

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Sandoz Private Limited
Unit number	N/A
Production Block	K-3 MDT-TB
Physical address	Plot no.8 A/2 and 8-B, TTC Industrial Area, Kalwe Block, village Dighe, Navi Mumbai 400 708, India
Postal address	As above
Date of inspection	14 - 17 February 2011
Type of inspection	Routine inspection
Dosage form(s) included in the inspection	Tablets
Summary of the activities performed by the manufacturer	Production, quality control and release of tablets - coated
Scope and type of inspection	Routine GMP inspection
Programme	Prequalification of Medicines Programme

Part 2: Summary

General information about the company and site

Sandoz Private Limited (SPL) is a NOVARTIS group company. SPL is primarily engaged in production of Active Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP).

SPL has three sites in India, at Turbhe, at Mahad and at Kalwe. All sites are located in Maharashtra State and are near Mumbai.

The Turbhe location is having 2 different sites. The one site produces cephalosporin products. The other site is Carbapenam API and sterile injectable manufacturing facility. The Mahad site is the API manufacturing facility.

The inspected Kalwe site is about six years old. Here manufacturing and packing of oral solid dosage forms (i.e. tablets & capsule) is done. This site has increased its

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

manufacturing capacity and expanded for manufacturing of Multi Drug Therapy (MDT) – TB products.

The Kalwe site also has a global Pharmaceutical Development Centre for API as well as FPPs. This development site is situated adjacent to Sandoz FPP manufacturing facility. SDC (Sandoz Development Centre) is involved in the generic product development and registration of API & FPP.

The building comprises of two floors (ground floor and first floor) which includes API development laboratories, FPP development laboratories, QC, validation and stability laboratories, bio-analytical laboratory, warehouse, FPP manufacturing facility and Kilo lab facility for scale-up & development trials and other supporting functions including regulatory, quality compliance, patents, and pharmacokinetics.

The Kalwe site started manufacture of validation batches of TB085 and TB090 in 2009. The production of these two FDCs was transferred from the Kolshet site. At the time of the inspection - no commercial batches had been manufactured.

At the time of the inspection the site employed approximately 472 full time employees operating 3 shifts, 6 days a week; 221 of which worked in pharmaceutical production activities, 149 in Quality Assurance (QA) and Quality Control (QC), 34 in Engineering.

History of WHO and/or regulatory agency inspections

The Sandoz Kalwe site was inspected by WHO in 2009.

The Site was approved and was inspected by:

- FDA India in 2005, 2007 and 2010
- US FDA in 2005, 2007 and 2009;
- TGA
- ANVISA
- ANMAT
- PMDA in 2008.

The company manufactured FPPs under license form 25 and forms 28 bearing number KD-548 and KD-390 respectively. The company holds licenses form 25-A and form 28-A for loan license manufacturing of Novartis India Limited Products (license number KD-2040-A and KD-2309-A). The license is renewed every 5 years. The current license is valid to 22/01/2013.

Focus of the inspection

The inspection focused on the production and control of prequalified products. The inspection covered all the sections of the WHO GMP text, including premises,

equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

2.1 QUALITY ASSURANCE

A system for quality assurance was established and covered all the basic elements of GMP. Organization chart was reviewed and found to be acceptable.

Product Quality Review (PQR)

SOP "Product Quality Review" and PQRs for prequalified products were reviewed.

Quality Risk Assessment

SOP "Quality risk management" (QRM) was reviewed. The tools what could be used to identify the risk were defined.

Change control (CC) SOP, Log books for Change Request 2010 - 2011 and reference matrix for impact analysis indicated selecting functions to do impact analysis and flow chart was reviewed: no comments were made.

Change controls review for period July-December 2010 was available, presented to the inspectors and reviewed. Change controls were presented graphically. Details of Types of Change Controls were also explained.

A number of Change controls were reviewed, no comments were made.

Deviation management SOP "Deviations & Investigations", flow chart and deviation register for 2010 were reviewed. Deviations related to the production were documented in Batch Manufacturing Reports/Batch Packaging Reports (BMR/BPR). According with the SOP QA personnel checked the deviation and decided that either a full scale product failure investigation must be performed. Deviation was defined as unplanned departure from an approved instruction or established standard or an unexpected observation. Deviations were investigated on Risk based analysis.

A number of deviation investigations were reviewed and found to be properly carried out.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language.

Qualification and validation were performed.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

Manufacturing and packing areas were cleaned according to approved written cleaning procedures.

2.4 QUALIFICATION AND VALIDATION

The company's approach to qualification, and validation was consistent with the WHO technical report series recommendations.

Cleaning validation

"Validation Master Plan - cleaning" and a number of cleaning validation reports were presented to inspectors. Sampling method applied for the cleaning validation studies was swab method.

Worst case molecule has been identified, equipment drawings were available.

Cleaning performance effectiveness was verified once in a year for the critical equipment and critical molecule.

Process validation Protocols were reviewed. Sampling points were identified

Process validation Reports and BMRs of specific batches were reviewed by the inspectors: no comments were made.

2.5. COMPLAINTS

The company approach to dealing with complaints was explained in the SOP. A Complaint register was available and shown to inspectors. The Responsible person for coordinating and processing the complaints was designated. Complaint investigation records were kept together with corresponding BMR. CAPAs were identified.

Complaints were classified as:

- Medical compliant
- Technical compliant

Complaints were received at the centralized Competence centers, afterwards complaints were registered in GCRS (Global complaints recording system). GCRS classified complaints as:

- Critical
- Major
- Minor

Ishikawa Fish bone tool was used for the 95% of complaint investigation. A number of T complaints investigations were reviewed and found to be properly carried out:

2.6. PRODUCT RECALLS

Dealing with recalls was explained in the SOP.

SOP "Product recall" was reviewed. Recalls were classified as:

- Class I
- Class II
- Class III

There were three recall levels specified:

- Level A Recall from the customers
- Level B Recall from all links in the distribution chain
- Level C Recall from certain links in the distribution chain

Evaluation of effectiveness of the recall - mock recall should be carried out once in a three years.

2.7. CONTRACT PRODUCTION AND ANALYSIS

Production activities were not contracted out. Some analysis was carried out in two contract laboratories. A number of contracts were reviewed: no comments were made.

2.8. SELF INSPECTION AND QUALITY AUDIT

The company had a basic self inspection program which consisted of reviews of all of its operations, and production activities. SOP "Quality audits", flow chart and Self inspection schedule and for 2011 were reviewed.

The SOP was applicable to the self inspection and vendors audits. Self inspection was carried out twice per year, according with the Check list. Contract manufacturer's audits were carried out once in 3 years and once in 2 years for sterile product manufacturers. Approved suppliers audits were carried out once in 3 years and once in 2 years for sterile product manufacturers. Audits for the GMP service providers were carried out every 3 years. After audit the report, incorporated to the Check list, was written and observations were specified. Audit reports were approved by the QA Manager. CAPAs were requested and evaluated. Vendor's audits in most cases were carried out by the corporate auditors. Approved vendors lists for APIs manufacturers and packaging material manufactures were available.

2.9. PERSONNEL

In general, the personnel met and interviewed during the inspection were confident in what they were doing. Job descriptions of key persons were available and the following were reviewed by the inspectors: no comments were made:

- Head QA, Kalwe FDF Operations
- Manager, QA. Designation QA - Regulatory and commercial support
- Senior Executive QA
- D.G.M (production)

2.10 TRAINING

The training needs were identified and training was organized as per the SOP "Training". The SOP and flow chart was reviewed by the inspectors. Several types of the training was specified.

The training types were subdivided in different training modules. Training effectiveness was evaluated based on the questionnaires with closed questions and demonstration of skills and self assessment. Training schedule for 2011 was available.

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. Level of personnel hygiene was observed to be appropriate.

2.12. PREMISES

During inspection attention was paid only to the (K-3 MDT_TB Block) production block. In general 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. In Process Laboratory was located in the production block. Quality control laboratories (separate for FPP's and APIs analysis) 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.

Access to the warehouses, production premises and Quality control laboratories was controlled.

2.13. EQUIPMENT

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.

Daily checking of analytical balances was carried out using two calibrated standard weights, fortnightly calibration was carried out using 6 calibrated standard weights,. Standard weights calibration certificates were presented to the inspectors.

Production equipment was cleaned on a scheduled basis as per written SOPs. Cleaning status was shown by a cleaning label. It was discussed with the company that it would be necessary to specify on the label "clean before use" in case if the cleaning hold time has been exceeded.

Equipment calibration schedule and planned preventive maintenance program (PM) of equipment and systems was in place. Spot checks showed that the schedules had been followed and records were maintained.

Production equipment and instrument calibration schedule and PM schedule were managed by the SAP system.

HVAC

The HVAC system was well designed and maintained. The filters specifications were given in accordance with ISO standard. A separate room was provided for the air filters washing and cleaning. An adequate number of spare filters were stored in a separate room. The HVAC system was provided with an alarm for T and RH. Filters' cleaning was properly documented. Preventive Maintenance schedule and check lists were presented to inspectors, no comments were made.

The utilities section was visited and specific AHU was checked. Filters were properly labeled, dampers positions were fixed and DOP ports were specified.

Purified Water System PW)

The PW system was installed in 2004. Radiographic report of orbital welding, and boroscopic Inspection reports, joints reports and welder certificate were available and presented to the inspectors. Print outs of orbital welding machine were available and presented to the inspectors. Boroscopic welding was recorded on photo films. PW was used only for production. In the QCL water was generated using Millique system.

Performance Qualification and Operational Qualification of the PW system was carried out in three phases. Phase I was for 14 days, phase II was also for 14 days and phase III was 11 months.

PW was manufactured by two stage reverse osmosis followed BY EDI (electro deionisation)

2.14. MATERIALS

Materials were properly quarantined and released by the QC. Temperature and Relative Humidity (RH) were controlled. T and RH were recorded every 20 minutes and print outs were reviewed next day. T mapping was carried out; reports were reviewed by the inspectors.

Printed packaging materials were stored in a locked area.

Materials were received via two unloading platforms; proper checks according the check list were carried out for incoming materials. Approved vendors list was available in the warehouse. All incoming materials were de-dusted before placing to the quarantine area.

Quarantine labels were placed on all items. Sampled containers were properly identified. Materials movement was managed by the SAP system.

100% sampling plan was applied for API sampling for identity tests. Excipient sampling plan for WHO products was also 100 % sampling.

Printed packaging materials were sampled following AQL, inspection level II. Defects - critical, major and others were defined.

There were five sampling rooms which had separate personal and material entrances. Sampling was carried out under the UDAF.

Finished goods were stored properly. There were two separated, locked Rejected and Returned goods storage rooms.

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. A system for version control was in place. Specifications and testing procedures were available. Documents related to the batch release were stored one year after the expiry date of the batch.

Current records of BMR issuance were presented to the inspectors.

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. During processing, materials, bulk containers, equipment, rooms and packaging lines were labeled. In-process controls were performed within the production area.

Punches and dies were stored properly, they were numbered and rotation was ensured. Food grade lubricant was used for punches and dies lubrication.

Finger bags were product dedicated.

The process flow for the specific products under inspection was logical and followed a defined pattern from receipt of the raw material from the delivery vehicle into a closed unloading platform, through a qualified and maintained de-duster cabin, and into a quarantine and store where Quarantine and Release were controlled by status labeling and color coding and SAP system.

T and RH were controlled in all production rooms.

2.17. GOOD PRACTICES IN QUALITY CONTROL (QC)

The QC function was independent from other departments. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods. Sufficient samples of starting materials and products were retained to permit future examination of the product. Analytical results were checked by the QC Manager.

HPLC chromatograms for stability studies and method validation for stability studies were checked on hard copies. Electronic copies were available.

Analyst's competency list was available for the FPPs testing laboratory.

Reference substances

SOP "Reference substance - Creation, Handling and use" and register were reviewed by the inspectors. Working standards (WS) were dispensed in 14 vials - 1 g per vial. Usage of standards was recorded. Standards were stored properly.

Stability studies

Walk in- stability chambers and retention samples storage rooms were located on the technical floor. Retention samples of FPPs, API's and bulk products were stored in the perforated boxes. Boxes were placed in the perforated movable racks. Retention samples storage rooms T and RH were maintained by the separate AHU.

SOP "Investigating OOS results", flow chart and OOS investigation reports were reviewed by the inspectors. The same SOP was applied for Out Of Trends (OOT) and Out Of Expectations (OOE) investigations.

A number of OOS investigation records were reviewed by the inspectors. OOS investigations reviewed was carried out properly and investigations were comprehensive.

Microbiological laboratory

Media preparation

The Media preparation SOP was available. A Growth promotion test using culture collection micro-organisms was carried out for each batch of dry media and each lot of sterilized media. Positive and negative controls were carried out.

Autoclave validation reports were available but not checked by the inspectors.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, Sandoz Private Limited, located at Plot no. 8 A/2 and 8-B, TTC Industrial Area, Kalwe (K-3 MDT_TB Block), Village Dighe, Navi Mumbai 400 708, India, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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.