Guidelines for GMP, Import, Export and Destruction of Investigational Medical Products (IMPs) for Clinical Trials Bangladesh

Directorate General of Drug Administration
Ministry of Health and Family Welfare
Govt. of the People's Republic of Bangladesh

Reference Documents: This Guideline has been developed based on following Guidance Documents:

GCP guideline 2015, Guidelines to Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use (volume 4) as per EU Directive 2005/28/EC and 2003/94/EC, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products - Annex 3 in the use of essential drugs.6 Report, WHO, 1995 ((WHO Technical Report Series, N°850)

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Revision History:

Sl. No	Version No.	Causes for Revision
01	00	Newly prepared SOP
02	01	Included the feedback mechanism to inform the NRA on quantities left over after the CT, how to keep the records of import and destruction of IMPs during and after the CT, application forms to import of IMPs, application form of NOC for IMPs

CONTENTS

1. ACRONYMS

SOP	:	Standard Operating Procedure
IMP	:	Investigational Medical Products
CT	:	Clinical Trial
QA	:	Quality Assurance
PI	:	Principle Investigator
IB	:	Investigational Brochure
NRA	:	National Regulatory Authority
DGDA:		Directorate General of Drug Administration

2. OVERVIEW

An investigational medicinal product is any medicinal product which is being tested within a trial or any product, including placebo, used as a reference in a clinical trial. The manufacturing, testing and distribution of investigational medicinal products (IMPs) are strongly regulated by the relevant authorities to assure high quality of medicinal products that are administered to patients in clinical trials. Full transparency and traceability from the origin of starting materials to dosing and finally destruction of the study medication is mandatory.

3. Legal Basis:

1) As per Gazette notification of Ministry of Health & Family Welfare memo no: 45.00.000.182.22.001.21.103 dated: 04 May 2021 and Government Gazette published on 28 June, 2021: sec: b (4),

Investigational Medical Products (IMPs) shall be manufactured complying cGMP by WHO. Sample of Investigational Product (IP) or Investigational New Drug (IND) or New Chemical Entity (NCE) shall be destroyed upon getting the approval of licensing authority.

4. RESPONSIBILITIES

4.1 This guideline will be used by DGDA CT staffs, investigators, sponsors & monitors, etc.

4.2 Responsibility for investigational product(s) accountability at the trial site(s) lies with the investigator/institution.

4.3 Where allowed/required, the investigator/institution may/should assign some or all the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.4 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.5 The investigational product(s) should be stored as specified by the sponsor in accordance with applicable regulatory requirement(s).

4.6 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.7 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.

5. GMP REQUIREMENTS

To manufacture IMP for clinical trial shall comply Good Manufacturing Practice (GMP)

i) The manufacturer should manufacture the product following WHO TRS-986 Annex 2 (general principle of GMP) & for sterile product TRS-961 Annex-6 or

ii) With the compliance of EU GMP, PIC/S GMP or US FDA CFR PART 21.

Sponsor or PI will submit investigational brochure (IB) which contains all information related to IMP. Also, they should submit GMP certificate of the manufacturing plant from the NRA of country of origin. Products of IND (Investigational New drug) or NCE (New Chemical Entity) are used for an indication not included in the summary of product characteristics for that product or used to gain further information about the product as authorized in the clinical trial authorization.

6. MANUFACTURING, PACKAGING, LABELING AND CODING OF IMPs

6.1 One of the most important aspects of the GMP based quality system is the final control of the IMP before it can be used in the clinical trial. To ensure the IMP has the required quality which is suggested by GMP certificate of concerned NRA

6.2 Investigational medical products should be produced in accordance with the principles and following the detailed guidelines of GMP for medical products. Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. For sterile products, the validation of sterilizing processes should be of the same standard as for products authorized for

marketing. To assure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.

6.3 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, (if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GCP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

6.4 The sponsor should determine, for the investigational product(s), acceptable storage temperature, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

6.5 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

6.6 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.

6.7 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

6.8 Quantity of IMPs and placebo is calculated and allowed to bring on the basis on human subject to be enrolled in the trial and dosed to be administered.

7. ROLE OF DGDA FOR IMPs IMPORT AND EXPORT

7.1 The manufacturer who supplies IMPs must obtain a relevant license from the appropriate Competent Authority (NRA).

7.2 The NRA has a legal responsibility to ensure that the IMPs has been manufactured in accordance with GMP and meets the conditions of the clinical trial authorization and the product specification file (PSF). In certifying a batch against the PSF **(Annexure-1)**, investigational medicinal product dossier or the clinical trial authorization (CTA) the NRA is providing certification. The manufacturer has to submit the GMP certificate of the IMPs.

7.3 Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step procedure: certification by the Qualified Person of NRA; and release by the sponsor for use in a clinical trial. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

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

7.5 The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

7.6 Product release based on GMP certificate; CoA & date logger reading is needed (**Annexure-2**). The sponsor may not start a clinical trial until the clinical trial authorization has been granted for the trial and all conditions of the authorization have been met; and an Ethics Committee positive opinion has been granted and each trial site has been approved.

7.7 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing and retrieval of unused product from participants, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement (s).

7.8 Sponsor should ensure timely delivery of investigational product(s) to the investigator(s). When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

7.9 The sponsor should update the Investigator's Brochure as significant new information becomes available.

7.10 Permission for bringing IMPs is issued NOC provided by DGDA Clinical Trial cell / NOC cell . In this NOC letter it is suggested that PI has to report DGDA the quantity of IMPs administered & quantity left over through letter to DGDA. (**Annexure-6 and Annexure-7)**

7.11 IMP records must be maintained to demonstrate adherence to the trial protocol and credibility and integrity of the data. (**Annexure-3**)

7.12 Labeling should comply with the requirements of NRA. The information in the (**Annexure-4)** should be included on labels, unless its absence can be justified.

7.13 CT cell head/an NRA officer may inspect the premises of the trial site/sponsor/CRO facilities to evaluate the following documents:

a) the Certificate of Analysis of each batch of the investigational product(s) as well as comparator (s), if relevant

b) a copy of the letter of approval of clinical trial

c) a copy of a valid GMP certificate of a pharmaceutical product 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. (**Annexure-5)**

8. RETURN TO SPONSOR OR DESTRUCTION OF IMPs

In the application of NOC for importing/locally collecting IMPs, the sponsor/ PI should mention the amount they want to import/collect with the justification. CT cell will verify the amount according to the protocol and they will issue the NOC. After finishing the trial, the PI/Sponsor will inform DGDA about the remaining and used amount of IMPs. (**Annexure-6)**

This procedure describes the methods to be used for return to the Sponsor or destruction of clinical study product used in clinical trials.

The procedures are as follows:

8.1 Procedure for the Return of Unused Investigational Product:

i) After the study has been completed, a comprehensive inventory of the product / devices is completed before returning them to the Sponsor.

ii) The manner of shipment of unused investigational product must be defined by the Sponsor and followed by site personnel. Returned investigational product must be packed and shipped with the documentation provided by Sponsor. The manner of shipment must have mechanism of being traced.

iii) The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug.

iv) Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.

v) Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

8.2 Procedure for Destruction of Investigational Product:

i) All investigational products used and unused must be accounted for by the Study Monitor/Sponsor. Disposal of used or unused investigational products must be initiated only after the written instruction from the Sponsor/Study Monitor had been obtained.

ii) Once accounted for, if the sponsor does not request that drugs need to be returned, then the products may be disposed of. The procedure for destroying used study drugs is as follows:

a. Safety and Regulatory Compliance Administrator must be contacted to arrange for pickup of used or unused investigational product for disposal as biomedical waste.

b. Prepare accounted drug and place them in a biohazard bag. Secure and tape the bag closed.

c. Keep bag with investigational product locked at site until it may be released to biomedical waste management personnel.

d. Document that drugs were disposed of according to policy.

Documentation shall be maintained concerning the disposal of the Investigational Product which shall contain:

- The quantity of the Investigational Product disposed of;
- The date and manner of disposal;
- The staff member who conducted the disposal;

A copy of this documentation shall be sent to the sponsor and kept with the research records.

9. ANNEXURES

Annexure-1 Product Specification File (PSF)

Title: Product Specification File (PSF)

Sl. No.	Types of documents	Availability of Documents			Remarks
		Yes	No	NA	
01	GMP Certificate of IMPs.				
02	Specifications and analytical methods for starting materials, packaging materials				
03	Specifications and analytical methods for intermediate, bulk and finished product				
04	Manufacturing methods				
05	In-process testing and methods				
06	Approved label copy				
08	Relevant clinical trial protocols				
09	Relevant technical agreements with contract givers, as appropriate				
10	Stability data				
11	Storage and shipment conditions				
12	Others if any:				

Note: The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the Qualified Person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of different Qualified Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

Annexure-2 Content of the Batch Certificate for Medicinal Products

Content of the Batch Certificate for Medicinal Products
[LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER]

1. Name, strength/potency, dosage form and package size
(identical to the text on the finished product package).
2. Batch number of the finished product.
3. Name of the destination country/countries of the batch.
4. Certification statement.

I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of NRA with the requirements of the Marketing Authorization(s) of the destination country/countries.

5. Name of the Qualified Person certifying the batch/QA manager.

6. Signature of the Qualified Person certifying the batch.

7. Date of signature

Annexure-3

Summary of labeling details:

a) name, address and telephone number of the sponsor, contract research organization or investigator (the main contact for information on the product, clinical trial and emergency unblinding);

GENERAL CASE

For both the primary and secondary

Packaging

(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;

(c) the batch and/or code number to identify the contents and packaging operation;

(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

PRIMARY PACKAGE

Where primary and secondary packaging remain together throughout

(e) the trial subject identification number/treatment number and where relevant the visit number;

(f) the name of the investigator (if not included in (a) or (d);

(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product

PRIMARY PACKAGE

Blisters or small packaging units

(h) "for clinical trial use only" or similar wording;

(i) the storage conditions;

(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.

(k) "keep out of reach of children" except when the product is for use in trials Where the product is not taken home by subjects.

[4] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

[5] The address and telephone number of the main contact for information on the product, clinical trial

and for emergency unblinding need not be included.

[6] Route of administration may be excluded for oral solid dose forms.

[7] The pharmaceutical dosage form and quantity of dosage units may be omitted.

Annexure-4

ANNEX 4: 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	
Name of the GMP certificate issued NRA	
Unique code number	
NDA approval number of clinical trial/IND no	
NDA reference number(s) of comparator drug(s) (if applicable)	
NDA 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	

	Submitted by (Sponsor/PI)	**Reviewed by (DGDA)**	**Approved/Authorized by (DGDA)**
NAME			
DESIGNATION			
SIGN & DATE			

Annexure-5

Report template of feedback to DGDA about the quantities left over and destruction of IMPs after the CT.

To be supplied by the sponsor/ PI to DGDA about the quantities left over and destruction of IMPs after the CT.

SI. No.	Types of document	Remarks
01	Study Title and phase of the study	
02	Protocol Number	
03	Study Drug	
04	Name of the GMP certificate issued NRA	
05	Unique code number	
06	NDA approval number of clinical trial	
08	NDA reference number(s) of comparator drug(s) (if applicable)	
09	NDA reference number(s) of concomitant drug(s) (if applicable)	
10	Recommended storage temperature	
11	Batch number(s) and expiry date: Study drug/	
12	Quantities of Imported/ Locally purchased IMPs	
13	Use amount of IMPs	
14	Rest amount of IMPs	
15	Sponsor Contact Person: Address Telephone number Fax number	

	Submitted by (Sponsor/PI)	Reviewed by (DGDA)	Approved/Authorized by (DGDA)
NAME			
DESIGNATION			
SIGN & DATE			

Anexure 6

Application Form of import of IMPs/Placebo

To

Director General

Directorate General of Drug Administration

Attention: Head of Clinical Trial Cell

Subject: Application of bringing IMPs for NOC application

In reference to approved protocol entitled "...." and protocol approval letter no.....I hereby apply to bring IMPs/Placebo. Required treasury chalan/bank draft copy and relevant documents has been duly filled and attached herewith. It is to be noted that study of PI.....sponsor..... study site/sites.....

Thanking you,

Name:

Designation:

Address:

Signature

Date:

Anexure 7

Checklist of NOC for IMPs:

1) GMP certificate
2) Certificate of analysis
3) IND certificate of IND product from country of origin.
4) Protocol approval letter
5) Name of PI, sponsor, Trial site in application for NOC
6)NOC fees