

WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**
Finished Product Manufacturer
Part 1: General information

Name of Manufacturer	Bayer de México S.A. de C.V.
Unit number	NA
Production Block	NA
Physical address	Ojo de Agua, Ixtaczoquitlán, C-94450 Orizaba, Veracruz, Mexico.
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Date of inspection	23 to 26 April 2013
Type of inspection	Initial Routine Inspection
Dosage forms(s) included in the inspection	Sterile Solution for injection packed in glass ampoules
WHO product categories covered by the inspection	Injectable Hormonal Contraceptive - Solution for injection
Summary of the activities performed by the manufacturer	Production, packing, testing and release of Finished Pharmaceutical Products (FPPs)

Part 2: Summary

General information about the company and site

Bayer Mexico site is located on a 16ha plot of land, in Ixtaczoquitlan, in the suburbs of Orizaba, State of Veracruz. The land and installations are property of Productos Químicos Naturales, S.A. de C.V. (PROQUINA), who is a manufacturer of active pharmaceutical ingredients and member of the Bayer Group. Installations of this site are physically and administratively separated from those of PROQUINA. There are no common areas for storage or production. The quality control and production processes are carried out in the same building, which is partially used as warehouse for raw materials and conditioning materials as well as for office operations.

The building started operations in 1967, and has since undergone several extensions and renovations. Between the year 2009 and 2011 the injectable area restructuring was carried out. The building complex has a total area of 8924m². The materials used are a mixed system of walls and modular soffits with conventional materials (bricks and cement plates).

The site was licensed as a factory or laboratory of drugs or biological products for human use by the Federal Commission for the Protection against Health Risks (COFEPRIS). The licence #30 085 02 0001 is valid for an indefinite time. The authorized manufacturing lines were the following:

- Oral-hormonal solids: sugar coated tablets
- Semisolids: suppositories, cream, ovules
- Sterile-hormonal: injectable solution in ampoule, injectable solution in syringe

Only products for human consumption were manufactured as finished products and 1 as product for clinical studies (IMP). Some of those products handled on site were imported from the Corporate Company and from other Group subsidiaries. This site had a GMP Certificate issued by COFEPRIS on January 13, 2011.

History of WHO and/or regulatory agency inspections

This was the first inspection by WHO-PQ. The following is what the company presented as the inspection history of the site:

Health Ministry	Country	Year*
National Agency of Health Surveillance (ANVISA)	Brazil	2012
Federal Commission for the Protection against Health Risks (COFEPRIS)	Mexico	2012
Landesamt fuer Gesundheit und Soziales Berlin (LAGeSo)	Germany	2011
National Drug, Food and Medical Technology Administration (ANMAT)	Argentina	2011
National Institute of Drug and Food Surveillance (INVIMA)	Colombia	2008

*Last Certification Date.

Focus of the inspection

The inspection focused on the production and control of a specific injectable hormonal contraceptive product. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1: 23rd April 2013

Inspection proceeded as follows:

1. Opening meeting:
 - a. Introduction of company staff present
 - b. Introduction of inspectors
 - c. Brief on the WHO prequalification of medicines programme (WHO-PQ) covering its history, policies, standards and procedures used.
 - d. Company presentation covering corporation business units, site organisation, capacities.
2. Personnel issues:
 - a. Organisation charts:
 - b. Template for job descriptions.
 - c. Flow chart for job descriptions
 - d. Job descriptions of key personnel
 - e. Catalogue of deputisation,
 - f. Training procedures and records
3. Quality management system:
 - a. Product quality review (PQR):
 - i. The directive on PQR.
 - ii. APR for the specific injectable hormonal contraceptive product for the period 01.01.2011 to 31.12.2012.
 - b. Handling OOS.

Day 2: 24th April 2013

Feedback was given on the previous day's inspection and the company was given an opportunity to provide clarification.

The inspection of the following issues and areas followed:

- a. Risk assessment:
 - a. Standard operating procedure, which was referred to as a directive, on risk assessment.
 - b. The procedure which employs the FMEA to assess risk throughout the product lifecycle.
 - c. Review of selected examples of application of risk management.

- b. Examples of change in the premises: dispensing areas for the API, compounding and filling areas.
- c. Review of selected relevant examples of deviation.
- d. Inspection of the Warehouse:
 - a. Material receiving procedures.
 - b. Selected examples received materials were reviewed.
- e. Plant tour inspection – presentation and tour observations:
 - a. Presentation of demonstration of entrance and gowning procedures – 3 levels of change (not over-gowning) with hand-washing and disinfection facilities. There are no exit air-showers.
 - b. Laundry for gowns used in the production area located next to the autoclave.
 - c. Dispensing and compounding area.
 - d. Contingency measures to prevent reversal of airflow due to reduction of pressure differential (ΔP) in case of power failure.
 - e. Flow of materials and monitoring of production areas.
 - f. Inspection of the production process.

Day 3: 25th April 2013

Feedback was given on the previous day's inspection and the company was given an opportunity to provide clarification.

The inspection of the following issues and areas followed:

- 1. Continued with inspection of the production area:
- 2. Packing hall:
- 3. Water treatment and distribution system:
- 4. Quality control laboratory:
 - a. Sample receiving procedures and records.
 - b. Review of records of sampling and testing materials.
 - c. The specifications of the injectable specific hormonal contraceptive product.
 - d. Review of analytical electronic raw data for selected batches.

Day 4: 26th April 2013

Feedback was given on the previous day's inspection and the company was given an opportunity to provide clarification.

The inspection of the following issues and areas followed:

- 1. Physico-chemical laboratory:
 - a. Records of qualification of one of the HPLCs by the supplier.
 - b. Computer access levels and rights of various QC staff.
 - c. Review of electronic analytical raw data for relevant API analysis.
- 2. The microbiology laboratory.

The microbiology lab had the following sections:

- a. Class E for:

- i. Microorganism identification and incubators.
 - ii. Biosafety cabinet for validation, identification and staining.
- b. Class A/B/C for:
 - iii. sterility testing
 - iv. Environmental monitoring: air, personnel and surfaces.
- c. An autoclave dedicated for decontamination of microbiology waste and another dedicated to the sterilisation of media.
- d. Incubators of different conditions.
- e. Review of sterility testing procedure and its validation (validation report). Records of testing selected relevant batch were reviewed.
- 3. HVAC system:
 - a. AHUs serving the preparation and filling system, the corridors and class D areas.
 - b. The HVAC system was controlled through a computer programme.
 - c. HVAC Qualification report dated 23.01.2013 was reviewed.
- 4. Change control:
 - a. The directive for change control was reviewed.
 - b. Changes in 2012 and 2013 and examples in database were reviewed.
- 5. Deviation management:
 - a. The deviation directive was reviewed.
 - b. Deviations in 2012 and 2013 were documented. Examples were evaluated.
- 6. Handling complaints and suspected counterfeits:
 - a. The relevant directive was reviewed.
 - b. Complaints in database for 2012 and 2013 were briefly reviewed and a selected example was reviewed in detail.
- 7. Product recall:
 - a. A directive on product recall was in place and classified recall according to the risk associated with the defect.
- 8. Qualification of Autoclave: Report of requalification on 11.01.2013 was available for a cycle of 121⁰C for 25 minutes.
- 9. Batch review: Examples of executed BMRs for solution preparation, filling and packaging were reviewed with no major issues noted.

At the closing meeting, the inspectors gave feedback on the inspection observations of the day and the entire inspection. The company was informed about the procedures and timelines for the report, Corrective and Preventive Actions (CAPAs) and WHO Public Inspection report (WHOPIR). The company expressed commitment to address the issues noted as part of Bayer's strategies for continuous improvement.

2.1 QUALITY ASSURANCE

Bayer Mexico had in place arrangements for evaluations and monitoring of the quality of the systems, procedures and products through self-inspection procedures and annual product reviews. There were procedures for equipment and systems qualification and validation of processes. There were written and approved procedures

to investigate, assess the impact of changes, deviations and Out-of-Specification results.

Annual Quality Product Review (AQPR)

Annual Product Review (APR) were conducted under a specific directive. The SOP provided that the PQR would cover 12 months but period could be extended if <7 batches are produced. All manufactured batches were required to be included, even if not released and the PQR had to be completed within 6 months of the review period.

There were two concepts:

- Annual Product Review (APR) which did not require the review of starting materials, variations, qualification status of equipment, validation, post-marketing commitments, technical agreements and recommendations of the previous report and effectiveness of CAPAs.
- Product Quality Review (PQR) which included the review of parameters as specified in WHO GMP. It also provided for review of trends using statistical tools like CpK, although it did not give guidance on its calculation and interpretation

So far only an APR had been produced for the product under focus and available for review. It covered the following:

- Bulk batches (in syringes and ampoules) of a fixed batch size and packed batches for commercial distribution with shelf life of either 60 months or 48 months depending on the market.
- Critical process parameters reviewed.
- Discussion of deviations was not detailed.
- Trend results were noted to be out of control limits, but these were not discussed and the CpK value was only stated without further discussion.
- Changes were discussed.
- On-going stability studies of a batch at 30⁰/65%RH.
- There were no returns, no recalls but a complaint related to a counterfeit was discussed.
- Qualification of the HVAC system (Annually and continuous monitoring for class A & B) and validation (process and analytical) were reviewed.
- The conclusion indicated that the changes did not affect the validation status of process but it did not make any comment or recommendation with respect to the OOT for yield.

Change control:

The directive for change control was reviewed. Changes were classified as global or local. Changes were classified as global if they affect quality, have regulatory impact or affect several sites. Changes were managed through a database. Examples of global changes were listed in the SOP:

Selected changes in the database were reviewed. A few issues were noted but submitted CAPAs demonstrated that these were adequately addressed.

Deviation management:

Deviations were managed under a directive which indicated that deviations were classified as:

- a. Critical: risk to health of patient or regulatory non-compliance with MA/licence of manufacture. These were investigated by Unit QA for root cause analysis (RCA) and impact with designation of CAPA and final classification but had to be referred to corporate QA.
- b. Major: Failure of GMP with a potential effect on quality. Unit QA was responsible for their evaluation and final classification.
- c. Minor: deviation from procedures without impact on drug quality. The initiating unit was responsible for their investigation, evaluation and final classification.

There were several deviations in 2012, some of which related to the product under focus and selected examples were reviewed. The investigations and impact analysis were generally comprehensive and the 5M risk evaluation technique was used for RCA followed by appropriate CAPAs. Examples were evaluated.

Risk Management:

Directive on risk assessment outlined the principles of quality risk management implementation and application. The corresponding SOP employed the FMEA to assess risk throughout the product lifecycle. A technical team was entrusted with the key responsibilities and decisions including but not limited to review and approval of reports plus evaluation of residual risk.

The process of risk management included identification, evaluation, control, communication and review of risk. This utilised evaluation of severity, detectability, occurrence, risk to quality, risk to business and CAPAs. The categorisation was considered not adequately granular to adequately characterise the risk.

An example of application to the filtration and filling process of product under focus was available and was reviewed. To reduce the risk identified, SOPs, control process and contingency measures were designed. Risk management was generally conducted in an acceptable manner and submitted CAPAs demonstrated that the issues noted were adequately addressed.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

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

The observations raised following the inspection were adequately addressed as demonstrated through submitted CAPAs, and these will be verified during the next routine inspection.

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. Cleaning procedures for equipment and premises in place were adequate to enhance hygiene on the site. Personnel were trained on how to maintain good hygiene. There were comprehensive factory entrance and changing procedures. Entrance and gowning procedures included 3 levels of change (not over-gowning) with hand-washing and disinfection facilities. The gowning was appropriate to class and level of activities.

In general, this area was found to be adequate.

2.4 QUALIFICATION AND VALIDATION

Validation Master Plan (VMP)

The Validation Master Plan (VMP) was in place defining the qualification and validation policies and requirements for equipment (machines, laboratory devices, installations and services) and processes (manufacturing, analytic, cleaning processes and computer systems). The VMP was not reviewed in detail. Each system was then described in a specific system validation master plan (for instance cleaning validation and qualification master plans).

Process validation

The system provided for a trigger of prospective validation following introduction of a new product and any major changes in existing product, process, cleaning, materials etc., and concurrent validation following minor changes, although the definition and extent of major and minor changes was not explained. These validation approaches required three consecutive batches. The manufacturing process of the product under focus had been validated; however, there was no documented justification why validation had not been considered when certain changes were made.

The media fill test had been performed to validate aseptic procedures. The microbiological monitoring reports reviewed only stated qualitative results (complies) and not quantitative results (cfu). Records of batch # 2 indicated OOL results from personnel monitoring but the investigation covered only laboratory aspects, there was no discussion of possible production causes and/or potential impact.

Equipment qualification

Qualification included User Requirements Specification (URS), Design Qualification (DQ), Factory Acceptance Tests (FAT), 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. Selected examples were selected for review.

In general, this area was found to be adequate.

2.5 COMPLAINTS

Complaints and suspected counterfeits were handled under a directive. Complaints were managed by Local QA using a Global database. Complaints were classified in 5 categories:

- a. 1 and 2 critical to be managed within 6 days for category 1 and 14 days for category 2.
- b. 3 and 4 were quality defects with no harm to health to be managed within 30 days. For category 3 – 4, time limit was extended to 60 days if a sample was required to be obtained.
- c. 5 of no responsibility of Bayer and no timeline was specified.

The database indicated several complaints in 2012 and in 2013, some of which related to the product under focus. Selected examples were reviewed. In general, this area was found to be adequately by the QMS.

2.6 PRODUCT RECALLS

Product recall was managed under a directive which classified recall as follows:

- a. Category I – Defects with serious risk of causing harm
- b. Category II – defects less likely to cause harm.
- c. Category III – defects with no risk of causing harm.

It was stated that recalls would be handed by a team of representatives of different departments including medical and Regulatory affairs. There was a provision to inform local health authorities with 3 days.

It was specified to evaluate annually the effectiveness of the procedure through a mock recall.

Some observations were noted but these were adequately addressed as demonstrated through submitted CAPAs, and the same shall be verified during the next routine inspection.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Activities on Contractors (Contract Manufacturer, Third Parties Laboratories) were under the charge of the Quality Management for External Products (QMEP) of the corporate Bayer Group.

The SMF listed a number of outside laboratories that were approved to conduct supplementary contract analysis for the site. It was stated that these laboratories had been authorized by the Health Department or by governmental entities, but this area was not reviewed in detail.

The site was also involved in labelling and secondary packaging of imported products for some third parties. Again this aspect was not reviewed.

2.8 SELF INSPECTION AND QUALITY AUDIT

There were procedures to conduct self-inspection at regular intervals for the purpose of monitoring the quality system and continuous improvement of the procedures. Records indicated that auditors had the skills and training to conduct the internal audits. Reports were written with follow up actions and timelines. The implementation of CAPAs and its effectiveness was regularly reviewed by management. Audits had to be closed within 6 months.

Supplier qualification

Excipients and active pharmaceutical ingredients were either manufactured and/or supplied by BHC Group and its affiliate companies. Primary, secondary and tertiary packaging materials were purchased from local and / or foreign manufacturers.

An annual program of audits to suppliers was prepared and prioritised based on the relevance for quality, processes and products and/or any acquired goods or services, as well as on the results of the last audits.

2.9 PERSONNEL

The site employed adequate numbers of skilled personnel to conduct production and quality control procedures. There was an organizational chart and job description to guide personnel. Organisation charts for the site, quality management, quality control, production and the template for job descriptions were reviewed. These indicated independence of Quality Assurance and quality control from production. The responsibility for batch review and release was assigned to Quality Assurance.

Job descriptions of the following key personnel were reviewed:

- a. Quality Assurance Manager,
- b. Head Validation,
- c. Head documentation,
- d. Quality Control Manager,

- e. One of the Raw material analysts,
- f. One of the FPP Analysts,
- g. One of the Microbiology analysts,
- h. Production Manager,
- i. Head Liquids Production,
- j. One of the Shift Supervisors.

There was a system in place to ensure that key personnel were effectively deputised in their absence. The catalogue of deputisation for the 1st Semester 2013 effective 31.01.2013 was available and reviewed.

In general, this area was found to be adequate and the observations made were adequately addressed as demonstrated through the submitted CAPAs.

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. This was managed under the directive on training.

Training plan for new staff outlined the topic, objective, summary of content and evaluation, although there was no detailed training module. There were PowerPoint presentations, but these were not referenced to the respective SOPs. There was a format for the administration of training activities. The following documents related to personnel training were reviewed:

- a. Flow chart for training of new personnel.
- b. Flow chart for integral concept of GMP/HSE training.
- c. Flow chart for training requirements and annual program.
- d. New staff training and qualification of aseptic areas.
- e. Evaluation questionnaire for personnel working in liquid parenteral section.
- f. Training matrix for GMP/HSE.
- g. List SOPs to be covered in training of staff of liquid compounding section.
- h. List SOPs to be covered in training of staff of liquid ampoules and injection filling section.
- i. List SOPs to be covered in training of staff of oily solutions section.
- j. Training records of one of the staff members.

A number of observations were made, but these were adequately addressed as demonstrated through submitted CAPAs. Personnel interviewed and the records checked reflected that initial and continuing training provided was generally adequate.

2.11 PERSONAL HYGIENE

There were facilities and procedures for changing and entrance into production areas which required staff members to wash their hands/feet, body and change into clean

factory garments. The facilities and procedures were generally adequate although there were no pictorial gowning instructions available before entering into the production areas. Production staff were required to undergo health checks on recruitment and thereafter regularly as required.

In general, this area was found to be adequate.

2.12 PREMISES

Production areas:

The premises were located, designed, constructed and maintained to suit storage, manufacturing, quality control and related operations. The layout and design of premises facilitated the logical flow of materials and personnel to minimize the risk of errors and permitted effective cleaning and maintenance. The areas where dust was generated were fitted with dust containment and extraction systems.

There were separate warehouses for raw materials, packaging materials and finished goods. They were generally well designed, controlled and monitored to provide appropriate temperature and Relative humidity conditions. There was a covered receiving bay and an area where in coming consignments are verified and cleaned with sponge and solution.

The laboratory is located in the same building as the production activities.

The laundry for gowns used in the production area is located inside the production area next to the autoclave further strengthening powder containment measures. There are no exit air-showers. A study of hormone exposure levels which was conducted in 2008 showed adequate containment and no exposure levels above acceptable Operator Exposure Limits. A new study was being planned following modification of the facilities and process.

Staff use masks with adequate solid and liquid particle filtration efficiency and able to remove a range of organic chemical fumes.

Dispensing was conducted inside production area under extraction cabinet in a room under negative pressure to the surrounding for containment.

Compounding was under a closed system in a room under negative pressure to the surrounding, further strengthening containment measures, minimising the risk of release of powder.

Contingency measures in case of power failure included sealing doors to the central corridor with tape to prevent reversal of airflow due to reduction of pressure differential (ΔP). An incident was witnessed during this inspection and inspectors witnessed deployment of these contingency measures.

Empty ampoules were purchased sealed and packed in plastic boxes. There were transferred into metallic trays; non-particle shedding cardboard boxes were used. Opening, filling and sealing the ampoule was performed under Class A conditions with Class B background. Class A area had a permanent sensor for continuous particle monitoring while Class B was monitored using a movable sensor. Both class A and B areas were monitored for viable particles throughout line set up to filling and sealing in all shifts. Filled ampoules were packed on similar (colour and size) metallic trays with appropriate labelling for content and stage of processing or status. Filled and treated ampoules were washed and visually inspected against white and black background and standard light intensity. After visual inspection, ampoules were packed in trays with appropriate labelling for content and stage of processing or status.

Packaging:

There were 5 packing lines:

- i. Enclosed packing line for preparation, filling and secondary packaging of ovules.
- ii. Packaging of syringes.
- iii. Labelling and packaging of individual ampoules.
- iv. Enclosed packing line for primary and secondary packaging of sugar coated tablets.
- v. Manual packing of ampoules in 100s.
- vi. Labelling of ampoules of the product under focus was done on line (ii) and then transferred to line (v) for manual packing in 100s.

Warehouse:

There were separate warehouses for raw materials, packaging materials and finished goods. They were generally well designed, controlled and monitored to provide appropriate temperature and relative humidity conditions. There was a covered receiving bay and an area where in coming consignments are verified and cleaned with sponge and solution.

There were 2 dispensing areas: one for API with an extraction cabin and another for excipients. The limits of pressure differential for the washing areas were indicated on the Magnehelic gauge. Sampling rooms and dispensing rooms were accessible only through the production area, with appropriate gowning. There was a cleaning procedure for sampling area between different materials and / or same product of different batches. Cleaning was recorded in log sheets. A common logbook was used for sampling booth and area.

Quality control laboratory:

The laboratory was located in the same building as the production activities. It consisted of the following sections:

- i. Microbiology laboratory

- ii. Physico-chemical laboratory consisting of chemical lab, preparation area and 2 instrument labs.
- iii. Wash area with sections for microbiology and chemical operations separated in space (separate table and sink) and time.
- iv. Documentation area.

HVAC system:

The preparation and filling system was served by a dedicated AHU and dehumidification unit. The corridors and class D areas were served by a separate AHU. Fresh air was serially filtered through primary and secondary filters, passed over cooling coil, fan and tertiary filters, humidity was controlled by heated steam and electric heater and air was terminally filtered through HEPA filters. Exhaust air was filtered via HEPA and secondary filters. Primary, secondary and tertiary filters were changed every 6 months.

The HVAC system was controlled through a computer programme. The pressure and temperature were monitored online with alarms visual and audial alarms set and recorded for any out of range condition > 1minute.

The latest HVAC Qualification report was reviewed. The information on air balance showed a design to keep a net negative pressure for hormone containment. The qualification procedure was referenced to ISO14644. The particle counter used had appropriate capacity and had been adequately calibrated. The HVAC system was generally adequately designed, maintained and monitored. The issues noted were adequately addressed as demonstrated through the submitted CAPAs.

Purified water system:

Water from the Municipality supply was collected in a reservoir, disinfected and mechanically filtered. Purification system included sand filter (PLC controlled backwash with water and air after specified interval or > above a specified pressure and sanitised once a year by clean steam), two softeners in series (regenerated after a specified volume), removal excess Cl₂, RO (disinfected regularly), EDI, heat exchanger and storage tank. A hot distribution loop was used and was fitted with 2 heat exchangers.

Water for injection was produced by a multi-column, multi-effect still and stored in a tank. Water was dumped if conductivity was above a specified limit. The water in the tank and loop is maintained at a specified hot temperature. Water for injection was used to produce clean steam. Tanks were fitted with level sensors, spray balls and hydrophobic vent filters. The generation system had a recirculation system when consumption is low. The flow rate in the loops was maintained within a specified range.

In general, this area was found to be adequate.

2.13 EQUIPMENT

There was adequate numbers of equipment for the production and testing products manufactured at the site. For the manufacturing of the product under the focus of this inspection, the product contact parts for all equipment were stated to be made of SS316. The QC laboratory had enough glassware for wet chemistry and other instruments. The equipment reviewed were well designed, qualified and were regularly calibrated. Balances were calibrated and records of daily verification using standard weights were available. There were procedures and records for equipment use, cleaning and preventive maintenance.

2.14 MATERIALS

The inspection of the warehouse followed the flow of materials covering receipt of raw materials, inspection, sampling, status labelling, sampling, storage and dispensing.

The parameters to be verified on receipt of consignments of materials were outlined in the SOP and the approved vendors were listed in SAP.

Consignments of certain raw and packaging materials were received with target samples taken by the supplier. A sample was taken for identity (ID) tests from each container and a composite sample was made from samples taken from selected containers for other tests.

Examples of 1ml ampoules and the corresponding labels indicated that the sample size was specified in SAP and was verified to be consistent with ISO2859 level 2.

Storage areas were available at ambient, below 25⁰C and 2⁰ to 8⁰C, as appropriate to the material.

Several weaknesses in material control were identified but these were adequately addressed through the submitted CAPAs, and the same shall be verified during the next routine inspection.

2.15 DOCUMENTATION

A documentation system was in place to guide production and control of products. These included: Site Master File (SMF); Validation Master Plan (VMP); standard operating procedures (SOPs); Batch Manufacturing and Packaging Instructions and records (MIs, BMRs, BPRs); specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records. There were corresponding records in the form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

Most documents were maintained electronically on a document server and there was a daily and weekly back up of the system.

QA department was responsible for the coordination and control of preparation, review, approval, distribution and review of documents. The system was generally comprehensive and well managed.

The observations raised following the inspection were adequately addressed through the submitted CAPAs, and the same shall be verified during the next routine inspection.

2.16 GOOD PRACTICES IN PRODUCTION

Production operations were guided by approved written procedures in form of manufacturing instructions (MIs) and batch manufacturing records (BMRs). Records reviewed and practices witnessed indicated that records were made promptly in the BMRs and any deviations were also recorded and handled in accordance with an approved procedure.

Line clearance was conducted before and after production and packaging operations. The check list used was not detailed enough to highlight all the checks that needed to be done. This was raised as an observation and adequately addressed through CAPA.

In-process controls were performed and documented at appropriate stages and intervals. There were provisions for checks on yields and reconciliation of quantities. Materials and equipment were adequately labelled with identity, stage of processing and status as appropriate.

At the time of dispensing, the APIs are also sampled for identity testing.

Charging of materials and compounding was conducted under a closed system. There were appropriate checks before and during compounding. The holding time of the bulk was 20 hours and the solution is controlled for bio-burden.

Bulk solution was then serially sterile filtered followed by filling into pre-sterilised ampoules. Ampoules filled were identified by a different lot number than bulk solution. This lot number was maintained until end of optical inspection. There was continuous particle monitoring during filling and the print out from continuous particle monitoring indicated very low counts for both 0.5µm and 5.0µm particles.

The ampoules were staged awaiting labelling and final packaging. These steps proceed prior to QC results, with the results required before batch release.

The primary and secondary packaging was controlled with a number of automatic sensors based on optics, weight and bar codes. Labelling of the product under focus was done on line (ii) and then transferred to line (v) for manual packing in 100s. Labels were purchased pre-printed with batch number, date of manufacture and expiry

date. The procedure for packing of ampoules was described in an SOP. The set-up of the labelling line was preceded with line clearance. A sample label was checked at the start of the process and kept in the BPR. There was an on line camera to check the label details based on PLC settings. In-process checks were conducted every 2 hours for duration of 14 hours per batch.

The label for the box of 100s was screen printed online with details of lot number, manufacture date and expiry date. There was label reconciliation and the balance was returned to the warehouse.

The observations raised following the inspection were adequately addressed, and the same shall be verified during the next routine inspection.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The laboratory was located in the same building as the production activities but separate from production areas and their functions were independent of other units including production. They were manned by qualified analysts and had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution.

There were separate Microbiology laboratory and Physico-chemical laboratories with sections for chemical lab, preparation area and 2 instrument labs in the latter.

Samples were received either from the supplier; from sampling rooms for incoming raw materials and packaging materials; and from production area. Received samples were recorded in registers before entering the records in LIMS and distributed to the different labs based on predetermined allocation. There were 2 sample registers: one for physico-chemical lab and another for microbiology. Samples for water, environmental monitoring and bio-burden were not entered in the register but directly in the work sheet. A dedicated member of staff received the samples, entered the details in SAP and distributed the samples to the different labs.

The heads of the respective labs allocated the samples to the different analysts. The sample code indicated the specifications and method to be used and a batch specific worksheet was generated from SAP. This also indicated the sampling size and plan. Records of selected samples were verified in the register and SAP.

Records of qualification of a specific HPLC by the supplier were reviewed.

The QC lab used double distilled water for injection for analysis and this water was used within 24 hours of production.

Volumetric glassware like burettes and measuring cylinders were of class A standard and certificates were available. The accuracy of Microbalances was verified daily over the working range using standard weights.

The microbiology lab was involved in the following testing:

- a. Product sterility
- b. Non-sterile products (TMC, Pathogens)
- c. Starting materials (TMC, Pathogens)
- d. Packaging materials (TMC, Pathogens and for ampoules; sterility and bio-burden)
- e. Stability samples: from the beginning and end of the studies.
- f. Water: potable water, purified water, water for injection and clean steam.
- g. Environment: air (static and dynamic), surfaces, personnel.
- h. Bio-burden before filtration.

The microbiology lab had the following sections:

- a) Class D for:
 - i. Microorganism identification and incubators.
 - ii. Biosafety cabinet for validation, identification and staining.
- b) Class A/B/C for:
 - i. sterility testing
 - ii. Environmental monitoring: air, personnel and surfaces.
- c) An autoclave dedicated for decontamination of microbiology waste and another dedicated to the sterilisation of media.
- d) Incubators of the following conditions:
 - i. 30⁰ – 35⁰C x 3
 - ii. 20⁰ – 25⁰C
 - iii. 45⁰ – 55⁰C for liquid media
 - iv. -70⁰ – -80⁰C for lyophilised cultures and 2nd passage
 - v. 35⁰ – 37⁰C
 - vi. 2⁰ – 8⁰C for working cultures, maximum of 4 passages allowed.

Each batch of prepared culture media was tested for growth promotion and pH. For growth promotion test (GPT), <100cfu/ml was used.

Sterility testing was by membrane filtration.

Reference standards

Primary reference standards were supplied from USP and Bayer when available or from the specific supplier with a certificate of analysis.

Working standards were taken from specific received batches. The working standards were tested for qualification against primary reference standards.

The observations raised following the inspection were adequately addressed through submitted CAPAs, and the same shall be verified during the next routine inspection.

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, **Bayer de México S.A. de C.V. Ojo de Agua, Ixtaczoquitlán, C-94450 Orizaba, Veracruz, Mexico** 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.