

# MEDICINES CONTROL COUNCIL



## AMENDMENTS

This guideline has been prepared to serve as a recommendation to the holder of a certificate of registration wishing to submit applications for amendment of a registration dossier of a medicine. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified.

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**REGISTRAR OF MEDICINES**  
**MS M HELA**

TABLE OF CONTENTS		Page
1	<a href="#">Format</a> of responses to Council	3
2	<a href="#">Amendment</a> submissions: Format	3
3	<a href="#">Proprietary name</a>	4
4	<a href="#">HCR/FPRR</a> and/or Manufacturer, Packer, FPRC	4
4.17	HCR - FPRR only - name only	6
4.18	HCR - FPRR only - address only	6
5	<a href="#">Pharmaceutical</a> and analytical amendments	7
5.7.1	Type A - Amendments that do not require prior approval and that may be implemented without prior notification	8
5.7.2	Type B - Amendments that require notification only	9
5.7.3	Type C - Amendments that require prior approval	9
5.7.4	<a href="#">Type D</a> - Amendments that are considered new applications	9
5.8	<a href="#">Once-off</a> manufacturing changes / amendments	9
6	Format of the <a href="#">amendment schedule</a> / covering letter	9
	<a href="#">Appendix A1</a> – Medicines Register Details	15
	<a href="#">Appendix A2</a> – Affidavit by Responsible Pharmacist	16
7	<b>Types of amendments</b>	<b>17</b>
7.1	<a href="#">Type A</a> – Prior notification not required	17
7.2	<a href="#">Type B</a> – Notification required	23
7.3	<a href="#">Type C</a> – Prior approval required	27
7.4	Type C – <a href="#">Inspectorate</a> : Prior approval required	36
8	<a href="#">List</a> of Acronyms	38
9	<a href="#">Legend</a> for stability requirements	39
10	<a href="#">Annual</a> viral strain changes for influenza vaccines	40
11	<a href="#">Revision</a> History	42

## AMENDMENTS

Amendments to the registration dossier are necessary to maintain the safety, quality and efficacy of a medicine and to ensure compliance with current technical requirements, to adhere to administrative aspects, to keep abreast of scientific progress, or to reflect new therapeutic indications / warnings or other safety matters.

It is therefore the objective of the MCC to process, as quickly as possible, amendment applications made by the

- holder of the certificate of registration (HCR) to registered medicines
- Applicant of old medicines
- proposed holder of the registration certificate (PHCR) / Applicant in response to committee recommendations.

This document has been prepared as a tool to address all matters concerning amendments to

- facilities, (including change in the HCR)
- pharmaceutical and analytical aspects of the medicine.

Comprehensive documentation to support the amendment application should be supplied and the conditions determined by Council, complied with.

For amendments to the clinical aspects of the package insert for human orthodox medicines MRF4 should be completed and should be submitted with a covering letter on the company letterhead.

### 1 FORMAT OF RESPONSES TO COUNCIL

- 1.1 Responses to letters from the Registrar of Medicines should be cross-referenced to the actual questions asked. A copy of the letter from the Registrar of Medicines being replied to should be included for easy reference.
- 1.2 Council resolutions/Committee recommendations should be addressed by stating the Council resolution/ Committee comments or recommendations followed by the relevant response. The format as per section 6 of this guideline should be used and the requirements of this guideline be complied with.

### 2 AMENDMENT SUBMISSIONS: FORMAT

- 2.1 **All** pre- and post-registration amendment submissions should be submitted with the following in addition to those reflected in section 7 of this guideline:
  - Amendment schedule / covering letter in accordance with section 6 of guideline; correct coding is important, as per General Information guideline section 13.
  - Administrative amendment fee, if relevant;
  - completed MRF1 PART 1A including 1Ac) Amendment history / CTD Module 1.2.1 and relevant front pages of the MRF1 PARTs/SUB-PARTs /CTD module 1.1 ToC
- 2.2 MRF1 PART 1Ac) Amendment history / CTD Module 1.2.1 f)
  - The MRF1 PART 1Ac) / CTD Module 1.2.1 f) Amendment history should reflect the particulars of the pharmaceutical and analytical amendments (if applicable) of all types.
  - The current amendment being applied for should not be included in this section as a submission with a response pending.
  - If any PARTs / Annexures / Modules or sub-Modules have not been approved, this should be indicated.
  - If the response to an amendment is pending, this should be indicated, rather than not reflecting this amendment at all.

**2 Amendment Submissions: Format continued**

- 2.3 An amendment application may not address more than one product unless
- the products constitute a range for which a single application for registration dossier was submitted at the time of application for registration
  - it is an application for change of only the name or address of the HCR, in which case details for a group of products may be submitted. However, each registration dossier should be updated in accordance with the change.
- 2.4 All applications for amendments should be properly bound on the left side. It is preferred that documents be punched (2-hole) and secured. The use of lever-arch files, metal file fasteners and any kind of paper clip is not recommended.  
Any single volume should not be thicker than 4 cm, including binder, also depending on the binder used. When submitting more than one volume of an application, they should be tied together.
- 2.5 All photocopies should be legible and the left margin of documents should be wide enough to allow for legibility after copying and binding. Shading, e.g. in tables, should be avoided.
- 2.6 The date of the amendment schedule/covering letter should be reflected in black on every page of the submission.
- 2.7 All pages should be paginated and the document indexed according to the existing MRF1 PARTs (e.g. page 3B.1 referring to PART 3B, first page) or tabbed in accordance with the CTD modules.
- 2.8 Dividers or tabs should be included where applicable to facilitate locating the different sections in the document.
- 2.9 The front pages of the amended MRF1 PARTs and the amended pages only of the PARTs should be submitted when amendments are made which involve a limited number of pages. The pages to which the amendments refer should be clearly indicated.  
The relevant ToC for CTD should be updated.
- 2.10 When extensive updating of the dossier is done, a completely updated dossier should be submitted and the amended PARTs / CTD Modules clearly indicated. The amended pages should reflect the date of the amendment schedule/letter and those not amended should reflect the relevant date of the previous submission/amendment. It is not acceptable to submit selected pages only when a full update is submitted.
- 2.11 All documents in a foreign language should be translated into English and certified or verified.
- 2.12 Amendments to applications for registration during evaluation prior to registration by Council are usually not permitted, unless recommended by the committees, or advised by or negotiated with Council.
- 2.13 Incomplete submissions or submissions which **do not comply** with the requirements as described or if not accompanied by the amendment schedule/covering letter in the format prescribed in section 6 of this guideline **will not** be evaluated. These should be **collected within 14 working days** of notification of the inadequacy, failing which such applications will be destroyed.

**3 PROPRIETARY NAME**

Changing of the proprietary name during the evaluation and registration phase will only be permitted if the Council has not accepted the name originally proposed by the HCR/applicant.

The policy on proprietary names is detailed in the General Information guideline.

The requirements in addition to those in 2.1 are summarised in section 7.4 of this guideline.

**4 HCR-FPRR and/or additional/change of MANUFACTURER, PACKER, FPRC**

- 4.1 Amendments to any of the above result in an update of the Medicine Register and the issue of an amended registration certificate for registered products.

The original medicine registration certificate should accompany amendments to registered products.

A copy of the medicine registration certificate will not be accepted as the original is to be replaced.

If the original certificate has already been submitted to Council, this should be indicated in the amendment schedule / covering letter (section 6 of this guideline).

- 4 HCR-FPRR and/or additional/change of MANUFACTURER, PACKER, FPRC – continued**  
(Original registration certificate already submitted with application dated ....., reference no. ....).
- 4.2 The processing of the application is not a mere formality; each application will be evaluated individually. The authorisation for change is dependent on various aspects including the proposed new HCR / manufacturer / packer / laboratory's infrastructure and its compliance with Good Manufacturing Practice (GMP) in terms of the guidelines as recommended by the SA Guide to GMP and the World Health Organisation.
- 4.3 In order to assess the suitability of the proposed HCR, manufacturer, packer or laboratory, an inspection by Council Inspectors may have to be performed prior to the authorisation of the change requested.  
An inspection by Council Inspectors may be required for manufacturers in countries outside the borders of South Africa other than those with which Council aligns itself.
- 4.4 An amendment will be considered final only once the HCR has been supplied with the new registration certificate or a letter of approval stating that the new registration certificate will follow for registered medicines, or a final letter of approval of the amendment in the case of an old medicine.
- 4.5 If the dossier has not been updated during the previous 5 years, or an application for a type C change is lodged, a fully updated dossier in CTD format should accompany an application for transfer of the certificate of registration or change in manufacturer.
- 4.6 The HCR should be familiar with the requirements in the current Guide to GMP. Attention is particularly drawn to the following:  
*"A Contract Giver should assure himself that the Contract Acceptor has adequate premises, equipment, and staff with sufficient knowledge and experience, to carry out satisfactorily the work placed with him. In order to do this the Contract Giver should audit the Contractor Acceptor's premises, equipment and systems both before the contract is given and at regular intervals thereafter. Audit reports should be issued and kept on record. A contract Giver may only use the contract manufacturer or packer as approved in the registration dossier."*  
The HCR is advised to discuss the latest MCC inspection report of the proposed Contract Giver with the Contract Acceptor prior to entering into an agreement with the Contract Giver.  
In the case of contract packaging by a third party, the relevant cGMP should be adhered to.
- 4.7 As the processing of these amendments results in the updating of the database/Medicine Register and the issue of amended registration certificates, the HCR should ensure that details with regard to approved facilities are current.
- 4.8 Should there be a discrepancy between the administrative data submitted with the amendment request and the relevant PARTs / MBR1 Annexures, the data in the Registration Dossier on file will be reflected on the registration certificate.
- 4.9 It is the responsibility of the HCR to
- ensure that details with regard to the facilities / laboratories applied for are correctly reflected in MRF1 Part 1A / CTD Modules 1.2.1, 1.7.1, 3.2.S.2, 3.2.P.3.1
  - check registration certificates for correctness and communicate discrepancies to Council within 30 days of receipt thereof.
- 4.10 If the HCR is of the opinion that the information reflected on the registration certificate is incorrect, the correct approved **information together with the letter(s) of approval by the Council** should be provided. An amended registration certificate will be issued free of charge should the error have occurred at this office.
- 4.11 Once a change in HCR-FPRR/manufacturer/packer/FPRC has been approved, the updated pages to the PARTs / Modules are placed on file. Subsequent updates of the dossier should *clearly* and unambiguously reflect these as approved. (It is often not clear whether the information submitted pertains to the same as the previous or a new amendment).

**4 HCR-FPRR, and/or additional/change of manufacturer, packer, FPRC continued**

- 4.12 The letter of cession from the current HCR should confirm that the complete registration dossier (MRF1/ MBR1 / CTD) and product history have been transferred to the proposed HCR. This letter must be signed by the Responsible Pharmacist as defined in [Section 22C(1)(b) of Act 101 of 1965].
- 4.13 The FPRR changes when a registration certificate is transferred. The MRF1 PART 1A / CTD Modules 1.2.1, 1.5.2 and 1.7 should be appropriately updated to reflect this change. *However, if the dossier has not been updated during the previous 5-year period, a fully updated dossier should accompany the application for transfer of the registration certificate.*
- 4.14 The Registration dossier should be fully updated to the current statutory format and current scientific standards within 12 months after transfer of the registration certificate. In the case of mergers the HCR should adhere to the programme of updating of dossiers as approved by the Council. The date by which the dossier will be fully updated should be clearly reflected in the amendment schedule/covering letter.  
*However, if the dossier has not been updated during the previous 5-year period, a fully updated dossier should accompany the application for transfer of the registration certificate.*
- 4.15 The proposed HCR should ensure that the registration dossier being acquired has been fully updated recently (at least during the last 5 years) and that the full product history is provided by the current HCR. An HCR should be in possession of all the information relevant to the product.
- 4.16 The current HCR remains legally responsible and liable until transfer of the registration certificate has been confirmed in writing.

The requirements in addition to those in 2.1 are summarised in section 7.

**4.17 HCR – FPRR ONLY – NAME ONLY**

In this case application to change the name of the HCR may be submitted for a whole range of products. Old medicines and registered products should be dealt with under separate cover.

The requirements in addition to those in 2.1 are summarised in section 7 of this guideline. The relevant documentation has to be submitted for each product.

**4.18 HCR – FPRR ONLY – ADDRESS ONLY**

- 4.18.1 The SMF has to be updated.
- 4.18.2 The front page of the Registration dossier / PART 1A / CTD Modules 1.2.1 and 1.7 have to be updated.
- 4.18.3 The letter addressed to the Registrar (section 6 of this guideline) has to reflect the code VAA (for the Medicine Register) and include Appendix 1 (CTD Module 1.5.2.1) reflecting the details of the change of the HCR's address.
- 4.18.4 The requirements for change of HCR will apply as this will result in a change in the registration certificate.  
The requirements in addition to those in 2.1 are summarised in section 7 of this guideline. The relevant documentation has to be submitted for each product.

## 5 PHARMACEUTICAL AND ANALYTICAL AMENDMENTS

This information is for the amendment of a registration dossier already lodged with the Medicines Control Council, pertaining to PART 3 (PART 3A to PART 3I) / MBR1 Annexures 2 to 13 / CTD Module 3 of the application for registration dossier.

It is practically difficult, if not impossible, to review all pharmaceutical amendments to every pharmaceutical product registered by Council. This document is also aimed at trying not to prejudice the HCR in terms of medicine regulation.

It is the HCRs responsibility to ensure that

- the requirements of this document and other policies/guidelines are complied with;
- any amendment made does not in any way negatively affect the quality, safety and efficacy of the medicine;
- the product stability is established; and
- appropriate validation and qualification procedures are instituted.

Should any doubt exist, prior written authorisation should be obtained.

Four different types of amendments are identified:

Type A - amendments that may be implemented without intervention of or prior notification to Council

Type B - amendments that require prior notification

Type C - amendments that require prior approval

Type D - amendments that should be considered new applications.

In all cases the HCR should record and report all types of amendment that have been implemented or applied for. Council Inspectors may audit such changes during inspections for whatever reason.

Implementation of amendments that require prior approval without due approval of the MCC would be contrary to the provision of this policy document.

Council retains the right to withdraw any concession granted to an HCR by virtue of the provisions of this guideline, should the HCR's manufacturing facility not comply with current Good Manufacturing Practice (cGMP) as determined by Council (SA GMP guideline) or should it subsequently be determined that the application for the amendment does not fully comply with the requirements of this guideline.

The requirements under sections 1 and 2 of this guideline are applicable and the process is valid only if the correct procedure is followed, the description of the type and category of amendment complied with, the conditions if any, are met, proof of efficacy and all the required documents are submitted. Data or a commitment to generate stability data should be provided where relevant.

- 5.1 All the differences between the current and the amended PARTs / Annexures / Modules (specifications, procedures, methods, data, etc *and* the page numbers that have changed), should be reflected in detail in the amendment list/table in the amendment schedule / covering letter (refer to section 6 of this guideline).

The current and proposed amended PARTs / Annexures / Modules should be compared carefully to identify any differences not specifically addressed by the originator/supplier of the document. This is particularly relevant for documents received from overseas.

General statements such as "specification change from in-house xyz to in-house xzz; specifications updated, routine update; updated final product control procedures; as is, old" are not acceptable. The individual items of each should be stated. The reasons for the changes should be clearly and succinctly stated. Again general statements such as "Council policy; routine update" are not acceptable.

**A column headed "Effect of amendment" is only applicable to PART 3B / Module 3.2.P.1 and should NOT be included for the whole table.**

Landscape format is recommended for this table.

- 5.2 ~~In the case of a general change in the manufacturer or specification of an active pharmaceutical ingredient (API), affecting more than one product (same dosage form), the updated PART 3A / Module 3.2.S of the product dossiers involved should be submitted only upon approval of the general change.~~

**5 Pharmaceutical and Analytical continued**

~~The additional supplier or change of specifications should be approved for one product first and then the PART 3A / Module 3.2.S of the various products involved updated. A copy of the letter of approval of the first product should be included in the subsequent updates.~~ [General changes in the manufacturer or specifications of an active pharmaceutical ingredient \(API\) affecting more than one product \(same dosage form\) will no longer be accepted. The specific change complying with all the requirements of the type and category has to be submitted for each product.](#)

- 5.3 In-house specifications and control procedures that are pharmacopoeial but presented in a standard in-house format should be identified as such in both the amendment schedule and the amended PARTs / Modules.
- 5.4 When a formulation amendment is applied for, the reason for the amendment and the effect of the amendment on the process and/or product specifications should be clearly stated. Confirmation should be given whether the specifications remain the same or change.
- 5.5 When extension of the shelf-life of a product is applied for, supporting stability data should be submitted in tabulated format, reflecting the specifications (titles and limits), and the proposed shelf-life according to the Stability guideline.
- 5.6 Only relevant data in support of the proposed changes/amendments should be submitted together with the reasons for submitting such data.
- 5.7 Compliance with the following general conditions is required whenever amendments are made:
- a) All amendments, including those not specifically listed in the table (section 7.1) must be justified and the effect of the amendment must be addressed, e.g. removal of IPI(s) – depending on the purpose of the IPI in the formulation these could be Type A, B or C. Ensure that the amendment is consistent with the definition of the type – see below.
  - b) Type A and/or B amendments may only be made to registered medicines or “Old Medicines”.
  - c) The intended date of implementation of Type B amendments should be indicated. This should take the actual date of delivery of the amendment to the Regulatory Authority into account.
  - d) Validation data (P&A and GMP Guidelines) should be available for inspection. If however, submission of the data is requested it should be supplied within 30 days of the request.
  - e) Compliance with the conditions relating to the specific amendment, [i.e. documentation, validation, stability, proof of efficacy (i.e. pharmaceutical and/or biological availability) and notification] summarised in section 7.
  - f) Type B and C amendments should be submitted in accordance with section 2.1 of this guideline and be clearly marked with the Type and category number of the applicable item in section 7 of this guideline. Any implemented Type A amendments (implemented or intended to be implemented) should be included (5.7.1). Type C amendments should also include any *implemented* Type B amendments relevant to the PARTs / Annexures / Modules being amended.
  - g) If Type B and C amendments are applied for simultaneously, either in the same PART / Modules or in different PARTs / Modules, the submission becomes a Type C amendment and the 30 day implementation date is not applicable.
  - h) Suitably authorised amended master documents should be prepared prior to the manufacture of such medicine.
  - i) A declaration should be made that
    - a) the amendments are in line with the relevant current guidelines and/or that a motivation for any deviation has been included and
    - b) no amendments other than those specified in the amendment schedule have been made.

**5.7.1 Type A Amendments that do not require prior approval and that may be implemented without prior notification** (section 7.1 of this guideline)

Type A amendments are such that there is unlikely to be an effect on the quality and performance of a dosage form. These changes should be recorded in the product review (Chapter 1 of the SA Guide to GMP) and be available for inspection.

**5.7.1 Type A continued**

At any point when an amendment application is submitted for a product, all Type A amendments pertaining to the product should also be included in the MRF1 PART 1Ac) / CTD Module 1.2.1 f) Amendment history and also be clearly addressed in the Amendment Schedule, and the latest amendments to any particular aspect should be submitted.

**5.7.2 Type B Amendments that require notification only** (section 7.2 of this guideline)

Type B amendments could have a significant impact on the quality and performance of a dosage form. Type B amendments should not be made with amendments that require prior approval.

Written notification of the type of amendment should be forwarded to this office **30 days prior** to intended **implementation**. (*Note: The covering letter becomes the notification – no separate fax should be sent.*)

The appropriately amended PARTs / Modules affected by the change should be submitted together with the relevant data/documentation. The submission should be clearly marked: "Type B amendment."

**5.7.3 Type C Amendments that require prior approval** (section 7.3 of this guideline)

Type C amendments are likely to have a significant impact on the quality and performance of a dosage form. The appropriately amended PARTs / Modules affected by the change should be submitted together with the relevant data/documentation. The submission should be clearly marked: "Type C amendment".

Written approval from the MCC should be obtained before the change may be implemented.

**5.7.4 Type D Amendments that are considered new applications**

- a) Change in the API to a different API
- b) Inclusion or removal of an API(s) from a multi-component product unless specifically required by Council
- c) Change in the quantity of one or more of the API(s), per dosage unit excluding overages and/or potency adjustments
- d) Change in the dosage form including, change from an immediate release product to modified-release dosage form or vice versa and change form liquid to powder for reconstitution, or *vice versa*
- e) A change in the route of administration.

**5.7.5** For amendments not covered by this document and/or if the specified conditions are not complied with, the normal data requirements apply and prior approval should be obtained.

**5.8 ONCE-OFF MANUFACTURING CHANGES / AMENDMENTS**

In the event of a once-off formulation or manufacturing procedure change the HCR should refer the application to **Council Inspectorate** as indicated under section 7.4 of this guideline.

**6 FORMAT OF THE AMENDMENT SCHEDULE / COVERING LETTER**

The following template for the covering letter should be followed for pre- or post-registration MRF1 / CTD amendments. Items not applicable to the submission may be omitted providing the omission is confirmed / identified.



<b>AMENDMENTS AFFECTING THE MEDICINE REGISTRATION CERTIFICATE</b>	
<b>PROPRIETARY NAME CHANGE – Application for name change</b>	
Amended MRF1 PART 1Aa) + b) / Module 1.2.1	
Appendix A1 Medicine Register Details / Module 1.5.2.2	
MRF1 PART 1C / Module 1.3 – PI & PIL	
MRF1 3B / Module 3.2.P.1	
<b>PROPRIETARY NAME CHANGE – Update following approval of name change</b>	
Copy of letter of approval	
Original medicine registration certificate	
Registration certificate amendment fee	
All the front pages of the MRF1 PARTs and sub-parts of PART 3	
<b>TRANSFER OF REGISTRATION CERTIFICATE [CHANGE OF HCR/FPRR]</b>	
Amended MRF1 PART 1Aa) + b) / Module 1.2.1	
Completed Appendix A1 Medicine Register Details / Module 1.5.2.2	
MRF1 PART 1C PI + PIL / Module 1.3	
Letter of cession & Letter of acceptance signed by the respective Responsible Pharmacists	
Affidavit regarding master documentation and all product information (Appendix A2) / Module 1.5.2.3	
Due date of update of dossier stipulated	
New applicant / HCR information (SMF, date of last inspection, organogram) / Module 1.7	
SMFs or SMF numbers for all sites	
Inspection flow diagram (IFD) / Module 1.7.12	
Copy of SAPC and Registrar of Companies registration certificates	
Original medicine registration certificate	
<b>if in addition</b>	
<b>MANUFACTURERS/PACKERS outside South Africa in recognised countries</b>	
Latest inspection report	
A copy of manufacturing licence <b>or</b> a GMP certificate <b>and</b> a WHO GMP certificate	
<b>and in addition</b>	
<b>MANUFACTURING PROCEDURE AND EQUIPMENT</b>	
<b>Identical</b> Appendix A2 affidavit / Module 1.5.2.3; fully updated dossier if not updated previous 5 years	
<b>Type B</b> Appendix A2 affidavit / Module 1.5.2.3; fully updated dossier if not updated previous 5 years	
<b>Type C Fully updated dossier, proposed VP or VR</b>	
<b>HCR, FPRR – NAME ONLY, SAME ADDRESS</b>	
Amended MRF1 PART 1A / Module 1.2.1	
Completed Appendix A1 Medicine Register Details / Module 1.5.2.1	
PART 1C PI + PIL / Module 1.3	
SMF and updated organogram (Module 1.7.13)	
Copy of SAPC and Registrar of Companies registration certificates	
Old and new company letterheads	
Original medicine registration certificates in alpha numerical order	

<b>AMENDMENTS AFFECTING THE MEDICINE REGISTRATION CERTIFICATE <i>continued</i></b>	
<b>HCR, FPRR and/or MANUFACTURER, PACKER, FPRC – ADDRESS ONLY</b>	
Amended MRF1 PART 1Aa) + b) / Module 1.2.1	
Completed Appendix A1 Medicine Register Details / Module 1.5.2.2	
PART 1C PI + PIL / Module 1.3.	
SMF, organogram (Module 1.7.13)	
Appendix A2 affidavit confirming same as previous / Module 1.5.2.3	
Original medicine registration certificate	
<b>ADDITIONAL OR CHANGE OF MANUFACTURER, PACKER, FPRC</b>	
Amended MRF1 PART 1Aa) + b) / Module 1.2.1	
Completed Appendix A1 Medicine Register Details / Module 1.5.2.2	
Affidavit regarding master documentation and all product information (Appendix A2) / Module 1.5.2.3	
Due date of update of dossier stipulated	
New site information (SMF, date of last inspection, organogram / Module 1.7.13)	
SMFs or SMF numbers for all sites	
Inspection flow diagram (IFD) / Module 1.7.12	
Copy of SAPC and Registrar of Companies registration certificates	
Original medicine registration certificate	
<b>if in addition</b>	
<b>MANUFACTURERS/PACKERS outside South Africa in recognised countries</b>	
Latest inspection report	
A copy of manufacturing licence <b>or</b> a GMP certificate <b>and</b> a WHO GMP certificate	
<b>and in addition</b>	
<b>MANUFACTURING PROCEDURE AND EQUIPMENT</b>	
<b>Identical</b> Appendix A2 affidavit / Module 1.5.2.3; fully updated dossier if not updated previous 5 years	
<b>Type B</b> Appendix A2 affidavit / Module 1.5.2.3; fully updated dossier if not updated previous 5 years	
<b>Type C</b> Fully updated dossier, proposed VP or VR	
<b>ADDITIONAL OR CHANGE OF FPRC ONLY</b>	
Amended MRF1 PART 1Aa) + b) / Module 1.2.1	
Completed Appendix A1 Medicine Register Details / Module 1.5.2.2	
Affidavit regarding master documentation and all product information (Appendix A2) / Module 1.5.2.3	
New FPRC information (SMF, date of last inspection, organogram / Module 1.7.13)	
SMFs or SMF numbers for all sites	
Inspection flow diagram (IFD) / Module 1.7.12	
Original medicine registration certificate	
<b>if an additional FPRC outside South Africa in recognised countries</b>	
<b>in addition</b>	
Latest inspection report	
A copy of relevant licence <b>or</b> a GMP/GLP certificate <b>and</b> a WHO GMP/GLP certificate	

PHARMACEUTICAL & ANALYTICAL			
<b>API</b>		<b>Supporting documents</b>	
Change of approved name		APIF	
Change of method of synthesis		Certificate of Analysis	
Change of source (manufacturer)		Physical / Chemical equivalence	
Other (Specify).....		Other (Specify).....	
<b>FORMULATION</b>			
Change of quantity of API		Updated final product specifications	
Change of quantity of IPI(s)		Updated formulation	
Addition of IPI(s)		Updated IPI specs & control procedures	
Deletion of IPI(s)		Stability data	
Substitution of IPI(s)		Efficacy data	
<b>SPECIFICATIONS AND CONTROL PROCEDURES FOR API and IPIs</b>			
Change of specifications		Updated specifications	
Change of control procedures		Update of control procedures	
<b>CONTAINER SPECIFICATIONS AND CONTROL PROCEDURES</b>			
Change of container material		Stability data	
Change of container specifications		Updated specifications	
Change of container control procedures		Updated control procedures	
Alternative container		Equivalency of containers	
<b>MANUFACTURING PROCEDURE</b>			
Change/addition of batch size		Updated manufacturing procedure	
Change of equipment		Updated packaging procedure	
Change of process		Validation protocol	
Change of process conditions		Stability data	
Change of in-process controls		Dissolution data	
Change of packaging process		Other, specify	
<b>FINAL PRODUCT SPECIFICATIONS AND CONTROL PROCEDURES</b>			
Change of specifications		Updated specification	
Change of control procedures		Updated control procedure	
Change of assay procedure		Validation data	
Other procedures			
<b>SHELF-LIFE</b>			
Extension		Stability data	
Confirmation		CoAs 0 months and x months	
Batch-specific extension			

**3 List of changes/amendments to the CTD / MRF1 / MBR1**

The MRF1 PART 1Ac) / Module 1.2.1 f) **Amendment history** reflects the particulars of the previous pharmaceutical amendments (if applicable). *Include this history here for amendments previously in the MRF1 format.*

Other amended PARTs/Annexures/Modules are as follows:

**Note:** Landscape format is recommended for this table. **A column headed “Effect of amendment”** is only applicable to PART 3B / Module 3.2.P.1 and should NOT be included for the whole table.

Annexures/ PARTs / Modules	Comparison between Annexures / PARTs / Modules		Reason for amendment	Reviewer’s comment
	Existing	Amended		
<i>Example 1 is <b>not acceptable</b> – it will take longer to evaluate as the changes have not been identified for easy reference. The format of example 2 is recommended as evaluation is facilitated by the identification of the specific items.</i>				
<b>Example 1</b> 10 (b)	Stability report: XXX	Stability report YYY replaces report XXX	Includes stability data on 2 batches stored for 36 months	
<b>Example 2</b> 10 (b)	Pages 10.0, 10.1, 10.3.1  Stability data on two production batches stored for 24 months at 25 °C/60 % RH and for 3 months at 40 °C/75 % RH submitted.	Pages 10.0, 10.2.1, 10.2.2, 10.3.1, 10.3.2  Stability data on the same two production batches stored for 36 months at 25 °C/60 % RH included.	Extension of the shelf- life to 36 months applied for.	
	No index in 10 (b), attached data only referred to.	Detailed index included in 10 (b)	Administrative update to facilitate review.	
10 (c)	Shelf-life of 24 months approved.	A discussion of the results is included and a 36 months’ shelf-life is inferred.	Extension of the shelf- life to 36 months applied for.	

*Note Stability specification limits should be reflected in the stability report.  
Out-of-specification results should be addressed.*

**4 I declare that**

- the amendments are in line with the relevant current guidelines and/or a motivation for any deviation has been submitted
- no amendments, other than those stated in the list of changes/amendments, have been made.

\_\_\_\_\_  
Signature of HCR/applicant or delegate

Name	Title	Qualification	Designation	e-mail	Tel number

Appendix A1 / Module 1.5.2.2 Medicine Register Details	<i>included</i>	Yes/no
Appendix A2 / Module 1.5.2.3 Affidavit by Responsible Pharmacist	<i>included</i>	Yes/no

**APPENDIX A1 / Module 1.5.2.2  
MEDICINE REGISTER DETAILS**

**1 Product to which this application refers**

Proprietary name of medicine	Registration/Reference number	Registered medicine (R) Old Medicine (OM)

**2 Details** (if there is no change to the "Current", indicate as such under "Proposed", do not state N/A)

	Current	Proposed
<b>Proprietary Name</b>		
<b>HCR/Applicant</b>		
Name and Address		
Contact person:		
Name		
Designation		
Telephone no		
<b>Manufacturer</b>		
Name and Address		
MCC Licence No.		
SMF Reference No.		
<b>Packer</b>		
Name and Address		
MCC Licence No.		
SMF Reference No.		
<b>FPRC</b>		
Name and Address		
MCC Licence No.		
SMF Reference No.		
<b>FPRR</b>		
Name and Address		
MCC Licence No.		
SMF Reference No.		
<b>Formulation</b>		**

\*\* If the formulation is the same, confirmation to this effect will suffice.

APPENDIX A2 / MODULE 1.5.2.3

Indicate clearly which of the following are relevant and/or not applicable by strikethrough

AFFIDAVIT BY THE HCR/APPLICANT (On company letterhead)

(In the case of transfer of the certificate of registration, this must be done by the proposed HCR)

PRODUCT NAME:

REGISTRATION NUMBER:

I, .....(insert full name and surname) Responsible Pharmacist [as defined in Section 22C(1)(b) of Act 101 of 1965] of ..... (insert Company name), confirm that:

- a) I am in possession of the master documentation pertaining to the above-mentioned medicine.
- b) This master documentation is the same as that which was in existence when the medicine was initially registered or which has been updated in accordance with amendments of the medicine registration form (MRF1/CTD) in accordance with the provisions of the regulations under the Medicines and Related Substances Control Act, 1965 (Act 101 of 1965).
- c) The master documentation conforms with the Registration dossier;
- d) The master documentation is properly authorised i.e. signed and dated by at least the responsible pharmacist, and the quality assurance or production manager as applicable;
- e) The master documentation has been supplied to the new manufacturer/packer or laboratory (state company and role) and that applicable control records have been compiled. I confirm further that I have signed these to indicate my approval that they contain all the requirements listed in the relevant master documents; namely
  - formulation and method of manufacture and packaging
  - in-process control procedures
  - specifications for ~~raw materials~~ [pharmaceutical ingredients](#)
  - specifications for the final product
  - specifications for the packaging material
  - specifications for the label
  - specifications for the package insert
  - testing procedures for the ~~raw materials~~ [pharmaceutical ingredients](#)
  - testing procedures for the final product
  - testing procedures for the packaging materials.
- f) I confirm that a technical agreement and/or signed contract(s) exist(s) with all third party manufacturer(s)/packer(s)/laboratory(ies) involved in manufacturing of this product.
- g) For an alternative/additional manufacturer:
  - I confirm that the manufacturing procedure (including equipment) is identical to the manufacturing procedure currently used **or**
  - I confirm that the manufacturing procedure (including equipment) differs, but falls within the Type A and/or Type B amendments **or**
  - I confirm that the manufacturing procedure (or equipment) is different from the manufacturing procedure (or equipment) currently on file outside of the Type A and Type B amendments and that comparative data (efficacy), stability data or protocol (as applicable), and a validation protocol for the first three production batches, are submitted.
- h) I confirm that the package insert will be updated to reflect the new HCR details and will submit the amended package insert with the first update of the dossier after authorisation of this amendment. (registration certificate transfer only)
- i) I confirm that the Registration dossier will be fully updated to the current statutory format and current scientific standards within 12 months of transfer of the certificate of registration, or approval of additional, or change of manufacturer. (Not applicable for Type C changes)
  - or**
  - I confirm that the Registration dossier will be fully updated to the current statutory format and current scientific standards by (stipulate date) in accordance with the programme as approved by the Inspectorate. (Not applicable for Type C changes)

Signature

Date

**7 TYPES OF AMENDMENTS** all amendment submissions should comply with section 2.1 in addition to those specified in this section

**7.1 TYPE A – Amendments** comply with the definition of type A and (i) do not require prior approval before implementation; (ii) do not require prior notification; (iii) should be recorded in the annual product report & be available for inspection; (iv) should be reflected under “Amendment History” MRF1 PART 1Ac) / Module 1.2.1 f).

TYPE A category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9) Stability and dissolution before and after change to be compared	NOTIFICATION
1	Change in the name and/or address of a manufacturer of the API whether or not a European Pharmacopoeia certificate of suitability is available	A formal document from a relevant official body (e.g. Registrar of Companies) in which the new name and/or address is mentioned.	The manufacturing <b>site</b> shall remain the <b>same</b> .	-
2	Deletion of colour/flavour/fragrance (including capsules shells) <b>Removal of</b> printing ink on the dosage form	PI + PIL; formulation; IPI specifications and control procedures; final product specifications and control procedures; manufacturing procedure.	Case A dissolution; stability (j)	-
3	Replacement or addition of colourant/ flavourant/ fragrance (final product <b>specifications excluding</b> description remains the same)	PI + PIL; formulation; IPI specifications and control procedures; manufacturing procedure.	FCD Act 54 of 1972 or FDA purity standards or EU commission directives; Case A dissolution; stability (b)	-
4	Granulating solution $\leq$ 20 % of the original stated granulating solution	Formulation; manufacturing procedure.	Case A dissolution	-
5	Change in the quantity of sugar or film coating material only: no change in final product specification except mass	Formulation; manufacturing procedure.	Case A dissolution; no API in the coating; stability (j)	-
6	Change in composition of the sugar coating material: no change in final product specifications except mass (either qualitative, or qualitative and quantitative, excluding change in sealant)	Formulation; IPI specifications and control procedures; manufacturing procedure.	Case A dissolution; Stability (a)	-

TYPE A category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9) Stability and dissolution before and after change to be compared	NOTIFICATION																																						
7	Quantity of pharmaceutical ingredient change ( <u>overages</u> ): <ul style="list-style-type: none"> <li>• Overage of API change: <math>\leq 10\%</math> of active</li> <li>• Overage of water soluble vitamins <math>&lt; 50\%</math> of vitamin content</li> <li>• Preservative* (semi-solid dosage form) <math>\leq 10\%</math> of preservative</li> <li>• Preservative* (other dosage forms) <math>\leq 20\%</math> of preservative</li> </ul> * <b>specifically refers to antimicrobial preservatives</b>	Formulation; IPI specifications and control procedures; manufacturing procedure.	Case A dissolution; stability (j)	-																																						
8	Change in inactive pharmaceutical ingredient (IPI) range: <ul style="list-style-type: none"> <li>- Immediate release solid oral dosage form.</li> <li>- Modified release solid oral dosage form (<i>only non-release controlling IPIs</i>)</li> </ul> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">IPI (<i>m/m</i>) per total target dosage form mass</td> <td style="width: 20%; text-align: right;">% IPI</td> </tr> <tr> <td>Filler</td> <td style="text-align: right;"><math>\leq 5\%</math></td> </tr> <tr> <td>Disintegrant:</td> <td></td> </tr> <tr> <td style="padding-left: 20px;">Starch</td> <td style="text-align: right;"><math>\leq 3\%</math></td> </tr> <tr> <td style="padding-left: 20px;">Other</td> <td style="text-align: right;"><math>\leq 1\%</math></td> </tr> <tr> <td>Binder</td> <td style="text-align: right;"><math>\leq 0,5\%</math></td> </tr> <tr> <td>Lubricant</td> <td></td> </tr> <tr> <td style="padding-left: 20px;">Ca/Mg stearate</td> <td style="text-align: right;"><math>\leq 0,25\%</math></td> </tr> <tr> <td style="padding-left: 20px;">Other</td> <td style="text-align: right;"><math>\leq 1\%</math></td> </tr> <tr> <td>Glidant:</td> <td></td> </tr> <tr> <td style="padding-left: 20px;">Talc</td> <td style="text-align: right;"><math>\leq 1\%</math></td> </tr> <tr> <td style="padding-left: 20px;">Other</td> <td style="text-align: right;"><math>\leq 0,1\%</math></td> </tr> <tr> <td>Filmcoat</td> <td style="text-align: right;"><math>\leq 1\%</math></td> </tr> </table> <p>The total effect of all IPI changes should not be more than 5 % <i>m/m</i> relative to the total dosage mass. Calculation example</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">API</td> <td style="width: 20%; text-align: right;">500 mg</td> </tr> <tr> <td>Total IPIs</td> <td style="text-align: right;">100 mg</td> </tr> <tr> <td>Total dosage mass</td> <td style="text-align: right;">600 mg</td> </tr> <tr> <td>Lactose: change from 30 to 45 mg (+15/600)</td> <td style="text-align: right;">= +2,5 %</td> </tr> <tr> <td>Cellulose: change from 50 to 35 mg (- 15/600)</td> <td style="text-align: right;">= - 2,5 %</td> </tr> <tr> <td>Absolute total change</td> <td style="text-align: right;">= 5 %</td> </tr> </table>	IPI ( <i>m/m</i> ) per total target dosage form mass	% IPI	Filler	$\leq 5\%$	Disintegrant:		Starch	$\leq 3\%$	Other	$\leq 1\%$	Binder	$\leq 0,5\%$	Lubricant		Ca/Mg stearate	$\leq 0,25\%$	Other	$\leq 1\%$	Glidant:		Talc	$\leq 1\%$	Other	$\leq 0,1\%$	Filmcoat	$\leq 1\%$	API	500 mg	Total IPIs	100 mg	Total dosage mass	600 mg	Lactose: change from 30 to 45 mg (+15/600)	= +2,5 %	Cellulose: change from 50 to 35 mg (- 15/600)	= - 2,5 %	Absolute total change	= 5 %	Formulation; final product specifications and control procedures; manufacturing procedure.	Case A dissolution; stability (a)	-
IPI ( <i>m/m</i> ) per total target dosage form mass	% IPI																																									
Filler	$\leq 5\%$																																									
Disintegrant:																																										
Starch	$\leq 3\%$																																									
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API	500 mg																																									
Total IPIs	100 mg																																									
Total dosage mass	600 mg																																									
Lactose: change from 30 to 45 mg (+15/600)	= +2,5 %																																									
Cellulose: change from 50 to 35 mg (- 15/600)	= - 2,5 %																																									
Absolute total change	= 5 %																																									
9	Change in mass of empty capsule shell (size)	Formulation; final product specifications.	Case A dissolution	-																																						

Registration of Medicines

Amendments

TYPE A category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9) Stability and dissolution before and after change to be compared	NOTIFICATION
10a including parenterals and biologicals	<ul style="list-style-type: none"> <li>Change to container dimensions, same content size</li> <li>Change of container presentation size (addition or removal), same container and closure system</li> </ul>	PI + PIL (if relevant); container specifications and control procedures; packaging procedure (if relevant). Validation (if relevant)	-	-
10b including parenterals and biologicals	Update of approved Storage Instructions to align with currently accepted wording and directives, e.g.: <ul style="list-style-type: none"> <li>Store at or below x °C</li> <li>Keep blister in carton until required for use</li> <li>Protect from light</li> </ul>	PI, PIL label(s)	-	-
11	Change to appearance/description (excluding scoring for dosage claim and shape of tablets) <b>restricted to:</b> <ul style="list-style-type: none"> <li>shape (surface area unchanged – otherwise it is Type B</li> <li>imprinting/embossing</li> <li>printing</li> </ul>	PI + PIL; IPI specifications and control procedures; final product specifications; manufacturing procedure.	Validation; Case A dissolution; FCD* Act, 54 of 1972 or FDA purity standards or EU commission directives	-
12	Change to dimensions of tablet or capsule, without any other change to the final product specifications	PI + PIL; final product specification and control procedures; manufacturing procedure.	Validation; Case A dissolution	-
13 including parenterals and biologicals	Pharmaceutical ingredient specifications and/or analytical methods <ul style="list-style-type: none"> <li>More stringent</li> <li>Additional</li> <li>Upgrading to latest edition of currently used pharmacopoeia</li> <li>Switching pharmacopoeia, provided that the new pharmacopoeial specification is more stringent (Any change resulting in deletion of specifications – refer to Type C 4)</li> <li>Minor change of method (same principle of analysis)</li> </ul>	Pharmaceutical ingredient specifications and control procedures	Validation of analytical methods if applicable; changes do not reflect a change in processing e.g. fine to micro-fine particle size	-

TYPE A category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9) Stability and dissolution before and after change to be compared	NOTIFICATION
13 cont.	Final product specifications and/or analytical methods <ul style="list-style-type: none"> <li>• More stringent</li> <li>• Additional</li> <li>• Upgrading to latest edition of currently used pharmacopoeia (BP; USP; Ph. Eur.)</li> <li>• Switching pharmacopoeia, provided that the new pharmacopoeial specification is more stringent (Any change resulting in deletion of specifications – refer to Type C 4)</li> <li>• Minor change of method (same principle of analysis)</li> </ul>	Final product specifications and control procedures		-
14 including parenterals and biologicals	Change of name of active or other ingredient to an INN or approved name	PI + PIL and label; formulation; pharmaceutical ingredient specifications and control procedures; manufacturing procedure. Registration certificate if relevant.	-	-
15	Change in: <ul style="list-style-type: none"> <li>• process timing and/or operating speeds (if validated), but same final product specifications and content uniformity</li> <li>• process temperature and/or humidity (within validation range), but same final product specifications and content uniformity</li> <li>• order of addition of pharmaceutical ingredients with same processing principles and same final product specifications</li> </ul>	Manufacturing procedure; validation protocol of critical steps.	Validation; Case A dissolution; Product not modified nor slow release; stability (j)	-

TYPE A category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9)
<b>BIOLOGICALS</b> – PART 3A, 3E (where indicated) and 3I only – amendments to other PARTs in accordance with above as indicated			
16	New Working seeds or Working cell bank derived from the Master seed lots or Master cell bank by the same process as already approved	Master and Working seed. Cell bank.	Batch information and comparative data on characterisation (e.g. demonstrate that master seed lot has not deteriorated and that the new working seed or cell bank is equivalent to the approved one)
17	New Stock seed (seed lot) derived from the Master seed lot or Working seed lot by the same process as already approved	Seed lot.	Batch information and comparative data on characterisation (e.g. demonstrate that master seed lot has not deteriorated and that the new stock is equivalent to the approved one)
18	Minor change in the harvesting and/or pooling procedures that does not affect the method of production, recovery, storage conditions, sensitivity of detection of adventitious agents or production scale	Production procedure.	Validation
19	Replacement of a reference standard according to SOPs and specifications that have already been approved	Include information on new reference standard.	Comparative data (specifications)
20	Tightening of specifications for the Master seed lot, Working seed lot and Stock seed	Specifications.	
21	Addition of equipment for manufacturing processes that is <i>identical</i> to the primary system and serves an alternate resource within the approved production room or area (PPL and FP)	Production procedure.	Validation
22	Replacement in equipment with same operating principle involving no change in process parameters (PPL and FP)	Production procedure.	Validation
23	Minor changes in fermentation batch size using the same equipment and resulting in no change in specifications of the bulk or final product	Manufacturing procedure	Validation



7.2 **TYPE B – Amendments** comply with the definition of type B and (i) require notification; (ii) should be recorded and made available for inspection and (iii) should be reflected under “Amendment History” in the MRF 1Ac) / Module 1.2.1 f) and submitted with also the administrative amendment fee if relevant, and the amendment schedule/covering letter as in section 6.

TYPE B category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9)	NOTIFICATION
		Stability and dissolution before and after change to be compared and submitted		
1a including parenterals	Change/additional source <b>to a different site of the same parent company</b> of API (route of synthesis and specifications the same) <b>** Statement re route of synthesis by each new site – if route of synthesis including purification step is identical</b>	Name and address of source; APIF / Module 3.2.S, if not previously included; CoAs; Statement **	Case A dissolution	X
1b	Change in batch size of <del>API active substance</del> or intermediate (excluding biological): <ul style="list-style-type: none"> <li>Up to 10-fold compared to the original batch size approved at the time of registration of the product</li> <li>Downscaling of any magnitude</li> </ul> Provided that <ul style="list-style-type: none"> <li>Any changes to the manufacturing methods are only those necessitated by scale-up or scale-down, e.g. use of different-sized equipment.</li> <li>The change does not affect the reproducibility of the process.</li> <li>In addition for Downscaling: The change should not be the result of unexpected events arising during manufacture or because of stability concerns.</li> </ul>	<ul style="list-style-type: none"> <li>The batch numbers of the tested batches having the proposed batch size.</li> <li>Test results of at least two batches according to the specifications for the proposed batch size.</li> </ul>	Case B dissolution	X
2	Film coating change from organic solution to aqueous solution ( <b>Qualitative</b> composition of components, excluding change in sealant if used e.g. modified release)	Formulation; IPI specifications and control procedures; manufacturing procedure.	Validation; Case A dissolution; stability (a)	X
3	Packaging material: <ul style="list-style-type: none"> <li>Changes in composition of the immediate container (at least equivalent in protection of light and moisture permeability to that of the existing container) *</li> <li>Composition not equivalent, but provides better protection to the product (stability not affected) *</li> <li>Changes to colour, at least equivalent in protection (light sensitive products) *</li> <li>Changes to closures in contact with product in compliance with the USP permeation test</li> </ul> *To prove equivalence use USP criteria for containers	PI + PIL (if relevant); container specifications and control procedures; packaging procedure (if relevant).	Excluding labelling; stability (a)	X

TYPE B category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9)	NOTIFICATION
		Stability and dissolution before and after change to be compared and submitted		
4a including parenterals	Storage conditions	PI + PIL and label; stability data and batch information.	Stability (g)	X
4b	Shelf-life reduction	PART 3G / Module 3.2.P.8	Data & Justification	X
5	Change in: <ul style="list-style-type: none"> <li>• Equipment or process machinery but with same processing principles e.g. low energy/low energy</li> <li>• Process timing and/or operating speed, but same final product specifications and content uniformity</li> <li>• Process temperature and/or environmental humidity, but same final product specifications</li> </ul>	Manufacturing procedure; affidavit confirming same as previous; site master file.	Validation; product not modified nor slow release; Case A dissolution; stability (a).	X
6	Change to shape of tablet if the surface area is different	PI + PIL; IPI specifications and control procedures; final product specification; manufacturing procedure.	Validation; Case A dissolution	X
7 including parenterals and biologicals	Scale-up and down to and including ten times the batch used to support stability and efficacy or the approved or validated batch using the same: <ul style="list-style-type: none"> <li>• Formulation</li> <li>• Equipment design and operating principles</li> <li>• Controls</li> <li>• SOPs</li> </ul>	Manufacturing procedure	Validation; Case A dissolution; stability (a)	X
8	Replacement of an IPI with a comparable* IPI with the same functional characteristics, resulting in no change in the dissolution profile for solid oral dosage forms. The final product specifications should remain unchanged. *in terms of chemical structure, physical form and/or pharmaceutical effect.	Formulation; IPI specifications and control procedures.	Validation; Case A or B dissolution; Stability (b)	X

**Registration of Medicines**

**Amendments**

TYPE B category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9)	NOTIFICATION
		Stability and dissolution before and after change to be compared and submitted		
9 including parenterals and biologicals	Automation of one or more process steps without change in process methodology	Manufacturing procedure	Validation Stability (a)	X
10 including parenterals and biologicals	Computer process control for steps to replace manual process control	Manufacturing procedure	Validation	X
<b>BIOLOGICALS</b> (PART 3A and 3I only – amendments to other PARTs in accordance with above as indicated)				
11	Changes to the site of production (same site) involving: <ul style="list-style-type: none"> <li>• Changes in responsible individuals specified in approved dossier</li> <li>• Relocation of equipment within an approved operating room, rearrangement of operating area or rooms where production is performed, or Relocation of equipment to another approved area to improve product/personnel/raw material flow and improve segregation of materials with no change in room air classification</li> <li>• Production of an additional product in a previously approved multiple product manufacturing area using same equipment and personnel, providing there have been no changes to the approved and validated and changeover procedures and there are no additional containment requirements</li> </ul>	Updated PART 3I/Module 3.2.A.1 Qualifications & experience.	Validation if applicable (Demonstrate integrity of the process e.g. avoidance of cross-contamination)	X
			Validation (Demonstrate integrity of the process e.g. avoidance of cross-contamination)	X
12	In order to ensure TSE compliance, obtaining the same raw material from a different source (non-animal origin) used in the manufacturing of seed lots	Raw material in PART 3A / Module 3.2.S	Equivalence between materials	X
13	Addition or reduction in number of pieces of equipment (e.g. centrifuges, filtration devices etc) to achieve a change in purification scale not associated with a process change	Production procedure.	Validation	X

**Registration of Medicines**

**Amendments**

TYPE B category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	CONDITION (Stability legend section 9)	NOTIFICATION
		Stability and dissolution before and after change to be compared and submitted		
14	Installation of a new or modification to an existing purified water system, not including pre-treatment systems for WFI	Production premises	Validation	X
15	Change of storage conditions of an intermediate of an <del>active raw material</del> API based on data from stability protocol in approved dossier, providing storage conditions of <del>API active raw material</del> API does not change	Stability data; Updated production procedure.	Stability data according to the approved protocol	X

**7.3 TYPE C – Amendments** comply with the definition of type C and (i) require prior approval before implementation; and (ii) should be reflected under “Amendment History” in the MRF1 1Ac) / Module 1.2.1 f) (refer section 2.2 of this guideline) and submitted with also the administrative amendment fee, if relevant, and the amendment schedule/covering letter as reflected in section 6. The letter “B” included after the category number indicates a biological medicine.

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
		Stability and dissolution before and after change to be compared and submitted as soon as available – applies to all Type C changes		
1 including parenterals	Inactive Pharmaceutical Ingredient (IPI): <ul style="list-style-type: none"> <li>Addition of one or more IPIs</li> <li>Ranges more than allowed for Type A or B changes for immediate release solid oral dosage forms and for modified release solid oral dosage forms (non-release controlling ingredient)</li> <li>Addition or removal or increasing or decreasing any release controlling ingredient</li> <li>Changes in technical grade i.e. Avicel PH102 to Avicel PH200</li> <li>Replacement of more than one IPI.</li> </ul>	Formulation; IPI specifications and control procedures; final product specification; manufacturing procedure; batch information of stability data.	Stability (c)	Proof of efficacy
2	Sugarcoat: Changes in composition (qualitative and/or quantitative), which result in a change in final product specification.	PI + PIL (if relevant); formulation; IPI specifications and control procedures; final product specifications; manufacturing procedure; batch information of stability data.	Stability (c)	Proof of efficacy
3	Overage greater than the overages allowed for in Type A or B changes. <ul style="list-style-type: none"> <li>Wide therapeutic effect</li> <li>No increase in the severity of known side effects</li> <li>No additional side effects</li> </ul>	Formulation; final product specifications; manufacturing procedure; batch information of stability data.	Stability (c)	Proof of efficacy
4 including parenterals	Pharmaceutical ingredient specifications and/or analytical methods <ul style="list-style-type: none"> <li>Less stringent requirement</li> <li>Deletion of specification</li> <li>Not in accordance with latest pharmacopoeia (full motivation)</li> </ul> Final product specification and/or analytical methods <ul style="list-style-type: none"> <li>Less stringent</li> <li>Deletion (excluding particle size)</li> <li>Not in accordance with latest pharmacopoeia (full motivation)</li> </ul>	Pharmaceutical ingredient specifications and control procedures.  Final product specifications and control procedures	Stability (c)	-

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
5 including parenterals	API (suspension dosage form): <ul style="list-style-type: none"> <li>Change in crystalline or polymorphic form</li> </ul>	Chemical details; API specifications and control procedures; final product specifications and control procedures. Justification for such change.	Stability (c)	Proof of efficacy, which may be supportive literature
6	Change to scoring of tablet (change in dosage regimen)	PI + PIL; final product specifications; manufacturing procedure.	Stability (c)	-
7 including parenterals	Packaging material: <ul style="list-style-type: none"> <li>Changes in composition of the immediate container affecting stability</li> <li>Changes to less protective colour (light sensitive products)</li> <li>Changes to closures in contact with product not in compliance with the USP permeation test</li> </ul>	PI + PIL (if relevant); container specifications and control procedures; packaging procedure (if relevant).	Stability (c)	-
8a including parenterals	Change/additional source of API <b>to a different company</b> (route of synthesis stated to be the same, specifications the same)	<a href="#">PART 3A / Module 3.2.S</a> Discussion of routes of synthesis, even if apparently the same, with emphasis on impurities; (Also refer to P&A Guideline section 3.1.7) (3.2.S, 3.2.R.4) <ul style="list-style-type: none"> <li>If CEP is submitted, comply with requirements of P&amp;A Guideline section 3.1.6 (3.2 R 3)</li> </ul> As for 8b below.	<a href="#">FP</a> Stability (b)	<sup>Φ</sup> BCS class 1 & 3 – Case A <a href="#">FP</a> dissolution All others – Case C <a href="#">FP</a> dissolution
8b	<ul style="list-style-type: none"> <li>Additional source/change in API source (route of synthesis not the same), or</li> <li>Minor change in route of synthesis (e.g. no change in crystallisation process or final purification),</li> </ul>	<a href="#">PART 3A / Module 3.2.S</a> From each source: <ul style="list-style-type: none"> <li>Name and address of source;</li> <li>Method of synthesis APIF/DMF/CEP</li> <li>Discussion of routes of synthesis (if no CEP)</li> <li>If CEP is submitted, comply with requirements of P&amp;A Guideline section 3.1.6 / <a href="#">PA CTD guideline</a> 3.2.R.3</li> </ul>	<a href="#">FP</a> Stability (b)	<sup>Φ</sup> BCS class 1 & 3 - Case B <a href="#">FP</a> dissolution All others – Case C <a href="#">FP</a> dissolution

<sup>Φ</sup> BCS Class 1 and 3 (highly soluble APIs, i.e. the highest dose is soluble in 250 ml or less of aqueous media over pH range 1,2 to 6,8) substantiated by WHO TRS 937 (Annex 8) or data

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
8b cont	resulting in <b>no change</b> of API specifications or <b>more stringent</b> API specifications, and no change in qualitative and quantitative impurity profile or in physico-chemical properties.	<ul style="list-style-type: none"> <li>CoA</li> <li>Demonstration of equivalence between material from each source / manufactured according to the currently approved and proposed process by a common laboratory. Refer to P&amp;A Guideline section 3.1.7 / <a href="#">PA CTD guideline 3.2.R.4 and/or 3.2.R.1.1.8</a></li> </ul> Verification of compliance also in tabulated form.		
8c including parenterals	Additional source/change in API source <ul style="list-style-type: none"> <li>route of synthesis not the same, or</li> <li>change in route of synthesis</li> </ul> resulting in <b>change</b> of API specifications	From each source: <a href="#">PART 3A / Module 3.2.S</a> <ul style="list-style-type: none"> <li>Name and address of each source;</li> <li>Tabulated comparison of old and new specifications</li> <li>Method of synthesis APIF/DMF/CEP *</li> <li>Discussion of routes of synthesis, with emphasis on impurities *</li> <li>CoA</li> <li>Demonstration of equivalence between material from each source by common laboratory. Refer to P&amp;A guideline section 3.1.7 / <a href="#">PA CTD guideline 3.2.R.4 and/or 3.2.R.1.1.8</a></li> </ul> * If CEP is submitted, refer to P&A guideline section 3.1.6. / <a href="#">PA CTD guideline 3.2.R.3</a> Verification of compliance also in tabulated form; API specifications and control procedures; Final product specifications and control procedures (if relevant); Justification if API specifications are less stringent, with special reference to safety.	API Stability <u>and</u> <a href="#">FP</a> Stability (c)	<sup>Φ</sup> BCS class 1 & 3 – Case B <a href="#">FP</a> dissolution All others – Case C <a href="#">FP</a> dissolution

<sup>Φ</sup> BCS Class 1 and 3 (highly soluble APIs, i.e. the highest dose is soluble in 250 ml or less of aqueous media over pH range 1,2 to 6,8) substantiated by WHO TRS 937 (Annex 8) or data

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
8d	Change in batch size of API (excluding biological): More than 10-fold compared to the original batch size approved at the time of registration provided that <ul style="list-style-type: none"> <li>any changes to the manufacturing methods are only those necessitated by scale-up, e.g. use of different-sized equipment;</li> <li>the change does not affect the reproducibility of the process.</li> </ul>	<ul style="list-style-type: none"> <li>Test results of at least two batches according to the specifications for the proposed batch size</li> <li>Demonstration of equivalence (batch analysis data in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes</li> <li>Batch data on the next two full production batches should be made available upon request and reported by the HCR if outside specification (with proposed action)</li> </ul>	-	<sup>Φ</sup> BCS class 1 & 3 – Case B <b>FP</b> dissolution All others – Case C <b>FP</b> dissolution
8e	Change in: <ul style="list-style-type: none"> <li>the re-test period of the <del>active substance</del> <a href="#">API</a></li> <li>the storage conditions for the <del>active substance</del> <a href="#">API</a></li> </ul> provided that the change is not the result of unexpected events arising during manufacture or because of stability concerns, and the <a href="#">API</a> <del>active substance</del> is not a biological substance.	Results of appropriate real time stability studies; conducted in accordance with the stability guidelines on at least two (three for NCEs products) production scale batches of the <a href="#">API</a> <del>active substance</del> in the approved packaging material and covering the duration of the requested re-test period or requested storage conditions.	API stability	-
8f	Change in: <ul style="list-style-type: none"> <li>the re-test period of the <a href="#">API</a> <del>active substance</del></li> <li>the storage conditions for the <del>active substance</del> <a href="#">API</a></li> </ul> due to a change that is the result of unexpected events arising during manufacture or because of stability concerns, and provided that the <a href="#">API</a> <del>active substance</del> is not a biological substance.	Results of appropriate real time stability studies; conducted in accordance with the stability guidelines on at least two (three for NCEs products) production scale batches of the <a href="#">API</a> <del>active substance</del> in the approved packaging material and covering the duration of the requested re-test period or requested storage conditions.	API stability <a href="#">FP</a> Stability (c)	<sup>Φ</sup> BCS class 1 & 3 – Case B <b>FP</b> dissolution All others – Case C <b>FP</b> dissolution

<sup>Φ</sup> BCS Class 1 and 3 (highly soluble APIs, i.e. the highest dose is soluble in 250 ml or less of aqueous media over pH range 1,2 to 6,8) substantiated by WHO TRS 937 (Annex 8) or data

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
9 including parenterals	Change in: <ul style="list-style-type: none"> <li>type of process used in the manufacturing of the product outside validation (i.e. completely different method of processing) e.g. change from dry to wet granulation</li> </ul>	Formulation (if relevant); pharmaceutical ingredient specifications and control procedures (if relevant); manufacturing procedure; validation protocol.	Stability (d)	Proof of efficacy
10 including parenterals and biologicals	Shelf-life extension (final product)	Stability data to cover the extension period, and batch information. Include all the stability data in support of the shelf-life extension (including previously submitted data for the relevant batches and accelerated stability testing data).	Stability (f)	-
10B	Extension of shelf-life of an intermediate of an <del>active raw material</del> <a href="#">API</a> , providing shelf-life and storage conditions of final <a href="#">API</a> <del>active raw material</del> does not change	Stability data; Updated production procedure.	Stability data according to the approved protocol for intermediate and final <a href="#">API</a> <del>active raw material</del>	
11 including parenterals	Different equipment/process machinery with different processing principles. (Note: if change occurs, current manufacturer, if retained, should follow same manufacturing procedures unless product integrity can be maintained by both processes)	Front Page / Modules 1.2.1/2.3.P formulation; pharmaceutical ingredient specifications and control procedures; final product specifications; manufacturing procedure; site master file if affected / change in manufacturer; validation protocol.	Stability (d)	Proof of efficacy
12	Change in process of combining phases in the production of semi-solid dosage topical dosage form	Manufacturing procedure	Stability (c)	-
13 including parenterals and biologicals	Change in sterilisation process and method (e.g. from filtration sterilisation to autoclaving) <b>Biological:</b> Provided that this is not part of virus inactivation (Note: Change in virus inactivation is critical, could result in type D change)	Manufacturing procedure; Validation	Stability (c)	-

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
14 including parenterals	Scale-up to more than ten times the size of the batch used to support stability and efficacy, using the same: <ul style="list-style-type: none"> <li>• Formulation</li> <li>• Equipment design and operating principles</li> <li>• Controls</li> <li>• SOPs</li> </ul>	Manufacturing procedure; batch information of stability data	Stability (i)	Proof of efficacy
15 including parenterals	Scale-up to more than ten times the batch size of the approved and validated batch	Manufacturing procedure, batch information of stability data	Stability (i)	Proof of efficacy
16 including parenterals and biologicals	<ul style="list-style-type: none"> <li>• Change from a glass ampoule to a glass vial with an elastomeric closure</li> <li>• A change to a pre-filled dosage form from another container system</li> <li>• A change that adds or deletes silicone treatment to container closure system</li> <li>• Changes in the size and / or shape of a container for a sterile drug product if the head space changes</li> <li>• A change to a flexible container system bag from another container system</li> </ul>	PI + PIL (if relevant); container specifications and control procedures; packaging procedure (if relevant). Compatibility with e.g. elastomeric closures	Equivalent protection or more protective, stability (a); Less protective, stability (c)	-
17	Proprietary name 1) Application for name change 2) Update following approval of name change	1) <i>Application:</i> <ul style="list-style-type: none"> <li>• MRF1 PART 1Ab)/Module 1.2.1</li> <li>• Appendix A1 Medicine Register Details/ Module 1.5.2.2</li> <li>• PART 1C PI + PIL / Module 1.3 PART 3B/ Module 3.2.P.1</li> </ul> 2) <i>Following approval:</i> <ul style="list-style-type: none"> <li>• Copy of letter of approval</li> <li>• Original medicine registration certificate</li> <li>• Registration certificate amendment fee</li> <li>• All front pages of dossier (MRF1)</li> </ul>		

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
<b>BIOLOGICALS</b> (PART 3A, 3E and 3I only – amendments to other PARTs in accordance with above as indicated) (Modules 3.2.S, 3.2.P.3, 3.2.A.1)				
18B	Process changes including, but not limited to, <ul style="list-style-type: none"> <li>• extension of culture growth time leading to an increase in number of cell doublings beyond validated parameters</li> <li>• new or revised recovery procedures</li> <li>• new or revised purification process, including a change in a column</li> <li>• a change in the chemistry or formulation of solutions used in processing</li> <li>• a change in the sequence of processing steps or addition, deletion, or substitution of a process step; or</li> <li>• reprocessing of a product without a previously approved reprocessing protocol</li> </ul>	Formulation; Production procedures; Validation.	Stability (c)	Final product: Proof of safety and efficacy.
19B	Any change in analytical methods that <ul style="list-style-type: none"> <li>• results in change(s) of specification limits or modification(s) in potency, sensitivity, specificity, or purity</li> <li>• establishes a new analytical method</li> <li>• deletes a specification or an analytical method</li> <li>• eliminates tests from the stability protocol; or</li> <li>• alters the acceptance criteria of the stability protocol</li> </ul>	Analytical methods; Validation.	Stability (c)	
20B	Any change in production processes that may <ul style="list-style-type: none"> <li>• result in change(s) of specification limits or modification(s) in potency, sensitivity, specificity, or purity</li> <li>• establish a new analytical method</li> <li>• delete a specification or an analytical method</li> <li>• eliminate tests from the stability protocol; or</li> <li>• alter the acceptance criteria of the stability protocol</li> </ul>	Production procedure; Analytical methods; Validation.	Stability (c)	Final product: Proof of safety and efficacy.
21B	Scale-up requiring a larger fermentor, bioreactor, and/or purification equipment (applies to production up to the final purified bulk)	Production procedure; Batch information for stability; Validation.	Stability (i)	Proof of efficacy
22B	Change in the composition or dosage form of the biological product or ancillary components (e.g. new or different excipients, or buffers)	Formulation	Stability (d)	Proof of safety and efficacy

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
<b>BIOLOGICALS</b> (PART 3A, 3E and 3I only – amendments to other PARTs in accordance with above as indicated) (Modules 3.2.S, 3.2.P.3, 3.2.A.1)				
23B	New lot of, new source for, or different, in-house reference standard or reference panel (panel member) resulting in modification of reference specifications or an alternative test method	Reference standard information; Revised specifications.		
24B	A change in storage temperature / conditions of final product	PI + PIL (if relevant) and label; PART 3G / Module 3.2.P.8 / 2.3.P	Stability (g)	Proof of efficacy may be required
25B	Installation of a new Water for Injection (WFI) system; or modifications to an existing WFI-system that would have a significant potential to stress or challenge the system, such as: <ul style="list-style-type: none"> <li>• lengthy or complicated distribution system extensions to service new or remote production areas</li> <li>• use of components of lesser quality or function</li> <li>• expansions of ambient temperature water distribution loops</li> <li>• conversion from hot loop to ambient loop</li> </ul>	Production premises; Specifications.	Validation	
26B	Change of the site(s) at which production, other than testing, is performed; addition of a new location (including donor centres manufacturing platelets and/or performing automated pheresis procedures); or contracting of a production step in the approved manufacturing procedure to be performed at a separate facility.	PART 3A, 3I / Module 3.2.S, 3.2.A.1, 2.3.P Final product: See also Type C (Inspectorate) category 26	Stability (c)	
27B	Conversion of production and related area(s) from single to multiple product manufacturing area(s).  (Addition of products to a multiple product manufacturing area could be submitted as a type B amendment if there are no changes to the approved and validated cleaning and changeover procedures and no additional containment requirements)	PART 3I /Module 3.2.A.1, 2.3.P		
28B	Changes in the location (room, building, etc.) of steps in the production process which could affect contamination or cross contamination precautions	PART 3I /Module 3.2.A.1, 2.3.P	Stability (a) Validation	

TYPE C category	DESCRIPTION	DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED	STABILITY legend section 9	EFFICACY (ref guidelines)
<b>BIOLOGICALS</b> (PART 3A, 3E and 3I only – amendments to other PARTs in accordance with above as indicated) (Modules 3.2.S, 3.2.P.3, 3.2.A.1)				
29B	Changes in location, involving or affecting environmentally controlled manufacturing or related support areas, such as <ul style="list-style-type: none"> <li>• new buildings</li> <li>• new production areas or room in existing buildings</li> <li>• aseptic processing areas</li> <li>• modifications to support systems with significant potential to affect air, water, or steam quality</li> <li>• installation of a new HVAC system involving or affecting environmentally controlled manufacturing or related support areas; or</li> <li>• modifications to an existing HVAC system that supplies aseptic processing areas</li> </ul>	Information required but not limited to PART 3A, 3E, 3I / Module 3.2.S, 3.2.P.3, 3.2.A.1, 2.3.P	Stability (c) Validation	
30B	Downgrade of room or area environmental quality classification except for aseptic processing areas.	Production procedure; Production premises.	Validation	
31B	Process changes e.g. <ul style="list-style-type: none"> <li>• leuko-reduction</li> <li>• irradiation</li> <li>• freezing/deglycerolizing/rejuvenating</li> <li>• manual to automated collection of Source Plasma, Fresh Frozen Plasma, or platelets</li> <li>• immunization programs</li> <li>• disease-state (as opposed to disease-associated) or</li> <li>• high risk donor collections</li> </ul>	Production process	Stability (c) Validation	Proof of efficacy may be required
32B	Annual viral Influenza strain changes ( <i>Note: Final approval will be considered by Council</i> )	Refer to Section 10		

## 7.4 INSPECTORATE

TYPE C category	DESCRIPTION	DOCUMENTS REQUIRED	CONDITION
18	All amendments (section 2.1 of this guideline)	<ul style="list-style-type: none"> <li>Amendment schedule and covering letter section 6 of guideline;</li> <li>Administrative amendment fee, if relevant;</li> <li>completed MRF1 PART 1Ac) Amendment history / Module 1.2.1 f)</li> </ul>	-
19	Batch-specific shelf-life extension (submit under working code VSE)	<ul style="list-style-type: none"> <li>As per 18 plus</li> <li>CoA of lot release (0 months) +</li> <li>CoA at time point of requesting extension.</li> </ul>	Stability (h)
20	Once-off formulation and /or manufacturing procedure changes	<ul style="list-style-type: none"> <li>As per 18 plus</li> <li>Batch manufacturing record and master;</li> <li>Motivation for change and dissolution data where applicable.</li> </ul>	Stability (j)
21	HCR only – Address only	<ul style="list-style-type: none"> <li>As per 18 plus</li> <li>HCR SMF</li> <li>Cover letter coded VAA plus Appendix A1 Medicine Register Details / Module 1.5.2.2</li> <li>MRF1 PART 1C PI + PIL if affected / Module 1.3</li> <li>Registration certificate amendment fee; original medicine registration certificate;</li> <li>Updated dossier within 12 months or full update if not updated within previous 5 years</li> </ul>	-
22			-
23	<p>HCR/FPRR name only (facilities and/or applicant) and / or Manufacturer/packer/FPRC-name only</p> <p>* for HCR/FPRR only name change</p> <p>** excluding FPRC if registration with SAPC is not required</p>	<ul style="list-style-type: none"> <li>As per 18 plus</li> <li>MRF1 PART 1Aa)+b) / Module 1.2.1; Appendix A1 Medicine Register Details / Module 1.5.2.2</li> <li>PART 1C PI + PIL * / Module 1.3</li> <li>Updated HCR (and other relevant SMFs if applicable) SMF within agreed time frame; updated organogram / Module 1.7.13;</li> <li>Copies of SAPC and Registrar of Companies registration certificates **;</li> <li>Copies of old and new letterheads*;</li> <li>Per product in alpha-numerical order of application/registration number:- registration certificate amendment fee; original medicine registration certificate;</li> <li>Updated dossier within 12 months or full update if not updated within previous 5 years*</li> </ul>	-

TYPE C category	DESCRIPTION	DOCUMENTS REQUIRED	CONDITION
<b>7.4 INSPECTORATE continued</b>			
24	HCR/FPRR and/or Manufacturer, Packer, FPRC <b>address only</b> i.e. <b>Site change</b> with same: <ul style="list-style-type: none"> <li>• Equipment</li> <li>• SOPs</li> <li>• Environmental conditions (e.g. temp and RH) and controls</li> <li>• Personnel competency</li> <li>• Common master manufacturing, packaging or testing procedures</li> </ul>	<ul style="list-style-type: none"> <li>• As per 18 plus</li> <li>• MRF1 PART 1Aa)+b) / Module 1.2.1; Appendix A1 Medicine Register Details / Module 1.5.2.2</li> <li>• MRF1 PART 1C PI + PIL if affected / Module 1.3</li> <li>• Appendix A2 affidavit confirming same as previous / Module 1.5.2.3</li> <li>• Updated SMF within agreed time frame; Organogram / Module 1.7.13; IFD / Module 1.7.12</li> <li>• Original medicine registration certificate; registration certificate amendment fee</li> </ul>	Dissolution if applicable, similar; stability (a)
25	HCR/FPRR (no change of manufacturer)	<ul style="list-style-type: none"> <li>• As per 18 plus</li> <li>• MRF1 PART 1Aa)+b) ) / Module 1.2.1; Appendix A1 Medicine Register Details / Module 1.5.2.2;</li> <li>• MRF1 PART 1C PI + PIL / Module 1.3</li> <li>• PHCR SMF; PHCR Organogram / Module 1.7.13; IFD / Module 1.7.12</li> <li>• Copies of SAPC and Registrar of Companies registration certificates;</li> <li>• Appendix A2 PHCR affidavit / Module 1.5.2.3; letters of cessation and acceptance;</li> <li>• Registration certificate amendment fee; original medicine registration certificate;</li> <li>• Fully updated dossier if not updated within previous 5 years</li> </ul>	Dissolution if applicable, similar
26	HCR/FPRR and/or additional or change of Manufacturer, Packer, FPRC	<ul style="list-style-type: none"> <li>• As per 18 plus</li> <li>• MRF1 PART 1Aa)+b) / Module 1.2.1; Appendix A1 Medicine Register Details / Module 1.5.2.2;</li> <li>• MRF1 PART 1C PI + PIL / Module 1.3</li> <li>• PHCR SMF; PHCR Organogram / Module 1.7.13; IFD / Module 1.7.12</li> <li>• Copies of SAPC and Registrar of Companies registration certificates;</li> <li>• Appendix A2 PHCR affidavit / Module 1.5.2.3; letters of cessation and acceptance;</li> <li>• Registration certificate amendment fee; original medicine registration certificate</li> <li>• SMF all sites if not already submitted</li> </ul>	Dissolution if applicable, similar

TYPE C category	DESCRIPTION	DOCUMENTS REQUIRED	CONDITION
26 cont.	Manufacturers / packers outside RSA	in addition	
	a) recognised countries	<ul style="list-style-type: none"> <li>• Latest inspection report;</li> <li>• GMP certificate WHO Certification scheme or GMP certificate by authority for the manufacturing site or copy of manufacturing licence</li> </ul>	
	b) non recognised countries	<ul style="list-style-type: none"> <li>• Inspection by MCC</li> </ul>	
	packer	<ul style="list-style-type: none"> <li>• Appendix A2 affidavit packing process unchanged / Module 1.5.2.3;</li> <li>• relevant MRF1 PARTs 3D and/or 3E / CTD Modules 3.2.P.7 and/or 3.2.P.3</li> </ul>	
	manufacturing procedure:	<ul style="list-style-type: none"> <li>• Appendix A2 affidavit identical procedure and equipment / Module 1.5.2.3;</li> <li>• Fully updated dossier if not updated previous 5 years</li> </ul>	Stability (a) Validation
<ul style="list-style-type: none"> <li>• if identical</li> <li>• if procedure and equipment differ Type A and/or B</li> </ul>	<ul style="list-style-type: none"> <li>• Appendix A2 affidavit Type A and/or B changes / Module 1.5.2.3;</li> <li>• Fully updated dossier if not updated previous 5 years</li> </ul>	Type A + B as per 7.1 +7.2	
<ul style="list-style-type: none"> <li>• if procedure and equipment differ Type C</li> </ul>	<ul style="list-style-type: none"> <li>• Fully updated dossier;</li> <li>• VP and VR; batch manufacturing documents to clearly state "Validation batch".</li> </ul>	Stability (c) and proof of efficacy as 7.3	

**8 LIST OF ABBREVIATIONS/ACRONYMS**

API	Active Pharmaceutical Ingredient	FPRR	Finished Product Release Responsibility
APIF	Active Pharmaceutical Ingredient File	HCR	Holder of the Certificate of Registration
IPI	Inactive Pharmaceutical Ingredient	FDC	Foodstuffs, Disinfectants and Cosmetics
FPRC	Final Product Release Control	SMF	Site master File
PHCR	Proposed holder of certificate of registration	FPP	Finished Pharmaceutical Product
IFD	Inspection flow diagram	FP	Final pharmaceutical product
VP	Validation Protocol	VR	Validation Report
PPL	Primary production lot		

## 9 LEGENDS FOR STABILITY DATA REQUIRED

Data to demonstrate efficacy and or stability should be derived from batches of at least 100 000 tablets or capsules.

For semi-solid dosage forms batch sizes greater than 100 kg are to be used.

*Note:* Where stability studies at 25 °C/60 % RH are referred to, 30 °C/65 % RH may be used.

For biological the storage temperatures / conditions are as per the approved protocol.

- (a) The results of an ongoing long-term study derived from the first production batch, stored at 25 °C/60 % RH, should be submitted as soon as 12 months' data are available. The approved shelf-life is retained. The study should continue till the approved shelf-life has been substantiated.
- (b) The results of an ongoing long-term study derived from the first production batch, stored at 25 °C/60 % RH, should be submitted as soon as 12 months' data are available, plus 3 months' data, storage at 40 °C/75 % RH. The approved shelf-life is retained. The long-term study should continue till the approved shelf-life has been substantiated.
- (c) Three months' stability data derived from at least one pilot batch, stored at 25 °C/60 % RH, plus three months' data, storage at 40 °C/75 % RH, should be submitted at the time of submission to obtain a tentative shelf-life of 24 months. This shelf-life should be substantiated on the first two production batches.
- (d) Nine months' stability data derived from at least one pilot batch, stored at 25 °C/60 % RH, plus three months' data, storage at 40 °C/75 % RH, should be submitted at the time of submission to obtain a tentative shelf-life of 24 months. This shelf-life should be substantiated on the first two production batches.
- (e) Three months' stability data derived from the product, stored at 25 °C/60 % RH, plus three months' data, storage at 40 °C/75 % RH, should be submitted at the time of submission to obtain a tentative shelf-life of 24 months. This shelf-life should be substantiated by submission of the results of the long-term study at 24 months. (**NB** This set of data would apply specifically to new applications for registration of medicines.)
- (f) Stability data derived from three production batches (products containing new chemical entities) or two production batches (products containing well established entities – generics) stored at 25 °C/60 % RH, for the full period of the requested shelf-life, and three months' data, storage at 40 °C/75 % RH, complying with all specifications, should be submitted. (Stability guideline to be followed)
- (g) Stability data derived from three production batches (new chemical entities) or two production batches (generics) stored at the maximum requested recommended storage conditions for the full period of the shelf-life, plus three months' data at least 15 °C higher than the recommended storage conditions, complying with all specifications should be submitted.
- (h) Follow-up stability data derived from the specific batch of the product stored at the maximum recommended storage conditions should be submitted every three months, till the end of the extended shelf-life.
- (i) Three months' stability data derived from a batch of the product stored at 25 °C/60 % RH, plus three months' data, storage at 40 °C/75 % RH, should be submitted at the time of submission. The approved shelf-life is retained. The long-term study should continue till the approved shelf-life has been substantiated.
- (j) Follow the stability schedule and place a batch as per schedule onto the stability programme. The data should be submitted as soon as the 12 months' data are available. The study should continue till the approved shelf-life has been substantiated.

## 10 ANNUAL VIRAL STRAIN CHANGES FOR INFLUENZA VACCINES

### 10.1 Introduction

There are several influenza vaccines registered and marketed in South Africa, all of which contain three influenza strains, usually two of type A and one of type B. Each year the manufacturer changes the viral strain composition to conform to those deemed most likely to cause outbreaks during the next influenza season [May to October] in the Southern Hemisphere.

The WHO, via the International Influenza Centres assisted by National Laboratories, studies the isolates, incidence and virulence of influenza viral strain around the world and generate strain recommendations, prior to the influenza season for each hemisphere. The WHO recommendations are intended for worldwide use and therefore need to be adapted to the epidemiological situation of each country.

The influenza vaccine manufacturers obtain viral strains that conform to the characteristics of the strains recommended by the WHO and develop manufacturing processes to incorporate these into their respective products. These formulations are then submitted for approval from the regulatory authority to amend the formula, the manufacturing processes (where applicable), the package insert and the patient information leaflet.

This guideline outlines the process to be followed when submitting an annual viral strain change to ensure standardized and adequate evaluation for quality, safety and efficacy, and to expedite the approval process.

This process is solely for routine annual vaccine viral strain changes and any related safety information to be included in the package insert and the patient information leaflet. No other amendments may be included in the process.

### 10.2 Time for submission

The application must be submitted to the Medicines Control Council as soon as the required information is available.

Submission of the application by the end of October of the year preceding the intended Influenza season will allow for comprehensive and diligent review.

The intention is to have routine annual vaccine strain changes approved by the end of February of the year of the relevant influenza season.

Late or incomplete submissions will lead to delays in the review and approval process.

### 10.3 Information and documentation required

The application to change viral strain involves changes to the Registration Certificate and therefore the relevant amendment fee should be paid and proof of such payment be included in the submission.

**The following information and the relevant documents must be included:**

- 1) WHO recommended strain list for the relevant Hemisphere.
- 2) Manufacturer's choice of strains for inclusion.
- 3) Details of manufacturing procedure (declaration if unchanged).
- 4) The source, history and master/working seed characterization of each strain included.
- 5) Egg/cell culture: Safety specifications and tests. (Declaration if unchanged.)
- 6) Final product release Specifications and results. This must include Endotoxin release limit.
- 7) Retrospective data about the "efficacy or performance" of influenza vaccines (preceding year / season).
- 8) Stability data (accelerated or from the most recent, or most similar batch of approved vaccine).
- 9) Copy of the approved Package Insert.
- 10) Copy of the proposed Package Insert indicating:
  - i) The year/season for which the vaccine will be used;
  - ii) WHO recommended strains;
  - iii) A statement that the vaccine complies with WHO (Southern or Northern hemisphere) for the year/season must be included.
- 11) Copy of the approved Patient information Leaflet.
- 12) Copy of the proposed Patient Information Leaflet indicating:
  - i) The year/season for which the vaccine will be used;
  - ii) WHO recommended strains.
- 13) All labels, immediate and outer container, must prominently indicate the year/season for which the vaccine will be used and a facsimile must be submitted as proof.
- 14) International core Data Sheet.

#### Approval

All amendments, including amendments to the package insert and the patient information leaflet, must be approved by the Medicines Control Council (MCC) before release of any batches of influenza vaccines.

## 11 REVISION HISTORY

Date	Reason for update	Version & publication
June 2003	First publication released for implementation and comment	Version 1 May 2003
July 2003	Deadline for comment	
November 2003	Date for finalisation/implementation	
December 2003	Edited version	Version 2
June 2006	Amended sections 1.2, 2.1, 2.2, 2.4, 3, 5.7, 5.7.1, 5.7.2, 6, Appendix A2, 7.1, 7.2, 7.3, 8, 9. Addition of section 10.	Version 3 June 2006
	1 Update of sections on <ul style="list-style-type: none"> <li>• Format of responses to Council</li> <li>• Format of Amendment Submissions and the covering letter, and general conditions</li> <li>• Proprietary name changes</li> <li>• Affidavit by the HCR/Applicant in Appendix 2</li> <li>• List of abbreviations / acronyms</li> <li>• Legends for stability data</li> </ul> 2 Inclusion of <ul style="list-style-type: none"> <li>• Types of amendments for Biologicals specifically</li> <li>• Section on Annual Viral Strain Changes for Influenza Vaccines</li> </ul>	
14 August 2006	Deadline for comment	
December 2006	Date of implementation	
October 2008	Amended sections Appendix A1 & A2, 4, 4.11, 4.12, 4.13, 4.17, 4.18, 5, 5.1, 6, 7.1 (1, 3, 8, 13), 7.2 (1a, 1b, 4), 7.3 (8), 7.4 (18, 19, 21, 22, 23, 24, 25, 26), 10.3 (7)	Version 4
	1 Amendment to sections on the HCR / PHCR to clarify requirements with regard to the FPRR. 2 Amendment to and addition of requirements with regard to changes to the Active Product Ingredient. 3 Clarification of requirements regarding pharmacopoeial changes 4 Replacement of proof of specific immunogenicity by the submission of retrospective data re efficacy for Annual Viral Strain Changes for Influenza Vaccines	
15 December 2008	Deadline for comment	
May 2009	*Date of implementation	
<i>* The required stability data have to be generated and submitted within six months for all applications for API changes made since January 2008 that would now be categorised as Type C changes for Fixed-dose Combinations. Further products may be added as determined by Council.</i>		
June 2010	Amendment of sections 1.2 and 5 for clarity	Version 4_1 June 2010
With immediate effect	Date of implementation	
July 2010	Correction of section 7.3 Categories 8a and 8b	Version 4_2 June 2010
With immediate effect	Date of implementation	

Date	Reason for update	Version & publication
March 2011	Renamed to "Amendments" guideline	Version 5, March 2011
	Amended to include reference to CTD modules, deletion of MBR1 Annexures where relevant	
	Expanded documents required for shelf-life extension in accordance with Stability guideline	
	Corrected FPRR acronym	
	Amended time of submission of annual vaccine strain changes	
	Amended sections: 2.1, 2.2, 2.4, 2.7, 2.9, 2.10, 2.12 4.5, 4.9, 4.11, 4.12, 4.13, 4.18.2, 4.18.3 5, 5.1, 5.2, 5.3, 5.7c), 5.7d), 5.7f), 5.7g) 5.7.1, 5.7.2, 5.7.3 6 Appendix A1, A2 7.1, 7.1 (24) 7.2, 7.2 (1a, 4b, 11, 12) 7.3, 7.3 (8a, 8b, 8c, 10, 11, 17, 24B, 26B, 27B, 28B, 29B) 7.4 (18, 21, 23, 24, 25, 26) 8; 10.4	
With immediate effect	Date of implementation	
July 2012	Amendment of 5.2; amendment to 7.1 Type A category 10 to include 10b re update of storage instructions; Replacement of active substance, active raw material and raw material with API, IPI and pharmaceutical ingredient as relevant Inclusion of CTD numbering and clarification of API and FP stability dissolution under Type C category 8.	Version 6, August 2012
August 2012	Date of implementation	