LICENSING AND ENFORCEMENT DIVISION

PIR cGMP INSPECTION REPORT OF PHARMACEUTICAL MANUFACTURER:

Name of company: **Therdose Pharma Pvt Ltd**

1.0 General information

1.1 Name of Inspected company	**Therdose Pharma Pvt Ltd**
1.2 Physical address	Plot No:118-122, Survey,No. 342, ALEAP Industrial Estate, Opp JNTU Lane, Pragathi Nagar, Gajularamaram (V) Quthbullapur (M), Medchal-Malkajgiri District- 500 090 Telangana State, India
1.3 Corporate address	Plot No:118-122, Survey, No. 342, ALEAP Industrial Estate, Opp JNTU Lane, Pragathi Nagar, Gajularamaram (V) Quthbullapur (M), Medchal-Malkajgiri District- 500 090 Telangana State, India
1.4 Summary of the main activities performed	Manufacture of the following finished pharmaceutical dosage forms: Oncology injectables liquid and lyophilized (vials)
1.5 Scope of Inspection	Product based inspection to verify compliance with cGMP guidelines for the manufacture of Oncology injectables liquid and lyophilized (vials)
1.6 Purpose of Inspection	To ascertain cGMP compliance to support new registrations and continued registration of products in Zimbabwe
1.7 Inspectors	Ms Martha Mwatseteza - **Co-inspector** Mr. Sly Mutyavaviri **–Lead-inspector**
1. Date of Inspection	3rd – 4th of March, 2025

2.0 Abbreviation list

Abbreviation	Expanded Form
AHU	Air Handling Unit
BMR	Batch Manufacturing Record
BPR	Batch Processing Record
CV	Cleaning Validation
EM	Environmental Monitoring
FPP	Finished Pharmaceutical Product
HPLC	High-Performance Liquid Chromatography
HVAC	Heating, Ventilation, and Air Conditioning
MACO	Maximum Allowable Carry Over
MCAZ	Medicines Control Authority of Zimbabwe
MFS	Media Fill Study
PDE	Permitted Daily Exposure
PQ	Performance Qualification
PQR	Product Quality Review
QA	Quality Assurance
SOP	Standard Operating Procedure
TD	Therapeutic Dose
TRS	Technical Report Series
WFI	Water for Injection
WHO	World Health Organization

3.0 Summary

3.1 Brief summary about the facility

TherDose Pharma Pvt Ltd is located at Plot No:118-122, Survey, No. 342, ALEAP Industrial Estate, Opp JNTU Lane, Pragathi Nagar, Gajularamaram (V) Quthbullapur (M), Medchal-Malkajgiri District- 500 090 Telangana State, India. The company manufactures general soft gelatin capsules. The Medicines Control Authority of Zimbabwe (MCAZ) Inspectorate audited the block manufacturing oncology injections. The audit was conducted from the 3rd to the 4th of March 2025. The company has been audited by other regulatory bodies such as Philippines, Ethiopia, Kenya, Tanzania, Syria, Nepal and Sri Lanka.

3.2 General Information about the Company and the Site

This was a routine inspection of the site by the Medicines Control Authority of Zimbabwe (MCAZ) Inspectorate, to support registration of products in Zimbabwe. The site had been previously audited by the MCAZ on the 9th to the 11th of February 2018. The inspection was product-based and focused on the products that were intended for the Zimbabwean market, as provided below:

Product	**Dosage form**	**Registration number**
Bortezomib 2mg lyophilized injection	injection	Pending registration
Carboplatin BP 150mg/15ml injection	injection	Pending registration
Carboplatin BP 450mg/45ml injection	injection	Pending registration
Carmustine USP 100mg lyophilized injection	injection	Pending registration
Sterile diluent for Carmustine/3ml	injection	Pending registration
Irinotecan 40mg/2ml injection	injection	Pending registration
Irinotecan 100mg/5ml injection	injection	Pending registration
Melphalan 50mg lyophilized injection	injection	Pending registration
Solvent for Melphalan 10ml injection	injection	Pending registration
Paclitaxel USP 30mg/5mlninjection	injection	Pending registration
Thiotepa 15mg injection	injection	Pending registration
Thiotepa 100mg lyophilized injection	injection	Pending registration
Zolendronic acid Concentrate for solution for infusion 4mg/5ml lyophilized injection	injection	Pending registration
Fulvestrat injection 250mg/5ml	injection	Pending registration

The first day activities comprised of an introductory meeting in which the MCAZ Inspectorate and the TherDose Pharma Pvt Ltd team introduced themselves. This was followed by a projected TherDose Pharma Company power-point presentation. Thereafter the scope of the inspection was defined, both parties agreed on the blocks to be inspected. Immediately extensive document review commenced. Later in the day a walk-through inspection was conducted, for the raw material warehouse and the production floor.

Second day activities encompassed further document review and the inspection of the Quality control laboratories chemistry section, the microbiology section, and the utilities block (HVAC system &Water Purification). The inspectors then held an inspectors' meeting in which findings from the inspection were discussed and there was consensus on the inspection findings.

The inspection was conducted with reference to and in accordance with the WHO Good Manufacturing Practices detailed in the Technical Report Series 986, Annex 2 of 2014, among other relevant current guidelines. The inspection was conducted in an open and cooperative atmosphere.

3.3 Areas inspected

- **Quality Management**: Product Quality Review (PQR), Quality Risk Management, Deviation control, finished product and starting material batch release, Contract agreements and Supplier approval.
- **Materials Management**: Receipt, handling, quarantine, sampling, release, reject, temperature (and humidity) monitoring and dispensing.
- **Good Practices in Production**: Production areas, production equipment, documentation and instructions, sanitation cleaning and maintenance, batch records, calibration, contamination control, in process controls.
- **Quality Control**: Review of test procedures and specifications.
- **Utilities**: HVAC, Purified Water,
- **Environmental Monitoring**: EM Program
- **Equipment qualification** and preventive maintenance

3.4 Utilities

a. Water Purification system
b. HVAC system
c. Compressed air system

3.5 Documents reviewed

As listed in the report

4.0 System Summaries

Pharmaceutical Quality System

Product Quality review

The SOP for Annual Product Quality Review was submitted for review. The PQRs were prepared in accordance with the TRS requirements. The critical material attributes, critical quality attributes were being reviewed. All the pharmaceutical quality system components had been reviewed. PQRs of the product under the scope of the inspection were reviewed. From the statistical evaluations, all the processes were in a state of control.

Complaints

An SOP for complaints handling was provided for review. There was provision of categorization of complaints according to the impact. The root cause investigation tools used were indicated. There was provision of putting in place immediate actions. The logs of complaints were submitted for review, and these were being adequately investigated. There were trend reports of complaints.

Deviations

The SOP for Handling of deviations was submitted for review. The deviations were classified as minor, major and critical. These were also managed with QA. Root cause identification and CAPAs for the deviations were being executed. Examples of deviations were taken for review to demonstrate implementation of the SOP.

Change Control

The SOP for change management was submitted for review. There was provision for impact assessment and risk evaluation as part of change management. There was provision of a multidisciplinary approach to change management. The log of changes were submitted for review. Examples of changes were evaluated to see implementation of the SOP.

Vendor Qualification

The SOP for vendor management was submitted for review. There was provision of an offsite questionnaire for initial evaluation of a vendor. This incorporated key declarations. This was followed with onsite inspection of the facilities. The SOP provided for the auditors and their qualifications. There was provision of an ongoing vendor monitoring program and this was acceptable.

Product Recall

The SOP for product recall was submitted for review. There was provision of voluntary and regulatory recalls. The procedure provided for receipt, evaluation, immediate action, classification and root cause identification for the defects or complaints resulting in the recalls. There was classification of recalls. The SOP provided for mock recalls.

Self-Inspection

The SOP for self inspection was submitted for review. There was provision of facility calendar for the same. A multi departmental approach under the supervision of QA was being taken. Audit observations were being handled in prescribed timelines.

Quality Risk Management

The SOP for risk assessment was submitted for review. The approach to risk identification, risk evaluation, risk mitigation and periodic review was specified. The different types of risk tools used were specified. Risk management was incorporated in the majority of the pharmaceutical quality system.

Utilities

Purified water system
The P and I.D diagrams for the water system was submitted for review. The sampling points, the inline monitoring parameters were indicated. The generation, purification and distribution processes were evaluated. The annual trend reports were submitted for review and these were acceptable.

Air handling units (AHU)
The AHUs of the critical sections were inspected. The approach to preventative maintenance was reviewed. The approach to monitoring of critical environmental parameters was specified. The approach to handling of the filters and cleaning of the filters was provided and this was satisfactory.

Materials Management

Procurement of starting materials was being done from approved vendors. The SOP for receipt of raw materials was provided. The materials were appropriately stored at the appropriate storage conditions. The environmental conditions were verified. The sampling area and the dispensing areas were provided.

Batch Manufacturing Records

The SOP for issuance, retrieval, review and archival of batch manufacturing records and BPR was submitted for review. The dispensing part was verified and there was provision of appropriate line clearance. The compounding stage was verified and the meta data for the cleaning process were submitted for review. The hold time study reports for the products under the scope of the inspection were submitted for review. The approach to filtration was verified in the BMR. The appropriate filters were being used. Vial washing and depyrogenation, filling, rubber stoppers handling was reviewed. The environmental records were reviewed and were satisfactory. The vial inspection was inspected and was satisfactory.

Disinfectant preparation

The SOP for disinfectant preparation was submitted for review and this was satisfactory.

Gases handling

The approach to handling of aseptic gas was verified and this was satisfactory.

Facility tour.

Filling line was inspected. The lyophilisation area was inspected. The autoclave area was inspected. The SOP for lyophilisation was submitted for review.

Qualifications

Manufacturing Tank performance qualification (PQ)

The PQ of the manufacturing tank was submitted for review and this was satisfactory.

Autoclave Qualification

The autoclave qualification report was submitted for review. All the critical parameters had been considered.

Depyrogenation tunnel

The Depyrogenation tunnel qualification report was submitted for review. This was being requalified at a frequency of 6 months. All the critical parameters had been considered.

Media Fill Study (MFS)

The video of the most recently executed MFS was reviewed during the inspection. All the interventions were being challenged and the worst case conditions had been considered.

Cleaning validations

The cleaning validation report for cytotoxic injections #TD/QA/CV/002. The MACO calculation were submitted for the 10ppm, dose criterion, the PDE criterion. The dose criterion

MACO was the least. The calculation of the swab and rinse limit were specified and the rinse limit was specified. The cleaning validation for paclitaxel injection 30mg/5ml #TD/QA/CV-R/002-01 was submitted for review.

Quality Control

Microbiology Laboratory

The sterility test area was inspected and was satisfactory. The approach to media handling, growth promotion tests, inoculation, incubation and enumeration was verified. Vertical inspection of water for injection (WFI) test reports were conducted and these were satisfactory.

Chemistry laboratory

There was provision of a sample receipt area. The samples were adequately labelled with respect to the tests to be executed. There was appropriate environmental monitoring. The approach to finished pharmaceutical products (FPP) specifications and Worksheets issuance was verified and this was satisfactory.

High Performance Liquid Chromatograph (HPLC)

The SOP for HPLC operation and calibrations were submitted for review. The good chromatographic SOP was submitted for review and

Laboratory incidences and audit trails

The SOP for handling of laboratory incidents in quality control was submitted for review. The log of incidences was inspected. These were being adequately investigated with corrective actions proposed.

4.0 Conclusion

Based on the areas inspected, the people met, and the documents reviewed including the observations listed in the Inspection Report **TherDose Pharma Pvt Ltd** located at **Plot No:118-122, Survey, No. 342,ALEAP Industrial Estate, Opp JNTU Lane, Pragathi Nagar, Gajularamaram (V) Quthbullapur (M), Medchal-Malkajgiri District- 500 090 Telangana State, India** was considered to be operating at an acceptable level of compliance with WHO TRS cGMP guidelines for the manufacture of oncology injections vials (liquid and lyophilized).

All the non-compliances observed during the inspection listed in the full report were addressed by the manufacturer to a satisfactory level prior to the publication of the MCAZ PIR

The site will be reinspected **3 years** from the date of the last inspection in line with the risk based reinspection frequency determination.

5.0 References

1. WHO good manufacturing practices for pharmaceutical products: main principles. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eight Report* Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2 http://www.who.int/medicines/publications/pharmprep/en/index.html

2. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8, https://www.who.int/publications/m/item/Annex-8-trs-1010
3. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3 https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf?sfvrsn=9440a5c_0&download=true
4. Supplementary guidelines on good manufacturing practices: validation. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report*. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4 http://www.who.int/medicines/publications/pharmprep/en/index.html

5. WHO good practices for pharmaceutical microbiology laboratories. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2 http://www.who.int/medicines/publications/pharmprep/en/index.html

6. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. *WHO Expert Committee on specifications for pharmaceutical preparations*. *Forty-third report.* Geneva, World Health Organization, 2009. (WHO Technical Report Series, No. 953), Annex 2 http://www.who.int/medicines/publications/pharmprep/en/index.html

7. WHO guidelines on quality risk management. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report* Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2 http://www.who.int/medicines/publications/pharmprep/en/index.html

8. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty Ninth Report* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929),

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http://www.who.int/medicines/publications/pharmprep/en/index.html

9. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty Ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/publications/pharmprep/en/index.html