A Compilation of WHO GMP Audit Points

Collected from WHOPIR of 28 companies

Part VII of VIII

Current article – Part VII – Quality Control

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QC:

QC Documentation Review:

- Specifications (selected API's and Finished Products)
- The preparation and standardization records for Perchloric acid were inspected
- The calibration record of the UV spectrophotometer was checked as well as the usage log for this period
- OOS, Investigation and reports ,SOP and records
- API and FP specifications
- Raw data on paper and electronic data (e.g. identity, assay, related substances/impurities, dissolution and residual solvents) related for testing of APIs and continuing stability was verified and found acceptable.
- Product Release specifications
- Method validation report for ID test and raw data
- Master Formula
- BMR and analytical reports including source data
- Selected OOS investigation and reports
- Record of analysis for several batches of products
- COA and record of analysis for several batches
- Calculations were made and verified against original calculations by analysts during the inspection including for dissolution data, assay and LOD - at selected packaging presentations, stability storage conditions and time intervals (for various products)
- Specifications for APIs and Finished products were reviewed and verified against analytical reports and source data (including review of electronically stored data) for selected batches and selected parameters including spectra and chromatograms.
- Selected chromatograms including those of reference standards used were checked on the computers
- GLASS WARE SOP WAS AVAIALBE FOR INSPECTION, PW was used for final rinse
- Standards were registered and their usage was traceable
- Handling of out of specification laboratory results"
- "Handling out of trends results during stability study
- AUTOCLAVE Validation using thermocouples were carried out and the results were available. The autoclave was re-validated every year
- URS, FAT was done for the new autoclave and documents were presented for inspection Protocol and Report for Heat penetration and temperature distribution study for the Cooling Incubator with PLC
- Buffer solutions for PH Meter prepared are purchased
- 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
- During inspection particular attention was paid to the Dissolution apparatus and HPLC apparatus, analyst training and qualification and Out of Specification (OOS) investigations

- Preparation of standard solutions, pH Meter buffer solutions and HPLC mobile Phases were reviewed.
- The calibration and/or operation of the leak tester was not appropriate, set to apply a vacuum pressure of up to 300mmHg but went up to 305mmHg
- Dry chemical and solutions expiry dates was set to 5 years after date of receipt or 2 year of opening the bottle of dry chemicals or 3 months after opening the bottle for solutions and volumetric solutions and reagents were properly labeled
- COA available for the columns and discard of the columns were recorded
- Purified water is used for the HPLC tests, and was checked for PH, CONDUCTIVITY Daily and recorded in the log book
- DISSOLUTION apparatus were calibrated by technicians, physical parameters such as RPM, TEMPERATURE, and WOBBLE AND CENTERING OF PADDLES were calibrated every three months and system stability tests were performed once per six months using USP Prednisolone and acetyl salicylic acid tablets were used
- RE-TEST POLICY
- LABORATORY audit SOP, Laboratories were re-audited after two years
- SOP was applicable for QCL equipment. Yearly and monthly calibration planners were available.
- Finished products were taken by methods and personnel approved of by the quality control department
- SOP on Assigning of Expiry date. The date of dispensing materials was the date of manufacture and was used to determine the expiry date
- Nitrogen, used in contact with the product was filtered through 0.01µ filters.
- SOP "Quality control of raw materials (API and excipient)"
- Retention samples from finished products and API's were kept for one year after the expiry date
- All instruments in the laboratory had Log books and were properly labelled, calibration status and due to date were identified.
- General SOP for Cleaning of Glassware
- List of personnel authorized to accept/reject and release the batches of Raw Materials, Bulks, Packaging Components and Finished Products
- All instruments in the laboratory had Log books and were properly labelled, calibration Status and due to date were identified.
- KBr used for the identification tests before analysis was dried at 105 ºC from 1 to 2 hours, after drying substance was kept in the dry box
- Reagent solutions and titration solutions were properly labelled and manufacturer's batch numbers were traceable from the solution preparation sheets
- Weaknesses were also noted in the records to support traceability of stability samples from charging, withdrawing and testing
- Pharmacopoeia methods as well as in house methods were validated
- Temperature was monitored and recorded two times per day
- Autoclave validation using thermocouples
- Acceptable contract agreements were in place for any analytical testing carried out by external laboratories. These laboratories were audited every two years using a pre- prepared check-list. However, this check-list did not include a check that analytical method validation was acceptable to the company

- Work allocation in (QC)
- Verification of the adequacy of the SOP for HPLC testing with regards to the requirements for time in between the injection of system suitability standards for long runs (e.g., 80 min)
- Training of production officer who performed IPC counting of tablets
- 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 laboratory had a fume hood for safe handling of volatile chemicals.
- QC equipment was evaluated using the dissolution testing equipment which was found to have been adequately calibrated by regularly checking the temperature probe, shaft eccentricity, RPM and paddle clearance, performance checks using the standard USP tablets (Salicylic Acid).
- SOP "Procedure for procurement preparation, qualification and handling of analytical Standards" was reviewed
- The data on assay, related substances, dissolution, content uniformity and residual solvents was verified and found acceptable. The data on IR was verified and whereas most IR showed natural variance, some IR were found to be too similar with evidence of only one sample weight.
- Traceability was ensured through the records, reference standards, technical data sheets which include AR numbers, source data, software - which are reviewed by a reviewer, lab QA and then approval
- Water used in the laboratory was produced in the laboratory.
- The water was tested against specification for purified water at quarterly intervals. The results were acceptable.
- A sample inward register was maintained. Some analytical reports were selected by the Inspectors for review including some batches of Nevirapine API. The reports were inspected and source data were further verified against the reported results for identification testing.
- The FTIR was inspected. The calibration was done as per SOP and the results were acceptable.
- The spectra reviewed met acceptable criteria. The HPLC chromatograms for one batch were Reviewed (XYZ). The assay value obtained was manually calculated and verified
- The dissolution tester (E-164) was inspected for physical calibration, performance verification test and use. Various parameters were included in the calibration such as level, temperature, rotations, time, wobble, distance, and vibration
- There was a quality control analytical group, and a QC lab support group (specifications, Documentations, sampling, validation, master preparation etc).
- The dissolution tester (E-164) was inspected for physical calibration, performance verification test and use. Various parameters were included in the calibration such as level, temperature, rotations, time, wobble, distance, and vibration.
- SOP for water sampling and monitoring. The samples were collected at monthly intervals (user Points) but the sampling point (return loop) was monitored on a weekly basis.
- The trend results were reviewed for 2010 for pH, conductivity (NMT1.3uS/cm at 25C), and TOC. Microbiology test results trending was then inspected for various points.
- For dissolution testing, the samples were withdrawn and filtered through a Whatman filter. The time lapse between withdrawal and filtration was not specified or limited. For Rifampicin, there was no specification to the type of filter other than the specified Whatman filter.
- FTIR and UV/visible spectrometers were regularly calibrated and were within specification for resolution, wavelength accuracy, absorption accuracy and stray light.

- Analyst validation report for one of the analysts for Assay of one of the APIs Specifications, Standard Testing Procedures and Analytical Data Sheets for selected APIs.
- Certificates of selected RS and impurity standards
- SOP on Post production stability studies
- The pH meter was regularly calibrated and the electrode was retained in the recommended solution in between use. The SOP on operation and maintenance of the pH meter did not cover the care and maintenance of electrodes. This was corrected with a proper change control procedure during the inspection.
- Thermometers were calibrated against a certified standard and the pH meter adequately maintained. Temperature profile data (mapping) was not available at the time for the drying oven and refrigerator, but this has been satisfactorily done
- Observations related to routine checking of both the shafts' eccentricity (wobble) and RPM have been addressed
- Glassware washing SOP was available for the inspection. PW was used for the final rinse. Glassware was dried at the temperature _ 90 ºC
- The autoclave was a basic top-loading vessel with a single drain mounted thermocouple. It was regularly serviced and a monthly calibration using a bio indicator (st. thermophyllus) was performed. A standard cycle produced a106 kill
- Sterilization followed a normal cycle 1200C for 15 to 20 minutes. Records were kept and F0 in excess of 8 was easily achieved
- Results from the past two months reported no growth

Assay Validation:

- All methods used were compendia (BP.USP.IP). Validation was restricted to checking recoveries.
- Against the label claim using dissolution test data.

ANALYST CERTIFICATION AND QUALIFICATION:

- Analyst records, work sheets, calculations, chromatograms, weight slips and related reports.
- Analyst competency and signature specimen lists were available
- Analyst certification
- The analyst certification procedure was reviewed
- An analyst competency list was available
- Analyst qualification involved practical evaluation where comparative tests on the same sample were conducted by the new analyst and an experience analyst

Analyst certification and qualification:

- Analyst's competency list was available. A number of analyst certification and validation records were reviewed and found to be comprehensive. Analyst qualification involved practical evaluation where comparative tests on the same sample were conducted by the new analyst and an experienced analyst

Sampling:

- The method of withdrawal of samples (dissolution) was verified through a

demonstration by the company in accordance with an SOP

- SOP "Sampling and analysis of raw materials
- After sample receipt QC manager assigned work to technicians using "Daily work output report".
- The method of withdrawal of samples (dissolution) was verified through a demonstration by the company in accordance with an SOP.
- Composite sample preparation was explained.
- Trending of water sample results
- Sop for sampling and sampling plan for packaging material
- All containers of API, Inactive were sampled and tested for identification, except excipients form in-house vendors or from manufacturers with dedicated facilities and approved by QA for reduced sampling based on their good history
- Note: A brief evaluation report was prepared to support each inactive material to be put on a list of approved materials for reduced sampling
- The reduced sampling for such inactive materials was 10 containers from a consignment of < 74 containers or square root of n+1 for more than 74 containers
- There was a procedure for making composites and the maximum number of
- Samples that could be pooled were defined
- "Critical" tests were defined for each material. Sampling for ID tests was performed in accordance to the formula $\sqrt{n} + 1$.
- Formula $\sqrt{n} + 1$ were applied for exicipients' ID tests.
- Packaging sample size has to be in line with iso2859 or bs6001

Purified Water Sampling:

- Sampling of water was done based on a weekly schedule. The use of water for production was documented.
- All purified water sampling points were sampled on rotational basis once per months
- Purified water sampling, testing and trend monitoring
- PW Tests were performed on 100 ml samples using the Millipore membrane filtration equipment.

Laboratory materials management:

a) Samples
b) Reagents
c) Stock Solutions
d) Reference and Working Standards

Environment Monitoring:

- The results of the last three months were reviewed. Typical values for one-hour exposure were 18 ± 3 cfu. This level would comply with a class D area at rest.
- Active air sampling was performed. Annual measurements were taken with a Biotester (strip media). The instrument collects 40 litres/minute for five minutes.
- Results were typically 8 ± 3 cfu/200 litres. This equated to 40 cfu/ cubic meter, well within the level 200cfu/m3 for a class D area
- Using a MET I particle counter, the blending area 0.5micron particulate count measured 10,000 / cubic feet and 200/cubic feet for 5 microns.

- Environment monitoring is based on sop uses settle plate and contact plate monitoring for bacteria and fungi of all production facilities the results were checked by trend analysis according to year wise
- SOP "MB monitoring of environment in production area" was reviewed and found to be satisfactory. MB monitoring was carried out monthly for ISO 8 areas and quarterly for Controlled areas
- Settle plates for the environmental monitoring were exposed for 4 hours. Settle plates and air sample locations were identified. Action and alert limits were specified. 4 hours settle plate exposure time was validated
- Sampling point layout for air sample and settle plates was available for inspection. Separate schedule was available for production, stores, MBL and other control areas. Trends were available for all sampling points, there was no OOS
- 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.
- Standard stock reference culture and subcultures were used and subcultures were discarded after 5 regenerations. Both positive and negative growth test were performed on all media
- Environmental monitoring included temperature, relative humidity, particles and microbes. A Schematic drawing was available indicating the locations of settle plates for micro monitoring
- The programmes of microbial air monitoring and general testing procedures were managed by following approved SOPs.
- A sample of air was collected under active air sampling and while Petri dishes were exposed for 4 hours under passive air sampling. Growth promotion tests had validated the 4 hour exposure time. The SOP gave details of both frequency and location of sampling. The work areas were claimed to be class 100,000 (Class D) at rest.
- Both active air and settle plate samples were taken and an SOP was followed. The procedure stipulated the sample site, the frequency of sampling and the technique to use.
- Settle plates were exposed for one hour and each site was checked every two months on a sequential basis. Typical results for the past 3 months were of the order of 30cfu/plate. The warning limit was set at 64cfu/plate and the action limit at 90cfu/plate.
- For class B and C areas, 1m3 active samples were taken with an SAS18 while 50 liters were collected for class D areas. Results plant wide for the past 3 months were of the order of 72cfu/m3 and warning and action limits were 125cfu/m3 and 400cfu/m3 respectively
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- The inspectors established that the major functions of the microbiology laboratory encompassed environmental studies, general microbiological assessment of raw materials and routine water testing. Entry to the microbiology suite was via a pressurized change room.
- Plate pouring and inoculation was performed under laminar airflow in a dedicated LAF cabinet. Incubators for all culture development were available, namely: 18 –240C, 20-250C, 35-370C, 30-350C. Cold storage between minus 5 and minus 200C was also provided.
- The incubators and refrigerator had been validated with respect to temperature Mapping

- The SOP on media preparation was reviewed
- Media sterilization cycle records showed an exposure at 1220C for 20 minutes
- A full record including Fo values far in excess of 8 was available. A log of media preparations was kept with positive and negative growth controls being performed for each batch
- Growth promotion was checked using the standard organisms taken from sub cultures of certified stock organisms. The test preparations are renewed from stock after the 4th generation
- A sample of 1.0 ml was tested by membrane filtration. This small volume had been validated after simultaneous testing of 1ml, 10ml and 100ml sample sizes gave similar results
- Plates were placed throughout the facility according to a set monthly schedule. They were exposed for 1 hour and not for 4 hours as recommended in cGMP Guidelines, but this had been validated
- Six monthly contact plate results for work surfaces and floors were well within guideline limits of 50/plate
- Organisms in any growth could be specifically identified if necessary but to-date no fungi, coliforms or other pathogens had been detected. Results routinely met class 100,000 at rest (Active air NMT 200cfu /m3 and settle plates NMT60 cfu/plate).
- Disinfectant Efficacy was tested by inoculating specimen surface areas with e coli and candida albicans (106). After the sanitising treatment, a 104 reduction was achieved

Analytical method validation:

- The validation method used was compliant with WHO and ICH guidelines. Data demonstrating specificity, linearity of response, precision, accuracy, LOD and robustness were available

Working Standard:

- **Diffractogram of a batch was inspected, evidence of working standard was sent to the contract** laboratory
- Records of preparation, storage and selected working standards were reviewed
- Review of preparation of analytical working standards, analytical working standards has to be prepared in the sampling area, and it has to be document in the logbook for the area The usage log for the working standard was reviewed, and it was verified that the WS was tested against an official standard. In this case, it was EP CRS lot # 1. The determination of the potency of the standard was verified and re-calculated
- WS were stored in a fridge _ 150C and had to be used within a maximum of one year and each opened vial had to be used within 2 months for all WS and within 1 day for one API
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- WS preparation and qualification records were evaluated and found to be satisfactory as the analysis was carried out in triplicate
- Working standards were dispensed in separate glove box
- Working standards (WS) were dispensed under the LAF, and were transferred to the amber glass bottles for single use .WS were qualified against primary reference standards in accordance with SOP "Laboratory reference standards"
- Usage of primary reference and WS was recorded; the standards usage log books were available for inspection

- SOP on Qualification and storage of laboratory working standards
- PRIMARY reference and working standards were properly stored. Working standards were dispensed under LAF and were transferred once per year to 24 amber glass bottles following qualified against primary reference standards in accordance with SOP after opening the bottle, the bottle was used for 15 days.
- Usage of primary and WS were recorded, the standard usage log book were available for inspection
- The material with the highest purity on dry and solvent free basis was selected for used in preparing Working Standards. Sampling was then done from each container of the selected batch and fully retested (Assay, appearance, IR, UV/Vis, Related substances, water content/LOD
- Opened vial had to be used within 2 months for all WS and within 1 day for one API
- Working standards were standardized against the pharmacopoeia standards the laboratory conducted water and environment monitoring settle plate for the environment monitoring were exposed for 2 hours settle plates and air sample locations were identified action and alert limit were specified
- SOP on Laboratory Reference Standards. The system for preparation, qualification, storage, issuance and use of Reference, Test and Working Standards was reviewed in detail.
- The procedures for preparation of working standards were comprehensive
- Working standards (WS) were dispensed in vials (2-5g) for monthly use.
- Usage of standards was recorded. WS were dispensed in un-controlled environment. Standards were stored properly.
- There were dedicated facilities (LAF, humidity chambers, refrigerator and controlled boxes with desiccators) for preparation and storage of reference and working standards).
- The conditions of storage were well monitored but the time taken for conditioning at ambient temperature before use (at least 30 minutes) and the time spent out of the fridge (NMT 60 minutes) for the RS which require cold storage were neither monitored nor recorded to confirm adherence to the requirements in the SOP
- According to the SOP on preparation and handling of working standards, only materials of at least 99.5% purity should be used to prepare working standards and an average of triplicate assays (which should not differ by >1.5% or 6 determinations of RSD _1.5%) should be used to determine the potency of a working standard
- A register for the use of working standards was maintained. It was ensured that only current references standards were used as these were checked against the catalogue (e.g.USP).
- Working standards were dispensed in separate glove box.
- Standards were registered and their usage was traceable
- There was a standard method of preparation of working standards to a high purity level by recrystallization in the appropriate solvent and retesting carefully selected APIs

Reference Standard:

- There were dedicated facilities (LAF, humidity chambers, refrigerator and controlled boxes with Desiccators) for the preparation and storage of reference and working standards
- Preparations of working standards were comprehensive (SOP
- Reference and working standards were well labelled and the records for standardization of working standards were well maintained.
- Only RS with potency were used for assay and preservative content testing, while those without potency were only used for identification by IR.
- It was provided that RS and WS be stored in the fridge (2 - 80C) and had to be allowed

30 minutes to equilibrate to room temperature before use. A limit of 60 minutes maximum exposure to ambient temperature at any one time was set.

- Access to the humidity chambers was password protected
- A batch of materials with an assay value of >99.5% and least impurity content was standardized against primary (pharmacopoeia) standards to prepare working standards. Triplicate assay were made.
- Primary reference standards were used to standardize Working standards. There was a standard method of preparation of working standards to a high purity level by recrystallization in the appropriate solvent and retesting carefully selected APIs
- Reference and working standards were well labeled and the records for standardization of working standards were well maintained
- Reference standards and working standards were kept in a refrigerator and deep freezer under lock and key. Working standards were prepared on site as well as obtained from contract givers.
- Records for reparation, storage, issuance and use of reference standards were maintained
- Primary Reference materials were used to qualify Working Standards according to an approved SOP.
- Triplicate determinations were made the acceptance criteria were Assay with RSD of NMT 0.5% each time 13 vials were prepared one for each months and one being a spare for one month. Records for reparation of selected WS were reviewed and they had been standardized against pharmacopoeia RS USP. Certificates for the pharmacopoeial RS were reviewed
- The SOP did not specifically require the reference materials kept in the fridge to be equilibrated to room temperature before use and did not specify that the RS be kept in the desiccators once out of the fridge.

Packaging material testing laboratory:

- Components were sampled according to an SOP following the Military Standard/BSI 6001guidelines.
- Samples were drawn for a level P inspection and normal rejection/acceptance AQLs were used in the decision chain
- A Pantone colour reference was not always included in the component specification. Authorized standard reference samples for all components were held.
- An aluminum foil was chosen for scrutiny of the testing record. PVC foil was similarly assessed. The records showed that the components were tested to specification with the AQL assessment indicating approval.
- SOP on operating the Illuminated Magnifier

Stability chambers and stability testing programme:

- Tests of stability samples were not always performed within the specified time frame, yet, the Company did not consider this as a deviation from its SOP
- Stability Study Records of their heat distribution and recovery studies plus temperature monitoring were reviewed
- First three production batches, and first batch per year is placed on stability
- The procedure for stability monitoring defined the time tolerances for loading, unloading and analysis of samples, record for the different activities could be provided. Activities were planned

in schedules, responsibilities for the collection of on-going stability samples were assigned

- The batches were put under 6 months accelerated stability studies at 400C/75%RH and the results were approved. Acceptable explanations and CAPAs to these and other observations related to purchasing and receiving procedures have been received
- There were two walk in stability chambers, one for accelerated and one for long term Stability studies.
- Stability chambers were equipped with alarm which was connected to the QC and security. Temperature was software controlled. Chambers were connected to the diesel power generators.
- Stability protocol was reviewed and found to be satisfactory.
- SOP "Stability studies" was reviewed and found to be satisfactory. Time point windows were specified. After withdrawal of the samples analysis should be initiated within 15 days. Acceptance criteria for the tests results were specified
- Stability study raw data including verification of data presented in product dossiers against raw / source data
- SOP on Stability Studies.
- Mean Kinetic Temperature Study for Stability Walk in Chambers for the years 2007 - 2008.
- Tests of stability samples were not always performed within the specified time frame, yet, the Company did not consider this as a deviation from its SOP
- Stability Study Records of their heat distribution and recovery studies plus temperature monitoring were reviewed
- The procedure for stability monitoring defined the time tolerances for loading and unloading and analysis of samples
- Activities were planned in schedules; responsibilities for the collection of on-going stability samples were assigned
- For every product in production at least one batch per year was taken into the ongoing stability program
- Stability program, Protocol, procedure were maintained
- Stability chambers were equipped with alarms which were connected to the QC and security
- Data on three stability batches was reviewed. Stability data for 58 months was available. According with ICH guidelines, assigned expiry data was 60 months; Initial protocol specified 36 months shelf life. Protocol for 60 months was not available.
- Stability sample withdrawal log sheet for Ethambutol HCl Tablets 400mg reviewed. Samples were withdrawn as per the SOP.
- Stability study data at 6M and 12M was reviewed and found acceptable. Stability study at 9M not conducted due to oversight
- Stability program and raw data (samples, chromatograms)
- Stability monthly plan
- Long-term study intervals were 0, 3, 6, 9, 18, 24 & 36 Months. Accelerated storage was for 6 months at 400C and 75% RH
- There were studies of the holding time of the cleaned status for 7 days, sanitisation status, 24 hours
- Stability Chambers charging and Withdrawal registers.
- One annual batch of 2009 was under storage conditions of 300C/65% RH and packaging: 28's Blister. Some transcription errors of dissolution data were noted. Due to oversight, the analysis of the sample at 9 months was not done by the company.
- Stability batches in 2006:
- Batch 1. Condition: 400C/75%, 300C/65% and 250C/60% and packaging: 28's Blister. No issues noted.

- Batch 2. Condition: 300C/65% Packaging: 28's Blister. Issues noted with assay data.

- There was a stability testing programme supported by stability chambers set at 40 C/75%RH and 30 C/65%RH.
- Weaknesses were also noted in the records to support traceability of stability samples from charging, withdrawing and testing
- Accelerated stability studies for 3 months was carried after reprocessing and if satisfactory the batch was released

HPLC:

- Mobile phases were freshly prepared and not reused
- Mobile phase was sonicated for 2-3 minutes
- KBrs used for identity tests were dried before use
- Routine qualification of the HPLC was reviewed using QC/143 Waters. It was done quarterly and parameters evaluated included pump flow rate and gradient; auto sampler reproducibility, injector linearity and carry over check; detector linearity and wavelength accuracy (273±2 using caffeine).
- HPLC COLUMN were dedicated for each product and properly stored in cabinets
- Each column had a usage log book
- What is the typical injection sequence on an HPLC
- Mobile phases were freshly prepared and not reused. Mobile phase was sonicated for 2-3 minutes and filtered under vacuum
- Verification of the adequacy of the SOP for HPLC testing with regards to the requirements for time in between the injection of system suitability standards for long runs (e.g., 80 min)
- The mobile phase expiry date was set as 7 days
- The IQ/OQ/PQ, flow checks, injection repeatability, detector wave length accuracy, linearity response well documented
- Peak threshold settings were set manually after visual assessment of the peak printouts. Similarly for the peak cut off point.
- The OQ report showed that it met the desired specifications for flow rate, detector wavelength calibration, linearity of response and auto injector performance.
- The reporting integrator was a data capture model with variable peak threshold setting. The operator set these after visual assessment of the initial chromatograms during set up. HETP, peak symmetry and resolution factors were automatically calculated and printed out. The peak efficiency in all cases gave well-defined start and finish integration points.
- The HPLC column log was well maintained and managed using an SOP. HETP values were recorded after each usage. The data was used to decide whether or not the column was suitable

MICROBIOLOGY:

Microbiology Laboratory:

- Personnel
- Premises, environment
- Equipment
- Reagents and culture media, preparation and control
- Reference materials and reference cultures
- Sample handling

- Purified Water monitoring
- Environmental monitoring
- Testing of materials and finished product
- SOP for Disposal of Microbial waste
- Swabbing of the rubber rollers of the inspection belt for microbiology testing had not been done The PH of media was checked before and after sterilization. Growth promotion checks, positive and negative controls were carried out
- Standard stock reference culture after 5 regenerations
- Application of the harmonized method for total viable counts, non sterile products was checked
- Media sterilization, growth promotion checks, water monitoring and microorganism identification was inspected
- The Media preparation SOP was available. A Growth promotion test using both culture collection micro-organisms and in house isolates was carried out for each batch of dry media and each lot of sterilized media. Positive and negative controls were carried out.
- In microbiology laboratory general Bio-burden testing, water purity monitoring and environmental studies were done
- There were separate areas for media storage, media preparation and media sterilization
- Plating out was carried out under a UDAF cabinet in a dedicated room operating under positive pressure related to the outer rooms
- Samples entered the room via a pass box fitted with mechanically locking double doors
- Standard stock reference culture and subcultures were kept with latter being discarded after 5 regenerations
- Media was prepared following a valid SOP, both positive and negative test were performed on all media according to a valid SOP
- Environmental monitoring both active air and settle plates were employed, the program me involved alternating between settle plate (3 hours exposure) and active air sampling (1 cubic meter samples)
- Trends for past 3 months were scrutinized, typical results for settle plates were tested for granulation areas, coating areas, compression areas and for inspection area
- Application of the harmonized method for total viable counts, non sterile products was checked.
- Media sterilization, growth promotion checks, water monitoring and microorganism identification was inspected
- Media Preparation A full range of solid media was available for the culturing of yeasts, moulds and bacteria. Media ware prepared either for plate pouring or slants
- The sterilization cycle reference number formed part of the BMR. A log of usage was maintained. Details of growth promotion checks and negative controls were also recorded.
- There was an autoclave for sterilizing media and equipment. It was subject to a regular validation and requalification which followed the requirements given in HTM 2010 empty chamber temperature studies; steam penetration, load configuration, vacuum and pressure hold times. The thermocouples used were calibrated externally
- The sterilization cycle times consistently confirmed that the drain probe temperature remained at 1200C for a minimum of 15 minutes. F0 values of the order of 29 were

achieved. A separate autoclave was used for destruction of used plates and unwanted media

Media preparation and use:

- A full range of solid media was stored and catalogued. Liquid media preparation followed an SOP. A preparation log was maintained and growth promotion tests, negative control results and the sterilization cycle reference number were included in the record.
- Growth promotion was carried out with standard reference cultures. Standards were re-cultured after five generations.
- The plate pouring room was a class C (10,000) and had a UDAF class A (100) with a horizontal air flow rate of 90 ft/min. (0.45m/sec).

The laboratory was divided into different areas such as:

- An instrumentation room with HPLCs, FTIR, UV
- Wet chemistry
- Reserve samples
- Microbiology laboratory
- Hot zone
- Wash area etc

Retention sample storage room:

- This included an examination of the time during which retention samples were being kept
- The temperature and humidity conditions (the method for data logger for humidity conditions and the responsible person's adequate resetting after readings was verified).
- The reserve sample procedure was examined, with a focus on the dates (samples taken on 11.06.2010) vs. the actual date of manufacturing and the date where the analyses were actually performed.
- Inspectors also verified the amount of time between actual QC analyses and the removal of stability samples from incubation, which was of only 2 days in the specific example that was examined

Weighing room:

- The calibration and daily verification methods for analytical balance FA-041 was verified by asking one of the analysts present how this was performed.
- He showed us the set of calibrated weights that were used as well as his method, which was generally acceptable

Chemistry Laboratory:

- Sample receipt was recorded in a ledger and all details recorded they include but are not limited to Name supplier, Lot No. AR No. Lot No, date of receipt and date of approval/. Rejection.
- The QC manager distributed samples amongst the analysts based on each analyst's technical competence.
- All preparations could be traced back to the bottle of solid reagent used.

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