# endTB Clinical Trials Pharmacy Manual

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## DEFINITIONS and ABBREVIATIONS

**Ancillary Drugs:** Drugs that will be provided centrally from MSF Logistique (or exceptionally from local distributors upon approval of the Central Trial Pharmacist) to treat the main known side effects related to the use of the Investigational Products (IPs).

**Central Medical Store (CMS):** Drug storage area in each participating country where the IPs and ancillary drugs will be received from MSF Logistique or from local distributors (the latter only for Bedaquiline (in few countries) and few ancillary drugs and upon approval of the Central Trial Pharmacist) and stored until distribution to the dispensary pharmacy (if any) or directly to the institution pharmacies. This Central Medical Store is under the responsibility of the Site Principal Investigator or delegated site pharmacy personnel.

**Concomitant medications (Con-med):** Drugs that might be procured locally for provision to patients suffering of concomitant diseases (e.g. HIV, HCV).

**Dispensary pharmacy**: Drug storage area in some participating countries that will be used for drug storage and dispensing. IPs and ancillary drugs will be received from the Central Medical Store and, after dispensing, distributed to the storage and distribution area(s) at peripheral location(s) by trained site personnel. This dispensary pharmacy is under the responsibility of the Site Principal Investigator or delegated site pharmacy personnel.

**Institution Pharmacy:** The location where the IPs and ancillary drugs will be stored at each site (institution) before being distributed to the applicable wards and DOT corners. This storage is under the responsibility of the Site Principal Investigator or delegated site pharmacy personnel.

**Investigational Products (IPs):** All the TB drugs listed in the endTB Clinical Trial Protocols are considered IPs in this study: Amikacin, Bedaquiline, Capreomycin, Clofazimine, Cycloserine, Delamanid, Ethambutol, Ethionamide, Isoniazid, Kanamycin, Levofloxacin, Linezolid, Moxifloxacin, PAS, Prothionamide, Pyrazinamide and Terizidone. In addition for endTB-Q protocol, Amoxicillin/Clavulanate and Imipenem/Cilastatin.

**Medicine administration:** Medicine administration refers to the intake by the participant of medicines as prescribed by a physician.

**Medicine dispensing:** Medicines dispensing refers to the process of preparing and giving a medicine to a named person on the basis of a prescription. It involves the correct interpretation of the prescription and the accurate preparation and labeling of the medicine for safe administration to the patient.

**Medicine distribution:** Medicine distribution refers to the process of transferring medicine from one storage location to another regardless of the medicine being already dispensed or not.

**Stringent Regulatory Authority (SRA) is** [[1]](#footnote-2)[1]**:**

* a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission (EU), the US Food and Drug Administration (US FDA) and the Ministry of Health, Labour and Welfare of Japan also represented Regulatory guidance by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or
* an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or
* a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015)

A synonym for SRA is **Highly Regulated Country** (HRC)

**Storage and distribution area(s):** the location(s) outside the pharmacies in each participating country where the IPs, ancillary drugs, and concomitant medication(s) will be stored before being distributed to the participants. These locations are under the responsibility of the Site Principal Investigator or delegated site personnel.

**Ward/DOT (Directly Observed Treatment) corner:** the location(s) where the IPs and ancillary drugs will be dispensed to the participants daily (except in the sites where the IPs will be distributed and then stored at patients’ home). These locations are under the responsibility of the Site Principal Investigator or delegated site personnel.

## CENTRAL PROCUREMENT OF IPs

### MSF Logistique

**MSF Logistique** is responsible of procuring the 19 IPs and the essential ancillary drugs (see Appendix A1 for the Ancillary drug list) to countries participating in endTB Clinical Trials.

**MSF Logistique**, a non-for-profit association under French 1901 law, is one of the supply centers for *Medecins Sans Frontieres* ([MSF](http://www.msf.org/)). MSF Logistique is based in Bordeaux, France.

**MSF Logistique** has extensive experience with medical supplies from purchasing through shipment, particularly with second-line anti-TB drugs supplies. MSF Logistique operates in compliance with the World Health Organisation Model Quality Assurance System for procurement agencies (WHO MQAS).

**MSF Logistique** is an approved "pharmaceutical establishment" by the French Ministry of Health since 1999. In 2007, MSF Logistique obtained the certificate of Good Distribution Practices in its capacity as wholesale pharmaceutical establishment for humanitarian projects. MSF Logistique is also certified by the European Commission as international humanitarian procurement center.

Fact sheet (Annual report 2017):

* 178 employees
* 102 M€ turnover
* 5 142 tons shipped
* 24,7 M€ worth of stock
* 21 661 m² storage capacity
* 15 357 product references

### MSF Quality Policy for Drug Procurement

The drugs supplied through MSF Logistique are selected according to the MSF quality policy for drug procurement. The MSF policy is consistent with the principles of the WHO’s Model of Quality Assurance for procurement agencies, and it covers the qualification of medicines, drug purchase, and drug supply to beneficiaries.

MSF’s qualification of pharmaceutical products is not intended to interfere with the WHO’s prequalification initiative (WHO PQ), nor is it to duplicate any existing qualification system, such as the Good Manufacturing Practices (GMP) inspections or product evaluations, carried out by a National Regulatory Authority (NRA) in a highly regulated country. The criteria where a pharmaceutical product would automatically be granted a product approval by MSF include:

* Any WHO pre-qualified product will be accepted by MSF; or
* Any product registered by a Stringent Regulatory Authority will be accepted by MSF.

If none of these above criteria is met, MSF will also accept products that have been reviewed and permitted for use by the Expert Review Panel (ERP) (category 1 and 2 only), which is co-managed by the Global Fund, Global Drug Facility (GDF) and WHO Prequalification program (WHO-PQ) for TB medicines.

### Selection of Manufacturers for a Clinical Trial

#### IPs

In order to ensure a steady supply and avoid bias, the endTB Clinical Trials will use only a single manufacturer for each IP, especially in cases where several validated manufacturers exist, through the duration of the study. MSF Logistique has selected medicines already approved by MSF quality policy (therefore even more stringent than International Conference on Harmonization - Good Clinical Practices guidelines) and the related manufacturers based on prior collaborating experience. MSF Logistique has secured procurement agreements with the selected manufacturers for the duration of the clinical trial. The list of manufacturers for each IP is as below.

Any deviation from this list will be documented by the Clinical Trial Pharmacist.

|  |  |  |  |
| --- | --- | --- | --- |
| **Item code** | **Description** | **Manufacturer** | **Clinical Trial** |
| DINJAMIK5A- | AMIKACIN sulfate, eq. 250 mg/ml base, 2 ml, amp. | **Medochemie** | **endTB and endTB-Q** |
| DORAAMOC5T1 | AMOXICILLIN 500 mg / CLAVULANIC acid 125 mg, tab. | **Remedica** | **endTB-Q ONLY** |
| DORABEDA1T- | BEDAQUILINE, 100 mg, tab. | **Janssen** | **endTB and endTB-Q** |
| DINJCAPR1V- | CAPREOMYCINE sulfate, eq. 1 g base, powder, vial | **Vianex** | **endTB and endTB-Q** |
| DORACLOF1C- | CLOFAZIMINE, 100 mg, soft caps. | **Novartis** | **endTB and endTB-Q** |
| DORACYCL2C1 | CYCLOSERINE 250 mg caps. | **Macleods** | **endTB and endTB-Q** |
| DORADELA5T1 | DELAMANID, 50mg, tab., blister | **Otsuka** | **endTB and endTB-Q** |
| DORAETHN2T1 | ETHIONAMIDE, 250 mg, tab., blister | **Macleods** | **endTB and endTB-Q** |
| DORAETHA4T1 | ETHAMBUTOL hydrochloride, eq.400mg base, tab. blister | **Macleods** | **endTB and endTB-Q** |
| DINJIMCI55V | IMIPENEM 500 mg / CILASTATIN sodium 500 mg, powder, vial | **Panpharma** | **endTB-Q ONLY** |
| DORAISON1T1 | ISONIAZID ,100 mg, breakable tab., blister | **Macleods** | **endTB and endTB-Q** |
| DORAISON3T1 | ISONIAZID ,300 mg, blister | **Macleods** | **endTB and endTB-Q** |
| DINJKANA1V- | KANAMYCIN sulfate, eq. 1 g base, powder, vial | **Panpharma** | **endTB and endTB-Q** |
| DORALEFX2T- | LEVOFLOXACIN hemihydrate, eq. 250 mg base, tab. | **Hetero** | **endTB and endTB-Q** |
| DORALEFX5T- | LEVOFLOXACIN hemihydrate, eq. 500 mg base, tab. | **Macleods** | **endTB and endTB-Q** |
| DORALINE6T- | LINEZOLID, 600 mg, coated tab. | **Hetero** | **endTB and endTB-Q** |
| DORAMOXI4T- | MOXIFLOXACIN hydrochloride eq. to 400 mg base, tab. | **Hetero** | **endTB and endTB-Q** |
| DORAPASA4S2 | PARA-AMINOSALICYLIC acid (PAS), del.rel.gran, 4g, sach.(25°C) | **Jacobus** | **endTB and endTB-Q** |
| DORAPRON2T- | PROTHIONAMIDE, 250 mg, tab. | **Microlabs** | **endTB and endTB-Q** |
| DORAPYRZ4T1 | PYRAZINAMIDE, 400 mg, tab., blister | **Macleods** | **endTB and endTB-Q** |
| DORATERI2C1 | TERIZIDONE, 250 mg, caps., blister | **Riemser** | **endTB and endTB-Q** |

#### Ancillary Drugs

MSF Logistique may choose any MSF-validated manufacturer for the supplies of essential ancillary drugs. The manufacturer selection is dependent on the availability of stock in house when the order is received from the countries. It is possible that the endTB Clinical Trial sites may receive from MSF Logistique ancillary drugs from different manufacturers when the orders are placed for the same drug. Nonetheless, the specifications of the received ancillary drugs, including the designation, dosage and forms, will always be the same.

The list of essential ancillary drugs, selected for endTB clinical trials, is available in Appendix A1 of this manual. For some of the ancillary drugs identified in the Appendix A1, a minimum stock should be maintained at the Central Medical Store (CMS).

#### IPs as concomitant medication (Con-Med)

IPs or any TB drugs should be avoided as Con-Med but their use is not disallowed unless they fall into the list of disallowed concomitant medications. In case a TB drug included in the endTB IP list is prescribed as Con-Med : a) it is advised to use drugs from the IP stock if quantities are sufficient (to ensure quality of the dispensed drug ); b) the Sponsor should be informed and the CAC (Clinical Advisory Committee) consulted (informed if the conditions of the patients are life threatening); c) the pharmacy should receive a prescription in the same format used for the ancillary drugs; d) a note should be written in the dispensing accountability logs saying that that quantity has been allocated as Con-Med and not as an IP to that patient; and e) a NTF is required to document the case.

### Transportation

MSF Logistique is responsible for ensuring appropriate transportation conditions for the drugs supplied to countries participating in the endTB Clinical Trials.

MSF Logistique will send all drug shipments by air. The supplies will be packed in pre-qualified, insulated boxes that maintain storage temperature between 15-25°C or 2-8°C (qualification done by a company certified by French authorities) as per MSF Logistique procedure. Each packing box will contain a data logger that starts tracking as the parcel leaves MSF Logistique until the box is opened in the Central Medical Store of the destination country.

In case of temperature excursion during the drug transportation process, i.e. data logger alerts, delegated site personnel should follow the actions as detailed in the Standard Operating Procedure (SOP) IP-003-CT IP Replenishment and Reception.

### Process of a Clinical Trial

**Before Initial IP shipment for a Trial**

Before the initial IPs shipment is sent to the country:

1. Mandatory documents prior to IP shipment must be available (see SOP IP-002-CT IP Release).
2. The Drug Storage Assessment Form must be completed by delegated site personnel and approved as “conform” by the Clinical Trial Pharmacist or designee on behalf of the Sponsor. One form must be completed for each of the following storages: Central Medical Store, dispensary and institution (hospital) pharmacies (see SOP IP-002-CTIP Release).
3. The IP Release Form must be completed by delegated site personnel and submitted to the Clinical Trial Pharmacist or designee for approval (see SOP IP-002-CT IP Release).

**Note: National IRB/IEC Approval + Local Regulatory Approval + Authorization of IP Importation = Start**

**During the conduct of a Trial**

1. Clinical Trial Pharmacist gives Greenlight to MSF Logistique on behalf of the Sponsor to trigger IPs shipment
2. Customs clearance of the shipment happens in the recipient country
3. Reception of the drugs happens at the Central Medical Store within the country (see SOP IP-001-CT IP Storage and IP-003-CT IP Replenishment and Reception)
4. Distribution, dispensing, and accountability of the drugs have to be conducted as per Sponsor provided/approved SOP (see SOP IP-004-CT IP Distributing, Dispensing, and Accountability)
5. Regular replenishments of IPs and ancillary drugs has to be performed to avoid stock-outs (see SOP IP-003-CT IP Replenishment and Reception)

**During the conduct and at the end of a Trial**

1. IPs returns from patients, damaged or expired drugs are returned to a designated area of the Central Medical Store (see SOP IP-005-CT IP Return).
2. Anytime IPs destruction is requested, the delegated site personnel must submit a list of items to be destroyed to the Clinical Trial Pharmacist for approval. Once destruction approval is received, the delegated site personnel should proceed to IP destruction in accordance with the national regulations. A certificate of destruction, usually issued by the local authority, must be obtained and retained (see SOP IP-006-CT IP Destruction for minimum content).

**Note:** All expired medicines must be destroyed. The expiry day when not indicated is always the last day of the month of the expiry date indicated on the packaging. For instance, if the expiry date is indicated as follow “Jan. 2020”, the exact expiry date will be the 31st of January 2020.

1. Final return and final destruction should occur once the last randomized trial patient in the country has finished his/her treatment (see SOP IP-006-CT IP Destruction).

 **Important note:** The decision on the fate of unused, not expired, sealed containers of IPs and ancillary drugs either present or returned to the Central Medical Store is the responsibility of the Sponsor. The Sponsor will discuss with the Site Study Coordinator, delegated site personnel and the Site PI all applicable options to minimize wastage. These drugs might be considered for use in the country outside of the clinical trial umbrella or for the endTB/endTB-Q trials if there is a need and following national regulatory authorities approval.

1. At the end of the study or at the closure of a site, the Sponsor (Clinical Trial Pharmacist) or the external monitor should complete the IP section of the endTB site close-out report including: IP final accountability, returned IPs accountability and temperature and Relative humidity reports review; destruction Sponsor authorization and destruction certificate and/or in case of donation Sponsor and NRA approval; and a comprehensive review of the Central Investigator File (CIF) and Investigator Study File (ISF) (see Section 2.7). The Site Internal Monitor may check on Site and provide the information required for completion of the Sponsor site close-out report.

### Pharmacy monitoring

In each participating site, the Site Internal Monitor will regularly check that IPs management is according to endTB Protocol, SOPs, Good Clinical Practices guidelines and national regulation. The Site Internal Monitor will proceed with the checks according to defined work instructions (to be reviewed and approved also by the Clinical Trial Pharmacist). Monitoring reports and findings will be shared and discussed as per need with the Sponsor (see endTB Site Quality Management Plan):

* the regulatory monitoring tool (containing a pharmacy section) will be shared with the Central Study Coordinator on a quarterly basis.
* the detailed pharmacy monitoring tool will be completed as per local work instruction and shared with the Clinical Trial Pharmacist as a minimum on quarterly basis.

All the  findings  of  the  report  should  be  discussed  with  the  site  pharmacist.

### Pharmacy Site File

The Pharmacy Site File corresponds to the Section 6 of the Investigator Site File (ISF) (see endTB ISF and CIF list). While the trial is on-going, the Pharmacy Site File must be updated by the delegated site personnel and kept at the Central Medical Store of each country/site (as appropriate). Some of the documents have to be uploaded on the Central Investigator File (CIF) (see endTB ISF and CIF list), the electronic Trial Master File platform provided by the Sponsor and available until the end of archiving period. At the end of the trial, the Pharmacy Site File will be archived as Section 6 of the Investigator Site File and retained with other essential trial documents on site.

All the documents listed in the Pharmacy Site File Index that exist in electronic version can be stored electronically. Providing the documents don’t contain any patient personal data, all electronic documents requested for archiving can also be retained on the “Central Investigator File” (CIF).

### IP Monthly Report to Sponsor

On the first Monday of each month, delegated site personnel must submit an IP monthly report to the Clinical Trial Pharmacist –by uploading it in the CIF section 6.12.

The IP monthly report is generated after the monthly update of QuanTB.

The delegated site personnel shall follow the steps below:

1. Change the reference date to the current date
2. Record the end of quantification date corresponding to two years after the end of the enrollment period
3. Complete the “enrolled cases”
4. Complete the “expected cases”
5. Complete the “stock of medicines” (see below )
6. Execute forecasting
7. Export to excel
8. Archive QuanTB file and exported excel file –in the CIF section 6.12.

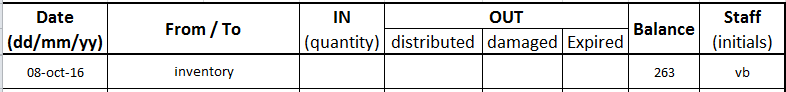
The Clinical Trial Pharmacist will be automatically alerted by the system that a new document has been archived in CIF section 6.12.

QuanTB and Excel files that must be submitted to the Clinical Trial Pharmacist on a monthly basis by uploading in the CIF must contain multidrug regimen (experimental arm) and Standard of Care regimen (control arm) preferably in one compiled file.

Delegated site personnel may report any relevant information to the Clinical Trial Pharmacist through email.

 **Important note:** To complete the stock of medicines, a physical inventory must be performed (for the CMS and the dispensary pharmacy if any).

The physical inventory has to be recorded on the “Drugs Global Accountability Log” and/or “Dispensation Log” as follows (see SOP IP-004-CTIP Distributing, Dispensing, and Accountability):



In some sites, a web-based software is used to monitor and record stock movements. Software print outs, dated and signed can be used instead of the Drugs Global Accountability Log to record inventory.

 Documents sent to Clinical Trial Pharmacist should not contain any patient personal data (e.g. names), only Study Subject ID can appear.

If the quantity found at the physical inventory is different from the theoretical balance (line above the inventory), the delegated site personnel must investigate to find out where the discrepancy occurred.

## REFERENCES

* Interim definition adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Technical Report Series (TRS) 1003 - Fifth first report. Who, Geneva, June 2017.

## SUPPORTING DOCUMENTS

* SOPIP-001-CTIP Storage (endTB Site Study Documents)
* SOP IP-002-CT IP Release (endTB Site Study Documents)
* SOP IP-003-CT IP Replenishment and Reception (endTB Site Study Documents)
* SOP IP-004-CT IP Distributing, Dispensing, and Accountability (endTB Site Study Documents)
* SOP IP-005-CT IP Return (endTB Site Study Documents)
* SOP IP-006-CT IP Destruction (endTB Site Study Documents)
* endTB Site Quality Management Plan (endTB Site Study Documents)
* endTB ISF and CIF list (endTB Site Study Documents)

## APPENDIX

|  |  |
| --- | --- |
| **Number** | **Title** |
| A1 | Pharmacy Manual\_A1- Ancillary drug list |

1. [1] Interim definition adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Technical Report Series (TRS) 1003 - Fifth first report. Who, Geneva, June 2017. [↑](#footnote-ref-2)