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Guideline for Variations

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This guideline replaces sections 3 of the MCA 'Guideline for Registration of Medicines' (MCA-GL-102), version 3, 15 April 2020 and MCA 'Guideline for Registration of Herbal Medicinal Products' (MCA-GL-106), version 3, 15 April 2020.

Comments should be provided by using the template (MCA-F-021/03) for Submission of Comments and sent to info@mca.gm.

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Acknowledgements

We duly thank the World Health Organization (WHO) and European Commission publishing their guidelines that contributed in several aspects relevantly to the development of this guideline.

Executive summary

The variation guideline helps the reader to classify changes that may occur related to all the major sections of a dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

The change categories for the quality aspects are organised according to the structure of the common technical document (CTD). The specific CTD sections associated with individual data requirements have been identified in order to assist in the filing of documentation (reproduced with corresponding numbers in bold). Changes are classified as major (Vmaj) only in those instances where the level of risk is considered to be high and it is deemed necessary to provide the Medicines Control Agency (MCA) with adequate time for an assessment of the supporting documentation. Particular circumstances are identified where lower reporting requirements (annual notification (AN), immediate notification (IN) or minor variation (Vmin)) are possible. In all cases where notification to MCA or acceptance by MCA is required to implementation,

assessment timelines will be published in order to provide predictable and reasonable timeframes.

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

This guideline is based on the has been developed by the Joint Technical Working Group for Guidelines in Marketing Authorization (TWG-MAG). The TWG-MAG consists of two representatives each of the national medicines regulatory authorities (NMRA) of Liberia (LMHRA, Liberia Medicines and Health Products Regulatory Authority), Sierra Leone (PBSL, Pharmacy Board of Sierra Leone), The Gambia (MCA, Medicines Control Agency), and Ghana (FDA, Food and Drugs Authority) and is facilitated by the GHPP PharmTrain2 Project team of the Federal Institute for Drugs and Medical Devices (BfArM, Germany). Version 1 of the Guideline on Variations for the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia was finalised on 03 July 2024 for preparation of the NMRA's own guidelines.

This document should be read in conjunction with the MCA Guideline for Marketing Authorisation (Registration) of Medicines (MCA-GL-102) and other applicable guidance.

1 Introduction (background)

1.1. This guideline is technically and structurally based on the European Union Institutions and Bodies Commission's Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. It is intended to provide supportive information on how to present an application to implement a change to a product.

1.2. A Marketing Authorisation Holder (MAH) is responsible for the safety, efficacy and quality of a product throughout its life-cycle. Therefore, the MAH is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the authorised product. Such changes, whether administrative or substantive, are referred to as variations and may be subject to acceptance by the Medicines Control Agency (MCA) prior to implementation.

1.3. Technical requirements for the different types of variations are set out in this guideline in order to facilitate the submission of appropriate documentation by MAHs and their assessment by MCA and to ensure that variations to the medicine (medicinal product) do not result in health concerns.

Objective

1.4. This guideline is intended to assist MAHs with the classification of changes made to the quality, safety and efficacy parts of a finished pharmaceutical product (FPP) and also to provide guidance on the technical and other general data requirements to support changes to the quality attributes of the active pharmaceutical ingredient (API) or FPP as well as the safety and efficacy of the FPP.

1.5. The classifications of changes and the conditions and requirements to support changes are summarised in the Annexes 1-4.

2 Legal basis

2.1. Part IV of the Medicines and Related Products Act, 2014 stipulates the legal requirements for registration (marketing authorisation) of medicines.

2.2. This guideline has to be read in conjunction with section 32 (3) of the Act which states that 'a person responsible for the registration of a medicine or related product who fails to inform the Agency of a change in the information submitted for its registration commits an offence'.

2.3. This document is coherent with the national and regional frameworks and policies.

2.4. The usage of the variation guideline by MCA is supported/embedded in section 64 of the Medicines and Related Products Act, 2014.

3 Scope

3.1. This guideline applies to MAHs intending to make changes to the quality, safety and/or efficacy sections of product dossiers for an active pharmaceutical ingredient (API) or a finished pharmaceutical product (FPP) for human and animal use.

3.2. This document is applicable only to APIs and excipients manufactured by chemical synthesis or semi-synthetic processes and FPPs containing such APIs and excipients. APIs produced by fermentation and APIs of biological, biotechnological or herbal origin are treated as special cases.

3.3. The notification requirements for API-related changes differ depending on the manner in which information on the API was submitted in the FPP application for marketing authorisation, namely, use of a WHO-prequalified API, use of a European Pharmacopoeia Certificate of Suitability (CEP), use of the API master file (APIMF) procedure, or as provided in full within the dossier.

3.4. The conditions and documentation stipulated in this guideline for API- related variations focus primarily on those FPPs that relied upon the provision of full API information within the FPP dossier. In general, FPPs that rely upon the APIMF procedure have reduced reporting requirements because the API manufacturers themselves have notified the relevant API-related change directly to MCA. Similarly, when an FPP relies upon a CEP or a prequalified API, FPP MAHs are required to notify MCA only when the associated CEP or Confirmation of API Prequalification document has been revised.

3.5. Guidance for API manufacturers on the technical and procedural requirements for changes to prequalified APIs and to APIs supported by the APIMF procedure is available on the WHO-Prequalification programme's web site. Regardless of whether the API-related change is notified primarily by the API manufacturer (API prequalification (API-PQ) procedure, APIMF procedure or CEP), or the FPP manufacturer (full API information in dossier) the technical requirements are in principle the same as those stipulated in this guideline.

3.6. For herbal medicinal products and biological substances and products the respective requirements stipulated in the European Commission guidelines apply.

4 Guidance for implementation

4.1 Reporting types

4.1.1. The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of quality, efficacy and/or safety related changes. Specific examples of changes are provided in this guideline.

4.1.2. However, it should be noted that a change not covered by this guideline, should be considered as a major change by default. Whenever the MAH is unclear about the classification of a particular change, MCA should be contacted. It remains the responsibility of the MAH to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and/or efficacy of the product.

4.1.3. Individual changes normally require the submission of separate variations.

4.1.4. Grouping of variations is acceptable only under the following circumstances:

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

b. when the same change affects multiple FPPs, e.g. addition of a new API manufacturing site for multiple FPPs;

c. when all the changes are annual notifications.

4.1.5. 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.

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

Notifications

4.1.7. Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and/or quality of the FPP. Such notifications do not require prior acceptance, but must be notified to MCA immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change.

4.1.8. It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the MAH must cease to apply the already implemented variation.

These reporting types are comparable to the EU procedure Type IA.

Annual notification (AN)

4.1.9. MAHs must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarised as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of

inspection. ANs do not require prior examination by MCA and should be submitted to MCA at the latest within 12 months from the date of the implementation of the changes. For convenience MAHs may group several AN changes as a single submission.

Immediate notification (IN)

4.1.10. MAHs must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by MCA within 30 calendar days of the date of acknowledgement of receipt of the application.

Minor variation (Vmin)

4.1.11. Minor variations are changes that may have minor effects on the overall safety, efficacy and/or quality of the FPP. MAHs must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

4.1.12. Such variations can be implemented if no objection letter has been issued within 30 calendar days. Should questions arise during this period, the MCA will request for clarification which should be submitted by the MAH within 30 calendar days. The change can only be implemented on receipt of a letter of acceptance from MCA. If the MAH does not amend the application within 30 calendar days as requested, the variation will be rejected.

This reporting type is comparable to the EU procedure Type IB.

Major variation (Vmaj)

4.1.13. Major variations are changes that could have major effects on the overall safety, efficacy and/or quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by MCA is required before the changes can be implemented. A letter of acceptance will be issued for all major variations if and when the variation is considered acceptable.

This reporting type is comparable to the EU procedure Type II.

New applications and extension applications

4.1.14. 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 as stipulated in the MCA *Guideline for Marketing Authorisation (Registration) of Medicines*. Examples of such changes are listed in Appendix 1.

Labelling information

4.1.15. For any change to labelling information (Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), labels not covered by the variation categories described in this document, MCA must be notified and submission of the revised labelling information is expected as per the MCA *Guideline for Labelling of Medicines for Human Use*.

4.2 Conditions to be fulfilled

4.2.1. 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.

4.2.2. In some circumstances Vmaj categories have been specifically stated for a given variation. This has been done to indicate to MAHs 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 MAH to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy and/or quality of the FPP.

5 Application for Variations

5.1 General Requirements

5.1.1. The Agency charges non-refundable application fees for variations as specified in the MCA Fee Schedule published in the *Gazette*. Evidence of payment as bank transfer should be submitted alongside the application. Note that any application not accompanied by the requisite proof of completed payment will not be given consideration.

5.1.2. An application for a variation of a medicine shall be made in writing via a completed Application for Variation form (MCA-F-114/01) available from the MCA website www.mca.gm, dated and signed by the applicant and accompanied by a cover letter.

5.1.3. In case of parallel submissions to other regulatory authorities, other forms (e.g. EU Application form) may be accepted on agreement with the MCA.

5.1.4. The duly signed cover letter shall be addressed to the Executive Director, Medicines Control Agency, Off Bertil Harding Highway, Kotu East, Kanifing Municipality, P.O. BOX 3162, Serekunda, The Gambia.

5.1.5. The documentation should be provided electronically as an USB flash drive. The cover letter and application form should be submitted both as a Word document and a scanned signed PDF, in addition to the printed version.

5.1.6. Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification.

5.1.7. It is also important to note that MCA may request information or material, or define conditions not specifically described in this guideline, in order to adequately assess the safety, efficacy and quality of an FPP.

5.2 Documentation required

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

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

a. Cover letter;

b. Application for Variation form (MCA-F-114/01).

c. An updated quality overall summary (QOS), if applicable

d. Replacement of the documentation in the relevant sections of the dossier as per CTD format;

e. Copies of SmPC, PIL and/or labels, if relevant. When a variation leads to a revision of the SmPC, PIL or labelling, the updated product information should be submitted as part of the application.

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

5.3 Decision on Major Variation

5.3.1. The Agency will acknowledge receipt of a valid application of a major variation and start the procedure.

5.3.2. As a general rule, a 60-day evaluation timetable will apply. This period may be reduced, particularly for safety issues, or may be extended to 90 days for variations concerning a change to or addition of therapeutic indications. The MCA will inform the MAH of the adopted timetable.

5.3.3. If additional data are requested, the MAH should provide the data within one (1) month, unless agreed otherwise with the Agency.

5.3.4. The evaluation procedure may take further 30 calendar days up to 60 calendar days depending on the complexity and amount of data requested for.

5.3.5. The accepted major variation(s) can be implemented after the holder has been informed about the acceptance of the variation(s). Variations related to safety issues must be implemented within a time-frame agreed between the Agency and the MAH.

Definitions

Interpretations and abbreviations contained in the MCA Glossary can be found on the MCA Website: **www.mca.gm.**

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

The interpretation of terms provided in the Act and Regulations apply, unless further defined in this guideline.

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

Active pharmaceutical ingredient (API) starting material
A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from

one or more suppliers under contract or commercial agreement, or produced in-house.

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Batch
A defined quantity of a starting material, packaging material or product manufactured in a single manufacturing cycle and which has homogeneous properties

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

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

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

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

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

Marketing Authorisation Holder (MAH)
A company or other legal entity that has the authorisation by a regulatory authority to market a medicine or related product and who is responsible for its quality, efficacy and safety and for compliance with conditions of authorisation (registration)

Officially recognised pharmacopoeia (or compendium)
Officially recognised pharmacopoeias recognised by the MCA

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

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

Reference Institution (RI)/ Reference Regulatory Authority
An authority or institution which assessment and its outcome serve as basis for regulatory reliance. As per WHO guidance (https://www.who.int/news/item/29-04-

2021-who-publishes-new-guidance-to-promote-strong-efficient-and-sustainable-regulatory-systems) this encompasses different levels of reliance.
In this document this term relates to a list of authorities/institutions determined by the NMRA including the transitional WHO listed authorities referred to as group B+C (https://www.who.int/publications/m/item/list-of-transitional-wlas) and WHO Prequalification Programme.

Supplier
A company or other legal entity providing pharmaceutical materials on request. Suppliers may be agents, brokers, distributors, manufacturers or traders. Where possible, suppliers should be authorised by a competent authority.

References

- WHO Guidelines on variations to a prequalified product, Annex 3, WHO Technical Report Series No. 981, 2013.
- European Commission. Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures. 2013 (2013/C 223/01)
- WHO - Quality Assurance of Medicines Terminology Database - List of Terms and related guideline, October 2023. https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cfc_10 (Accessed June 2024)
- Medicines and Related Products Act, 2014
- MCA Guideline for Marketing Authorisation (Registration) of Medicines (MCA-GL-102)
- MCA Guideline for Labelling of Medicines for Human Use (MCA-GL-101)
- MCA Guideline for the Investigation of Bioequivalence (MCA-GL-121)
- MCA Guideline for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (MCA-GL-123)

Annex

Annex 1: Administrative changes

Annex 2: Quality Changes, Active Pharmaceutical Ingredient

Annex 3: Quality Changes, Finished Pharmaceutical Product (FPP) or drug product

Annex 4: Safety and Efficacy Changes

Annex 5: Applcation for Variation (MCA-F-114/01)

Appendix 1: Examples of changes that make a new application or extension 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
Documentation in fulfilment of the requirements outlined in the MCA *Guideline for Marketing Authorisation (Registration) of Medicines*	

Appendix 2: Changes to excipients

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