

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1: General information about the inspection

Name of manufacturer	Aspen SVP Pty (Ltd) a Manufacturing division of Aspen Pharmacare
Physical address	8B Gibaud Road, Korsten, 6020 Port Elizabeth, South Africa
Unit	SVP unit “6000/hr Vial line”
Contact address	PO box 4002 Korsten 6014 Port Elizabeth, South Africa
Date of inspection:	22-26 April, 2013
Type of inspection	Routine inspection, covering selected aspects of GMP for sterile aseptically filled products
Dosage form included in the inspection	Sterile powder for injection
Summary of the activities performed by the manufacturer	The scope of activities of Aspen SVP is manufacturing, quality control and batch release of sterile finished pharmaceutical products – Liquid Filled Vials, Freeze Dried Vials and Eye Drops. The following hazardous products (hormones) are manufactured on site: Nur-Isterate and Medroxyprogesterone Acetate
WHO product category covered by the inspection	Powder for Injection for treatment of Tuberculosis

Part 2: Summary

Background information

Aspen Holdings was incorporated in 1999 in South Africa. Aspen has businesses in South Africa, Mexico, Venezuela, Brazil, Ireland, Germany, Kenya, Uganda, Tanzania, United Arab Emirates, Mauritius, Hong Kong, Philippines and Australia. Aspen has 18 manufacturing facilities at 13 pharmaceutical manufacturing sites on five continents. Four of the sites are located in South Africa, four in Australia, and one in each of Kenya, Tanzania, Brazil, Mexico and Germany.

In one building there were two completely separated production facilities (suites):

- Multi-Product Facility (Suite) – Aseptically filled Liquid and Lyophilized Vials and Eye Drops
- Hazardous Product Facility (Suite) - Aseptically compounded Vials and Ampoules.

Facility design incorporated completely separated entities for the production, inspection and packing of hazardous and the multi-products. HVAC systems were completely separate and were housed in separate Plant Rooms. Hazardous products facility HVAC was housed in a contained Plant Room with air-lock protection and safe filter element change and disposal. Conditioned air was supplied to and extracted from the hazardous and multi-product suites via separate duct systems. Dedicated operational staff was used for Multi product and Hazardous product facilities.

The plant employed a total of 311 people: 179 in Production, 50 in Quality Control and 27 in Quality Assurance.

History of WHO or regulatory agencies inspections

This was the first WHO and MHRA inspection (joint inspection) of the company.

Manufacturing site was inspected by the following authorities:

- Medicines Control Council (MCC) South Africa in 2009/2011
- Health Canada and Medicines Sans Frontiers in 2011
- Food and Drug Administration (FDA) US and Therapeutics Goods Administration (TGA) Australia in 2012

Focus of the inspection

The inspection focused on the production and control of Powder for Injection for treatment of Tuberculosis. The inspection covered sections of the WHO GMP for sterile products text, including quality assurance, premises, equipment, documentation, validation, production, and manufacture.

Inspected Areas

- Quality Assurance
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Vendors evaluation
- Contracts
- Premises

- Equipment
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

In general Quality Assurance (QA) system was established and adequately maintained.

Batch release

SOP “Review and release of finished product in the SVP” and SOP “Quarantine Shipment of Third party product” were reviewed. First release was done as quarantine shipment to transfer the product from the inner warehouse (WH) to off-site WH (Aspen distribution centre). In off-site WH products were held until the final release was carried out. At this stage laboratory results were not available. After shipment the full audit of the “batch book” was carried out by the Document Review Pharmacist or delegate. Batch Manufacturing Records (BMR), Batch Packaging Records (BPR) and Quality Control Laboratory (QCL) records were reviewed according to the documentation audit check list.

Product Quality Review (PQR)

According to the company terminology PQR was named Annual Product Review (APR). In general APR was found to be adequate.

SOP Annual Product Review (APR) was reviewed. Batches manufactured in one year were included in the review. At least 3 batches should be used for the review. In case, if 3 batches had not been manufactured, the review could include batches manufactured previously. APR should be approved within 3 months from the date of manufacture of the last batch for the review period. APR was evaluated during the Quality System (QS) Management Review (MR) and decision then was made to initiate Corrective Actions and Preventive Actions (CAPAS) if required.

A specific APR review period 1 September 2011 to 31 August 2012 was reviewed.

Non-compliances observed during the inspection that was listed in the full report regarding reviewed APR were addressed by the manufacturer to a satisfactory level.

Management review (MR)

SOP “Management review” was reviewed. In general MR was found to be acceptable and comprehensive.

Management review was discussed during the general Management meetings what were held monthly. ICH Q10 principles have been integrated in MR, responsibilities were specified. Separated support meetings were also carried out. MR covered review of the outputs of the support meeting minutes and trends for example:

- Monthly management meetings
- Monthly QS MR

QS MR included the following: topics

- Management
- Personnel
- Documentation
- Facilities and equipment
- Material and product control
- Process assurance
- Laboratory controls
- Incident managing
- Overall effectiveness of QMS

The following monthly meetings were held:

- Environmental monitoring meeting
- Stability review
- Validation review
- Deviation review meeting

Production and Engineering daily meetings were also held.

Key areas required improvement were listed were recorded in the MR report. Scoring system was used for evaluation of the system. Review of CAPAs was part of the MR. MR was signed by the senior management.

Quality Risk Management

Quality Risk Management in general was found to be adequate. Quality Risk Management SOP was reviewed. Approach was based on ICHQ9. Risk assessments were performed by a multidiscipline team. States that risk assessments may be used for evaluation of new equipment and processes, preparation for key projects and handling problems in day to day activities. Main steps were:

- Risk analysis
- Assess likelihood
- Assess severity
- Risk evaluation
- Probability of detection
- Risk control/reduction
- Risk communication.

Change control also prompts for consideration of risk assessment to be performed.

Change control (CC)

Change Control management in general was found to be adequate.

Management of Change Control SOP was reviewed. These were managed by the Process Compliance system. A risk assessment was performed and the SOP defines evaluators from each department. Regulatory Affairs performed an assessment if the change was likely to impact dossiers. Customers were notified if required by the Technical Agreement. The QA Manager gave approval to proceed. Evidence was required to be attached for each action.

Either a short term or long term effectiveness review can be selected. A weekly review of outstanding actions and overdue changes was performed.

Deviation management

Deviation management in general was found to be adequate. Deviation Procedure was reviewed. Customers were notified as per technical agreement. These were managed by the Process Compliance system. Attachment included guidance on problem solving and root cause analysis techniques. Monthly, quarterly and annual trending was performed at management review meeting. The specific trend was reviewed. Although the trend looked at high level issue types and which departments the deviations originated from, it was encouraged to trend deeper against root cause analysis types. Reference was made in the BMR that a deviation raised on batch to ensure it was visible to the batch release pharmacist. A multidisciplinary team perform a formal risk assessment for critical issues, less critical issues may have an informal review performed.

A number of deviations and incident reports were reviewed and found to be adequate.

Corrective Action and Preventive Actions (CAPAs)

Dealing with CAPA in general was found to be adequate. CAPA SOP was reviewed. The source of CAPAs was wide ranging and included complaints, deviations, audits, PQRs and risk assessments. Evidence must be attached for action completion and an effectiveness review performed. These were also tracked via Process Compliance System.

A number of CAPAs were reviewed and found to be adequate.

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. The concept of qualifications and validations was implemented. Operators were trained, and records were made during manufacture.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. Environmental monitoring was undertaken. Premises and equipment were cleaned and disinfected following written procedures.

2.4 QUALIFICATION AND VALIDATION

Validation Mater Plan (VMP)

VMP version 9 was reviewed. In general VMP was found to be adequate. Calibration and Maintenance was covered in this document as well as PRAGMA, which was the planned maintenance and calibration program. VMP was a High Level Plan that was an umbrella plan for the entire project and provided a summary to SVP overall validation philosophy and approach. Purpose of the VMP was to present overview of the validation operation, organizational structure, key validation activities, and the planning schedule related thereto validation. The following activities were specified in the VMP:

- HVAC
- Utilities
- BMS
- Production Equipment
- Aseptic Process simulation studies
- Product validation
- Cleaning validation
- Lab equipment qualification
- Empower
- Computer related validation
- Method Validation
- Clean room ISO compliance

Validation schedule was spot checked.

SOP “Re-validation appraisal” was reviewed. The purpose of this document was to define the requalification / revalidation approach and to document re-validation intervals for equipment. It also provided periodic review of the process to establish whether re-qualification /revalidation was required for key GMP processes which do not have fixed requirements for re-validation, requalification.

Building Management system (BMS)

In general BMS was found to be adequate. Updated SOP was reviewed as well as completed log book. The BMS system which was a network was primarily used for monitoring and control of the facility HVAC system relative to classified areas.

The BMS was capable of system monitoring, controlling, alarming, point trending, point adjustments, and overrides. The system was capable of generating an audit trail for all user actions, which included user name, date, time, and terminal ID. Data was stored on dedicated servers and all access was via dedicated workstations by multi-level password control.

The system was validated. Validation report was reviewed. All parameters tested met the performance criteria.

The BMS status was part of the Quality Management Review System (QMRS) on monthly basis in which the previous month’s data was assessed and a report on this assessment was done.

SOP “BMS alarm and warning response procedure Multi product and Hazardous product” was reviewed. This SOP defined the actions and practices to be undertaken in case of BMS alarms and warnings for humidity, temperature and pressure.

Non-compliances observed during the inspection that was listed in the full report regarding BMS were addressed by the manufacturer to a satisfactory level.

Freeze dryer validation

In general Lyophilizer validation and cleaning was found to be adequate.

Multiproduct site Lyophilizer validation report was revived. The equipment was used to freeze dry vials of sterile parental product. The lyophilisation process provided removal of moisture from aqueous product, without affecting its biological, chemical or structural changes. The equipment was set on an annual re-validation program.

Basic operations were following:

- System leak testing
- Filter sterilization
- Filter integrity test
- System CIP and SIP

Lyophilizer cleaning system - the system was design to clean, sterilize, and dry the chamber, shelves, and door and condenser. Fixed spray nozzles were provided to perform complete cleaning of all internal surfaces. The spraying system included an automatic purging system. The washing system operated on a recycling basis, the water being re-circulated during the cleaning cycle. The final rinse was performed using WFI which was drained out. During the cleaning cycle, the shelves were moved by the stoppering system to ensure complete cleaning.

The cooling system was assisted by the circulation of cooled thermal fluid in the chamber and shelves, enabling the cooling from 120°C to 40°C had to be achieved in less than 2 hours. The entire CIP/SIP was under Programmable Logic Computer (PLC) control

Aseptic process validation (Process Simulation Trials)

A list of media fills which have been performed on the Vial Lyo line since its installation was seen. Initial validation was performed in April and June 2009. The simulations were performed in 3 phases. Initially 6000 vials were filled and partially stoppered and loaded into the lyophiliser top and middle shelf. Another 5000 vials were fully stoppered and immediately capped to reflect products which do not undergo lyophilisation. Finally another 3000 vials were partially stoppered and loaded into the lyophiliser bottom shelf. A vacuum was pulled at ambient temperature and held for 30 minutes. The chamber was backfilled with compressed air and stoppers fully inserted. These were then transferred back to the machine for capping and inspection. Any vials which would be rejected during routine production were not incubated.

The requirement was for 6 monthly media fills to be performed per line, with a 1 month tolerance from the due date permitted. These were planned into the production schedule and also listed on Pragma calibration system. It was confirmed that the company were meeting this criteria. Alternate studies of 10ml size and 20ml size were performed. The routine duration of production was typically 1 shift, but media fills were performed over 2 shifts.

Non-compliances observed during the inspection that was listed in the full report regarding aseptic process validation were addressed by the manufacturer to a satisfactory level.

Production autoclave validation

In general autoclave validation was found to be adequate. Autoclave Validation report was reviewed. Validation was performed on 3 runs. Load patterns were fixed. 12 Thermo couples (TCs) and Biological indicators (BIs) were used for validation studies. For heat distribution only TCs were placed only on shelves. For heat penetration TCs and BIs were located in bags. Bags were sterilized as part of autoclaving and not a separate load. Bags were once use and then were throw away. The validation studies showed that the equipment inside the bag was sterile.

In total 17 load patterns were validated. SOP “Load patterns for Fedegari Autoclaves” was reviewed.

Microbiology autoclave validation

Microbiology autoclave validation report was not reviewed. Observations were made that the validated cycle was for 48 x 1000ml bottles, when routine practice was for a mixed load ranging from 100ml to 1000ml in the same load.

Non-compliances observed during the inspection that was listed in the full report regarding microbiology autoclave validation were addressed by the manufacturer to a satisfactory level.

Depyrogenation Oven re-qualification

Fedegari Depyrogenation Oven annual re-qualification protocol and report were reviewed. In general Fedegari Depyrogenation Oven re-qualification was found to be adequate.

Empty chamber T distribution studies were done at equipment initial qualification stage.

Depyrogenation Oven HEPA filters were re-qualified by engineering department. Re-qualification was found to be adequate. “Particle re-qualification Multiproduct Area including LAFs and dispensary down flow booth” was reviewed. Depyrogenation Oven HEPA filter qualification was covered by this report. Re-qualification was carried out. Air to the oven was taken from the Grade C room and filtrated via H13. Re-qualification was carried out every 6 months. The following tests were carried out:

Two particle counters were used for re-qualification studies. Particle counters calibration certificates were presented to the inspector. Calibration was done 17 September 2012 and due date was 17 September 2013.

Non-compliances observed during the inspection that was listed in the full report regarding DOP test for HEPA filters installed to the Depyrogenation oven were addressed by the manufacturer to a satisfactory level.

Sterilizing Filter Validation

Filter validation was reviewed. Data seen was from Pall validation when Lilly manufactured the product.

Non-compliances observed during the inspection that was listed in the full report regarding Sterilizing filter validation were addressed by the manufacturer to a satisfactory level.

Cleaning validation

Cleaning validation studies were found to be adequate.

Cleaning Validation Plan (VP) was reviewed. The VP provided the documented evidence that the cleaning methods within the facility consistently control potential carry-over of previous product, cleaning agents, and /or extraneous materials to subsequent product to determined levels. The initial validation was carried out on three consecutive batches.

Cleaning validation protocol for specific product was reviewed and found to be acceptable.

AHU (air handling units) qualification

SOP “Control of Engineering Maintenance Management System – Pragma” was reviewed. The purpose of the SOP was to define the control procedure that must be in place to control and maintain the validated state of the computerized Engineering Maintenance Management System used at Aspen SVP facility. It was said that the system was validated. Validation was not checked during the inspections

HEPA H14 filter DOP testing carried out for vial filling area report was reviewed.

SOP “Air profile Studies” was reviewed. Purpose of the studies was to utilize smoke studies to determine airflow over equipment and personnel so as to minimize undue disruption of airflows and thus determine the best siting of these resources within the room to minimize undue disruption of airflows. The smoke generator was of Liquid Nitrogen type. A camera was used to capture the smoke patterns in the various positions.

The specific qualification document was reviewed in relation to the Lyo line. The studies concluded that airflow patterns were acceptable for Grade B flow pattern checks.

HEPA filtered systems Re-Qualification report was reviewed.

Non-compliances observed during the inspection that was listed in the full report regarding HEPA filters qualifications were addressed by the manufacturer to a satisfactory level.

2.5 COMPLAINTS

In general complaints management was found to be adequate. SOP “Customer complaints procedure”, register and trends were reviewed. Complaints were received by Medical Affairs department and registered to centralized Aspen Event Logging (AEL) database and send to the SVP department for investigation. QA manager or delegate was responsible for complaints investigation, trend analysis and CAPAs if required. Complaints were trended monthly. Complaints were investigated by the investigation team and root cause should be established if required. Risk assessment was also carried out. Complaints review was carried out monthly, 6 monthly and annually. According to the SOP complaints should be investigated within 10 days.

Complaints were classified as:

- Minor
- Major
- Critical

2.6 PRODUCT RECALLS

In general recalls management was found to be adequate. SOP “Product recalls procedure” and mock recall report were reviewed. Information required for the recall should be provided to the MCC within 3 days about recalls and recall types were classified by MCC as:

- Class I
- Class II
- Class III

and

Types:

- A
- B
- C

According to the SOP Mock recall should be executed under simulated recall scenarios at least once in 2 years. Three mock recalls were executed till the date of inspection. The first mock recall was international mock recall for eye drops for US market, second was for the local market and related to powder for injections recall. Third mock recall was for the local market and was related to the eye drops recall.

Till the date of inspection there was no real recall initiated.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Contracts with laundry facilities permitted the contract giver to audit the facilities of the contract acceptor, contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver’s prior evaluation and approval of the arrangement. Reviewed contracts were found to be adequate.

Laundry of sterile garments and garments used in Class C/D was contracted out to two laundry companies. Technical Agreements (TA) were reviewed.

Non-compliances observed during the inspection that was listed in the full report regarding TA for laundry of garments were addressed by the manufacturer to a satisfactory level.

2.8 SELF INSPECTION AND QUALITY AUDIT

SOP “Internal Audits” and schedule was reviewed. In general self-inspection was found to be adequate. According to the SOP all work areas and activities should be audited at least once in a year or more frequently at the discretion of the QS Manager and /or QA Manager. After audit report was written and decision was made on classification of audit findings as:

- Critical
- Major
- Minor

After the audit the report was issued to the area manager and CAPAs or CC for all critical and major findings should be submitted and supported by evidence in within two weeks after receipt of the report. CAPAs and submitted evidence was evaluated by the auditor and QS Manager. If CAPAs and evidence were found to be acceptable the audit was closed. If CAPAs were not accepted those were sent back to the area Manager and discussed.

Internal auditors Assessment/questionnaire was spot checked. Training was evaluated using multiple choice assessment questionnaires. External certificate of the Lead auditor was presented.

QS Manager was responsible for co-ordinating internal audits. For a person to be selected to be an internal auditor they need to be in possession of a relevant qualification from accredited training provider or they have extensive internal auditing experience.

Supplier's audits

In general supplier's audits were carried out adequately. Risk based approach to Vendor Audit management was reviewed. Suppliers were reviewed every 3 years by means of history of performance and desktop questionnaire. Suppliers were assessed in line with a risk algorithm to determine audit priority. The maximum time between audits was 5 years.

Audit report contractor for clean rooms garments washing and sterilization was reviewed. The facility was considered to be in compliant with general GMP requirements and was approved as Aspen supplier.

A number of audit reports were reviewed.

Non-compliances observed during the inspection that was listed in the full report regarding audit reports were addressed by the manufacturer to a satisfactory level.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Job descriptions were not checked during this inspection. Minimum number of personnel required was present in clean areas. Periodic health checks were carried out for all personnel working in clean areas. Vials visual inspection operators had to pass eye checks once in a year and had to have breaks for 15 minutes every hour.

SOP "Segregation of the Aspen SVP Multiproduct and Hazardous Product Suites" was reviewed. Prevention of personnel related cross contamination (hazardous production facilities to multi source production facilities) was explained. If person should enter the Multisource production facilities after being in Hazardous Product facilities he/she first has to shower or allow 12 hours period before entering.

2.10 TRAINING

Training was adequately carried out.

SOP “Training and development Systems” was reviewed. The following training modules were provided:

- Business orientation training of new staff
- GMP training for new staff
- Grade C training
- Clean room registration
 - Introduction to Microbiology (MB)
 - Environmental Monitoring (EM)
 - Personnel health and hygiene monitoring and gowning methodology
 - Aseptic techniques and clean room behaviour
- Good documentation Practice (GDD)
- Ovens and autoclaves
- Media fill inspector training
- Pharmacist training

Job related training was provided additionally – this training covered all relevant SOPs.

Training effectiveness was assessed by multiple choice assessment questionnaires and open questions. Aseptic techniques and clean room behaviour refreshing sessions for the personnel qualified to work in the clean areas was given every 3 months. Annual gowning re-assessment was carried out.

Two commercial training packaged (CDs) were provided for the induction training of all personnel:

- GMP of personnel hygiene
- Understanding sterile production

Sterile operator Job related SOP and Clean room registration training files as well as senior microbiologist training files were spot checked. Training records were maintained as individual training files.

Microbiologist qualification was found to be adequate.

For the analysts working in microbiology, qualification was carried out by performance evaluation of an “audit blank” sample being given and results were compared with previous results. Formal qualification certificate for general MB tests was under development.

Sterility testing re-qualification results reports for one microbiologist was spot checked. This report had written prove that the test had passed. Microbiologist had to pass sterility test re-qualification.

According to the SOP “Sterility testing” “All sterility testing microbiologists had to test one previously released batch using the appropriate method of analysis on an annual basis.

Analyst's qualification

Till the date of inspection only two analysts were involved in qualification. It was explained that periodic re-qualification was in progress. Two analysts performed the test at the same time. The sample was tested in 6 replicates. Results between two analysts were compared. SOP training (theoretical) training matrix was presented to the inspector.

2.11 PERSONAL HYGIENE

All personnel, prior to and during employment had to undergo health examinations. Direct contacts were avoided between the operator's hands and starting materials, primary packaging materials, intermediate and finished product.

High requirements were set up for personnel working in clean areas e.g. smoking, eating, drinking and keeping food, drink, smoking material and personal medicines was prohibited. Wrist-watches, make-up/cosmetics and jewellery were not permitted to be worn in clean areas.

SOP "General Behaviour in Clean Rooms" and SOP "Special Requirements for Working in a Sterile Environment" were reviewed.

2.12 PREMISES

Production

The production of sterile preparations was carried out in clean areas, entries to which were through airlocks. Clean areas were supplied with terminal HEPA filtered air.

Non-compliances observed during the inspection that was listed in the full report regarding production facilities were addressed by the manufacturer to a satisfactory level.

Utilities

Water

Water for Injection (WFI) was produced in the following way:

Municipal city water → multimedia filtration → reverse osmosis (RO) → distillation.

WFI was distributed via separate distribution loops into two separate storage tanks, one for Multiproduct facilities, and one for Hazardous product facilities. WFI was maintained at minimum temperature of 70 °C. WFI system was found to be adequate.

Compressed air

Compressed air was generated using compressor PFF02PQ04. Dry, oil free and particulate free air was supplied to various points of use. In the system there were 3 compressors, air dryer and air receiver. Compressor filters were changed by outsourced company and the schedule was as per operating manual.

The following filters were installed in the system:

- Dust Filter 1 micron
- Primary filter 1 micron particulate
- Secondary filter 0.01 micron

Final filters before the point of use "Ring main" were validated 0.22 micron filters.

Compressed air class complied with ISO 8573-1 class 2 requirements. Compressed air quality checks were carried out yearly.

The compressed air should comply with the following specifications:

- Water at pressure Dew Point <-40
- Free water <0.12
- Oil mg/m³ < 0.1
- Air quality (particle counts) > 0.5µm was 3520 and > 5.0 µm was 20
- Microbial limit < 1CFU/m³

Test results presented and reviewed meet "PASS" criteria.

Non-compliances observed during the inspection that was listed in the full report regarding compressed air were addressed by the manufacturer to a satisfactory level.

Nitrogen

Nitrogen was supplied from the gas farm via the loop. Nitrogen gas was used as excipient for plant, process and laboratory requirements. The primary distribution piping branches off to feed the High Potency area, Multiproduct area and laboratory. Nitrogen quality was assured by the inclusion of filtration units - 0.2 micron microbial retentive filters in the nitrogen distribution system, excluding the laboratory supply.

Nitrogen gas purity was tested using oxygen analyser. The following parameters were tested:

- Test Gas Particulate Ref ISO 14644-2 Grade A
- Particle size > 0.5 µm max particles is 3250 per m³
- Particle size > 5.0 µm max particles is 20 per m³
- Total viable count- ref ISO 14644.2 incubation conditions included both aerobic and anaerobic conditions < 1cfu/m³
- Dryness - test gas using 5-200mg/m³ water dragger tubes

Nitrogen system was found to be adequate

Steam

The production of “factory” steam was contracted out and was generated on site by a third party. Steam condensate was tested for chemical purity and endotoxins.

Clean steam and pure steam were used interchangeably and required to meet the same quality standards. Clean steam was generated in the first stage of the Multitron multi-stage effect distillation and was supplied the Multi products and Hazardous products facilities. Steam was piped in 316 Stainless Steel (SS).

The multitron was interfaced with the Reverse Osmosis (RO) unit to ensure continuous (on demand) supply of treated water to the distillation units and generation of clean steam and WFI.

Clean steam parameters were referenced to HTM 2010 and EN285. The test parameters were following:

- Dryness Factor / value test > 95 and > 90 respectively

- Superheat test <25C
- Non condensable gas test <3.5%
- TOC < 500pb
- Conductivity 2.1 micro s at 25 °C
- Nitrates < 0.2 ppm
- Heavy metals < 0.1 pp
- Endotoxin < 0.25 endo/unit

The sampling points were a close to the intake valves of the autoclave (there were three autoclaves).

Certificate for 316 SS as well as risk assessment were reviewed.

Steam system was found to be adequate

Ventilation

Hazardous product and Multi product HVAC systems were built as separate entities with separate HVAC systems that were further separated into independent systems for each area classification. Air was exhausted form the Hazardous product facilities via HEPA filters. HVAC system was monitored by Building Management System (BMS) which was validated.

Multi product facilities production areas were divided into class Grade A-D (class 100 to 100000). Final HEPA H 14 filters were terminally installed.

Quality control areas

Quality control laboratories were separated from production areas. Separate areas were provided for biological and microbiological tests.

Adequate storage space was provided for samples, reference, solvents, reagents and records.

2.13 EQUIPMENT

Planned Preventive Maintenance (PPM)

PPM was found to be carried out adequately.

PPM schedule was presented and reviewed. PPM schedule was generated for the following month. List of maintenance tasks was prepared for each piece of equipment. Maintenance tasks were entered into PPM schedule. PPM was carried out in accordance with Work orders. GMP compliance / impact were assessed by the QA department. Completed PPM schedule was evaluated and problems / outstanding issues to be corrected were identified.

Non-compliances observed during the inspection that was listed in the full report regarding PPM were addressed by the manufacturer to a satisfactory level.

Equipment calibration

Equipment calibration was found to be carried out adequately.

SOP “Equipment calibration was reviewed. This procedure was applicable for Calibration procedure contracted out. SOP described the Calibration procedure to be followed by the Contractors performing calibration of Critical devices at Aspen SVP.

SOP “Calibration of Critical equipment” was reviewed. This procedure was applicable for Calibration procedure performed in-house. SOP described the Calibration procedure to be followed by the Engineering performing calibration of Critical devices at Aspen SVP.

Production

SOP described the segregation of Aspen SVP Multiproduct and Hazardous Product Suite. Good segregation controls were in place regarding personnel, clothing, storage and waste disposal.

Non-compliances observed during the inspection that was listed in the full report regarding moving equipment between the Hazardous suite and the Multiproduct plant were addressed by the manufacturer to a satisfactory level.

Entry to production Grade C areas had the requirement to remove outdoor clothing and don ‘scrubs’, wear plant shoes and hat in a primary change room. There was a second change room where non-sterile lint free containment one piece suits, face mask, overshoes, glasses and another hat were worn. Suits may be worn for one shift.

Laboratories

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

2.14 MATERIALS

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. Consignments were checked for integrity of package and for correspondence between the order, the delivery note, and the supplier’s labels. Damage to containers were recorded and reported to the quality control department. If one delivery of material (starting and packaging) was made up of different batches, each batch was considered as separate for sampling, testing and release.

Warehouse

Received stock may be stored outside while unloading but the procedure stated that in inclement weather stock had to be received undercover.

A Supplier Vehicle Material checklist was used to confirm acceptability of the stock, which includes a check against the approved supplier list. This specified supplier name and manufacturers name and address. Stock was booked on against the purchase order and went into quarantine status. Labels were also applied to each container with item code and lot number. Hazardous APIs were stored in a dedicated store, which had a separate entry from the Multi-product warehouse.

A sampling booth and dispensary were located within the warehouse. Weight tickets were printed for dispensed items and APIs were dispensed last.

The warehouse was orderly and bar codes were scanned to confirm the correct item had been picked up. These were also checked by the pharmacist.

The cold store was visited. Temperature probes in the cold store and the ambient storage areas were linked with the Building Management System (BMS) and SMS alerts were sent if there were any excursions.

Evidence of pest control was seen within and outside the warehouse. Insect lamps and rodent boxes were used.

Finished goods were sent to the off-site Distribution centre and held in quarantine until all testing and batch documents were reviewed.

Samples were collected for all raw materials and packaging components, although often the samples were collected by the supplier and placed in a stand-alone bag called a ‘satellite’ sample. Stoppers came ready to use and were depyrogenated, siliconised and sterilised by gamma irradiation.

Caps were ethylene oxide sterilised.

All containers of raw materials were sampled for ID testing. Disposable sterile tools were used. Printed components sampling was done according to statistical samples. All testing was performed by QC department.

An AQL was applied for the sampling of vials and samples were provided by the supplier. Critical, major and minor defects were specified in the SOP for printed components and non-printed components such as plastic containers, closures, fillers and plastic bags.

SOP “Component Sampling Plans” was reviewed. Sterile primary packaging components were pre-sampled by the manufacturer during the production run. The sample sizes must correspond to the sampling plans for normal inspection general inspection level II in accordance to AQL.

Stopper specification was also reviewed and Vial Glass specification was reviewed. Critical, major and minor defects were specified.

2.15 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by appropriate responsible persons. Documents were regularly reviewed every two years and kept up to date. Documents related to the manufacture and QC were kept for 10 years. Records were made or completed when any action was taken.

Document Management System Qumas was used to hold approved versions of procedures. The system logged when a copy was printed and that individual receives an email when a

new version of the procedure was made effective. Generally there was a good level of detail included in SOPs.

Batch Manufacturing records (BMR)

The Batch Manufacturing Instruction for specific product under assessment was reviewed. This contains all the registered information submitted in regulatory dossiers. These are approved by Regulatory Affairs. 100% Visual inspection of freeze dried vials was carried out on black and white background.

Batch Packaging Records (BPR)

BPR for specific product under assessment was reviewed. Line clearance was carried out before the packing started. QC laboratory analysis report was spot checked.

2.16 GOOD PRACTICES IN PRODUCTION

Although good aseptic technique was witnessed during the inspection, the design of the facility was not conducive to minimising the microbial and particulate contamination of aseptically manufactured products.

Non-compliances observed during the inspection that was listed in the full report regarding design of the facility were addressed by the manufacturer to a satisfactory level.

Components were transferred from warehouse, cardboard boxes were removed and bags wiped before placing in the hatch which off loads into the component preparation Grade C room.

Stoppers were pre-sterilised and came double wrapped. The transfer process was to submerge in a sporicidal solution and hold in transfer hatch for 10 minutes.

Caps were purchased triple wrapped and the outer layer was removed during the hatch transfer from Grade C to Grade B.

Vials were washed with WFI. Trays used to hold depyrogenated vials had perforations on the lid and base which would not minimise the contamination of the vial during the manual transfer process. These trays have been replaced with non perforated trays. Post depyrogenation, vials were then offloaded into a mobile LAF in the aseptic core.

A separate transfer hatch was available for the movement of dirty equipment out of the aseptic core to be washed. Washing was done with WFI only, no detergents were currently used. Cleaning stickers were attached to the batch record.

SOPs were available which described the wrapping of components prior to sterilisation, and the loading pattern for the autoclave. Pictures were used to show the location of equipment. Acceptance criteria for the different autoclave cycles were also specified. The logbook was reviewed: daily Bowie Dick tests were performed and weekly leak rate and pressure test were also performed. Failed cycles cannot be offloaded in the sterile area.

A bioburden sample was taken prior to first sterilisation; limit was 10cfu/100ml. A second bioburden sample was taken prior to final sterilisation at the point of fill, limit was 0cfu/100ml. Product sterilisation filters were single use and integrity tested pre-autoclave and post use. The company were moving towards integrity testing post autoclaving and post use.

Filing machine set up was observed. Autoclaved parts had a 72 hour hold time. Machine parts were sterilised for a specific batch and autoclave records were filed with the batch record. There was a mix of double and single wrapping of parts seen. Product contact parts generally had 2 layers of protection, with one layer of protection removed at the Grade B/A interface, and the final layer removed just before fitting to the machine. Single wrapped items e.g. engineers tools and EM plates were sprayed with IPA at the Grade B/A interface and removed from wrapping just before they were placed in position. Filling pumps were assembled as much as possible prior to autoclaving with filling needles attached to minimise connections in the aseptic area.

Filling of a trial batch (WFI) was observed. The line appeared to run well. A list of permitted interventions was available. High risk interventions involved opening the machine door, which causes all vials exposed to be rejected. Medium risk interventions were done through “port holes”. The operator puts on a new sleeve and opens a small round door to perform the intervention. Forceps were used to minimise exposure.

Non-compliances observed during the inspection that was listed in the full report regarding design of the facility were addressed by the manufacturer to a satisfactory level.

The lyophiliser was CIP/SIP prior to each use. Both stages had phases where the shelves were collapsed and fully expanded to ensure all exposed surfaces were clean and sterile. A leak test was also conducted prior to use. The cycle was PLC controlled and a print out if the cycle was included with the batch record. Shelves compress on each other to inset the stoppers fully into the vials. The condenser was defrosted at the end of a batch.

Different products were identified by different colour caps. Trays were labelled with product and batch number.

The aseptic processing rooms and equipment were cleaned with disinfectant on each day of use. A weekly clean using sporicidal agent was also performed, even when rooms were not in use. It was stated the disinfectants had been validated.

Environmental monitoring (EM)

During initial qualification in 2008, an intensive EM sampling schedule was performed ‘in operation’ across 3 shifts for 3 days. Data did not indicate any worst case locations.

Viable and non-viable monitoring was performed during set up of filing machine.

Non-viable monitoring of Grade A areas samples of 1ft³ every minute which equals 1m³ every 35 minutes. If three consecutive minute samples were above limits, it was investigated and a comment made in the batch record. If no immediate explanation can be found, a mobile

counter was brought in to verify the result. An assessment was made if a deviation was required.

The risk assessment for viable monitoring of the Vial Lyo line was seen and deemed acceptable.

The rationale for monitoring performed during set up, production and post-production was based on man and material movements. Operators perform sampling in the Grade A, microbiology personnel sampled the grade B areas. Monitoring was a mix of continuous active air (SMA), settle plates and post production swabs and contacts, which included the filling needles. Active air samples using MAS samplers were performed in the Grade B twice per shift. All samples were logged in the BMR and used to support batch release, including data from changing rooms and the Grade B corridor on the days of filling. All personnel were monitored on every exit from the aseptic area and comprise of contact plates from head, chest, arm and gloves. Samples were either taken by microbiology or a separate operator.

Grade C monitoring was performed with settle and contact plates. These were sampled weekly by microbiology. Action limits were in line with Annex 1. Grade D areas in the micro lab and entry to change rooms were also done weekly. Alert limits were not based on historic data.

A rolling 12 month trend was seen.

Personnel were trended separately. The USP standard 1116 to aid in trending personnel monitoring was used.

Out of Specification Investigations included a section on managing micro excursions. If there was a trend of alerts limits or an action excursion, a Micro Data Deviation (MDD) investigation was raised. The template included a prompt for a micro lab investigation, production investigation, engineering investigation, compliance review and a final impact assessment performed by QA.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. QC personnel had access to production areas for sampling and investigation.

Certificates of Analysis (CoA) were approved by the QC Manager/delegate and QA Manager/delegate.

Samples were logged into an excel system for the purpose of tracking. A LIMS system was planned to be introduced for use in the near future. A unique laboratory number was given to each sample. The materials item code was linked with the specification and referenced the method of analysis to follow. Raw data was recorded in the analyst's workbooks.

Chemistry laboratories included:

- Instrument room (for stability testing, particle counting and packaging component testing)

- HPLC room
- Wet chemistry laboratory
- Balance room which also included Karl Fischer.

Only Grade A glassware was used. Laboratory glassware, except pipettes and burettes, was cleaned in automatic glassware machine. Volumetric flasks were dried at 60 °C.

All laboratory instruments had usage log books.

Only USP primary reference standards were used for Capreomycin analysis. Records of use were kept and checks were made that the lot remained current.

Each analyst had his/her own record book. Analytical raw data was checked by the Laboratory Quality Review Group and compared with the report sheet.

Logbooks for HPLC equipment and columns were seen. It was explained that back up of HPLC chromatograms was done monthly on internal server and every 3 months recorded on CDs. HPLC columns were not reversed. Upon receipt of a new column plate counts were carried out and compared with column manufactures CofA. HPLC calibration was contracted out and was done yearly. HPLC verification on site was not done. System suitability tests were carried out for every analysis. PPM was done monthly.

Calibration of the HIAC particle counter was seen. This used standards traceable to NIST (the South African National Standard Institute).

Printed packaging components were given a unique code which was printed on the component and changes when the artwork was updated. Overlays were used to check text against. These were approved by a packing technologist who checks against regulatory data.

Balances daily checks were carried out, standard weight certificates were presented to the inspectors. Weekly balances linearity checks were also carried out.

UV-VIS verification checks were carried out monthly

Non-compliances observed during the inspection that was listed in the full report regarding PPM were addressed by the manufacturer to a satisfactory level.

Stability studies

Stability data summary for all storage conditions for a specific product under assessment were spot checked. These batches were kept in upright position.

Stability schedule was maintained electronically by SLIM system. The system was validated; validation report was not checked during the inspection.

Microbiology laboratory

Media used was a mix of in house prepared and purchased. All batches of media were challenged with growth promotion in line with Pharmacopoeial requirements plus environmental isolates.

It was noted that media for sterility testing was purchased. R2A agar used for WFI testing was also purchased.

Total Viable Counts and endotoxin testing were performed under LAFs. Turbidometric test was used for endotoxin. No failures had ever occurred.

Incubators were located in the plate reading room, which was well lit and had a plate counter. Alert level excursions had gram stain performed and if objectionable organism found would go for species identification. Action level excursions were fully identified using Vitek system. The performance of the Vitek was challenged weekly using 7 different types of organisms. Challenge cultures used were a maximum of 4 passages.

Non-compliances observed during the inspection that was listed in the full report regarding microbiology laboratory and related analysis were addressed by the manufacturer to a satisfactory level.

WFI monitoring

WFI trend data from 1 March 2012 to 24 April 2013 was seen. All points were sampled throughout week, with worst case locations e.g. return loop sampled daily. Chemical and micro data was satisfactory with Total Viable Counts (TVC). Counts usually were 0 cfu/100ml. When water was used in the manufacture of a batch, an additional sample was taken prior to use.

Handling of OOS results

SOP “OOS” and SOP “OOS Investigations” (MB OOS) were reviewed.

Non-compliances observed during the inspection that was listed in the full report regarding OOS investigations were addressed by the manufacturer to a satisfactory level.

Sterility testing

In general sterility testing was found to be adequately performed.

Samples for sterility testing were taken from the beginning, middle and end of filling. Twenty samples were tested. In addition, if a high risk intervention was performed during filling, extra samples were taken and tested.

Sterility testing was performed in Vapour Hydrogen Peroxide (VHP) gassing isolators within a Grade D room. Isolators were cleaned with IPA prior to use and materials were wiped with IPA prior to loading. Loading patterns were described in a SOP. The PLC controlled the gassing cycle and included a leak test. The print out confirmed if the cycle passed or failed and included a check if critical parameters were met and the required quantity of VHP was used.

The VHP solution was a QC released material. Residual VHP levels were checked prior to starting testing. Settle plates and open broth bottles were exposed during testing and contact swabs and plates were taken at the end. The incubator log confirmed date and time of incubation. These had chart recorders which were checked daily.

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, Aspen SVP (Ltd) a Manufacturing division of Aspen Pharmacare locate at 8B Gibaud Road, Korsten, 6020 Port Elizabeth, South Africa, 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 2 years, provided that the outcome of any inspection conducted during this period is positive.