

**Prequalification of Medicines Programme**
**WHO INSPECTION REPORT**
**Finished Product Manufacturer**
**Part 1: General information**

Name of Manufacturer	Cipla Ltd
Unit number	Unit V
Production Block	Oncology injections
Physical address	Verna, Goa, India
Date of inspection	14 - 17 February 2011
Type of inspection	Routine
Dosage forms(s) included in the inspection	Vinblastine injection
Summary of the activities performed by the manufacturer	Production and control

**Part 2: Summary**
***General information about the company and site***

After arrival, the inspectors were taken to the "new" building hosting a conference room. The inspectors as well as the company representatives introduced themselves.

The company gave a presentation covering an overview of the site and the activities performed in the 9 manufacturing units that were located at this site. Unit V was dedicated to oncology product manufacturing. This Unit was added in 2003. About 230 people were working in Unit V. There were three shifts operational - 0830-1700 (general), 1500-2315 and 2315 - 0700. Warehousing was dedicated for Unit V (receiving of raw materials and primary packaging materials). Utilities for Unit V were dedicated except for boiler steam and compressed air.

Changes since the last inspection in 2007 and anticipated future / planned changes were reviewed

### ***History of WHO and/or regulatory agency inspections***

Inspections of the Unit included:

- TGA 2008
- MHRA 2009
- WHO 2007
- US FDA 2009
- MCC 2004
- ANVISA 2007
- And others

### ***Focus of the inspection***

The scope of the inspection was clarified and it was mentioned that several of the WHO GMP texts had been revised. The activities and scope of PQ was explained including WHOPIRs and NOC. The inspectors explained that the inspection would focus on the production and control of injectable oncology products. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, personnel, validation, sanitation and hygiene, production, quality control and utilities.

### ***Inspected Areas***

After the opening meeting, the inspectors started the inspection by reviewing the organization charts and the job descriptions for Head Quality Control and Functional Head. The job description specified that the Head Quality Control would execute the responsibilities of the Head Quality Assurance in his absence, instead of the responsibilities of the Head Unit Quality Assurance.

The training SOP (CQA) was reviewed. Training records (2010) according to the training schedule were requested and checked for aseptic technique and media fill. Needs assessment for training was to be done according to the SOP. The attendance sheets for specified training were available. Assessment of the training success was done by means of a questionnaire.

The process flow chart for the manufacture of Vinblastine injection was reviewed. The company explained all stages and steps for production, material flow as well as component flow and preparation. Various questions were asked about the process.

General questions were raised regarding the process and validation approach.

The specification for polythene bags (in which material is dispensed) was reviewed. Parameters included identification and dimensions. The sampling plans and AQLs were specified as per ANSI/ASQ Z1.4-2003 and MIL-STD-105E.

The SOP for PQR was reviewed (CQA). The PQR report for 2010 was inspected for Vinblastine sulphate 10mg/10ml vial for batches that were manufactured in the review period



of January 2010 to December 2010. None of the batches had to be rejected. Reprocessing and reworking was not allowed for injectable products. There were no OOS results reported. No complaints or recalls were recorded. Various aspects of control were included in the PQR.

After a lunch break, the warehouse was inspected (receiving and storage of raw materials and primary packaging materials). Various checks were done on materials during receiving such as the purchase order, expiry date, approved supplier and batch number. Materials were controlled through an IMS (computer system). Raw Material codes were checked for Vinblastine sulphate. Passwords were used by operators of the IMS.

The storage of rubber stoppers, seals and raw materials was then inspected. There was no protective plate for the filters in the LAF that was used for sampling of rubber stoppers. There was a separate area for rejected materials (which was empty at the time of the inspection). Vinblastine sulphate was stored in a deep freezer (-10 to -20C). The temperature was monitored and recorded; the indicator and sensors were calibrated.

Separate sampling areas existed for excipients and APIs which had PALs and MALs. APIs were sampled in a bio-safety cabinet. Air was exhausted through a double HEPA filtration system, and pre-filters were maintained by means of a bag-in-bag-out system. A pressure suit was worn for sampling of APIs, which was fed by compressed air. Suits were dedicated to a specific API and could be used for 6 months before incineration. A different gowning procedure was in place for the wash area where the vacuum cleaner was cleaned. (The vacuum cleaner was used to de-dust suites after sampling).

Dispensing of excipients and APIs were done in separate areas. MALs and PALs were in place. The PAL was designed as a bubble airlock and the pressure cascade was monitored through the BMS. Dispensing of APIs was done in a RLAF cabinet (not a bio safety cabinet) which was fitted with a single HEPA filter in the exhaust.

A summary of deficiencies and observations made during the day was given to the company at the end of the day.

On the **second day**, the inspection of the quality control laboratories was started with a short walk-through through the premises. Sufficient space was available to carry out testing activities. Environmental conditions in the chemical laboratory, the refrigerators, the deep freezers and the stability chambers were monitored and recorded. Refrigerators, deep freezers and stability chambers are equipped with temperature and hygrometers as applicable and linked to an audio-visual alarm system. No excursions have occurred.

Reserve samples are kept for specified time periods.

Chemicals are purchased, checked, and labelled according to written procedure (QCP). Expiry dates are allocated, if no expiry dates of the manufacturers are available.

Official reference standards are purchased to be used for the preparation of working standards (SOP QCP). Vinblastine sulphate working standard was characterized against a primary standard by Cipla, Bangalore, and been distributed to the different Cipla sites. For the bulk working standard a retest period of two years is allocated, based on stability data available.

The bulk working standard is divided into single use aliquots, equally controlled by allocation of subplot numbers. Registers for the usage of the standards were kept and were – as far as checked – accurate.

Water for analytical purposes was produced in the laboratory. The water was tested against the specification for purified water on a regular basis.

A sample inward register was used, allocating an individual number to every sample to be analysed. The register was used for all types of samples, covering raw materials, packaging materials, environmental, and stability samples.

The procedure for conducting stability studies (QCP) as well as the schedule and record for the stability study for Vinblastine sulphate 10mg/10ml (Lot XYZ, 24 M, 2- 8 °C) were reviewed and found to be acceptable.

Out of specification procedure (QCP), the register and details to handling two out of specification results that were recorded in 2010 were reviewed. Investigation and testing was performed according to procedure and corrective actions were taken as asked for. Trending of out of specification results was performed. (Selected OOS investigations were requested and inspected).

The analytical reports for Vinblastine sulphate USP FW were reviewed. 8 containers were received, and samples were taken from each container for analysis (chemical as well as micro). The source data for identification were verified for each sample. The preparation of the KBr pellets was explained. The batch manufacturing record for Vinblastine sulphate finished product (lot XYZ) including results for environmental monitoring were reviewed.

After lunch, the microbiology laboratory was inspected. Media preparation, handling of test cultures, register and loading patterns of the autoclave, testing of the autoclave, and records for the testing of water for injection for the year 2010 were reviewed and found to be acceptable. A general procedure for sterility testing was available. However, no detailed instruction to carry out the sterility test was described for Vinblastine sulphate finished product (e.g. wash solution, volume of wash solution to be used, inactivation).

A summary of deficiencies and observations made during the day was given to the company at the end of the day.

On the **third day**, the OOS records selected by the inspectors, for primary packaging materials, including the investigations and rejection records for glass vials were reviewed.

Other documents and records inspected included:

- Media fill protocols and reports
- Process validation
- Qualification of the autoclave (rubber stoppers were sterilized in the autoclave)
- Qualification of the sterilizing tunnel (sterilization and depyrogenation of vials)
- Batch Manufacturing Records

- Area classification and monitoring

The company explained that media fill was done six monthly. Media fills were said to be done at different speeds of filling. Three runs of media fill are done based on risk assessment (worst case). In two years, all vial sizes are to be covered in accordance with a matrix prepared. All personnel involved in the filling of product were involved in the media fill exercise. The records were inspected. This included the actual media fill, the environmental monitoring at the time (non-viable and viable) as well as interventions performed. The different times, records and associated documents were verified during the inspection including incubation records and results. A growth promotion test as well as a container closure integrity test was done after incubation.

For Vinblastine sulphate 10mg/10ml, three batch sizes were used. All batch sizes have been validated. During the inspection, the process validation protocol and report for the 200l batch size were inspected. Three batches were subjected to validation for the 200l batch size in 2007.

Complete qualification for heat distribution and heat penetration of the autoclave (rubber stoppers were sterilized in the autoclave) was performed initially and will be repeated at defined intervals. Re-qualification is done at intervals, covering heat penetration studies. A matrix is prepared for different loads to be covered in a year. The sensors were calibrated before as well as after the study. A maximum load of stoppers was used. Records were verified. Chemical and biological indicators were included in the load. The results were acceptable. Although one load of the maximum load was included in the penetration study, six different loads are used in a year for the heat penetration study. The vacuum leak test was also done and the pressure was monitored during the study. Steam quality is also tested at regular intervals for compliance with the specification.

Qualification of the sterilizing tunnel (sterilization and depyrogenation of vials) was inspected. The heat distribution study was done initially (and to be repeated every X years), and the heat penetration was done every six months and all vial sizes were covered once a year. The results for heat penetration were reviewed. The temperature in the tunnel was monitored every 10 seconds. The conveyer speed was specified and was the same as in the BMR.

Validation of depyrogenation of the vials was done. A positive control is kept. The information in the BMR was verified against the validation outcome.

#### Area classification and monitoring

Filling area line II - class A:

The area is classified at regular intervals, PQ being done every 3 months (velocity, particles) and DOP 6 monthly. A schematic drawing of the areas indicated the different area classes.

Classification is done at rest and in operation.

The results for various parameters were checked and found as follows:

For particle monitoring, X locations were identified under the unidirectional air flow. 1000 l were sampled. Air flow velocity and uniformity of velocity records were reviewed. Verification was done at supply and working levels.

After lunch the inspectors went to the production areas and observed the set up of line II and operation that was ongoing on line I. They inspected the filled vial storage area and the visual inspection of vials. They also inspected the packaging line and finished product stores area.

The procedure for batch record review and batch release was verified. The implementation thereof was checked against the review of Vinblastine injection, batch XYZ. It included general aspects as well as viable and non-viable monitoring records.

A summary of deficiencies and observations made during the day was given to the company at the end of the day.

On **day 4**, the inspection was started by reviewing the planned preventive maintenance schedule for Unit V. The records for monthly and quarterly PPM for filling line I (OCP) and II (OCP) were checked for 2010 and 2011. The PPM for the sterilizing tunnel (OCP) was checked for monthly, six monthly and annual schedule.

An in house SOP is followed for calibration frequency. A master plan is prepared for every year, listing the equipment. A schedule is prepared (frequency) and is followed. The schedule for calibration of the HVAC system and autoclave in Unit V was inspected. Calibration intervals were specified and records were maintained including labels and certificates. The certificate for several sensors were checked. The calibration of instrumentation for the HVAC system was done for inter alia air velocity, temperature, humidity, and pressure differential. The pressure cascade specifications and limits were checked (tabulated) against the schematic layout of the site. A separate SOP was in place as well as a schedule for the calibration of laboratory instrumentation. The calibration procedure for the HPLC (XYZ) was checked.

The records for self inspection were checked, including the schedule, corrective actions taken and follow-up.

The SOP for complaint handling (CQA), and the register for complaints received in 2010 were inspected. A matrix was available for the product complaint investigation referring to BMR, BPR review, analytical record review etc.. The inspectors reviewed complaint number XYZ. The trending of complaints was done six monthly and the report generated for all of 2010 was checked.

A containment study was performed. The company performed a risk assessment to identify areas of risk and the need for upgrade of the site.

A procedure and records existed for risk assessment done in different areas of work. Some of the risk assessment reports were reviewed. FMEA was used as the tool of choice in performing risk assessment. RPNs were calculated.

Eye tests and medical examinations were done according to the company procedure (not inspected).

The training record for an identified employee was reviewed. There were three certificates in the file for 2010 for attendance of training.

Several draft documents were presented addressing changes in regard to observations made by the inspectors during the last 4 days. The initiated changes were noted, however, the documents were not checked in detail.

A summary of deficiencies and observations made during the day was given to the company at the end of the day.

A summary of the findings was presented in the closing meeting.

## **2.1 QUALITY ASSURANCE**

The company had systems in place to ensure the quality of products manufactured. There was a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It was fully documented and its effectiveness was monitored through audits and self-inspections. All parts of the quality assurance system were adequately staffed with competent personnel, and there were suitable and sufficient premises, equipment, and facilities.

The system of quality assurance ensured that:

- (a) pharmaceutical products were designed and developed in a way that takes account of the requirements of GMP;
- (b) production and control operations were clearly specified in a written form and GMP requirements were adopted;
- (c) managerial responsibilities were clearly specified in job descriptions;
- (d) arrangements were made for the manufacture, supply and use of the correct starting and packaging materials;
- (e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations were carried out;
- (f) the finished products were correctly processed and checked, according to the defined procedures;
- (g) pharmaceutical products were not sold or supplied before the authorized persons had certified that each production batch had been produced and controlled in accordance with the requirements of the dossier;
- (h) satisfactory arrangements existed to ensure, as far as possible, that the pharmaceutical products were stored by the manufacturer and distributed;
- (i) there was a procedure for self-inspection that regularly appraised the effectiveness and applicability of the quality assurance system;
- (j) deviations were reported, investigated and recorded;
- (k) there was a system for approving changes that may have an impact on product quality;

(l) regular evaluations of the quality of pharmaceutical products was conducted (Product Quality Review) with the objective of verifying the consistency of the process and ensuring its continuous improvement.

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

Products were consistently produced and controlled to the quality standards appropriate to their intended use and as required.

Systems were in place to reduce the risk of cross-contamination and mix-ups. These included: (a) all manufacturing processes were clearly defined and systematically reviewed, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;

(b) qualification and validation were performed;

(c) all necessary resources were provided, including:

(i) appropriately qualified and trained personnel;

(ii) adequate premises and space;

(iii) suitable equipment and services;

(iv) appropriate materials, containers and labels;

(v) approved procedures and instructions;

(vi) suitable storage and transport;

(vii) adequate personnel, laboratories and equipment for in-process controls;

(d) instructions and procedures were written in clear and unambiguous language, specifically applicable to the facilities provided;

(e) operators were trained to carry out procedures correctly;

(f) records were made during manufacture to show that all the steps required by the defined procedures and instructions had in fact been taken and that the quantity and quality of the product were as expected; any significant deviations were fully recorded and investigated;

(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, were retained;

(h) the proper storage and distribution of the products;

(i) a system was available to recall any batch of product from sale or supply;

(j) complaints about marketed products were examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

## **2.3 SANITATION AND HYGIENE**

A high level of sanitation and hygiene was practised on site. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination were eliminated through an integrated comprehensive programme of sanitation and hygiene.

## **2.4 QUALIFICATION AND VALIDATION**



Cipla Unit V identified what qualification and validation work was required to prove that the critical aspects of their operations were controlled.

Qualification and validation were performed and showed that:

(a) the premises, supporting utilities, equipment and processes had been designed, installed, and operated in accordance with requirements. The validation provided evidence that the production processes (for the product inspected) consistently produced a product meeting its predetermined specifications and quality attributes.

Validation studies were conducted in accordance with predefined and approved protocols and written reports summarized the results and the conclusions reached.

## **2.5 COMPLAINTS**

There was an SOP for handling complaints. All complaints and other information concerning potentially defective products were reviewed according to written procedures and the corrective action was taken.

## **2.6 PRODUCT RECALLS**

There was a system to recall from the market, promptly and effectively, products known or suspected to be defective.

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

Not inspected.

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

A self-inspection programme was in place and was designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections were performed routinely. A team was responsible for self-inspections. Recommendations for corrective actions were implemented. The procedure for self-inspection was documented, and there was an effective follow-up programme.

## **PERSONNEL**

There were sufficient qualified personnel to carry out all the tasks for which the manufacturer was responsible. Individual responsibilities were defined and recorded as written descriptions. There were an adequate number of personnel with the necessary qualifications and practical experience. All responsible staff had their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Delegated duties were not always clearly defined. Organization charts and job descriptions were in place, however, some discrepancies were noted (see observations below).

## **2.9 TRAINING**

Training was provided in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories. Training records were generally kept.

## **2.10 PERSONAL HYGIENE**

A high level of personal hygiene was observed by all those concerned with manufacturing processes. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Personnel were wearing clean body coverings appropriate to the duties they performed, including appropriate hair covering. Used clothes were stored in separate closed containers until properly laundered.

Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines was not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.

Personal hygiene procedures included the use of protective clothing for all persons entering production areas including contractors' employees, visitors, senior managers, and inspectors.

## **2.11 PREMISES**

The premises was located, designed, constructed, adapted, and maintained to suit the operations carried out. The layout and design of the premises aimed to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

In areas where dust was generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), appropriate measures were taken to avoid cross-contamination and facilitate cleaning.

## **2.12 EQUIPMENT**

Equipment was located, designed, constructed, adapted, qualified and maintained to suit the operations to be carried out. The layout and design of equipment also aimed to minimize the risk of errors and permitted effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

## **2.13 MATERIALS**

Materials were sourced from approved suppliers. All incoming materials and finished products were quarantined immediately after receipt until they were released for use or distribution. All materials and products were stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation.

## **2.14 DOCUMENTATION**

Documents were designed, prepared, reviewed and distributed with care. They complied with the relevant parts of the product dossiers. Documents were approved, signed and dated by the appropriate responsible persons. Documents were laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible. Documents were regularly reviewed and kept up to date.

## **2.15 GOOD PRACTICES IN PRODUCTION**

Production operations followed clearly defined procedures. All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution was done in accordance with written procedures or instructions and, where necessary, recorded.

Deviations from instructions or procedures were avoided, and when deviations took place, these were handled in accordance with an approved procedure.

Checks on yields and reconciliation of quantities were carried out.

Materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used were labelled with an indication of the product or material being processed.

Access to production premises were restricted to authorized personnel.

## **2.16 GOOD PRACTICES IN QUALITY CONTROL**

The quality control unit was concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests were carried out and that materials were not released for use, nor products released for sale or supply, until their quality had been judged to be satisfactory.

Quality control was independent from production. The basic requirements for quality control were met in terms of:

- (a) adequate facilities, trained personnel and approved procedures were available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and for monitoring environmental conditions for GMP purposes;
- (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by methods and personnel approved of by the quality control department;
- (c) qualification and validation was performed;
- (d) records were made demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations had been fully recorded and investigated;
- (e) the finished products contain ingredients complying with the qualitative and quantitative composition of the product described in the dossiers;
- (f) records were made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment included a review and

evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

(g) sufficient samples of starting materials and products were retained to permit future examination of the product if necessary; the retained products were kept in its final pack.

### **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, Cipla Ltd India, Verna, Goa (Unit V) was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

The manufacturer responded to all observations listed in the inspection report in a satisfactory manner.