



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

Part 1: General information

| | |
|---|--|
| Name of Manufacturer | Novartis Pharmaceuticals Corporation, Suffern, USA |
| Unit number | NA |
| Production Block | NA |
| Physical address | Novartis Pharmaceuticals Corporation, 25 Old Mill Road, Suffern, NY 10901, USA Phone: 845 368-6000 Fax: 845-368-6612 |
| Contact person and email address. | Julie Sanchez Director, Compliance Novartis Pharmaceuticals Corp., PH, PO-Compliance, PHJMG00000, Compliance USSF, 550-1-1737 Novartis Pharmaceuticals Corp., Pharmaceutical Operations Suffern 25 Old Mill Road Suffern, NY 10901 USA Phone: +1 845 368 6292 Fax: +1 845 368-6556 Cell: +1 845 406 7308 Email : julie.sanchez@novartis.com |
| Date of inspection | 25, 26, 27 and 28 October 2010 |
| Type of inspection | Routine Inspection |
| Dosage forms(s) included in the inspection | Tablets |
| WHO product categories covered by the inspection | Finished Pharmaceutical Products (FPPs) used in the management of Malaria (MA) |
| Summary of the activities performed by the manufacturer | Manufacturing, packaging, quality control and batch release of tablets, capsules and transdermals. |

Part 2: Summary

General information about the company and site

The facility inspected was **Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA**, here after referred to as **Novartis Suffern**. According to the Site Master File, Revision 5 and the company presentation, Novartis Suffern, was located on a 53,884m², piece of land, 17,652m² of which was occupied by the production facility. Tablets, capsules and transdermals were manufactured and packaged at the facility for human use only. Secondary packaging of some parenterals products was also handled at the site. A total of 19 active ingredients were used in the products handled at the site, including a synthetic hormone. It had 5 manufacturing lines and 15 packaging lines. It operated in 3 shifts per day and in 3 process teams: Cardiovascular, Specialty Medicines and third party manufacturing.

According to the company presentation and SMF, the company employed a total of 426 people.

History of WHO and/or regulatory agency inspections

This was the second inspection by WHO, the first was in March 2008. According to the company presentation, the site was also previously inspected by the following authorities:

- New York State Board of Pharmacy (March 2008),
- MHRA, UK (April 2008)
- USFDA (July 2008; March 2009; January, February and September 2010)
- Drug Enforcement Administration (DEA) (August and October 2008; August 2010)
- NAFDAC Nigeria (September 2010)

The registration number for the site by the different authorities is as follows:

- USFDA: is 2416082
- New York State Board of Pharmacy: 101181
- US Drug Enforcement Administration: PG0013754
- New York State licence to handle controlled drugs: 010033.

Focus of the inspection

The inspection focused on the production and control of **two Artemisinin based products**. The inspection covered selected sections of the WHO GMP text, including premises, equipment, documentation, materials, personnel, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards with the key staff of Novartis, Suffern. The inspectors explained the history and procedure for the WHO Prequalification Programme, the procedures and standards used for inspection and timelines for the processing the report and company responses to the inspection observations. The procedures for closing the inspection including the WHO public inspection report (WHOPIR) and Notice of Concern (NOC) were explained. The tentative inspection plan was discussed and confirmed. It was agreed that the inspection will focus on WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010



aspects related to or that would impact on the product and control of the two Artemisinin based products. The company made presentations on the site overview, changes related to product under focus, a project to increase access to and cost of the products in focus. Copies of the presentations were obtained and will be filed in the company file.

The Coartem related changes highlighted included:

- Created materials airlocks between the warehouse and the sampling booth.
- Implemented ID test on each container of the APIs used in the products under focus.
- Included WHO among the authorities to be notified in case of a product recall.
- Conducted airflow visualization test to confirm effectiveness of the dust collecting system design.
- New locker room created allowing direct access to zone 2, eliminating the need to transition.

The inspection of the following areas and aspects followed:

Quality Management System review (2008 & 2009):

- Personnel Policies: *Organization charts, Job descriptions, Training, Health and Hygiene.*
 - The role profiles (job descriptions) of some staff in the following functional areas were selected for detailed review: consumer complaints; analyst; MDV Scientist/Cleaning validation; Calibration/qualification of QC Equipment; Supplier auditing.
 - The training records for some staff recruited in 2010 were selected for detailed review.
- Product Quality Review reports for 2008 & 2009:
 - SOP No. SOP-5002485, Annual Product Review
 - PQR for the period 1st July 2009 to 5th February 2010 for products under code two codes (295 batches of commercial packs and 2 batches of bulk exported for packaging). The batches were tested according to standard testing procedures for Australia and for USA. It covered 2 complaints/ADRs, 1 compliance investigation, 59 approved changes, 7 validation batches and 17 occurrences (deviations). There were no rejected batches, no reworked/reprocessed batches and no recalls. A variability in the uniformity of dosage unit for one active ingredient was observed.
 - Data was evaluated using table, trend charts, RSD, proves capability (assay, uniformity of dosage unit and dissolution).
 - Some deficiencies were noted as described in the table of observations.
- Deviations + related SOPs and registers for 2009 and 2010:
 - SOP on "Occurrences and investigation Procedure".
 - Reports of selected occurrences (deviations) were reviewed in detail:
 - on wrong expiry date: Sept. 2009 instead of Sept.2011.
 - on incorrect material code on the shipper.
 - on a sampling scoop found in the IBC on transferring material from the IBC to the mixer.
 - It was noted that a significant proportion of occurrences/deviations were noted as attributable to human error.
- List of SOPs/SOP Index.
- Reprocessing/Reworking policy + SOPs:
 - SOP on "Creation and Issuance of Rework Orders".
 - SOP on "Dumpback of a packaging Batch".

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010



- Novartis Quality Manual: Reprocessing and Rework of Materials, Module N10.8 Edition 02.
- Change control + related SOP and register for 2009:
 - SOP on “Local Change Management”
 - Change Control relating to packaging transfer.
 - Change Control relating to change from unprinted foil to preprinted foil
 - Change Control relating to “Upgrade of granulation suite 1, using end point detection equipment”
- Self inspection (SOP, Plans, reports): not reviewed in detail.
- Complaints handling system (SOPs and registers for 2009 & 2010)
 - SOP on “Complaint Processing”
 - Complaint related to a suspected counterfeit
 - Complaint related to lack of efficiency on the Batch
- Product recall system (SOPs and registers for 2009 and 2010):
 - SOP on "product Recall Procedure".
 - There were 2 recalls in 2009 and 3 in 2010 but none involved the products under focus.
- Product Master Files, codes, specifications for APIs and FPPs, plus List of approved vendors:

Inspection of Receiving and storage areas + procedures:

- Starting materials, packaging materials and components receiving, quarantine, sampling and storage areas + SOPs and records in SAP. Records of selected materials were reviewed in SAP:
 - The APIs appeared under different codes.
 - It was noted that materials from different manufacturers were controlled under the same code.
 - The manufacturers of materials supplied to the Suffern site through Novartis Pharma "Turn table" were not indicated in SAP.
 - The manufacturers of some split batches were not indicated in SAP as the field was simply left blank.
 - PVC/PCTFE/PVC.
 - Laminated Aluminium Foil - pre-printed.
 - Package insert (PI).
- Finished goods warehouse + distribution records
- Temperature + RH mapping and monitoring
- Pest control procedures
- Vendor approval, qualification and maintenance system:
 - SOP on "Supplier Monitoring; Qualification and Certification".
 - Selected vendor audit reports were reviewed:
 - supplier of quality control micro-organism products (reference culture).
 - supplier of PA/AL/PVC foils.
 - supplier of printed folded inserts.
 - supplier of PVC/PE/PVdC Film laminate.

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010



Day 2

The inspectors started by giving feed back on observations of the previous day and obtained preliminary clarifications from management where deemed necessary. The inspection then proceeded with a review of the following issues outstanding from the previous day:

- Testing of packaging materials:
 - 49 rolls (3,403kg) of PVC/PCTFE/PVC based on a specification which specified S4 level of sampling for physical tests with AQL of 0 for critical, 2.5 for major and 4.0 for minor defects. All rolls were inspected, an IR test was done and the rest were evaluated based on the supplier CoA.
 - 104 rolls (2004kg) of Laminate foil was tested against a specification with similar sampling level and AQL as above for physical attributes and G1 level with AQL of 0 for printed defects. A hard copy proof sample was used for text accuracy testing and full analysis was done.
 - 249 containers (302,535 pieces) of PI was tested against an approved specification. A hard copy proof sample was used for text accuracy testing and Pantone colour charts were used for colour controls.

The inspection of the following areas followed:

- Cold storage: selected batches of APIs were noted for further evaluation:
- Staging area: Each drum of API had a "sampled" sticker.
- Dispensing:
 - Dispensing rooms each with a bubble material airlock.
 - Staging areas.
- Production, packaging and in process controls.
 - Staging areas.
 - Granulation suite consisting granulation fluid kettles, Powrex HSM, Comil (Fitzmills and Frewitt), Glatt FBD.
 - Frewitt Oscillator screen and Bin blender.
 - Fette 3090i Compression machine (75 stations) with online dedusters and metal detectors. Compression was going on. IPC in the room included: tablet weight, thickness, diameter, friability and hardness plus challenge of the metal detector.
 - Holding time for materials from dispensing to bulk tablets was specified as maximum 30 days and the holding time for bulk tablets was 6 months.
 - Log books for cleaning, use and preventive maintenance.
 - Wash areas for IBCs, equipment parts and other tools.
 - Punches and dies: sets for the products under focus and lubricants.
 - Storage area for FBD bags and screens.
 - Packaging lines: Lines 16 and 17 (B. No. F2111) for wallets; line 13 for blisters.
 - IPC: sensors for foil joints; various cameras and sensors; bar code readers; blister and wallet seal integrity;

Review of Plant Layout and Utilities (HVAC, Dust control, and Water Purification and Compressed air systems):

1. Site Plans and Plant layouts

- Site layout, Floor plans with material and personnel flow, area classification and Pressure differentials, AHU distribution.
 - Singled out specific AHUs for evaluation:
 - AHU 11A/B supplying dispensing rooms including Room No. 1205.

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010



- AHU 1A/B supplying granulation areas including rooms 101 and 201.
- AHU 2A/B supplying compression rooms 108 and 207.

2. Compressed air system

- Site Diagram
- Monitoring Report dated 1 May 2010
- Compressed Air Sampling Check-list

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

Day 3

The inspectors started by giving feed back on observations of the previous day and obtained preliminary clarifications from management where deemed necessary. Inspection proceeded with review of the following aspects:

Validation Master Plan

- The Pharma Ops US Site VMP was subdivided into the following sections:
 - Process VMP
 - Equipment qualification master plan
 - Packaging VMP
 - Computer system VMP: obtained list of software used on the site and their uses.
 - Analytical methods VMP
 - Change control master plan (Revision 01): changes managed using Adaptable Quality Workflow application (AQWA) software.
 - Cleaning VMP (Version 5.0): Used worst case approach monitoring visually; residues of actives, excipients and detergents, (NMT 10ppm or 0.1% of normal dose in maximum daily dose of next product); and microbial contamination.
- Qualification, validation and calibration policies and schedules plus status.

Equipment qualification and preventive maintenance:

- Equipment qualification/Requalification (DQ, IQ, OQ and PQ for major equipment)
 - Requalification/re-evaluation of Fette 3090i in 2005 and 2008.
- Preventive maintenance schedules and records
- Calibration

Water purification system:

- PW system drawings and summary of specifications and capacities: Potable water from the mains - 5µm filter - Multimedia - Softener - Carbon filter - break tank - 2 pass RO - CDI - 2 Purified Water (USP) tanks (Production: 2780 gallons; Labs: 879 gallons) - UV lamp in each supply loop and Ozone generator in the return loop.
- Qualification/Requalification/Monitoring/sanitisation of the PW system (*Sampling and trend analysis*)
- Inspection of Water Generation and Purification System installations.
- Review of maintenance and cleaning records for the RO/CDI and Carbon filter.

HVAC and Dust Control system:

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010



- Qualification/Requalification/Monitoring the HVAC + Dust Control System
 - ΔP and ACPH were requalified annually while particle counts were requalified every 6 months and alarms were last challenged in 2008.
- Inspection of the HVAC + Dust extraction technical area
 - Focused on AHU 1A/B: Primary filters - Pre-heat coil - Steam Humidifier - Chilled water system - supply air fan - secondary filter - final filter (HEPA). The filters were monitored by magnehelic gauges.
 - Inspection of BMS. Set conditions and actual reads; alarm records.

- Review of BMRs/BPRs/Testing records - selected batches.

The company presented information on the following outstanding areas:

- Sampling of packaging materials and AQL.
- SOP on "Blister packaging operation". Section 4.2 provided for holding the samples at a vacuum of 15 inches of Hg for 2 minutes.
- List of computer operations and their use.
- SOP on "Cleaning procedure for manufacturing area". Section 4.2 provided for cleaning the drains every product change over.
- Records of sampling and testing of a batch of one API. Records showed that each drum was actually sampled and tested for identity. Other parameters were accepted based on the CoA from the manufacturer who was considered certified. Retention sample was picked from one drum.
- Stability commitment report and SOP on "MES procedures for dispensing materials" to clarify on the requirement for one API requiring cold storage to be returned to the cold room within 72 hours.
- Reports of audits suppliers of packaging components for products under focus.

Validation

Process validation and revalidation for the product in focus

- Site Validation Master Plan.
- Equipment Qualification .
- Qualification report, related to tablet press FETTE # 3090.
- Analytical Methods Validation Master Plan.

Cleaning validation

- Cleaning Validation Master Plan.

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

Day 4

The inspectors started by giving feed back on observations of the previous day and obtained preliminary clarifications from management where deemed necessary. The following aspects were then reviewed:

- BMS alarms for ΔP , RH and Temperature for Rooms 201 and 1205 for the period 27 September to 27 October 2010.
- Records of preventive maintenance of Carbon Filter from January to September 2010.
- List of suppliers of raw and packaging materials and their qualification status.

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010



- Siemens report for preventive maintenance of RO/CDI/Ozone system performed on 29.07.2010.
- SOP on "Supplier monitoring, qualification and certification".
 - Each container of APIs purchased from certified suppliers was sampled and tested for identity and the rest of the parameters based on evaluation of CoA from the supplier. One batch was fully tested once a year. The last batches fully tested for the APIs used in the products under focus were noted.

Quality control laboratory

There were 5 laboratories for: (1) Packaging materials (2) Raw materials (3) Finished products (4) Stability testing (5) Microbiology. The following aspects were evaluated:

- Analyst training was in place but no competence matrix had been compiled to facilitate sample allocation.
- Sample receipt, storage and allocation in LIMS (SAP-QM)
- Wet chemistry laboratory
- Instrumental laboratory
 - Qualification, calibration, preventive maintenance
 - Balance No. 0428 did not have a printer attached.
 - Congestion was noted in the storage area for equipment which stored waste.
 - Old out of use equipment was still in the RM lab (e.g. UV- Vis No. 1292 since 31.03.2010 and Balance No. TR603D since 11.01.2007).
- Laboratory materials management (Samples, Reagents, Stock Solutions, Reference and Working Standards)
 - The RM lab was supplied with de-ionized waster which was purified in the lab and tested once a week.
 - Working standards in FFP Lab. Policy was to use the vial till its expiry date (2 years) but actually used in less than a month.
- Starting materials and finished products specifications, testing and release.
 - Records of sampling, testing and use of selected batches of APIs.
 - Raw data including sequence of injection on HPLC No. 145 plus and results of testing on FPP batch were reviewed.
- Testing of Packaging Materials and Components
- Microbiological laboratory
 - Room and equipment
 - Media preparation and product testing:
 - Growth promotion test for media: Phosphate modification; SCDA; SAB.
 - SOP on "Routine ATCC stock culture maintenance". Reference cultures were received at passage 3 and not more than 5 passages were allowed. A log of the monthly dilutions and counts was kept.
 - PW monitoring
 - Environmental monitoring
- Stability testing programme (*Protocols, programme, records and data*).

At the end of the day, the team reviewed the activities of the entire inspection, gave feed back on activities of the day and wrap up for the inspection. Preliminary reactions from the management of the company were received. This included recognition of issues about the washing rooms and WHO Public Inspection report (WHOPIR):

congestion in the RM lab and indicated that work had already been initiated to upgrade these areas. The timelines and procedures for the report, CAPAs and WHOPIR were outlined.

2.1 QUALITY ASSURANCE

There was an organizational chart and job descriptions specifying the responsibilities and reporting relationships of the various staff. There were documented and approved procedures to guide routine operations and activities. Starting materials, intermediate products, finished goods were controlled and approved by QC/QA before release for use or distribution.

Policies and procedures were in place for qualification and validation of equipment and systems, change control and deviation management, self inspection and product quality review.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

There were facilities and procedures for the production and quality control of the products in focus and their level of execution and/or maintenance was generally adequate to ensure products of consistent quality.

Never-the-less, the observations described in the sections that follow and summarized in the table hereafter required attention to ensure continuous improvement. There was no reference to either WHO GMP or EU GMP in a number of SOPs where GMP was referenced, despite the fact that products under focus were registered in Europe and Prequalified by WHO.

2.3 SANITATION AND HYGIENE

The site had facilities and procedures for sanitation and hygiene. Materials for production, containers and products for cleaning were handled in a manner to minimize their chances of becoming a source of contamination to the product. Management was called upon to strengthen dust control in granulation suite No. 2, improve level of cleanliness in the washing areas, and improve the facilities and drainage in the room for bin washing.

2.4 QUALIFICATION AND VALIDATION

There was a general validation master plan which outlined the policy and approaches to be followed in qualification of equipment and validation of systems and processes. Qualification included Design Qualification (DQ), Factory Acceptance Tests (FAT), Site Acceptance Tests (SAT), Installation Qualification (IQ), Operation Qualification (OQ) and Performance qualification (PQ).

Validation and qualification were guided by approved protocols. The schedules and frequencies for executed and planned requalification, validation and revalidation were outlined in annexes to the VMP.

The principles for cleaning validation were established plus the policies on number of cleaning cycles, discussion of worst case, setting of limits, justification of the limits and analytical methods used and general documentation.

2.5 COMPLAINTS

There was a procedure for handling customer complaints. The cases reviews revealed that the investigation of complaints and documentation on follow up of implementation of CAPAs were generally well handled.

2.6 PRODUCT RECALLS

The company had an established product recall procedure which classified the deficiencies ((Class I, II and III) that would require a recall, the means of communication to be used, the timelines to conclude the recalls, composition of the recall committee and the parties and Health Authorities to be informed while conducting a recall. Novartis was committed to informing WHO in case of recalls involving WHO Prequalified products.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The facility also packed products manufactured by other sites or manufactures and also used some other sites and companies for packaging. There was a team to manage third part manufacturing. Some analytical procedures were outsourced to external laboratories. These arrangements were governed by technical agreements and there were provisions for auditing such vendors before entering into such agreements.

2.8 SELF INSPECTION AND QUALITY AUDIT

The company had procedures and a schedule for self inspection. This covered the quality system, packaging and labelling, production system, facilities and equipment system, materials system and laboratory system plus any other areas as deemed necessary. This activity was not reviewed in detail.

The QA Compliance department also audited suppliers of their raw and packaging materials, either independently or jointly with Novartis Group Quality Operations. Extracts of selected reports reviewed indicated that the programme was well executed.

2.9 PERSONNEL

The site engaged adequate numbers of skilled personnel to conduct production and quality control procedures. There was an organizational chart and job description to guide personnel. These indicated independence of quality control from production. The responsibility for batch review and release was assigned to Quality Assurance.

2.10 TRAINING

There was a system designed to ensure that newly recruited staff members received orientation plus training in basic GMP, hygiene & safety, written procedures, technical skills and SOP training as well as continuous training for continuous improvements and new procedures. Training records were maintained by Human Resources Department in the Pharmaceutical Operations computerized training documentation system.

Records of training of selected personnel recruited since January 2010 were reviewed and indicated that recording of implementation of Basic GMP training and general evaluation of effectiveness of training could be strengthened further.

2.11 PERSONAL HYGIENE

There were facilities and procedures for changing and entrance into production areas which required staff members to wash their hands and change into clean factory garments. The facilities were generally adequate.

Production staff were required to undergo health checks on recruitment and thereafter regularly as required.

2.12 PREMISES

a) Ancillary areas

The premises were designed so that entrance to the production, quality control and packaging areas was through change rooms with hand washing facilities.

b) Storage areas

There was a receiving and dispatch bay well designed to protect materials and products from adverse weather conditions. The high rise (10 storied) fully automated warehouse had adequate space and shelves for storage of raw materials, packaging materials and finished goods. It was supplied with filtered and conditioned air. The environmental conditions were monitored using sensors connected to a central computer system. There were sampling rooms for raw materials and packaging materials. These has separate material and personnel airlocks

c) Production areas

Production areas were constructed, arranged and utilized in independent manufacturing lines made up of integrated granulation suites, compression, capsulation, and coating rooms. Each area was served by two separate alternate AHUs and separated by a clean corridor. Most doors were designed to open on the low pressure side and not the high pressure side. There were green and red lights acting as visual alarms to alert staff if environmental conditions were out of the specified limits.

Production areas were designed and controlled as class ISO 8 or class 100,000, supplied with recirculated air filtered through G4, H11 and H13 filters for dispensing areas (AHU11A/B) and compression rooms (AHU2A/B) while single pass air filtered through G4 and H11 filters was

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,

25 - 28 October 2010



used in the granulation room. The filters were monitored using magnehelic gauges and not via BMS although the limits and frequency of monitoring needed to be reviewed. The design of the walls, floor and ceiling plus installation of electric and other fittings could facilitate adequate cleaning and maintenance. Both centralized and localized dust extraction systems were used but their effectiveness in some rooms needed to be reviewed (*e.g. Granulation suite No. 2*). The premises generally had adequate space for orderly operations. The Environmental conditions (temperature, RH and ΔP) were regularly monitored and recorded in a central computer system (BMS) with an alarm system in case parameters went out of limits. The limits were supplemented with a visual system utilizing green and red lights.

d) Packaging area

The packaging area had 14 packaging lines: 6 bottle lines (Line 1, 2, 3, 5, 6 and 8) with shrouding around open product and bottle until capping; 5 blister lines (lines 13, 14, 16 and 17, the last 2 with walleting capabilities) with shrouding around product and foil until sealing step; 2 transdermal lines and one line (line 15) dedicated to secondary packaging of a Nasal Spray.

e) Quality Control

The quality control facilities consisted of separate laboratories for testing: packaging materials; raw materials (Excipients and APIs); 2 for finished products; Stability testing and Microbiology.

The water purification plant was located on the technical floor. It obtained its supply of potable water from the mains which was filter/treated through a 5 μ m filter, Multimedia, Softener, Carbon filter, stored in a break tank and then treated through a 2 pass RO, CDI and finally stored in 2 Purified Water (USP) tanks, one for the production loop: 2780 gallons; and the other for the laboratory loop: 879 gallons. There was a UV lamp in each supply loop and Ozone generator in the return loop.

2.13 EQUIPMENT

The design and installation of production equipment was mainly of closed systems utilizing gravity feed thus reducing human touch. For example, in granulation suite 2, the HSM, Comil and FBD were integrated. The most of the machine parts that came into contact with the products was made of SS 316L. Most were PLC controlled and were adequately labelled. There were SOPs to guide the operation and cleaning of the equipment reviewed. Records reviewed indicated that the equipment had been adequately qualified and were regularly cleaned and maintained.

Quality control equipment had been qualified and was regularly calibrated. There were balances of adequate operating ranges in various locations and these were verified daily with at least three standard weights. The management of punches and dies plus old production and QC equipment needed attention.

2.14 MATERIALS

a) Starting materials

There was a system to approve vendors of raw materials. Vendors were classified as approved (*full testing*), qualified (*reduced testing after comparative testing of 3 - 10 lots or 1 year consignments and full analytical + microbiological testing of at least 1 lot/year with good history of performance*), qualified for tailgate sampling (*sample shipped to Novartis for testing, trained in sampling and result of 3 lots*) or certified (*ID test and evaluation of supplier of CoA after comparative testing of 3 - 10 lots or 1 year consignments and full analytical + microbiological testing of at least 1 lot/year with excellent history of performance*). Raw materials were sampled, computer quarantined and tested, in accordance with the classification of the supplier, before release. Each container of API was tested for ID.

The storage conditions of the various materials were controlled and monitored. Requisition, issuance and reconciliation of materials were controlled both electronically using Automated Storage and Retrieval System (ASRS) and SAP (Systems, Analysis and products).

Some weaknesses were noted in the system to facilitate compliance regulatory requirements for sources of APIs: manufacturers of materials supplied to the Suffern site through Novartis Pharma "Turn table" were not indicated in SAP and; the manufacturers of some split batches were not indicated in SAP as the field was simply left blank.

b) Packaging materials

Packaging materials were purchased from approved, qualified or certified vendors. Each consignment was sampled quarantined using ASRS/SAP computer programme and tested before release for use.

c) Intermediate and bulk products

Bulk intermediates (dispensed materials, granules, blends, bulk tablets, etc) were stored in IBCs which were stored in holding areas until release for the next step of processing or final packaging. The hold times of these intermediates and bulk products had been determined and were systematically monitored.

d) Finished products

Products were not released for distribution unless each batch was tested and its production, packaging and testing records were reviewed and found in compliance with GMP and regulatory requirements. They were transported to the off-site warehouse for distribution.

2.15 DOCUMENTATION

A documentation system was in place to guide production and control of products. These included: Site Master File; specifications of starting materials, packaging materials, packaging components and finished products; production and packaging instructions and batch processing and packaging records; standard testing procedures, analytical records and certificates of analysis; standard operating procedures; validation master plan, qualification and validation protocols,

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010

schedules and reports. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

QA department was responsible for the control of preparation, review, approval, distribution and review of documents. Some incidences during inspection indicated that some documents/records were not always up to-date (e.g. Role profiles).

2.16 GOOD PRACTICES IN PRODUCTION

Production procedures were established and controlled and had been validated. Production was guided by electronic batch manufacturing instructions using Manufacturing Execution System (MES). Production facilities were designed to utilize mainly closed systems and gravity feed thus minimizing human contact. In addition, a campaign approach to production minimized the chances of cross contamination. There were dust extraction and control systems mainly at the point of generation, although their effectiveness in some of the rooms (e.g. granulation suite 3) needed to be reviewed.

Spot checks on the use log for punches and dies showed that their issue and use were well recorded but were not systematically rotated to ensure uniform ware and tare.

Line clearance checks were conducted before use of each production equipment and packaging line. In-process, yield and reconciliation checks were conducted at the appropriate stages, although there was no evidence that the vacuum used during leak tests for blisters and wallets was appropriately monitored as required by the SOP. Environmental conditions were monitored. Readings for ΔP , temperature and relative humidity were monitored and recorded centrally using BMS.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Quality control laboratories were separate from production areas. They were manned by qualified analysts. The major QC equipment included HPLCs, GC, FTIR, NIR, UV/Vis spectrophotometer, Dissolution apparatus, analytical balances and other miscellaneous laboratory glassware. The microbiology laboratory had different autoclaves for waste management from that used for media preparation. It also had incubators for the different conditions 20⁰ - 25⁰C and 30⁰ - 35⁰C. The laboratory equipment had been qualified and was periodically checked and calibrated.

Starting materials, packaging materials, intermediate products (e.g. blends), bulk products and finished products were sampled and tested using approved methods and (manual and electronic) records maintained. Different software were used not manage QC records, including LIMS/QDIS/SAP-QM and Empower data Acquisition Management System (EMP).

Reference standards used were supplied from Novartis Basle. Records of their receipt, issue and use sometimes were not detailed enough to facilitate traceability and accountability.

Samples of starting materials and finished products were retained for future analysis. Finished products were put on initial and continuing stability studies and the hold time for intermediates and bulk products had been scientifically established..

WHO Public Inspection report (WHOPIR):

Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA,
25 - 28 October 2010



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, **Novartis Pharmaceuticals Corporation, 25 Old Mills Road, Suffern, NY 10901, USA** 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

The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years had lapsed.