LICENSING AND ENFORCEMENT DIVISION

PUBLIC cGMP INSPECTION REPORT OF PHARMACEUTICAL MANUFACTURER:

Name of company: **4care Lifesciences Pvt. Ltd c/o Gliesse Pharmaceuticals**

1.0 General information

1.1 Name of Inspected company	**4care Lifesciences Pvt Ltd**
1.2 Physical address	Survey No. 23/3P & 24, Opp. Jeans Factory, Daduran Vistar, Village- Bagdol, Taluka: Kathalal, District: Kheda. Pin-387630
1.3 Corporate address	AKIK, 1st Floor Opp. Lions Hall, Mithakhali Six Roads, Elisbridge, Ahmedabad, Gujarat – 380006
1.4 Summary of the main activities performed	Manufacture of the following finished pharmaceutical dosage forms: General Oral Solid Dosage forms (Tablets and Capsules)
1.5 Scope of Inspection	Product based inspection to verify compliance with cGMP guidelines for the manufacture of: General Oral Solid Dosage forms (Tablets and Capsules)
1.6 Purpose of Inspection	To ascertain cGMP compliance to support registration of new products in Zimbabwe
1.7 Inspectors	Ms. Martha Mwatseteza - **Co-inspector** Mr. Sly Mutyavaviri **–Lead-inspector**
1.8 Date of Inspection	21st – 22nd of February, 2025

2.0 Abbreviations list

Abbreviation	Expanded Form
AHU	Air Handling Unit
BMR	Batch Manufacturing Record
BPR	Batch Processing Record
CV	Cleaning Validation
EM	Environmental Monitoring
ENFORCEMENT	Not defined in document
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

4care Lifesciences Pvt Ltd located at Survey No. 23/3P & 24, Opp. Jeans Factory, Daduran Vistar, Village- Bagdol, Taluka: Kathalal, District: Kheda. Pin-387630. The company manufactures general oral solid dosage forms tablets and capsules. The company was a contract manufacturer for Gliesse pharmaceuticals products that had been submitted to Zimbabwe through Emcure Pharmaceuticals.

The Medicines Control Authority of Zimbabwe (MCAZ) Inspectorate audited the block manufacturing tablets. The audit was conducted from the 21st to the 22nd of February 2025. The company has been audited by other regulatory bodies as follows:

Country	**Agency**
India	WHO
Cambodia	DDF
Philippines	FDA
Yemen	SBDMA
Kenya	PPB
Peru	DIGEMID
Gabon	DMP

3.2 General Information about the Company and the Site

This was a new inspection of the site by the Medicines Control Authority of Zimbabwe (MCAZ) Inspectorate, to support registration of products in Zimbabwe. 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**
Dapagliflozin Propanediol Monohydrate 5mg tablet IH	Tablet	Pending registration
Metformin hydrochloride 1000mg/Dapagliflozin 10mg BP extended-release tablet	Bilayer tablet	Pending registration

The first day's activities comprised of an introductory meeting in which the MCAZ Inspectorate and the 4care Lifesciences and the Gliesse Pharmaceuticals team introduced themselves. This was followed by a projected 4care Lifesciences Company power-point presentation. Thereafter the scope of the inspection was defined, both parties agreed on the blocks to be inspected. Immediately after, extensive document review commenced. Later in the day a walk-through inspection was conducted for the raw material warehouse, production block for the tablets and utility area (Water Purification and HVACC).

Second day activities encompassed further document review and the inspection of the quality control laboratories chemistry section and the microbiology section. 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

1. As listed in the Final Inspection report

4.0 System Summaries

Pharmaceutical Quality System
Product Quality review

The SOP for PQR was provided. The approach to erection of the PQRs was as per the WHO TRS. All the elements of the PQRs had been covered. The PQRs were being produced annually. The approach to statistical evaluation was provided. The critical quality attributes CpK showed that the processes were in a state of control. The PQR of one of the products under review was submitted for review and this was acceptable. There was satisfactory review of all the starting materials (API and excipients) and all the components of the pharmaceutical quality system.

Complaints

There was provision of complaints handling procedure. There was an effective categorization of the complaints. There were specified investigation periods for the different categories. The log of complaints for the past two years were reviewed and examples of complaints were reviewed to show application of the SOP. The complaints were being investigated with root causes identified and the corrective and preventative actions (CAPA) provided.

Vendor Qualification

SOP for vendor management was submitted for review. This provided for the initial vendor qualification, shipper sample receipt and testing. Key components of the vendor approval and declarations were captured in the SOP. The approach to routine vendor monitoring was specified. There was provision of audit teams and a qualification process for these was specified. The planner of vendor qualification was verified against the approved vendor list. The approach to disqualification was specified in the SOP.

Deviations

Handling of deviations was being managed through an SOP that was provided. The deviations were classified as critical, minor and major. These were also managed by QA and there was a multi-disciplinary approach. The root cause for the unplanned deviations were being investigated with risk principles being proposed and impact assessment for the same. The CAPAs for these were being provided. There was provision of trending of the deviations. The logs of deviations for the past two years were reviewed, and examples of deviations were taken for review to show the implementation of the procedure.

Change Control

The Change Management Process SOP was provided. This detailing the process of initiation, evaluation, approval, implementation, review, closure of changes and change effectiveness review. There was provision of classification of the changes according to the inherent risk and impact on the processes. Change control effectiveness would be verified at a frequency of 3 months and 6 months. Change control number CC/24/139; CC/24/197 and CC/24/57 were submitted for review and were found to be satisfactory.

Product Recall

Procedure for product recall was provided for review. The recalls were generally classified into voluntary and statutory recalls. These were classified further into class A, B, C and depth level type for consumers, retailers and wholesale distribution levels. The classes were clearly defined in the SOP and relevant examples were provided. This SOP also covered the mock recall procedure. The timelines for product recalls were defined in the SOP. An example of a mock recall was provided and this had been satisfactorily conducted.

Self-Inspection

SOP for self-inspection was presented. Self inspections for each department would be carried out bi-annually by a multidisciplinary team. The annual schedule was prepared at the beginning of the year. There was a qualification process for inspectors which was under QA. Inspectors were chosen based on experience and technical skills there was provision of observations categorization. The internal audit program was effectively being managed from audit observations categorization, CAPA handling and closure. These finding were tabled at the management review meetings. The calendar was reviewed and this was satisfactory.

Training

Training Program SOP was presented for review. This provided for all the types of trainings. There was provision of training needs identification. Training files were being kept for all employees. There was provision of training effectiveness verification. The training calendar was submitted for review and this was satisfactory.

Quality Risk Management

The SOP for quality risk management was submitted for review. There was provision of a multidisciplinary approach to risk handling. Different risk assessment tools were being used and the circumstances under which these would be used were specified in the SOP. Risk principles were part of the whole quality management process.

Preventive maintenance

There was an SOP on preventive maintenance was submitted for review. There was provision of a preventative maintenance planner. The PM frequencies were outlined in the SOP according to risk principles. The preventive maintenance plan for 2024 & 2025 and executed preventive maintenance records were reviewed. These were found to be satisfactory.

Facility Tour

Materials Management

Material management was in state of control. Procurement of starting materials was being done from approved vendors. SOPs for receipt of materials was provided and this was satisfactory. There was provision of material dedusting, quarantining, sampling and release. The SOPs were submitted for review. The approach to weight verification was provided. There was effective environmental monitoring and the records were verified. Temperature mapping had been executed. Sampling, dispensing areas and wash areas were provided which were in a good state of repair. The logbooks for traceability of the processes were submitted for review.

Production tour (Packing line)

The packing lines were inspected. The critical process parameters were defined. IPQC parameters were specified. All necessary challenge tests had been executed according to the SOPs and BMRs.

Air Handling Units (AHUs)

The AHU service floor was inspected. There was provision of appropriate air filtration system and temperature control. There was provision of a filter cleaning room. The filter cleaning area was inspected. The filter cleaning SOP was submitted for review and this was acceptable.

Area Qualifications

The SOP for area qualifications were submitted for review. The key concepts such HEPA leakage, Air Changes per hour, non viable particle counts, viable counts, room recover studies, relative humidity and pressure differentials. The frequencies for requalification were defined. The results for the areas reviewed had passed.

Purified Water System (WFI & PW)

The source of the PWS was specified. The approach to monitoring of the feedwater was specified and this was adequately monitored. The action and alert limits of the critical parameters to be monitored on the waters system were specified. The approach to sanitization of the system was specified. the sanitization records were verified. The approach to verification of the dumping systems was also verified. The water trend reports for 2024 were verified. The water system was in a state of control.

Batch Manufacturing Records

There was an SOP that controlled the issuance of blank manufacturing records. This was being followed in the issuance of the BMRs that were reviewed. The BMR of some of the products that were under the scope of the inspection were verified. The approach to line clearance, environmental monitoring, IPQC, yield verification and release were reviewed. The BMR were satisfactory. The dispensing, granulation, drying, blending, compression, coating and packing stages were provided.

BPR

The batch packing records were submitted for review. There was provision of adequate line clearance. Yield reconciliation was being done.

Batch release

SOP for batch release of finished product was submitted. There was provision of a checklist and the final batch release was being signed by the authorised person.

Facility tour

There was provision of hand wash facilities, the premises were adequately maintained with provision of covings and cleanroom walls.

Dispensing areas was provided. This had an RLAF for dispensing of active materials. The approach to handling of accessories such as cable tires and poly bags was specified.

Granulation room

Granulation room was inspected. This had a sifter, a Rapid Mixer Granulator, Fluidised bed drier and a blender. These were qualified. The SOPs for operation for the same were submitted for review. The room was being maintained in a good state of repair.

Tooling room

A tooling room was provided for the storage of punches and dies. The punches were stored in food grade oil. The approach to inspection and polishing of the punches was provided. Punches of the products in question

Capsule manufacturing

A capsule manufacturing area was provided. There was provision of capsule filling, polishing

and metal detection. The IPQC were also being monitored.

Coating area
An autocoater was provided. The SOP for operation was verified.

Tablets inspection area
There was provision of a tablets inspection area.

Validations and Qualifications
Hold time studies
The SOP for hold time studies was submitted for review. These had been executed in line with current guidelines. The hold time studies were verified for the container of use, the headspace, IPQC and the Critical Material or Quality Attributes were verified.

Cleaning validation
The SOP for cleaning validation was submitted for review. The worst case product matrix was submitted for review. The approach to calculation of the maximum allowable carry over limit (MACO) was specified. The MACO from the permitted daily exposure limits, therapeutic dose and 10ppm had been considered. The swab limits and rinse limits had been appropriately calculated. The routine SOPs were verified against the validation parameters.

Dirty equipment and clean equipment hold time studies
Dirty equipment and clean equipment hold time protocols and reports were submitted for review.

Equipment Qualification
Validation master plan was submitted for review. The scope covered most of the validation requirements. The protocols and SOPs for the validation criterions were referenced in the VMP. Schedule for qualification for qualification was submitted for review. The fluidised Bed Drier (FBD) and the rapid mixer granulator (RMG) were submitted for review.

Quality Control
The QC laboratory was inspected. The approach to receipt, storage and allocation of samples was specified. There were specified timelines from receipt of samples to analysis and these were being adequately monitored. There was adequate temperature conditioning and monitoring.

OOS and incidents handling

SOP for handling of OOS was submitted for review. A flow diagram showing the stepwise phase investigation was presented. The responsibilities of the key personnel were defined. A

step-by-step procedure for the investigation of an OOS was provided. The SOP provided for the approach to Phase 1a, 1b and phase 2 investigation. The root cause determination methods to be used were described. There was provision for trending of OOS annually.

Stability Studies

SOP for the management of the stability program was submitted for review. There was provision of an adequate number of stability chambers. Samples were being appropriately stored according the climatic zones. Stability protocols were provided and products were being tested according to these. The stability program was in a state of control. There were noted deviations to the stability program. The reports for the products under the scope of the inspection were reviewed and these were satisfactory.

Conductivity meter and pH meter

The SOP for preparation and calibration of pH meter was submitted for review. These were adequately calibrated and the approach to preparation of the buffers was reviewed.

Dissolution apparatus

The SOP of operation and calibration and cleaning of the dissolution apparatus was submitted for review. The frequency of calibration was specified as 6 monthly. The calibrated parameters were indicated. The geometric mean and coefficient of variations were calculated for both amd these were acceptable.

Disintegration apparatus

The SOP for operation, cleaning and calibration of the disintegration test apparatus #QCD-056 was submitted for review. The parameters verified were as per the SOP and the current compendia.

Volumetric Solutions

The volumetric solution area was inspected. The SOP for preparation and standardisation was submitted for review. There was traceability of the records.

Glassware cleaning

The SOP for cleaning of glassware #QCD-055 was submitted from review and this was acceptable.

Specifications, Analytical Methods and reference standards

The SOP for production of specification and the analytical methods was provided. Examples of specifications were reviewed.

Microbiology

The microbiology laboratory was inspected. The approach to media receipts, growth promotion, microbial limit testing, plate incubation, colon counting was inspected. This was satisfactory.

HPLC

The SOP for good chromatographic practises was submitted for review. This provided the approach to handling of columns and operation of the HPLCs.

5.0 Conclusion

Based on the areas inspected, the people met, and the documents reviewed including the observations listed in the Inspection Report **4care Lifescience Pvt Ltd** located at **Survey No. 23/3P & 24, Opp. Jeans Factory, Daduran Vistar, Village- Bagdol, Taluka: Kathalal, District: Kheda. Pin-387630** was considered to be operating at an acceptable level of compliance with WHO cGMP guidelines for the manufacture of general oral solid dosage forms (tablets and capsules).

All the non compliances observed during the inspection those 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

   WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 1033), Annex 2
   https://www.who.int/publications/m/item/annex-3-trs-1033

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), Annex 3
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