MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

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POST-IMPORTATION TESTING

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration 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. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

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POST-IMPORTATION TESTING OF MEDICINES

1 INTRODUCTION

The integrity of imported products could be compromised during transit. It is therefore important that the applicant confirms the imported product's integrity prior to release for sale in South Africa. In terms of Regulation 15 (Annexure 9A) of Act 101 of 1965, this is done by:

This should be done by:

1.1 Identification and assay, and other relevant tests performed locally on the final product.

Or

1.2 Return of samples to overseas testing laboratories or the manufacturers that supplies the product, for identification and assay and other relevant testing.

Note: The MCC prefers local testing of the final product and may recommend a local laboratory.

2 EXEMPTIONS FROM ~~RE~~ POST-IMPORTATION TESTING (PITE)

2.1 Exemptions ~~to~~ from post-importation testing will be considered in the following circumstances:

2.1.1 When very small quantities are imported for "selected" patients, or groups of patients. A ~~suitable motivation is required and a~~ projection as to the annual usage of the relevant product must be submitted.

~~2.1.2 If the identification and assay cannot be performed in South Africa the applicant should submit full justification and motivation.~~

2.1.2 In cases where there are pharmacopoeial analytical methods available for substances, post-importation exemption will not be considered unless a substantiated motivation for the request is provided.

2.1.3 ~~Any other reason deemed by the applicant as being of such nature as to qualify for consideration for this exemption~~. Post-importation exemption may be considered if there is no established monograph available for the substance, for example new chemical entities or products still under patency.

~~2.1.4 Continuous monitoring of temperature and humidity, where relevant of each shipment with validated monitoring devices according to SOP as well as performing a physical identification of the product.~~

2.1.4 If the identification and assay cannot be performed in South Africa due to complexity of testing, absence of the technology/equipment or lack of resources at local laboratories to perform such testing, proof thereof should be submitted with the application.

2.1.5 Other reasons may be proposed by the applicant to be considered for exemption of testing. Such reasons should be defined in terms of quality. Reasons related to economic factors would not be deemed relevant.

2.1.6 The product under discussion must be transported in a validated container. Calibrated monitoring devices (both minimum and maximum) must be placed inside the container to record the conditions (temperature and relative humidity) whilst the product is in transit. Note that products sensitive to vibrations/agitation must be transported in vibration/agitation controlled conditions.

2.2 The applicant must in all instances provide full motivation for exemption from post-importation testing.

Products which are exempted from post-importation testing are not exempt from meeting regulatory release parameters, including, but not limited to, product release specifications and absence of environmental condition excursions i.e. temperature and humidity.

2.3 Requirements: submission of PITE requests (refer to Attachment 2)

2.3.1 Completed application letter for post-importation testing exemption and relevant fees, if applicable.

2.3.2 Continuous monitoring and control of transport conditions. See Attachment 1 (transportation of products) for monitoring and control of transport conditions.

2.3.3 A summary of the number of shipments, shipment details, including quantity of product imported during previous period of exemption.

2.~~2~~4 Validity of approved exemptions

2.4.1 Exemption, if approved, will be valid for three years ~~(renewable thereafter)~~ provided that all requirements are complied with.

2.4.2 Only one renewal of post-importation testing exemptions for a further period of two years will be considered, provided that the following are submitted:

2.4.2.1 Renewal application form and relevant renewal fees submitted three months prior to expiry of the approved exemption.

2.4.2.2 Records of quantities imported during the previous exemption period.

2.4.2.3 Evidence of compliance with the appropriate transport-storage monitoring and control of conditions.

2.4.2.4 Line listing of all serious adverse drug reactions reported in South Africa, in relation to the imported medicine.

2.4.3 Post-importation testing exemption for a product is valid only for the manufacturers/packers listed in the exemption.

2.4.4 Any changes to the transport monitoring and control equipment, methods and validations previously submitted, invalidate the post-importation testing exemption granted.

2.4.5 An applicant may re-apply for post-importation testing exemption as per 2.3.

3 GUIDELINES FOR MONITORING OF TRANSPORT

3.1 Monitoring and control of transport, that is, evidence that the conditions during transport are continuously monitored ~~by temperature and, where relevant, humidity recorders.~~ and controlled, including relevant parameters, such as temperature, humidity, vibration and freeze conditions.

3.2 The transport monitoring and control conditions ~~(temperature and humidity, where relevant)~~ of each shipment are recorded by a suitable device which provides a printout that will form a permanent record of the specific shipment and is filed with the batch release documents. Should the printout relate to different products of the same shipment, a QC certified copy of the print-out should be filed with the batch release documents.

3.3 An SOP, specifying the details of inclusion of the recorders, should be available for inspection. The procedure should include amongst others, the number of recorders, position of placement, date of activation and inactivation (on leaving the place of dispatch i.e. factory, and on receipt by the applicant i.e. warehouse) and evaluation of the printout with the reference to the stability data.

3.4 The monitoring and control mechanism should be qualified and/or calibrated as applicable and relevant records should be available for inspection. Thermo logger locations must be scientifically justified. Vibration studies to ensure that physical stresses encountered during transport do not negatively affect the stress sensitive products and the control of vibrations during transportation are submitted.

3.5 Data obtained through accelerated and long-term stability studies would not be considered as justification for release of products which have been exposed to environmental excursions observed during product transportation. This would include products sensitive to vibrations and lower temperatures. Note that

monitoring as well as control of these parameters must be assured throughout transportation.

3.6 Please note that exemption is applicable only for shipments monitored and controlled (refer to attachment 1). ~~subsequently evaluated for compliance with the stability profile~~. Shipments not in compliance should therefore be identified and assayed and other relevant tests performed as stated in point 1 above.

4 SUBMISSION REQUIREMENTS ~~TO MCC FOR EXEMPTION BASED ON MONITORING OF TRANSPORT~~

The following must be submitted:

4.1 A copy of the accelerated stability data of the formulation being applied for, packed in the final container as specified in ~~MRF1 PART 3D / MBR1 Annexure 8~~ Module 3.2.P 7 (Container closure system) (to determine if the humidity should be monitored). The submission should include the necessary supportive stability data~~.~~ Post-importation testing exemptions are only applicable for product packed in the final container.~~ If previously submitted, a statement to this effect will suffice.~~

4.2 The transport monitoring and control method, ~~or transport conditions~~ and parameters ~~should~~ must be specified in the master release document.

4.3 A tabulated summary indicating the method of transport ~~utilised and~~, the conditions during transport as indicated below and the method of controlling the respective conditions should be submitted. Data from a minimum of five printouts are required, giving an account of the same product or five different products, provided that the products require the same storage conditions, and provided that the products are dispatched from the same site but by different shipments.

4.4 A copy of ~~MRF1 PART 3F / MBR1 Annexure 7A. /~~ Module 3.2.P.5.1 and 3.2.P.5.2 (Control of pharmaceutical product, Specifications and Analytical procedures) ~~(Final Product Control)~~ including special conditions of handling and storage ~~for~~ e.g. "*do not freeze*", "*do not shake or agitate the contents*" and "*store at or below X°C"*.

~~4.5 An indication as to whether the request is for bulk product or for the product packed in the final container.~~

4.~~6~~5 A copy of the proposed master release document (MRD) in ~~accordance with MRF1 PART 3F~~ Module 3.2.P.5.1 reflecting the specifications pertaining to the product in question (example attached). The MRD should include:

4.5.1 The type of recorder used in transit.

4.5.2 A specification that the received certificate of analysis is valid, is complete (reflects the actual results of the tests performed) and reflects compliance with the registration requirements.

4.5.3 Visual identification of the product and dosage form.

4.5.4 A consignment reference e.g. GRN (goods received notice) or invoice. (Batch numbers on the invoice should concur with the batch numbers of the products).

4.5.5 Confirmation of the integrity of the containers, seals, and labels. Each aspect should be specified and controlled to ensure that no damaged articles are accepted.

4.5.6 Outcome of the evaluation of the transport conditions and relevant action, i.e. further testing to be performed.

4.6 Evidence to support that the product imported is not subject to transport delays/repackaging that may result in tampering / counterfeiting of the imported product.

5 CONDITIONS OF EXEMPTION

5.1 The MCC may grant exemption from testing of the product upon importation which is subject to conditions which the MCC may deem necessary.

5.2 The MCC may grant permission for skip testing i.e. full exemption is not granted.

5.3 Appropriate fees may apply.

Post-importation Testing exemption does not negate the need for the applicant to assume full responsibility for product quality and for the release of products which are safe, effective and of high quality.

NB The Medicines Control Council reserves the right to withdraw the exemption, should the applicant give cause.

ATTACHMENT 1: *a) Summary of data: transportation of product*

NAME OF PRODUCT:
REGISTRATION NUMBER:
DOSAGE FORM:
APPROVED STORAGE CONDITION:
ASSURANCE: TEMPERATURE RECORDED IN EACH SHIPMENT

Name of Product	Batch Number	Maximum and minimum temperature recorded	Other transport sensitive conditions e.g. vibration measurements	Maximum humidity recorded (where relevant)	Duration of transport (Date commenced and date terminated)	Mode of Transport	Signature of responsible pharmacist who verified the printouts

ATTACHMENT 1: b) *Example* of Master Release Document (MRD)

COMPANY MASTER RELEASE DOCUMENT (MRD) PRODUCT NAME: Code:			Page x of y Date: Supersedes ... of	
Batch number				
Approved storage conditions				
Final product specification reference number				
Receiving notice number (GRN)				
Dates of dispatch and of receipt				
Transit period specification, actual and conformity			YES	NO
Quantity dispatched				
Number of containers received				
Test	**Specifications**	**Result**		**Signature**
Temperature and humidity printout (storage and transport conditions)	Present, attached; conforms to ~~stability profile submitted~~ product specific storage and handling requirements			
Certificate of Analysis	Present, valid (batch specific), conforms to ZA CTD/~~MRF1~~, complete			
Visual Identification	e.g. Product description, labelling, container, batch number, expiry date			
Shipping containers' condition	Clean, undamaged	Number approved, Number rejected		

Shipping container label	~~Untampered~~Not tampered with		
Shipping container seal	Present, intact		

Conclusion: Conformance	YES	NO	Further testing required?	YES refer to …..	NO
Comments					
Position/Function					

Originator		**Approved**		**Authorised**	
Designation		**Designation**		**Designation**	
Signature		**Signature**		**Signature**	
Date		**Date**		**Date**	

ATTACHMENT 2: *Template of application for post-importation testing exemption*

Company letterhead
Date

The Registrar of Medicines
Department of Health
Private Bag X828
Pretoria
0001

VIA

Dear Sir / Madam

REQUEST FOR POST-IMPORTATION TESTING EXEMPTION

Product Proprietary Name					
Application Number					
Registered medicine		Old medicine		Reply to MCC Response on VIA	

First time request for exemption	YES	NO
Renewal of existing exemption	YES	NO
Date first time exemption granted		
Motivation for exemption	*Summary of reasons why exemption should be considered*	

1 Attached herewith:

ZACTD Module 1.2.1	
Copy of medicine registration certificate*	
Records of quantities imported during the previous exemption period	
Evidence of compliance with the appropriate transport, storage and handling conditions	
Evidence that the transport monitoring and control equipment used are qualified	
Copy of Previous Post-importation Testing Exemption (if applicable)	
Submission requirements as per point 4 of the Post-importation Testing Guideline	
Application/Renewal fee, if relevant	

2 I declare that

- the request for post-importation testing is 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 amendments history, have been made.

_____
Signature of HCR

Name	Title	Qualification	Designation	e-mail	Tel number

UPDATE HISTORY

Date	Reason for Update	Version & Publication
May 2003	First publication released for implementation and comment	v1 May 2003
Nov 2003	Release for additional comment	v1 November 2003
Dec 2003	Date for finalisation/implementation	v1 December 2003
27 March 2015	Section 2: • Clarification and expansion of requirements • Requirements for application included Section 3: Expansion on monitoring and control conditions Section 4: Updated format requirements and clarification Attachment 1: • Additional column included for transportation sensitive conditions • Expansion on data required Attachment 2: Inclusion of template cover letter	v2 January 2017
November 2016	Section 4.1, 4.4 ,4.5 and Attachment 1: change from MRF1 to CTD	
31 March 2017	Due date for comment	