Quality Medicines for Malawi

PHARMACY AND MEDICINES REGULATORY AUTHORITY

DIRECTIVE FOR IMPORTATION AND RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS

For Clinical trials to be conducted in Malawi

Table of Contents		
		Page

1 Introduction

Investigational medicinal products which are unregistered medicines may only be brought into the country after ethical approvals are in place, the clinical trial application has been approved and a letter of authorisation has been issued by the Pharmacy and Medicines Regulatory Authority.

The National Drug Regulatory Authority of the producing country should be responsible for assurance of compliance with GMP for the manufacture and lot release of clinical batches and vaccines.

They should take all appropriate measures to ensure that the holder of the authorisation referred to above has permanently and continuously at his disposal the services of at least one qualified person who is responsible in particular for ensuring:

(a) in the case of investigational medicinal products that each batch has been manufactured and checked in accordance with internationally accepted standards of good manufacturing practice for medicinal products for human use, in accordance with the product specification file, and that each production batch has been checked in accordance with the information submitted in the application for authorisation;

(b) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information submitted in the application for authorisation.

In so far as the provisions laid down in (a) or (b) above are complied with, investigational medicinal products shall not have to undergo any further testing if they are imported into the country in which the clinical trial is to be conducted, together with batch release certification signed by the qualified person.

In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfies the provisions as stated above. The said register or equivalent document should be kept up to date as operations are carried out and shall remain at the disposal of the agents of the competent authority for a period of not less than five years.

2 Scope

This guideline applies to all investigational medicinal products, including vaccines, which do not have marketing authorisation in the country of intended use.

All procedures should apply to the placebo product, if applicable to the relevant clinical trial.

During the period of validity of the trial authorisation any subsequent importations should be subject to the same procedures.

3 Responsibilities of the Sponsor

The sponsor should not supply an investigational medicinal product until the sponsor obtains all required documentation (e.g. approval from COMREC and Pharmacy and Medicines Regulatory Authority.

The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP and is coded and labelled in a manner that protects the blinding, if applicable.

The sponsor should determine for the investigational medicinal product(s) acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any.

The sponsor should:
- ensure timely delivery of investigational product(s) to the investigator(s);
- maintain records that document shipment, receipt, disposition, return and destruction of the investigational product(s);
- maintain a system for retrieving investigational product(s) and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim);
- maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

The sponsor should also:
- take steps to ensure that the investigational product(s) are stable over the period of use; this data should be available on request and for inspection purposes. If non-compliance with the specifications becomes evident in the stability studies during the period of use in the clinical trial, the sponsor should notify the investigators and arrange to take appropriate steps;
- maintain sufficient quantities of the investigational product(s) used in the trial to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

4 Labelling and Packaging

The labelling of investigational medicinal products should comply with the relevant NRA requirements.
The particulars should appear in at least the official language of the country on the outer packaging or, where there is no outer packaging, on the immediate packaging.

The particulars should include at least the following information:
- state clearly that it is clinical trial material
- the product name or unique code
- storage temperature and conditions
- expiry date
- sponsor contact details

Investigational medicinal products should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

The investigational product(s) should be stored as specified by the sponsor, and in line with Good Pharmacy Practice (GPP), Good Manufacturing Practice (GMP), and the Pharmacy and Medicines Regulatory Authority regulations and conditions.

In blinded trials the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5 Importation and Release

Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.

A pre-clearance inspection should be carried out at the port of entry by the Pharmacy and Medicines Regulatory Authority. This should include the shipping documentation and overall physical condition of the consignment. (See point 6 below.)

If specific storage conditions are essential to ensure the quality of the product, e.g. maintenance of cold chain in the case of vaccines, a device that will confirm that storage temperatures were not exceeded during transport should be included with the shipment.

6 Documentation

Documentation that should accompany each consignment of IMP should enable the Pharmacy and Medicines Regulatory Authority at the port of entry to release the product to the investigator(s) responsible for conducting the clinical trial in the country.

This documentation should include at least:

- the Certificate of Analyses of each batch of the investigational product(s) as well as comparator(s), if relevant.
- a copy of Pharmacy and Medicines Regulatory Authority letter of approval of clinical trial.
- a copy of a valid Certificate of Manufacture issued by the competent Regulatory Authority in the country of origin.
- a copy of a valid WHO Certificate of a Pharmaceutical Product (CoPP) issued by the competent Regulatory Authority in the country of origin.

The Cover Sheet should be completed by the sponsor and should accompany each consignment of investigational medicinal products. ***See Annex 1.***

The Check-list may be used by the sponsor to ensure that the required documents are attached and correct, but a blank document should be submitted with the Cover Sheet for use by the relevant NRA staff responsible for authorizing the importation of the IMP. ***See Annex 2***

7 Definitions and Abbreviations

CoA: Certificate of Analysis

GMP: Good Manufacturing Practices

IMP: Investigational Medicinal Product
It is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

PMRA: Pharmacy and Medicines Regulatory Authority

Sponsor: An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

ANNEX 1

COVER SHEET ***(to be completed by the sponsor)***	
IMPORTATION AND RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS	
Fees (if applicable)	
Study Title and	
Phase of the study	
Protocol Number	
Study Drug	
Unique code number	
PMRA Reference number of clinical trial	
PMRA reference number(s) of comparator drug(s) (if applicable)	
PMRA reference number(s) of concomitant drug(s) (if applicable)	
Sponsor	
Applicant	
Trial site(s)	
Sponsor Contact Person: Address Telephone number Fax number Cell number E-mail address	
Batch number(s) and expiry date: Study drug Comparator drug(s)	
Quantities	
Blinding done or not	
Recommended storage temperature	

ANNEX 2

CHECK-LIST of required documentation

To be supplied by the sponsor for use by the PMRA staff responsible for authorising the importation of the IMP

IMPORTATION AND RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS			
CHECK-LIST of required documentation			
Are the following documents attached and correct, as indicated:		**YES**	**NO**
1	Copy of PMRA letter of approval of clinical trial		
2	Certificate(s) of Analysis (CoA) Study drug Comparator (if applicable)		
3	Does the CoA reflect at least the following information:		
	Product name or code		
	Name of company / Sponsor		
	Batch number		
	Expiry date		
	Date of issue		
	Signature, qualification and title of responsible person		
	Results of physical and analytical tests		
4	Copy of valid Certificate of Manufacture issued by the competent Regulatory Authority in the country of origin		
5	WHO certificate of a pharmaceutical product issued by the competent Regulatory Authority in the country of origin		
6	Device / Proof of maintenance of cold chain (if applicable)		
7	Labelling: *outer packaging, immediate container* Does the label clearly indicate		
7.1	that the product is clinical trial material, e.g. "For use in clinical trial only"		
7.2	Product name or unique code (if blinded)		
	Does this concur with the information on the Cover Sheet		
7.3	Storage temperature		
	Does this concur with the information on the Cover Sheet		
7.4	Storage conditions (e.g. protection from light)		
7.5	Batch number		
	Does this concur with the information on the Cover Sheet		
7.6	Date of Manufacture		
7.7	Expiry date		
	Does this concur with the information on the Cover Sheet		
7.8	Sponsor contact details		

IMPORTATION AND RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS			
CHECK-LIST of required documentation			
Are the following documents attached and correct, as indicated:		**YES**	**NO**
	Does this concur with the information on the Cover Sheet		
8	Is the physical condition of the consignment acceptable?		