

## WHO PUBLIC INSPECTION REPORT

### (WHOPIR)

#### Finished Product Manufacturer

#### Part 1: General information about the inspection

|                                                                                                                                                                                   |                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of manufacturer                                                                                                                                                              | Shasun Pharmaceuticals Limited                                                                                                                                                                                                                                  |
| Physical address                                                                                                                                                                  | R.S. No. 32-34, PIMS Road,<br>Periyakalapet, Puducherry, India 605 014                                                                                                                                                                                          |
| Unit                                                                                                                                                                              | Formulation Unit II                                                                                                                                                                                                                                             |
| Postal address                                                                                                                                                                    | As above                                                                                                                                                                                                                                                        |
| Telephone number                                                                                                                                                                  | 00914132655697/2655698/2655946                                                                                                                                                                                                                                  |
| Fax number                                                                                                                                                                        | 00914132656052                                                                                                                                                                                                                                                  |
| Summary of activities of manufacturer<br>(e.g. manufacturing, packing).<br><br>Indicate dosage forms and type of<br>products (e.g. tablets; cephalosporin<br>containing products) | Manufacturing, quality control and batch<br>release of FPP: solid oral dosage forms<br>(film coated, sugar coated and enteric<br>coated tablets), hard gelatin capsules.<br><br>Cephalosporin's and Beta lactam<br>Antibiotic products were not<br>manufactured |
| Focus of inspection - products in WHO PQ<br>program covered in the scope at the time of<br>inspection with the WHO reference<br>number                                            | <b>Products under WHO assessment</b><br>HA525: Lamivudine / Tenofovir<br>disoproxil fumarate 300/300mg tablets<br>and HA 527: Efavirenz / Emtricitabine /<br>Tenofovir Disoproxil Fumerate<br>600/200/300mg tablets                                             |
| Scope and type of inspection                                                                                                                                                      | Routine inspection, covering all aspects<br>of GMP                                                                                                                                                                                                              |
| Date of inspection                                                                                                                                                                | 13 – 16 March 2012                                                                                                                                                                                                                                              |
| Project (if any)                                                                                                                                                                  | Prequalification of Medicines Programme                                                                                                                                                                                                                         |

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March 2012

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## **Part 2: Summary**

### **Background information**

Shasun Pharmaceuticals Limited was established in the year 1976. A site was set up at Velachery, Chennai for the manufacture of Analgin, the active pharmaceutical ingredient (API)..

In 1986, the site at Puducherry (Unit-I) was set up to manufacture Ibuprofen API.

Another production unit was started in 1991 in Cuddalore to manufacture Ranitidine Hydrochloride API.

The Shasun Research Centre at Keelakottaiyur, Chennai, was set up in 2005. Process development for generic products and custom synthesis are being carried out.

Shasun started the manufacture of formulations in year 2005. Formulation Unit II was constructed adjacent to the API Plant (Unit I) at Puducherry for the manufacture of oral dosage forms such as tablets and capsules.

Shasun is a contract manufacturer for HA525: Lamivudine / Tenofovir disoproxil fumarate 300/300mg tablets and HA 527 Efavirenz / Emtricitabine / Tenofovir Disoproxil Fumerate 600/200/300mg tablets. Ranbaxy is the marketing authorisation holder of these products.

The total number of employees was about 482 of whom 237 employees were involved in production, 67 in quality control, 36 in quality assurance, 31 in storage and distribution and 35 in engineering and support services.

Normally the site was running 3 shifts for manufacturing and 2 shifts for packaging. 99 % of all manufacturing activities were contract manufacturing.

### ***History of WHO or regulatory agencies inspections***

Shasun Pharmaceuticals had never been inspected by the WHO team.

The Puducherry Formulation Unit (Unit II) was inspected by:

- Health Canada
- MHRA UK
- US FDA
- Local State Food and Drug Administration

### **Focus of the inspection**

The inspection focused on the production and control of HIV products under WHO assessment. The inspection covered all the sections of the WHO GMP text, including quality

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

As of yet, only pilot scale validation batches of the above-mentioned products had been manufactured at the site. These batches were manufactured in the Pilot plant of Unit II. Pilot plant and Commercial plant have been inspected.

### ***Inspected Areas***

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

## **2.1 QUALITY ASSURANCE**

In general, a system for quality assurance was established.

### **Quality Risk Management (QRM)**

The SOP quality risk management was reviewed. According to the SOP, FMEA was used as a risk assessment tool and involved 4 steps:

- Risk assessment - identification, analysis and evaluation
- Risk control – mitigation plan, risk reduction or acceptance
- Risk communication – QRM process communication between team members
- Risk review – review of output/results of the risk management process

The QRM was applied, but not limited to:

- Buildings and facilities/ utilities / equipment's / instruments
- Systems and procedures
- Critical operations / process

The Formulation site QRM assessment log was presented to the inspectors. Quality risk assessment for Phase – II expansion of the Formulation Unit was spot-checked.

**Product Quality Review (PQR)**

The term “annual product review (APR)” was used for PQR.

The SOP on annual product review (APR) and APR for a specific product from January to December 2011 were reviewed. Different APRs were prepared for products manufactured for different markets. In the SOP, a link was described for capturing all quality related issues; this aspect was not covered during the inspection.

**Change control**

The change control SOP had been approved on the corporate level. Cases were categorised based on impact area – utilities, production, etc. Cases No 4 and 6 related and cases No 42, 84, 94 and 101 were checked from the register/logbook for 2011.

**Deviation management**

The SOP deviation management was applicable to the Puducherry site and to the Cuddalore API site.

Deviations were defined as:

“Activities that are planned temporarily which is to be deviated from standard systems/standard instructions that covers document, process, testing, equipment, product, material and others in the GMP operations. Deviations were approved by Unit QA in charge or designee”.

Deviation trends were presented.

Three deviation logs were presented to the inspectors:

- Production
- Formulation development, technology transfer (transferring production from the Pilot plant to the Commercial plant), quality assurance, project management, packaging development, raw materials stores.
- Quality control, AR&D, engineering, material management.

A number of deviation requests were reviewed.

**Incidents**

The SOP on incidents was applicable for the Puducherry site and the Cuddalore API site.

Incidents were defined as:

“Incident is unplanned event that is in variance with the designated system of procedure in the facility. An incident may get identified and reported during the operation itself or during subsequent review”. Incidents were approved by Unit QA in charge or designee.

Incident trends were presented.

Incidents were classified as:

- Quality impact incident
- Quality non-impact incident

Three incident logs were presented to the inspectors:

- Production, formulation development, analytical R&D and quality assurance
- Quality control, material management, FCQA
- Technology transfer, quality assurance, raw material stores, regulatory affairs, packaging development, utility.

A number of Incident reports were reviewed.

**Management review and CAPAs** procedure was implemented. CAPAs were compiled on quarterly basis. Shasun Pharmaceuticals management representative (SCMR) was responsible for CAPAs review and prepared quarterly reports. CAPAs implementation reports were related to:

- Product
- Process
- Deviation
- Complaint
- Audits
- Recall
- Others

“Fish bone” approach was used to identify the problem and listing of major factors involved.

## **2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

Good manufacturing practices generally were implemented. The necessary resources were provided. Manufacturing processes were defined and reviewed. Qualification and validation were performed. Operators were trained to carry out procedures, and records were made during manufacture.

## **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.

Clean areas were cleaned in accordance with approved written procedures. Environmental monitoring was regularly undertaken.

The SOP environmental monitoring and trends was spot-checked. Action and alert levels were specified for:

- Passive air sampling
- Active air sampling
- Surface of floors and wall
- Surface of equipment
- Personnel
- Drain point

## **2.4 QUALIFICATION AND VALIDATION**

The company had identified what qualification and validation work was required. The key elements of the qualification and validation programme were defined in the validation master plan (VMP).

The Validation Master Plan was spot-checked. VMP was applicable for:

- Facility
- Equipment / laboratory instruments
- Utilities (water system / HVAC system / compressed air)
- Analytical methods
- Computer system
- Manufacturing process
- Processes
- Cleaning procedures

The company applied their technology transfer (TT) approach to shifting production from the Pilot plant to the Commercial plant.

### **Process validation:**

Validation protocols/reports were checked for the products under WHO assessment. On spot-checks validation studies were carried out properly.

### **Hold time studies:**

In general hold time studies were carried out for the following stages:

- Granulation
- Blending
- Compression
- Coating

### **AHU serving Phase-II expansion granulation room qualification**

OQ report PRO/SFPRN/EA/OQ/005 was spot-checked.

PQ covered:

- Air velocity
- Number of air changes

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- Air flow Pattern test
- Pressure control test
- HEPA filter integrity tests
- Particle counts at rest

PQ was also spot-checked.

PQ covered:

- T and RH
- Non-viable particle count in operation
- Viable particle count at rest

### **Cleaning validation**

The SOP cleaning validation program was spot-checked. Maximum allowable carryover (MACO) NMT 10 ppm approach was used. Validation studies were carried out using swab samples and rinse samples.

## **2.5 COMPLAINTS**

Complaints and other information concerning potentially defective products were reviewed according to a written procedure. Complaints concerning a product defect were recorded and investigated. Register/log for 2012 and cases No 02, 07, 09, 10 were checked.

It was recommended to classify complaints from the aspect of risk to health, in order to facilitate review and enable consistency in decisions.

## **2.6 PRODUCT RECALLS**

The SOP Product recall was checked.

Head – Quality Management was responsible for recall decision and execution in the case of Shasun marketed product. Head – Quality Management also took part in decision for recall by customer / contract giver in case of Shasun manufactured but customer marketed product.

Recalls were classified as:

- Class I defect
- Class II defect
- Class III defect
- Class IV defect

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

Production operations were not contracted out. Some analytical tests were contracted out to six contract laboratories.

The SOP contract laboratory – certification, sample testing and audit schedule was spot-checked. Audits and laboratories certifications were carried out every 2 years. Audits were

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carried out by Corporate Quality Control (CQC) and site QA according with a checklist. After audits reports were written and observations were classified as:

- Critical
- Major
- Minor

CAPAs were requested from the audited laboratories. CAPAs appropriateness and implementation was followed up by CQC.

A number of Contract agreements were spot-checked.

External laboratories audit schedule for 2011 and 2012 was presented to the inspectors. Laboratory audits in 2011 were carried out according with audit schedule.

## **2.8 SELF INSPECTION AND QUALITY AUDIT**

Self-inspections were performed regularly. Self-inspection covered basic GMP topics.

The SOP internal quality system audit (self-inspection) was spot-checked. SCMR and Unit QA were responsible for self-inspections. SCMR also was responsible to monitor and ensure effectiveness of corrective actions. Self-inspections were carried out by certified personnel, every 6 months according to audit check list. On spot-checks the audit schedule was followed. Audit reports were written and non-conformities were listed.

### **Supplier (vendor) qualification**

The SOP vendor qualification was applicable for:

- API
- Excipients
- Primary packing materials
- Secondary packing materials

API and packaging materials audits were carried out every 3 years. Head Corporate Quality Assurance (CQA) was responsible for supplier approval and certification.

After audit report was written, deficiencies were identified and classified as:

- Critical
- Major
- Minor
- Area for improvement

Proposed CAPAs were evaluated by the team leader. CQA was responsible for implementations of CAPAs and if required for follow-up audits.

Audit schedule was presented and spot-checked. On spot-checks the audit schedule was followed.

## **2.9 PERSONNEL**

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Organisation charts were presented. Job descriptions of key personnel were checked; the documents were available and the persons had given a signed consent.

Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

## **2.10 TRAINING**

Training was provided in accordance with a written program for all personnel whose duties take them into manufacturing areas or into control laboratories. Personnel received initial and continuing training, including hygiene instructions, relevant to their needs. Training plans were prepared. Certain training modules had been established. The concept of monitoring training effectiveness was applied. Records were kept systematically. On spot-checks, personal files were available.

## **2.11 PERSONAL HYGIENE**

Periodic health checks were carried out for staff workers and senior management. SOP personnel and SOP personal hygiene and medical examination were reviewed.

Changing and washing followed a written procedure. Direct contact was avoided between operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas.

## **2.12 PREMISES**

Change rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Change rooms were equipped with mirrors. Airlock doors did not opened simultaneously.

### **Ancillary areas**

Rest and refreshment rooms were separate from manufacturing and control areas.

### **Storage areas**

Storage areas were generally of sufficient capacity.

Receiving and dispatch bays were separated and protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products. There were separate sampling areas for starting materials and primary packaging

materials. Sampling was carried out under reverse laminar airflow. Dedicated dispensing tools were used for sampling different APIs.

### **Weighing areas**

Dispensing was carried out in the warehouse in two separate dispensing booths. Dispensing was carried out under reverse laminar airflow. Dedicated dispensing tools were used for dispensing different APIs.

### **Quality control areas**

QC laboratories were separated from production areas. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Separate air-handling units were provided for microbiology laboratories.

### **Pest and rodent control**

SOP, observation of rodent traps & gum pads and contract with service provider was reviewed. Pest and rodent control was carried out by a contract company.

### **Utilities**

HVAC had an adequate filtration designed.

Water production system was run at ambient temperature (which could mean > 30 °C, depending on outside temperature conditions). UV units were installed in the system. Recirculation was arranged. Purified water was produced by ultrafiltration of RO and DM water. Chemical sanitisation was applied at stages before the production of purified water, thermal sanitisation was applied downstream.

Compressed air was supplied from an oil free system. Appropriate filters were installed in the system.

## **2.13 EQUIPMENT**

Fixed pipework was labeled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Production equipment was cleaned on a scheduled basis. Laboratory equipment and instruments suited to the testing procedures undertaken.

The SOP calibration of weighing balance and electronic weighing balance monthly (February 2012) and specific equipment calibration report were spot-checked.

Equipment was subject to planned maintenance and calibration. On spot-checks, frequencies of PPM and calibration were generally satisfactory and the schedule was followed.

The site conducted calibration themselves, using devices calibrated externally. Records were available on spot-checks (T sensors in granulation equipment), in-house calibration devices had certificates referring to outside calibration.

The SOPs cleaning for RLAF dispensing booth and cleaning of RLAF sampling booth were spot-checked.

The following equipment usage log books were spot-checked:

- Dispensing booth – I
- Sampling booth – I and II

## **2.14 MATERIALS**

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under appropriate conditions. Check lists were used for materials receipt and verification.

### **Starting materials**

Starting materials were purchased from approved suppliers. For each consignment, containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material was recorded and reported to the QC department. If one delivery of material was made up of different vendor batches, each batch was considered as separate for sampling, testing and release. Starting materials in the storage area were appropriately labeled.

There were appropriate procedures in place to ensure the identity of the contents of each container of API. Bulk containers from which samples were drawn were identified.

The AQL was applied for sampling of excipients

The SOP on code-to-code transfer of material was reviewed. Material code numbers were linked to manufacturers/suppliers and material specifications.

### **Packaging materials**

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure conditions. Each delivery of batch of printed or primary packaging material was given a specific reference number or identification mark.

### **Intermediate and bulk products**

Not specifically inspected. During the site tour no adverse situations were noticed.

### **Finished products**

Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer.

**Rejected, recovered, reprocessed and reworked materials**

Rejected materials and products were marked as such and stored separately. Product was claimed to not be reprocessed or reworked. However acceptable minor reprocessing such as de-blistering of tablets from foils was performed.

**Recalled products and Returned goods**

A secure storage space, under lock and key, was provided for storage of recalled and returned goods.

**Reagents and culture media**

Records for the receipt and preparation of reagents and culture media were available. Reagents made up in the laboratory were prepared according to written procedures and appropriately labeled. Culture media was stored orderly. Growth promotion tests were carried out.

**Reference standards**

Official reference standards were used as well as working reference standards prepared by the manufacturer. Working standards were properly labeled and stored at 2- 8 °C. Working standards were dispensed in individual vials for one month use. Dispensing was carried out under RLAF in the microbiology laboratory. The temperature in the reference standards storage fridge was monitored using 4 sensors. Temperature was recorded every 30 minutes. The fridge was equipped with an alarm. Reference standards usage logs were maintained.

**Waste materials**

Not inspected.

**2.15 DOCUMENTATION**

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Records were made or completed when any action was taken.

**Labels**

In general, labels applied to containers, equipment and premises were clear and unambiguous. However some containers were seen not properly labeled.

**Specifications and testing procedures**

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products as well as for intermediate and bulk products.

**Master formulae**

Authorized master formulas were available.

**Packaging instructions**

Authorized packaging instructions were available.

**Batch processing records**

Batch manufacturing records (BMRs) were kept for each batch processed. Before any processing begins, checks were made that the equipment and work station were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded and were part of the BMR.

**Batch packaging records**

A batch packaging record (BPR) was kept for each batch processed. Before any packaging operation begins, checks were made that the equipment and work station were clear of previous products, documents or materials, and that equipment was clean and suitable for use.

**Standard operating procedures and records**

SOPs and associated records of actions taken were available.

**Assessment of the Site Master File**

The Site Master File was available in electronic form before the visit was made to the manufacturing site. In general, it complied with the guidelines on preparation of the SMF.

**2.16 GOOD PRACTICES IN PRODUCTION**

Handling of materials and products was carried out in accordance with written procedures. Checks on yields and reconciliation of quantities were carried out.

**Processing operations**

Before processing operations were started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Necessary in-process controls and environmental controls were carried out and recorded.

**Packaging operations**

Before packaging operations were started, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously.

Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

## **2.17 GOOD PRACTICES IN QUALITY CONTROL**

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements were effectively and reliably carried out. QA personnel had access to production areas for sampling and investigation.

### **Sampling**

The SOP sampling of raw materials (non-sterile) and sampling plan of primary, secondary and printed packaging materials packaging was checked.

### **Control of starting materials and intermediate, bulk and finished products**

Tests followed instructions given in the relevant written test procedure. Tests results were recorded in “Record of analysis” data sheets. Tests results were reviewed by a review group and approved by the head of QC or section head, QC.

### **Test requirements**

#### *Starting and packaging materials*

In general, before releasing a starting or packaging material for use, the QC Head or section head, QC ensured that the materials had been tested for conformity with specifications. An identity test was conducted on a sample from each container of APIs. Each batch of printed packaging materials was examined following receipt.

For more details see section 5 “Observations”.

#### *In-process control*

In-process control records were maintained and formed a part of the batch records.

#### *Finished products*

For each batch of a medicinal product, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release. CoA`s were approved by the head of QC or section head, QC.

### **Batch record review**

QC records were reviewed as part of the approval process of batch release.

### **Retention samples**

Retention samples from each batch of finished product were stored for 1 year after expiry date. APIs samples and batch documents related to the batch manufacture and release were stored 5 years. Maximum expiry time for finished products was 3 years. Finished products were kept in their final packaging and stored under the recommended conditions. Retention samples were stored under appropriate conditions. It was recommended to store API samples simulating their original packaging.

### **Stability studies**

A written programme for ongoing stability studies was developed and implemented. The SOP stability management was spot-checked. According to the SOP, stability studies should be initiated within one week of completion of packing of all packs.

Walk in – stability chambers were equipped with alarm system. Temperature (T) and relative humidity (RH) was monitored continuously. 8 sensors were placed in each chamber and T and RH were recorded every 20 minutes.

### **Analyst's qualification**

The SOP qualification of analyst for analytical techniques was spot-checked.

A specific analyst Qualification record was spot-checked. Analyst qualification matrix was presented to inspectors. The matrix identified analyses for which each analyst was qualified.

### **Microbiological laboratory**

The microbiological laboratory was briefly visited and was in a good order in general.

### **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, as well as the corrective actions taken and planned, Shasun Pharmaceuticals Limited, Formulation Unit II, R.S. No. 32-34, PIMS Road, Periyakalpet, Pondicherry, India 605 014, 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.