



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information about the inspection

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| Name of manufacturer | Varichem Pharmaceuticals (Pvt) Ltd |
| Physical address | 194 Gleneagles Road Willowvale Harare Zimbabwe |
| Postal address | As above |
| Telephone number | +2634620181 - 6 |
| Fax number | +2634620180 |
| Contact person | Mr Archibald Taurayi Chimuka REGULATORY AFFAIRS DIRECTOR chimukaa@varipharm.co.zw |
| Summary of all the activities performed by the manufacturer (e.g. manufacturing, packing). Indicate dosage forms and type of products (e.g. tablets; penicillin or cephalosporin containing products) | Manufacturer and packer of non-sterile oral solid dosage form products - tablets, hard gelatin capsules, creams, ointments, dry syrups and liquids No penicillins or cephalosporins are produced. |
| Scope of inspection | General and Product Specific GMP inspection with data verification. |
| Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference number | HIV products under assessment |
| Date of inspection | 10 - 14 May 2010 |
| Programme | Prequalification of Medicines Programme |

Part 2: Summary

The manufacturing site of Varichem, located in Harare, Zimbabwe was inspected by a WHO prequalification inspection team on 10 - 14 May 2010.

General information about the company and the site. History of WHO or regulatory agencies' inspections

The site was previously inspected by the WHO team on 14, 17 and 18 December 2007.

Background information:

Varichem Pharmaceuticals (Pvt) Limited, commenced operations in October 1986 in Msasa, Harare. In 1988 the company completed a self-contained pharmaceutical manufacturing facility and commenced manufacture of tablets and liquids.

In August 1992 the present facility in Willowvale was constructed and manufacturing of non-penicillin pharmaceuticals shifted to the new plant. Major renovations to the facility were undertaken in 1996 and another upgrade had been carried out in 2006.

The site manufactures non-sterile non-penicillin pharmaceutical products - tablets, capsules, creams, ointments, dry syrups and liquids.

The site was inspected and approved by:

- MCC (South Africa)
- DRU (Botswana)

In total there were approximately 110 employees working at the site.

Focus of the inspection

The focus of this inspection was to verify production and quality control activities for above mentioned products and to assess compliance with WHO GMP.

The areas inspected included the following:

- Receiving areas (raw materials and packaging materials)
- Storage areas for starting and packaging materials
- Sampling and dispensing areas
- Production areas related to the product such as granulation, compression, coating and packaging areas
- Quality control laboratory (chemical, stability testing, microbiological laboratory)
- Quality assurance and documentation
- HVAC
- PW
- Compressed air
- Garments laundry

Documents reviewed included (but not limited to):

- Quality Risk Management

- Schematic drawings of AHUs
- Qualification protocol/report and data for specific AHU
- Batch records
- Deviations
- Complaints
- Product Quality Review
- Out of Specifications
- Equipment/instrument re-qualification schedule
- Preventive maintenance schedule for facilities and equipment
- Cleaning validation
- Self inspection and schedule
- Vendor qualification
- Personal hygiene
- Sampling of packaging materials
- Water sampling
- Environmental monitoring
- HVAC primary filters cleaning SOP
- Microbiological tests methods
- Autoclave validation
- Batch review and release
- Contracts
- Garments laundry
- Stability study, annual stability schedule and monthly stability planner
- Training plans and records
- Analyst certification
- Microbiological monitoring of environment
- Calibration and qualification procedures and records
- Insect and rodent control procedure
- Stability testing
- Reference standards
- White mineral oil Certificate of Analysis
- Specific products specifications and test methods
- Preparation of mobile phase
- Friability testing
- Operation of BMS
- Contracts
- SOP Batch document review and procedure for release of product for sale
- Job descriptions:
 - QA manager
 - QC manager
 - Production manager

2.1. Quality Assurance (QA)

A quality assurance system generally was implemented and maintained.

Product release was the responsibility of the QA manager (Authorized person), hierarchically independent from production. The Validation manager was designated to deputize the QA manager for product release. QA manager was also responsible for dealing with other QA related activities, such as handling of complaints, change control and out-of-specification (OOS) result investigations, internal and external audits. QA personnel were involved in all the production and quality control activities.

Managerial responsibilities were specified in job descriptions.

Change Control

A formal system for change control was described in a written procedure and flow chart. Changes were classified as:

- Minor
- Major

Changes were classified by the QA manager and Regulatory affairs director. The change register was maintained. If relevant, customers and Drug Regulatory Authorities were informed about the changes.

SOP was applied to:

- Systems
- Processes
- Materials
- Products and procedures associated with the manufacturing of pharmaceutical products.

Records of several changes were reviewed.

Deviation management

Deviation management was described in a written SOP and flow chart. Deviations were classified as:

- Planned
- Unplanned

The deviation register was available. Copies of deviation cases were kept in a dedicated folder. Original deviation forms were attached to the Batch Manufacturing Records. Deviations were approved by the QA manager.

Records of several deviation investigation reports were reviewed.

Product Quality Review (PQR)

PQR was applied as a concept of Annual Quality Review (AQR) .

PQR's for products under assessment were reviewed.

Quality risk management (ORM)

A quality risk management procedure was approved in June 2008. Procedure was explained in the QRM Master Plan and was applied to:

- Equipment qualification
- Cleaning validation
- Failure and CAPA

Tools listed in the ICH Q9 had been selected. Explanation was given for the application of the tools.

2.2. Good manufacturing Practices for Pharmaceutical products

Good manufacturing practices were implemented and generally maintained.

Necessary resources were generally provided, including qualified and trained personnel, adequate premises and space, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, suitable storage, adequate personnel, laboratories and equipment for in-process controls.

Manufacturing steps were recorded in batch manufacturing and packaging records; records were made during manufacture.

Instructions and procedures were generally written in clear and unambiguous language.

Qualification and validation were performed.

2.3 Sanitation and Hygiene

The topic was not specifically covered during the inspection; no notable concerns were identified during the inspection, however see section “observations” about the use of garments. Production personnel hygiene was monitored by taking swabs from the operator’s hands.

2.4 Qualification and Validation

The key elements of the qualification and validation program were defined and documented in Validation Master Plan (VMP). Re-validation/qualification periods were specified.

Process validation protocols/reports for products under assessment were reviewed.

Cleaning validation

The "worst case scenario" and 10 ppm approach was applied for the cleaning validation studies. Swab samples were collected for the analysis.

Validation studies were carried out for three batches. Cleaning VP was reviewed after 5 years. Validation reports were reviewed.

HVAC / clean area qualification

AHU's re-qualification reports and available raw data were reviewed for specific rooms.

The following tests were carried out during the AHUs re-qualification:

- Particle counts - every 6 months
- Pressure differentials - every 12 months
- Air change rate - every 12 months
- UDAF velocity - every 12 months
- Recovery rate - every 24 months
- DOP - every 24 months

Pressure differentials and T&RH were monitored and recorded every day.

2.5. Complaints

Dealing with complaints was specified in a written SOP. The complaints register was maintained. The QA manager was responsible for investigations of complaints.

Complaints were classified as:

- Technical complaints
- Efficacy complaints
- Adverse Drug Reactions

Complaints were reviewed during Management meetings.

Relatively few complaints had been recorded, however it was understood that manufacturing activities had been limited over the last years. Some complaints were reviewed.

2.6 Product Recalls

The system to recall the products from the market was in place. The authorized person responsible for the execution and coordination of recalls was designated and was the QA manager.

Recalls were classified as:

- Class I
- Class II
- Class III

2.7 Contract production and analysis

Manufacturing activities were not contracted out.

One contract laboratory was used for some analytical tests (particle size, residual solvents and polymorphic form determination). Pest control, garment cleaning, HVAC qualification and laboratory equipment preventive maintenance (PM) activities were carried out by external agencies.

2.8 Self inspection and Quality Audits

Self inspection was carried out once in six months for all departments according to a written SOP and audit schedule. Check lists were used to carry out audits for different

departments. Critical, major and minor observations were identified. Corrective Actions (CA) were proposed after the audit and follow-up was carried out by the audit team. In general the procedure was found to be satisfactory.

Supplier audit and approval. Vendor qualification

SOPs for approval of raw material suppliers and quality auditing of API manufacturers were reviewed. New suppliers were requested to submit CoA, Drug Master Files and raw materials samples. APIs from a single supplier were used in the manufacture the products under assessment. Supplier audit was carried out. Observations were classified as critical, major and minor. The audit report was reviewed and found to be satisfactory.

Packaging material suppliers were audited every year, audit schedule was available for inspection.

The following approved suppliers lists were available for inspection:

- Raw materials
- Excipient
- Packaging materials

2.9 Personnel

In general, the personnel met and interviewed during the inspection were experienced, skilled and conscientious.

The following Job descriptions were reviewed:

- QA Manager
- QC Manager
- Production Manager

GMP duties were specified. Deputies were specified in the deputy's job description.

2.10 Training

The training needs were identified and training was organized as per the written SOP. The training effectiveness was evaluated by open questions. Training records and annual training plan were maintained. A training schedule was available for the inspection.

Theoretical training files for two operators were checked and found to be satisfactory. Training effectiveness was evaluated by open questions.

2.11 Personal Hygiene

Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product. All changing rooms were provided with photographs which described the gowning procedures.

2.12 Premises

The buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production

operations. Premises were designed to ensure the logical flow of materials and personnel. A pest control procedure was in place.

Storage areas

Receiving area protected materials and products from adverse weather conditions. Sampling of starting materials and primary packaging materials was carried out in a single sampling room.

Production areas

Production areas were laid out in a way to provide logical flow and required cleanliness level. Attention should be paid to the production premises maintenance. Some of the production rooms and corridors were not smooth and free from cracks and open joints.

Dispensing areas

Dispensing was carried out in separate dispensing rooms located in the production area.

Quality control (QC) areas

Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Sufficient space was provided for samples, reference standards, solvents and reagents.

2.13 Equipment

Process equipment was installed and maintained in a manner that minimized the risk of error and contamination. Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibrated standard weights used for in-house checking of balances were available.

Calibration due date labels were attached to the equipment. Weighing range was not indicated on balances anywhere in the production.

Production equipment was cleaned on a scheduled basis.

Laboratory equipment and instruments were suited to the testing procedures undertaken.

A planned preventive maintenance program (PM) of equipment and systems was in place. Critical equipment were identified. PM SOPs were available for all equipment and systems. PM was carried out following check lists. On spot checks the schedules and SOPs generally had been followed and records were maintained in a good way.

Quality control laboratory (QCL) instruments' PM was contracted out.

Purified water (PW) was used when appropriate. Pre-treatment had basic system elements installed, double-RO and related equipment was operational.

Oil free compressed air was used in production. Qualification documents were available. Microbiological monitoring programme covered compressed air.

2.14 Materials

Materials were stored in high bay racks. Materials were properly quarantined and released by QC. Temperature and RH was controlled. Temperature mapping was carried out.

Materials were managed by electronic system and on paper records.

Upon receipt, materials were checked against purchase orders. Starting materials were sampled 100% for identity tests and labeled with "sampled" labels.

Procedure for sampling, inspection, checking/analysis and release of packaging materials was reviewed. Statistical sampling was applied, sampling plan was based on Acceptable Quality Limit (AQL). The procedure had been implemented recently and was partially still in a trial phase.

Entrance to the sampling unit was via airlock for personnel and via hatch for materials. If samples have to be taken from large containers, these were brought in to the sampling room. Samples were taken under UDAF. UDAF was run continuously, pressure differentials were checked every day.

Entrance to the dispensing rooms was via airlocks, separate for personnel and materials. Dispensing was done under UDAF. Dispensing was done by two persons belonging to the warehouse and checked by the QA personnel. Balances were verified daily using appropriate range of calibrated standard weights.

2.15 Documentation

In general, the documentation system was established and maintained, documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. Alterations made to documents were signed and dated. Specifications and testing procedures were available.

Check lists were used for verifying analytical test results, Standard Manufacturing Records (SMRs) and Master Packaging Documents (MPDs).

Documents related to the production and quality control were stored one year after product expiry date.

2.16 Good practices in production

Handling of materials and products was done in accordance with written procedures and was recorded, checks on yields and reconciliation of quantities were carried out. In general, during processing materials, bulk containers, equipment, rooms and packaging lines being used were labeled. In-process controls were performed within the production area.

Temperature and relative humidity in the production rooms were continuously monitored by the Building Management System (BMS).

The general design of the facilities was appropriate. Maintenance of premises should be improved.

Processes were generally under control.

Pharmacopoeia grade liquid paraffin was used for punches and dies. Punches were numbered and rotation was ensured. The use of punches was recorded in the punch stock card. Punches were inspected before and after use. Punches were dedicated for each product and were stored in locked cabinets.

Fluid Bed Drier finger bags were dedicated for each product.

PW was used for final rinsing of the equipment. Equipment was dried in ambient conditions.

IPQC room was provided with instruments for controlling compression parameters such as thickness and hardness, disintegration and friability.

Primary and secondary packaging

Tablet production activities were inspected and in general found to be satisfactory.

2.17 Good practice in Quality Control

Adequate facilities, personnel and approved procedures were available. Records of analysis were checked. Analytical work sheets were reviewed and approved.

Instruments were calibrated by the laboratory personnel on regular intervals following the calibration schedule. Instruments were identified by unique numbers.

HPLC sample vials were single-use.

HPLC and Dissolution apparatus calibration records were checked.

Analysts' competency list was available.

Reagents and mobile phases were appropriately labeled and stored. Expiry dates were specified for reagents.

On spot check identity tests for Sucrose were reviewed. There were 130 bags in the consignment. Samples had been taken from all bags and IR spectrograms for all 130 samples were available.

Glassware washing SOP was available for the inspection. PW was used for the final rinse. Glassware was dried at the temperature ≤ 90 °C. Glassware calibration SOP was in place.

Out of Specification (OOS) and Out of Trends (OOT) results were investigated in accordance with a written SOP, which included a flow chart. There were separate SOPs for the microbiology and water OOS and OOT.

Retention samples were appropriately stored.

Stability studies

Accelerated and on-going stability studies for products under assessment were reviewed.

Reference substances

On spot checks, primary and working standards were available.

Storage conditions for standards were suitable.

Microbiology

Dry media was stored appropriately.

The pH of media was checked before and after sterilization. Growth promotion checks, positive and negative controls were carried out. Microbiological growth had been detected and microorganisms identified when appropriate. Raw/municipal water was also monitored, seasonal variations had been identified.

Part 3: Conclusion

Based on the facilities inspected, the personnel met and the documents reviewed, and considering the inspection observations listed in the inspection report, Varichem Pharmaceuticals (Pvt) Ltd, located at 194 Gleneagles Road Willowvale Harare Zimbabwe, was considered to be operating at an acceptable level of compliance with WHO GMP.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.