

# MEDICINES CONTROL COUNCIL



## IMPLEMENTATION OF THE POST-REGISTRATION AMENDMENTS GUIDELINE

This guideline has been prepared to serve as a recommendation to the holder of a certificate of registrations wishing to submit applications for amendment of registration dossiers of medicines. 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. This guideline is also intended to address the current backlog of amendments and to streamline the process for the future.

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REGISTRAR OF MEDICINES  
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## IMPLEMENTATION OF THE POST-REGISTRATION AMENDMENTS GUIDELINE

### 1 Background

The form used for detailing amendments as per Circular 6/96 was instituted in order to facilitate evaluation of amendments. If this form is completed in detail, it is possible to evaluate the submission from the form, with limited cross-checks in the actual Annexures/PARTs of the dossier, such as stability data and dissolution profiles.

The Amendments Unit has experienced that the details supplied in the “List of amendments” in the form as per 6/96 are often incomplete and do not comply with the MCC requirements or guidelines.

As a consequence, the reviewers have to spend an unnecessarily long time to properly review the submissions. This causes a significant delay in the processing of submissions, while the MCC is specifically committed to speed up this processing.

The following recommendations are intended to rectify the situation and facilitate a speedy review process.

An adapted version of Circular 6/96 will now be used and referred to as the “Amendment Schedule” (refer to the Post-registration amendments guideline). This amendment schedule includes all the information previously contained in

- a) the covering letter,
- b) the old Circular 6/96,
- c) the forms MRF 3A and MRF 3B and
- d) any other information relevant to the amendment application.

Therefore, a separate covering letter and amendment forms will not be required.

### 2 Guidance

Any applications for amendments submitted after the date of implementation of the Post-Registration Amendments guideline should comply with the requirements regarding data submitted and the format of the submission.

Applicants who have submitted applications for amendments to which replies are still pending, from July 2002 to date, are requested to do the following:

- 2.1 Apply the classification of types of amendments retrospectively to the relevant submission, and submit a letter referring to the submission awaiting review, indicating the classification (type A, B and / or C) – see point 2.3 below.
  - Indicate all types if the application involves a combination of different types.
  - Indicate clearly whether the same update is submitted separately for other products, e.g. a product range.
  - If more than one update/amendment was submitted for the same product from July 2002 to November 2003, submit these letter templates together, in order that the amendments can be handled together.

**2**      *Guidance continued*

- 2.2 Check the presentation of the submissions. If the List of Amendments is not sufficiently detailed, submit another list to **replace** that awaiting review – no new data should be included, only the List of Amendments.
- 2.3 Use the attached letter template when submitting the requested information, as the same letter will be used by the Post-registration Amendments Unit to respond to the applicant.
- 2.4 Submit the above information no later than 28 February 2004.

**3**      **Amendment Schedule**

Please also refer to the notes in the Post-Registration Amendments guideline.

- 3.1 It will be helpful to approach list of amendments from the point of view that the evaluator does not know the product, what the amendment is or why it is required.
- 3.2 To compile the AMENDMENT SCHEDULE properly, it means that the applicant should, in effect, sit with the current and proposed amended dossiers open next to each other and compare them.
- 3.3 If a response to a previously amended Annexure / Part is still pending, but the amendment was minor and this Annexure / Part is used as the current, this should be clearly indicated.
- 3.4 Include a header or footer indicating the page number.

An example of the required format is included in the Post-Registration Amendments guideline.

A further example of the List of Amendments including different ways of indicating the pages to be replaced, is attached.

**List of amendments:**

- 1 Present this table in landscape format.
- 2 Please note that a formulation amendment (Annexure 2 / Part 3B) should include the effect of the amendment in the “Reason for amendment” column.

*Italic font* denotes examples of statements or information that are not acceptable.

Normal font denotes examples of statements or information which would be required / accepted.

An \*asterisk denotes a recommendation and not an actual example.

PRODUCT NAME AND APPLICATION NUMBER				
Annexure / PART	Current Annexure / PART	Amended Annexure / PART	Reason for amendment	Comment of reviewer (for office use only)
3	<i>ABC approved supplier.</i>	<i>XYZ included as alternative supplier.</i>	<i>Routine update</i>	<i>Not acceptable</i>
3	ABC approved manufacturer.	XYZ included as alternative manufacturer. *List the information that has been included in support of the new manufacturer. *Confirm that the information for the approved manufacturer remains the same.	ABC cannot keep up with the demand, and an alternative source has to be available.	
	No index included in 3C.	Full index included in 3C.	Administrative amendment to facilitate location and review of data.	
	Replaced entire Annexure 3 with the amended Annexure submitted or Replaced pages 3.1 and 3.2 with the amended pages submitted, and included pages 3.20 to 3.30			

PRODUCT NAME AND APPLICATION NUMBER				
Annexure / PART	Current Annexure / PART	Amended Annexure / PART	Reason for amendment	Comment of reviewer (for office use only)
4	<i>Raspberry flavour In-house specification RF1</i>	<i>Raspberry flavour In-house specification RF2</i>	<i>Routine update</i>	<i>Not acceptable</i>
4 p 4.1 and 4.3.1	<u>Raspberry flavour:</u> In-house specification RF1	<u>Raspberry flavour:</u> In-house specification RF2	Updated to new manufacturer's in-house specification.	
	1. Appearance: ABC	1. Appearance: ABC	No change – included for the sake of completeness	
	2. Identification: The sample and standard chromatograms are comparable (GLC)	2. Identification: The sample and standard chromatograms are comparable (GLC) or The IR-spectrum is concordant with an authentic sample	Inclusion of IR spectroscopy as an alternative test.	
	3. Flavour: -	3. Flavour: XYZ	Additional test	
	4. Microbial contamination: -	4. Microbial contamination: Ph. Eur.	Additional test	
5	<i>Raspberry flavour: In-house method RF1</i>	<i>Raspberry flavour: In-house method RF2</i>	<i>Routine update</i>	<i>Not acceptable</i>
5	<u>Raspberry flavour:</u> In-house method RF1	<u>Raspberry flavour:</u> In-house method RF2	Updated to new manufacturer's in-house methods.	
	Appearance – Visual	Appearance - Visual	No change – included for the sake of completeness	
	Identification: GC method GM20	Identification: GC method NM-GC-02	GC method of the new manufacturer – no actual change, same operating conditions, different format only.	

PRODUCT NAME AND APPLICATION NUMBER				
Annexure / PART	Current Annexure / PART	Amended Annexure / PART	Reason for amendment	Comment of reviewer (for office use only)
5 (cont.)	-	IR method NM-IR-1	Additional test, method of the new manufacturer included.	
	Flavour: -	Flavour: Method described.	Additional test	
	Microbial contamination: -	Microbial contamination: Ph. Eur.	Additional test	
	Replaced pages 5.1 & 5.3 with amended pages 5.1 & 5.3.1 to 5.3.3			
6	<i>Raspberry flavour</i>	<i>Raspberry flavour updated tests stated</i>	<i>Update in line with Annexure 4</i>	<i>Not acceptable</i>
6	<u>Raspberry flavour:</u> Appearance Identification	<u>Raspberry flavour:</u> Appearance Identification Flavour Microbial contamination	Updated in line with the amended An. 4 (due to the change in manufacturer).	
	Annexure submitted in full for the sake of completeness. Amendment is on page 6.2 only.			
7A		<i>Updated final product specifications submitted</i>	<i>Routine update</i>	<i>Not acceptable</i>
7A	*List each parameter as in approved MBR1.	*Indicate each parameter as proposed.  *If most remain unchanged, only those to be changed need be stated, with confirmation that the other parameters remain the same.	*State reason for each change.	
	Replaced the entire Ann 7A with the amended Annexure submitted.			

PRODUCT NAME AND APPLICATION NUMBER				
Annexure / PART	Current Annexure / PART	Amended Annexure / PART	Reason for amendment	Comment of reviewer (for office use only)
7B		<i>Updated final product control procedures.</i>	<i>Routine update in line with Annexure 7A.</i>	<i>Not acceptable</i>
7B	*List the current procedures that are being amended.	*List the procedures that have changed.	*State the reasons for each change. *Indicate if it is a change in format only and no actual change to the method.	
		Replaced pages 7B.0 to 7B.3 and included pages 7B.8.1 to 7B.9.2		
10		<i>Updated stability data included.</i>	<i>Updated to MCC requirements.</i>	<i>Not acceptable</i>
10 (b)	Pages 10.0, 10.2.1, 10.3.1 Stability data on two production batches i.e. XYA and XYB 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 requested.	
	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 requested.	

The Registrar of Medicines  
Medicines Control Council  
Private Bag X828  
PRETORIA  
0001

Date



Dear Sir / Madam,

**PRODUCT NAME – Application number**

Date of amendment: \_\_\_\_\_

Reference: \_\_\_\_\_

Type	Category/ies
A	
B	
C - General	
C - Shelf-life	
C - Inspectorate	

These amendments were also submitted for other products in the range: Yes\_\_\_ No\_\_\_  
List product names and numbers.

*Amendment schedule*

List of amendments detailed: Yes \_\_\_\_\_ No \_\_\_\_\_

List of amendments replaced: Yes \_\_\_\_\_ No \_\_\_\_\_ N/A \_\_\_\_\_

Signed: \_\_\_\_\_  
(Typed name)

\_\_\_\_\_ Designation

**FOR OFFICIAL USE ONLY**

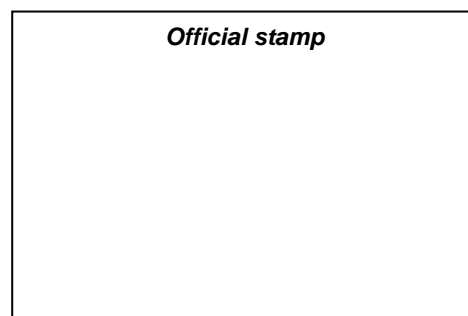
Dear Sir / Madam,

We acknowledge receipt of the above letter.

( ) The amendment/s has/have been placed on file.

( ) The amendment/s will be evaluated and you will be notified of the outcome in due course.

Yours faithfully



**REGISTRAR OF MEDICINES**