APIMF holder	

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 method is an alternative method and is equivalent to a currently accepted method
6. The change has previously been accepted through the APIMF procedure.

Documentation Required:

1. S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent.
2. Justification for deletion of the analytical procedure.

4.2. S.7 Stability

21. Change in the retest period or shelf-life of the API:

21. Change in the retest period or shelf-life of the API involving:		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
21a)	any change (APIMF procedure)	4	4	IN
21b	reduction	3	1-2	**IN**
21c	extension	1-2	1-3	Vmin
21f	Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol	1-4	1-3	Vmaj

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.
4. The revised retest period has previously been accepted through the APIMF procedure.

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.
4. A copy of the APIMF acceptance letter.

22. Change in the labelled storage conditions of the API

22. Change in the labelled storage conditions of the API involving:		**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
22a	any change in storage conditions (APIMF procedure)	1	1	IN
22b	any change in storage conditions	2	2	Vmin
22c	Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol	2	2	Vmin

Conditions to be fulfilled:

1. The revised storage conditions have previously been accepted through the APIMF procedure.
2. 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. A copy of the APIMF acceptance letter.
2. (S.7.1) Stability and/or compatibility test results to support the change to the storage conditions.

3.2. P Drug product (or Finished Pharmaceutical Product)

2.2. P.1 Description and composition of the FPP

23. Change in the composition of a solution dosage form

23. Change in the composition of a solution dosage form:		Conditions to be fulfilled	Required Documentation	Reporting type
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, osmolarity, 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 registered.

Documentation required:

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.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 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted.

24. Change in the colouring system or the flavouring system currently used in the FPP

24. Change in the colouring system or the flavouring system currently used in the FPP involving:	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
24a. reduction or increase of one or more components of the colouring or the flavouring system	1-3, 6	1, 4, 6-7	AN
24b. deletion, addition or replacement of one or more components of the colouring or the flavouring system	1-6	1-7	**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 should be made by an excipient which currently makes up a major part of the finished product formulation.
3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion or addition of an identification test.
4. Any new proposed components must comply with section 3.2.P.4 of the MCAZ Guideline on Submission of application for registration of a medicine.
5. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current WHO Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products (www.who.int/biologicals) or the EMS's Note for Guidance on Minimizing the Risk of Transmitting Anima Spongiform Encephalopathy Agents via Human

and Veterinary Medicinal Products (www.emea.euopa.eu/ema) or an equivalent guide of the ICH-region and associated countries.

6. Where applicable, the change does not affect the differentiation between strengths and for paediatric formulations it does not require submission of results of taste acceptability studies

Documentation required:

1. Sample of the new product.
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. Either a European Pharmacopoeia certificate of suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by am NMRA in the ICH region or associated countries and shown to comply with the scope of the current guideline in the countries of the ICH region or associated countries. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
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) Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.
6. (P.8.1) Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 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.

25. Change in weight of tablet coatings or capsule shells

25. Change in weight of tablet coatings or capsule shells involving:	Conditions to be fulfilled	Required Documentation	Reporting type
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 bio-batch.
2. The coating is not a critical factor for the release mechanism.
3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.

Documentation Required:

1. Justification for not submitting a new bioequivalence study according to the current MCAZ Guideline on Bioequivalence.
2. (P.2) Comparative multi point 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 bio-batch.
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 3 months of accelerated (and intermediate, as appropriate) and 3 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.

26 Change in the composition of an immediate-release solid oral dosage form:

26. Change in the composition (excipients) of the finished product		Conditions to be fulfilled	Required Documentation	Reporting type
26a.1	replacement of a single excipient with a comparable excipient at a similar concentration	1-5	1-10	Vmin
26a.2		None	1-10	Vmaj
26b.1	quantitative changes in excipients	1-4	1-4, 7-10	Vmin
26b.2		None	1-4, 7-10	Vmaj
26c	Change that relates to a biological/immunological product	None	Relevant sections of the dossier	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 MCAZ Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part (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 3 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 bio-batch.
5. The change is not the result of stability issues and/or does not result in potential safety concerns, i.e. differentiation between strengths

Documentation Required:

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequvalance study according to the current WHO guidelines on bioequivalence.
2. (P.1) Description and composition of the FPP.
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles obtained on at least two batches of pilot- or production-scale of the proposed product and the bio-batch (depending on the solubility and permeability of the drug, dissolution in the 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.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 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch, and confirmation that there are no changes to the production documents other than those highlighted.

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

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:		Conditions to be fulfilled	Required Documentation	Reporting type
27a. changes in imprints, embossing or other markings		1-3	1-2, 5-6	IN
27b. deletion of a score line		2-5	1, 5-6	IN
26c.1	addition of a score line	2-4	1, 3, 5-6	Vmin
26c.2		None	1, 3-6	Vmaj

Conditions to be fulfilled:

1. Any ink complies with section 3.2.P.4 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part.
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 MCAZ.
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 if the tablet portions, where 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.

28 Change in dimensions without change in qualitative or quantitative composition and mean mass:

28. Change in dimensions without change in qualitative or quantitative composition and mean mass of:	Conditions to be fulfilled	Required Documentation	Reporting type
pessaries other than those stated in change no. 28b	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.
3.

Documentation Required:

1. For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence. 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. 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 the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

29 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same:

29. Change in concentration of a single dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same:	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
29a. Deletion of the solvent/diluent container from the pack	None	1, 2	IN

Conditions to be fulfilled:
None

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 medicinal product.
2. Revised product information.

3.2. P.3 Manufacture

30 Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP

30. Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving:	**Conditions to be fulfilled**	**Required Documentation**	**Reporting type**
30a. Secondary packaging of all types of FPPs	2-3	1	IN
30b. Primary packaging site of:			
30b.1. solid FPPs (e.g. tablets, capsules), semisolid FPPs (e.g. ointments, creams) and solution liquid FPPs	2-4	1, 8, 10, 11	IN
30b.2. other liquid FPPs (suspensions, emulsions)	2-5	1, 5, 8, 10, 11	IN
30c.1 all other manufacturing operations except batch control and/or release testing for non-sterile products	1-3, 5	1-10	Vmin
30c.2 Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products	1, 2, 3, 5	1, 3, 5, 6, 7, 12	Vmaj
30c.3 Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes	1, 2, 3, 5	Relevant sections of the dossier	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 in the last three years either by MCAZ, WHO or an SRA.
3. Site appropriately authorized by an NMRA (to manufacture the pharmaceutical form and the product concerned).

4. The change does not concern a sterile FPP.
5. Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production-scale batches in accordance with the current protocol.

Documentation Required:

1. Evidence that the proposed site has been appropriately authorized in the last three years, for the pharmaceutical form and the product concerned:
   i. A copy of the current manufacturing authorization, a GNP certificate or equivalent
   ii. document issued by the NMRA
   iii. A GMP statement or equivalent issued by WHO or SRA
   iv. date of the last satisfactory inspection concerning the packaging facilities by WHO or an SRA in the last three years
2. Date and scope (with indication as to whether scope was e.g. product-specific or related to 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 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 bio-batch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the bio-batch 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 bio-batch results with f2 calculation as necessary.
6. (P.5.1) Copies of revised FPP release and shelf-life specifications.
7. (P.5.4) Batch analysis data on one production-scale batch from the proposed site and 33 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. The variation application should clearly outline the "present" and "proposed" finished product manufacturers.
11. Copy of current medicine registration certificate.
12. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.

Example of a comparative schedule for variation of manufacturing site for a tablet formulation:

	Currently approved product details	Proposed product details	Comments
Product name	ABC 50mg tablets	ABC 50mg tablets	No variation
Batch size	One batch size 30 000 tablets (30kg)	Two batch sizes 150 000 tablets (150kg) and 300 000 tablets (300kg)	Two batch sizes both higher than previous
Unit composition	• Specifications for API in-house • Excipient specifications International Pharmacopoeia and in-House	• API specifications now USP • Excipient specifications now B P/Ph. Eur	• API specifications now in official pharmacopoeia • Excipients specifications variation due to new markets in UK and Europe
Material Sifting	• Sifting of excipients X and Y in mechanical sifter • Sifting of extra granular material in mechanical sifter	Sifting in two lots (A and B) in Co-mill	• Equipment variation due to increased batch size and unavailability of same equipment. • The sifting process is however using the same principle. See attached Description
Granulation	In single lot	In two lots (A and B)	Equipment variation due to increased batch size
Drying	Drying at 50 – 55°C for 10 –15mins, till LOD is NMT 2.5% w/w	Wet mass dried at 60 - 65°C for 10 minutes, till LOD at not more than 2.5% w/w for both lots	• Equipment variation with new achieving optimum at higher temperature in a shorter time. • Process under validation • Higher drying temperature acceptable based on previously submitted pharmaceutical development data

Blending	Single cone blender for 20 Minutes	Cage blender and blended for 5 minutes	• Equipment variation. • The principles of operation of both blenders basically similar. See drawings and description of process. □ Under validation
Compression	• 16 station rotary press • Oval shaped, biconvex tablets with single break line and plain on the other side	• 32 station card compression machine. • Oval shaped, biconvex tablets with single break line on one side and embossed	• Similar equipment only increased number of stations • Process validated (see attached report) • New embossing included

31 Replacement or addition of a site involving batch control testing:

31. Replacement or addition of a site involving batch control testing:	Conditions to be fulfilled	Required Documentation	Reporting type
31a. Replacement or addition of a site involving batch control testing	1-2	1-3	AN
31b. Replacement or addition of a site where batch control/testing takes place for a biological or immunological product and any of the test methods performed at the site is a biological/immunological method	1-2	Relevant sections of the dossier	Vmaj

Conditions to be fulfilled

1. Site is appropriately authorized by the NMRA and satisfactorily inspected either by MCAZ, WHO or an SRA.
2. Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

Documentation Required:

1. Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application.
2. Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected either by WHO or and SRA or by MCAZ.
3. (P.5.3) Documented evidence of successful transfer of analytical procedures from the current and the proposed site.

32 Change in the batch size of the FPP:

32. Change in the batch size of the FPP involving:		Conditions to be fulfilled	Documentation required	Reporting type
32a	up to and including a factor of 10 compared to the bio-batch	1–7	2, 5–6	IN
32b	downscaling	1–5	2, 6	AN
32c	other situations	1–7	1–7	Vmin
32d	a batch size that has been accepted for one of the approved manufacturing sites of the product being implemented at the other approved FPP site	1-4, 8	2,3,4,6	AN
32e	The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study	None	1-8	Vmaj
32f	The scale for a biological or immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	1, 3, 4. 5, 6, 8	2, 3, 4, 5	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 three production-scale batches has been successfully undertaken in accordance with the current validation protocol.
5. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6. The change does not require supporting in vivo data.
7. The bio-batch size was at least 100 000 units in the case of solid oral dosage forms.
8. Formulation, controls on starting materials, manufacturing process, in-process controls, specifications and packaging materials remain the same at both sites.

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 bio-batch 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 three batches of the proposed batch size or validation protocol (scheme).
3. (P.5.1) Copies of release and shelf-life specifications.

   4. (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two 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 guidelines on bioequivalence.
8. (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 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing. For biologicals/immunologicals: a declaration that an assessment of comparability is not required.

33 Change in the manufacturing process of the FPP

33 Description of change		Conditions to be fulfilled	Documentation required	Reporting type
33a	Change in the manufacturing process of the FPP	1–9	1–4, 6–7	AN
33b		1–3, 5–9	1–7	Vmin
33c	The product is a biological/immunological medicinal product and the change requires an assessment of comparability	None	1-7	Vmaj
33d	Introduction or increase in the overage that is used for the active substance	1-5, 7-9	1-7	Vmaj

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 bio-batch.
3. The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet 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.
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 guidelines on bioequivalence.
2. (P.2) Discussion on the development of the manufacturing process; where applicable:
   i. 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 bio-batch results; data on the next two production batches should be available on request or reported if outside specification);

ii. 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 bio-batch results; data on the next two production batches should be submitted or be available on request);

iii. 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 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme.
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.

34 Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:

34. Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:		Conditions to be fulfilled	Documentation required	Reporting type
34a	tightening of in-process limits	1–2, 5	1	AN
34b	deletion of a test	2, 4	1, 6	AN
34c	addition of new tests and limits	2–3	1–6	AN
34d	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

35 Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin.

Description of change: Change in source of an excipient or reagent with TSE risk		Conditions to be fulfilled	Documentation required	Reporting type
35a.	Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin.	1	1	AN
35b.	For excipients or reagents used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product	None	1, 2	Vmaj

Conditions to be fulfilled:

1. No change in the excipient and FPP release and shelf-life specifications.

Documentation required:

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Study of equivalence of the materials and the impact on production of the final material and impact on behaviour (e.g. dissolution characteristics) of the finished product.

36 Change in the specifications or analytical procedures for an excipient involving:

36 . Change in the specifications or analytical procedures for an excipient involving:		Conditions to be fulfilled	Documentation required	Reporting type
36a	deletion of a non-significant in-house parameter	2	1–3	AN
36b	addition of a new test parameter or analytical procedure	2–3	1–2	AN
36c	tightening of specification limits	1–2, 4	1–2	AN
36d	change or replacement of an analytical procedure	2–3	1–2	Vmin
36e	Deletion of a test for heavy metals	5, 6	4	AN
36f	Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue	3	1,2, 5-8	Vmaj
36g	Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent	None	1-8	Vmaj

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.
5. Information about the elemental impurities in the excipient(s) should be available to the FPP manufacturer.
6. The FPP manufacturer should conduct associated risk assessment on elemental impurities which should be available in case requested by assessors or for verification by the MCAZ inspection team.

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.
4. The revised specifications of the excipient (with version history) should be submitted with the notification
5. Details of any new analytical method and validation data, where relevant.
6. Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters.
7. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. 8. Justification for not submitting a new bioequivalence study according to the relevant (Human, Veterinary) Guideline on Bioavailability, if appropriate.

37. Change in specifications of an excipient to comply with an officially recognized pharmacopoeia

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
37	**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).
2.

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
38a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard	1–3	1–5	AN
38b	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 38a or 38d 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.

39 Change in the specifications of the FPP involving test parameters and acceptance criteria:

39. Change in the specifications of the FPP involving test parameters and acceptance criteria:		Conditions to be fulfilled	Documentation required	Reporting type
39a	deletion of a test parameter	5	1, 6	AN
39b	addition of a test parameter	2–4, 7	1–6	AN
39c	tightening of an acceptance criterion	1–2	1, 6	AN
39d	relaxation of an acceptance criterion	2, 4, 6–7	1, 5–6	IN
39e	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, 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.

40. Change in the analytical procedures for the FPP

40 . Change in the analytical procedures for the FPP involving:		Conditions to be fulfilled	Documentation required	Reporting type
40a	deletion of an analytical procedure	5	1, 6	AN
40b	addition of an analytical procedure	3–4, 6–7	1–5	AN
40c. 1	modification or replacement of an analytical procedure	1–4, 6–7	1–5	AN
40c. 2		2–4, 6–7	1–5	Vmin
40d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph	None	1–5	AN
40e	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
40f	Substantial change to, or replacement of, a biological or immunological or immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol			Vmaj

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.

1.2 P.7 Container-closure system

41 Replacement or addition of a primary packaging type:

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
41a.1	Replacement or addition of a primary packaging type	1	1–2, 4–7	Vmin
41a.2		None	1–7	Vmaj
41a.3	Sterile medicinal products and biological/immunological medicinal products			Vmaj
41c	Change in qualitative and quantitative composition of immediate packaging of Sterile medicinal products and. biological/immunological medicinal products Change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life			Vmaj
41d	The qualitative and quantitative composition of immediate packaging			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.
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 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photo-stability studies.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation 5.
7. Copy of current MCAZ registration certificate.

4.2 Change in the package size:

42.Change in the package size involving:		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
42a	change in the number of units (e.g. tablets, ampoules, etc.) in a package	1–2	1–3	IN
42b.1	change in the fill weight or fill	1–3	1–2	IN
42b.2	volume of non-parenteral multi-dose products	1–2	1–2	Vmin
42c	Change in the fill weight/fill volume of sterile multi-dose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	1–3	1–3	Vmaj

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 WHO guidelines for products where stability parameters could be affected.
3. Current MCAZ registration certificate.

43 Change in the shape or dimensions of the container or closure

43. Change in the shape or dimensions of the container or closure for:		Conditions to be fulfilled	Documentation required	Reporting type
43a	non-sterile FPPs	1–2	1–3	AN
43b	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.
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 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photo-stability 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.
5. Current MCAZ registration certificate.

44 Change in qualitative and/or quantitative composition of the immediate packaging material

44. Change in qualitative and/or quantitative composition of the immediate packaging material for:		Conditions to be fulfilled	Documentation required	Reporting type
44a	solid FPPs	1–3	1–3	IN
44b	semisolid and liquid FPPs	1–3	1–3	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 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photo stability studies.

45 Change in the specifications of the immediate packaging:

45. Change in the specifications of the immediate packaging involving:		Conditions to be fulfilled	Documentation required	Reporting type
45a	tightening of specification limits	1–2	1	AN
45b	addition of a test parameter	2–3	1–2	AN
45c	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.

46. Change to an analytical procedure on the immediate packaging

46. Change to an analytical procedure on the immediate packaging involving:		Conditions to be fulfilled	Documentation required	Report -ing type
46a	minor change to an analytical procedure	1–3	1	AN
46b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
46c	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.

47 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).

Description of change		Conditions to be fulfilled	Documentation required	Report -ing type
47.	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.

48 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:

48. 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:		Conditions to be fulfilled	Documentation required	Reporting type
48a	addition or replacement	1, 2	1–2	IN
48b	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

49 Change in the shelf-life of the FPP (as packaged for sale):

49. Change in the shelf-life of the FPP (as packaged for sale) involving:		Conditions to be fulfilled	Documentation required	Reporting type
49a	reduction	3	1–5	IN
49b	extension	1–2	1–5	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. Copy of current medicine registration certificate.
5. Revised product information.

50. Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):

50. Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):		Conditions to be fulfilled	Documentation required	Reporting type
50a	reduction	1	1, 3	IN
50b	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. Copy of current medicine registration certificate

51. 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

Description of change: 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		Conditions to be fulfilled	Documentation required	Reporting type
52a.	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
52b.	Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	None	1–3	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.

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. Copy of current medicine registration certificate

6.0 KEY RELEVANT DOCUMENTS

1. World Health Organisation (WHO) guidelines on variation to a prequalified product: TRS 981 Annex 3 https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3TRS-981.pdf?ua=1
2. European Union (EU) Guideline on dossier requirements for type IA and type IB notifications http://www.ikev.org/docs/eu/GdVarTypIAB_rev0_200307.pdf
3. Food and Drug Administration (FDA) Guidance for Industry: Changes to an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA)", https://www.fda.gov/media/115733/download
4. Guidance for industry: Scale-up and Post-Approval Changes (SUPAC) guidelines. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-ir-immediate-release-solid-oral-dosage-forms-scale-and-post-approval-changes-chemistry

7.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	New document
N/A	N/A	

APPENDICES

APPENDIX I: 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.

APPENDIX II: Examples of Variations That Would Make A New Application Necessary

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. Replacement of the strain(s) in a seasonal, pre- pandemic or a pandemic vaccine against human influenza

APPENDIX III: Examples of changes that should be submitted as major variations:

(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)

1. Addition of new API source with a new APIMF.

2. Qualitative or quantitative changes in composition of the product that may have a significant effect on the quality, safety, or efficacy of the product (required to be supported by a bioequivalence study).

3. Addition of a new manufacturing site and/or new production block which has not been satisfactorily inspected by WHO or by an SRA.

4. Major change in the manufacturing process of product that requires a new bioequivalence study, e.g. from dry to wet granulation, from one type of drying process to another for products containing insoluble APIs.

5. Change in manufacturing process that may affect the sterility assurance of a sterile product (e.g. change from aseptic processing to terminal sterilization or vice versa), including changes in the sterilization method for packaging materials (e.g. gas, dry heat, irradiation).

6. Change in the limit of an impurity exceeding the ICH qualification threshold which requires supportive toxicological data.

7. Change in the qualitative/quantitative composition of primary packaging of a sterile product

Examples of changes which are not described in the Variation guideline and can be classified as minor change or notification.

(The category and required conditions, if applicable, are given for each specified change. 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)

1. Change in the manufacturing process of the FPP - Change in the holding time of an intermediate (Vmin) **Conditions:** Supportive hold time study data are available.

2. Change in in-process limits (relaxation) for immediate release products based on trend data for a minimum of 10 consecutive commercial batches, e.g. hardness, blend fines, bulk density (IN) **Conditions:**

   i. No change in the manufacturing process and specifications of the final product (except hardness, if applicable); ii. Similarity of dissolution profile to the bio-batch dissolution profile is demonstrated under routine dissolution condition (in the case of change in hardness)

3. Change in FPP specification - introduction of skip testing of microbial limit for non-sterile dosage forms (IN) **Conditions:** Results for at least 5 commercial batches showing compliance with the acceptance criteria. At least one batch should be fully tested at regular intervals (one batch for every 10 batches or one batch in a year, whichever is sooner). Full testing must be reinstated as soon as any batch failure is observed or conditions under which skip testing was approved are no longer met.

4. Elimination or reduction of an overage from the batch formula which was previously used to compensate for presumed manufacturing losses (IN) **Conditions:** N/A

5. Change in location of manufacturing (including terminal sterilization of finished product) within the accepted facility or site with no changes to currently accepted formulation, batch size(s), manufacturing process, equipment, in-process controls, finished product specifications, and packaging materials. The Quality systems, standard operating procedures, and manufacturing batch records will remain the same except for administrative information (AN)
   Conditions: The accepted facility or site, including the proposed location, has a satisfactory GMP status confirmed by WHO or by an SRA. Please note that such changes should follow proper change control procedures which should include but not be limited to risk assessment, qualification of new facility, equipment and process validation.

APPENDIX IV: Examples of changes that do not need to be filed as variation applications but should be implemented as per GMP change control

1. Reduced testing frequency of API, excipients, packaging material etc. by the finished product manufacturer on receipt of batches, whether the finished product manufacturer performs all of the tests listed in the approved specifications or accepts some of the results (except Identification) based on the certificate of analysis provided by the suppliers. The specifications should remain unchanged (a complete specification must be maintained for full periodic retesting). The reduced testing scheme should be documented and will be subject to review during a GMP inspection. Normally periodic or skip testing should only be implemented for the testing of regular commercial batches.
2. Reduced testing frequency of in-process controls of intermediates (e.g. final blend, core tablets) based on trend data of a sufficient number of commercial batches (e.g. more than 10 batches). The specifications of intermediates should remain unchanged. The reduced testing scheme should be documented and will be subject to review during a GMP inspection. The manufacturer needs to perform continued process verification to demonstrate that process is well controlled. Full testing must be reinstated as soon as any batch failure is observed or if there is a change in the validated manufacturing process which might have a possible impact on the quality of product.
3. Changes to the dossiers including spelling mistakes, editorial revisions made to documents such as Validation protocol and/or Reports, Analytical Procedures, SOPs, Batch manufacturing records, for added clarity that have no impact on the safety, efficacy and quality of the product.
4. Change in the in-process controls performed at non-critical manufacturing steps (e.g. a process/step that has no impact upon purity and impurity profile or requires no specific facility considerations, such as, buffer and media preparation, storage of intermediates, and packaging)
5. Replacement of equipment with that of the same design and operating principle, when there is no change in the approved process methodology or in-process control limits. An equivalency study is recommended. However, for terminal sterilization of product, change from a qualified sterilization chamber to another, the new chamber and load configurations are required to be validated to operate within the previously validated parameters. This will be verified during a GMP inspection.
6. Addition of a new GMP compliant storage warehouse for raw materials, and drug substance, packaging materials.
7. Change in supplier of excipients without a risk of TSE contamination and without change in the technical grade and specification.
8. Change in dimensions of secondary packaging.
9. Change in tertiary packaging components (including tertiary pack size) of drug substance or drug product that do not affect stability.
10. Change in the color, design of label art work without change in the contents

APPENDIX V: WEB-LINKS

1. **Guideline on dossier requirements for type IA and IB notifications July 2003"** *http://pharmacos. eudra.org/F2/eudralex/vol-2/C/GdVarTypIAB_rev0_20030 7.pdf*
2. ***Pharmaceutical Quality Information Form (MC8 FORM) http:/www.mcaz.co.zw/MC8.pdf***
3. ***Guideline on Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis [GuideGeneric]***
4. *http://mednet3.who. int/prequal/documents/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAn nexes.pdf*
5. **WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-fourth report, 1996: 114-154 (WHO Technical Report Series, No.863)" and Good Clinical Practices** *http://whqlibdoc.who. int/trs/WHO_TRS_863_(p99-p194).pdf*
6. **Note for Guidance on Validation of Analytical Procedures: Methodology**
7. **(CPMP/ICH/281/95)** *http://www. emea.eu. int/pdfs/human/ich/028195en.pdf*
8. **Note for Guidance on Validation of Analytical Methods: Definitions and Terminology**
9. **(CPMP/ICH/381/95)**
10. *http://www. emea.eu. int/pdfs/human/ich/038195en.pdf*
11. **Note for Guidance on Quality of Biotechnological Products: Viral safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin**
12. **(CPMP/ICH/295/95)**
13. *http://www. emea.eu. int/pdfs/human/ich/029595en.pdf*
14. **Note for Guidance on Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products**
15. **(CPMP/ICH/139/95)**
16. *http://www. emea.eu. int/pdfs/human/ich/013995en.pdf*
17. **Note for Guidance on Quality of Biotechnological Products: Stability Testing of**
18. **Biotechnological/Biological Products (CPMP/ICH/138/95)**

    http://www. emea.eu. int/pdfs/human/ich/013895en.pdf

19. **Note for Guidance on Quality of Biotechnicological Products: Derivation and Characterization of Cell Substrates used for Production of Biotechnological/Biological Products**
20. **(CPMP/ICH/294/95)**
21. *http://www. emea.eu. int/pdfs/human/ich/029495en.pdf*
22. **Note for Guidance on Biotechnological/Biological Products Subject to variations in their Manufacturing Process (CPMP/ICH/5721/03)***http://www. emea.eu. int/pdfs/human/ich/572103en.pdf*
23. **Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for**
24. **Biotechnological/Biological Products (CPMP/ICH/365/96)**

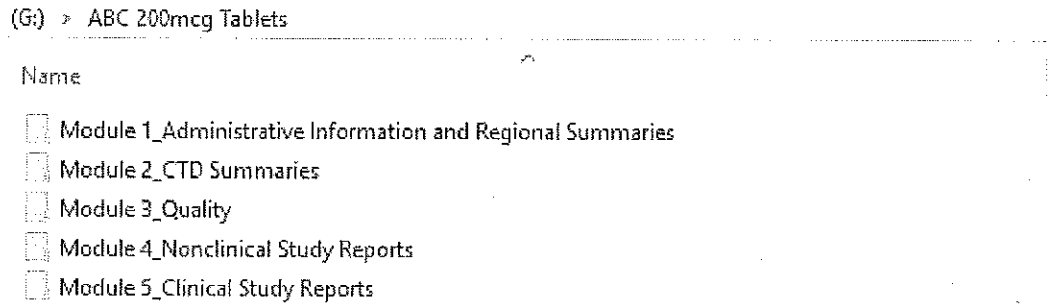
    http://www. emea.eu. int/pdfs/human/ich/036596en.pdf

25. **WHO-Guideline on Transmissible Spongiform Encephalopathies in relation to Biological and**
26. **Pharmaceutical Products**
27. *http://www.who. int/entity/bloodproducts/publications/en/WHO_TSE_2003.pdf*
28. **Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform**

29. **Encephalopathy Agents via Human and Veterinary Medicinal Products** (EM EA /410/01 rev 2)
30. *http://www. emea.eu. int/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf*
31. **Good manufacturing practices for Pharmaceutical Products: Main principle. Annex 4, WHO Technical Report Series 908, 2003** *http://whqlibdoc.who. int/trs/ WHO_TRS_908.pdf#page= 46*
32. **Note or Guidance on Stability Testing of New Drug Substances and Products (ICH Q1A (R2),**
33. **CPMP/ICH/2736/99)**
34. *http://www. emea.eu. int/pdfs/human/ich/23699en.pdf*

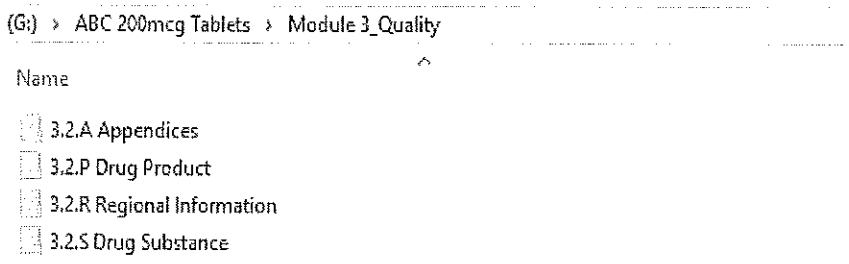
APPENDIX VI: The format for saving documents

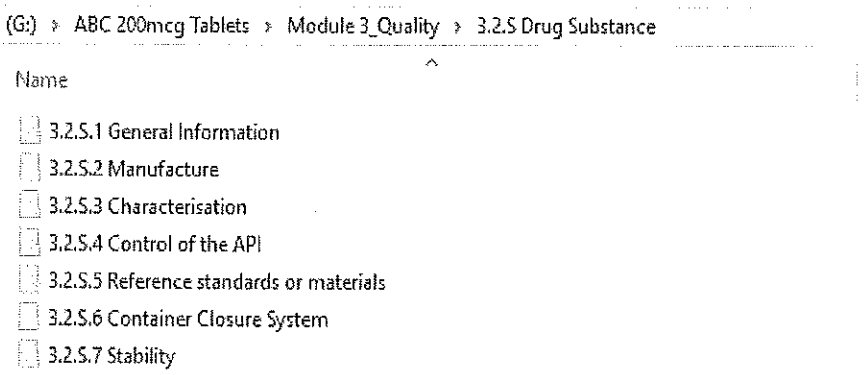
The format for saving documents in the USB flash drives or CDs shall be as follows;



Module folders shall be further granulated according to the applicable sections e.g.

Module 3:





(G:) › ABC 200mcg Tablets › Module 3_Quality › 3.2.P Drug Product

Name

- 3.2.P.1 Description and Composition
- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3 Manufacture
- 3.2.P.4 Control of Excipients
- 3.2.P.5 Control of Drug Product
- 3.2.P.6 Reference Standard
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability

(G:) › ABC 200mcg Tablets › Module 3_Quality › 3.2.R Regional Information

Name

- Blank Master Documents
- Executed Master Documents