A Compilation of WHO GMP Audit Points

Collected from WHOPIR of 28 companies

Part IV of VIII

Current article – Part IV – Quality Systems

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QUALITY SYSTEMS

Documentation:

- The Site Master File stated that no contract manufacturing was done but analysis of some materials for specific tests that could not be carried out at the site were contracted out
- The site master file (SMF) was not appropriately prepared to provide accurate information about the site including the responsibilities of the key site personnel, job descriptions, site lay out and equipment etc
- A clear explanation as to who is responsible for packaging and starting materials receipt, rejection and release and approval of COA has to be mentioned.
- The site plans showing material and personnel flow, area classifications, air changes and pressure differentials.
- The presentation highlighted the capacities, Quality Management System and inspection history of the site
- The organization charts were reviewed showing some discrepancies between the charts and job descriptions of some QC staff. Other SOPs reviewed included Deviation, Change Control, Batch Release and OOS.
- The company made a presentation about the company and the site to be inspected.
  The presentation highlighted the capacities, Quality Management System, Product range and other specific features of the site. A copy of the presentation was obtained and will be filled in the company file.
- Their manufacturing and process flow charts were reviewed which revealed that their formats were not standardized and some of them either not approved and/not dated
- The organization charts were completed down to the level of the different production blocks. The link between all organizational charts was clarified in the corrective actions.
- There were written procedures and records to manage the receipt, quarantine, sampling, labelling Storage and dispensing of materials; cleaning of equipment and premises; processing, packaging and distribution of products.
- SOPs on preparation, review, approval, control and revision of standard operating procedures.
- Critical control points were specified. According with SOP risks should be Re-evaluated after 3 years.
- The assembly of some sops was sub-optimal in that it did not have the revision history and the reason for revision attached.
- SOP on Preparation, review and control of formats
- CAPA SOP
- Yields were monitored at different stages of products with adequate reconciliation and investigation in case limits were exceeded.
- Documentation infrastructure consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance.
- Generally designed and developed in a way that took account of the requirements of GMP.
- Containers, equipment, rooms and packaging lines were at all times appropriately labeled according to their status
- The handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution was done in accordance with written procedures and, where necessary, recorded
- The manufacturing process charts for the various products reviewed (5) did not have standard

format (layout, presentation, and level of detail), some did not bear signature of approval and others were not dated

- QA has to maintain archive section
- The SOP on Pest Control, Rodent Control, Fly Control & Inspect control was reviewed and found satisfactory. **HOWEVER, LAY OUT OF THE BAIT STATION WAS NOT CLEAR**
- SOP on transfer of material from one grade to another
- SOP for handling any new API introduction, including the technology transfer check list
- SOP and cleaning validation matrix were reviewed; worst case was selected in terms of Toxicity, solubility and maximum carryover (MACO).
- SOP for change control of Software upgrade for FTNIR
- The list of both corporate and site specific standard operating procedures (SOPs) were reviewed plus the SOP for creation, distribution, utilization, operation and destruction of SOPs.
- SOP on Operation of Reverse Laminar Air Flow
- SOP on Cleaning cubicles and related cleaning logs
- SOP on Preparation, usage, storage and destruction of disinfectants, cleaning and deactivating solution
- SOP on Cleaning and sanitization of washing area and drainage points
- SOP on transfer of material from one grade to another
- The SOP for the newly installed FBE and checklist of PPM done were checked.
- **For products reviewed**, the was a master formula, specification of starting and Packaging materials, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and corresponding results.
- The documents carried a unique number and their documentation, change and retrieval were wellcontrolled by the quality assurance department
- **Job Description of key personnel along with personnel designated to deputies the key personnel** in their absence
- List of new personnel since January, 2010 (That inspection year, starting month)
- SOP and documentation preparation, review and control
- SOP Index for all the departments and block on the site
- SOP - Product Quality Review (PQR)
- SOP for Batch Numbering System
- SOP on Handing of Out-of-Specifications. An OOS report concerning a zero result on the 5th vessel of a tablet dissolution test was reviewed. Discussion showed that the sample taken from the vessel for analysis had been poorly prepared
- SOP on Entry and exit of Male and Female Staff
- SOP on Cleaning and utilization of FBD finger bag and RMG filter bag
- Classification of clean zones
- Corporate quality manual (selected items)
- Specifications for PVC, wallets, artemether and lumefantrene
- Some of the SOPs were not linked or cross-referenced which sometimes led to duplication
- The change rooms had cross-over benches, running water and had disinfectants
- The SOPs in the ETP laboratory did not have any obvious evidence that they had been reviewed within the stipulated time.
- The assembly of some SOPs was sub-optimal in that the revision history and the reason for revision were in an annexure which was no always attached
- The primary change rooms for the workers had hand wash basins, soap and hand driers but their design did not promote unidirectional flow (workers used the same entrance and corridor

passage before and after changing into factory gowns and shoes), they were congested and the floor was wet. A secondary change before entering the production area had been put in place to address this deficiency

- During the inspection of the receiving area, it was noticed that it was protected by an air curtain
- The SOP on production planning
- SOP on the batch numbering system
- A number of SOPs presented for the inspectors' review did not have their revision history attached. The copies of SOPs and other documents that were made and given to the inspection team to take home for review were not stamped as "Uncontrolled" as was required by the SOP on Creation, Distribution, Utilization, Operation and Destruction of SOPs
- Changes were grouped as either documentation related.
- **(Prefixed D), product related (prefix P), system related (prefix S) or facility based (prefix F).**
- The process started with identification of the need for change followed by impact analysis.
- Relevant departments were involved in the approval/rejection process.
- Master Batch Records (MBRs) for a particular product trade name / combination were Retrievable. MBR for a particular product included item codes of starting materials, by this indicating also suppliers /manufacturing sites of APIs. Title pages of MBRs carried a "Formulation code".
- The SOPs on allocation of batch numbers including split up batches were reviewed.
- Batch related documents were kept for 5 years.
- The study identified the hottest point which was used for regular monitoring of the environmental conditions in the warehouse.
- Temperature and relative humidity in the production rooms were continuously monitored by the Building Management System (BMS).
- Check lists were used for verifying analytical test results, Standard Manufacturing
- Records (SMRs) and Master Packaging Documents (MPDs).
- Entry was by a changing room where overshoes, hats and overalls were donned
- Additionally all watches and jewellery were surrendered and secured pending exit from the area
- During change over from the same product different batches, line clearance was carried out and recorded by two production officers. During product change over line clearance was carried out and recorded by two production officers and QA officer.
- FTNIR was used for ID testing of several materials
- SOP "Electronic data (software)/projects backup/retrieval
- The computer system was inspected to establish the code numbers for the various APIs
- Validation policy. ⇒ Validation Master Plan. ⇒ Calibration policy.
- Master Manufacturing formula and BMR for one of the products
- SOP on Assigning of analytical reference number.
- Work allotment record
- The cleaning SOP was common for warehouses and production cubicles, cleaning Records were maintained.
- Head of production and quality control responsibilities were in line with GMP requirements
- The "cleaned" status label for Sieve No. 30 did not indicate the previous product in which it was used.
- In the ETP testing laboratory the SOPs had been authorized on 12.01.2005 and there was no obvious evidence that they had been reviewed within the stipulated 2 years. It was explained that they had been review and found that no change was necessary but were not Stamped "**Reviewed, No Change required**" as required by the SOP.

- Conducted training on the use of the change rooms
- The system for management of changes was described in a procedure. Requested changes were listed in a register, documents about approval and implementation of changes were achieved separately. The reviewed changes were in general sufficiently documented. Responsibilities were defined; decisions about further investigations and actions were recorded
- Traceability of dispatched batches was ensured with data included in the batch record.
- Watches and other loose jewelry were not allowed beyond the change rooms
- The facilities and requirement for washing hands before entering production areas were inadequate as staff would have to enter toilet areas to wash their hands. There have been subsequently adequately addressed.
- SOP was applied to:
  a) Systems
  b) Processes c) Materials
  d) Products and procedures associated with the manufacturing of pharmaceutical Products.
- Product release was the responsibility of the QA manager (Authorized person), hierarchically independent from production. The QC Head was designated to deputize the QA manager for product release
- Printed outs of rejections in particular year was requested for selected material groups
- Cleaning was performed between the dispensing of two different starting materials. Dedicated utensils were used
- SOP For cleaning and CIP of In process bins
- Job Description of key personnel along with personnel designated to deputies the key personnel in their absence
- APR was prepared in accordance to SOP
- Reconciliation of issuance of BMR/BPR, batch numbering system and designation of person and Date of Manufacture
- Reference numbering of organization Charts
- Reference numbering and assembly of various registers
- Equipment was attached with calibration due dates. Whenever equipment is moved to new location re-qualification protocols / reports has to be prepared
- Materials code given to ERP PURPOSE has to be APPROVED BY QA
- The system was secure with regular password Changes.
- SOP for Archiving of Documents Authorization to supervisors to perform tasks has to be clearly mention sop for preparation, review, approval, distribution and retrieval of sop
- PQR a year is calculated from APRIL TO MARCH
- INTERIM PQR
- Waste collection procedures
- SOP of clean log book and batch records
- Product Master Files, codes, specifications for APIs and FPPs, plus List of approved vendors
- SOP for cleaning of equipment, area and utensils and handling and storage of work in process.
- Report of the Hold time study for dirty and clean equipment.
- Hand sanitization using validated sanitizing agents were practiced
- Reporting system was following QC Manager reports to the Unit QA Manager who reports to the Corporate QA Manager who in turn reports to the Joint Managing Director.

- Products were released for sale after certification by QA head.
- Batch related documents were kept for 7 years. Records of analysis were 100% checked by QA staff and the C of A was signed by the technician who carried out analysis, checked by the QC manager and approved by QA manager
- They reviewed various job descriptions, section organization charts and training records for selected persons, including General Manager of Main Pharma
  Block, QC manager and other persons in relation to key responsibilities and delegations
- Samples receiving flow chart was available for starting materials, packaging materials, Finished products and bulk finished products
- Separate sampling check lists for line clearance were available for starting, primary Packaging and secondary packaging materials
- In some instances, pictorial presentation on gowning and de-gowning were not available, e.g. sampling and microbiology lab.
- The process flow chart for the manufacture of PARTICULAR PRODUCT was reviewed.
  The company explained all stages and steps for production, material flow as well as component flow and preparation
- Dust extractors were not switched on during the sifting process Where required, lubrication was done with "food grade" lubricants which were approved by QC.
- All products production procedures were validated every 2 years
- The contracts were available. The contracts permitted to the contract giver to audit the facilities of the contract acceptor. The responsibilities of contract giver and contract acceptor were defined
- Contract laboratories were audited regularly. Laboratory audit SOP and schedule were available. Laboratories were re-audited after two years
- The responsibility of Departments heads and the person who deputize them in their absence is clearly mentioned.
- An SOP described the purchase and control of stereos
- Unused stereo sets were kept in locked portable box fitted with labeled trays
- Product release was the responsible of the QA manager, hierarchically independent from production
- The QC manager was designated to deputize the QA manager for product release
- Packing material sampling was carried out in accordance with ACCEPTABLE QUALITY LEVEL (AQL)
- The SOP for FPP release was reviewed. A checklist is used to verify the BMR
- The weight check limits were set to the highest and lowest weights of the first 10 completed packs. This may be an adequate control setting but the company may wish to consider determining the mean and standard deviation of 30 packs and setting a 95% confidence limit as a range (30 units are sufficient for a simple Null Hypothesis statistics)
- There were systems for control and approval by Qc/Qa of starting materials, intermediate products, finished goods 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.
- A procedure and records existed for risk assessment done in different areas of work.
  Some of the risk assessment reports were reviewed. FMEA was used as the tool of choice.
- All responsible staff had their specific duties recorded in written descriptions and Adequate

authority to carry out their responsibilities. Delegated duties were not always clearly defined.

- SOP Out of trends.
- Instructions and procedures were generally written in clear and unambiguous language.
- Standard operating procedures gave detailed directions to staff and employees on items such as restrictions on smoking, eating, and toilet procedures. This was found to be satisfactory
- The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.
- SOP "Procedure for Personal Hygiene Practices" was reviewed.
- Manufacturing and packing areas were cleaned according to approved documented Cleaning procedures.
- SOP "Procedure for selection and approval for Contract Testing Laboratories" was Reviewed. Four testing contract laboratories were used if necessary. Contract laboratories have been audited once in a year.
- A system for version control was in place for documentations.
- Operators were required to update the logbooks at the time of operation.
- People on contract worked mainly in secondary and tertiary packaging and cleaning.
- Cleaning check lists were available for all equipment.
- SOP "Procedure for preparation of calibration planner and tolerance" was reviewed.
- Cleaned equipment hold time studies were carried out.
- The noted low yield after inspection and packaging was attributed to high rejects due to sticking of coated tablets because of problem of inlet temperature but review of BMR showed that all the temperature readings were within the limits.
- Actives, Drug Master File (DMF), stability data, audit and re-audit every 3 years
- BMR's were not constructed in a way to enable clear yield evaluation of each production
- Stage; yields were calculated with reference to the start of batch production (it is remarked here that bulk may be packaged in several separate packaging runs).
- It was noted that the company had drawn new BMR/BPR formats in MS Word to enable the evaluation in question, and also to include additional data for equipment settings (e.g. compression speed).
- Finished product specification
- Product in process specifications
- Product release specification
- SOP on Document and Data Control
- SOP on Issue and Control of Formats and Books/Registers
- Product related documents were stored in QA archive for 6 years
- Approved procedures for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and for monitoring environmental conditions for GMP purposes
- **A recall** had been defined together with the means of notification to be used, the timelines to conclude the recalls, levels of recall and the parties to be informed while Conducting a recall
- **Analytical procedures** were contracted out and in such circumstances there was a contract that complied with the principles of GMP. The contracts defined the responsibilities if the contract giver and contract receiver, although it did not adequately specify how to dispose of left over samples

Number Of API Handled At the Site:

Example: A total of 19 active ingredients were used in the products handled at the site

- SOP "Batch split up"
- SOP "Receipt and storage of expired and recalled/withdrawn products"
- SOP "Reprocessing and reworking"
- SOP "Testing of samples and reporting of results"
- SOP "Handling of returned/rejected goods"
- SOP "Password system for computers"
- SOP "Batch release system of formulations"
- SOP "Pest control":
- SOP "Personal hygiene"
- SOP "Batch failure investigation":

Handling of out of specification laboratory results" and related flow chart was checked. The SOP was applicable for:

- APIs
- In-process samples
- FPPs
- Stability samples

Personnel were checked at every exit from the grade B rooms. Samples were taken from the Following places:

- Finger dabs
- Hand cuffs
- Forehead
- Chest
- Elbows

The training plan and program for the year 2009 was available. Training records were maintained in the employees personal files. The training file contained the following information:

- Job description
- Training records
- Training assessment
- External training
- Attendance certificates

A qualification record and competency list was available for each analyst. The performance of each analyst was re-evaluated every two years

CONTRACT MANUFACTURING:

- Contract production and analysis was defined, agreed and controlled in order to avoid Misunderstandings that could result in a product or work or analysis of unsatisfactory quality.
- The flow of information to ensure that an appropriate PQR was prepared, was not addressed in the agreement with a contract laboratory.

GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS:

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

Systems were in place to reduce the risk of cross-contamination and mix-ups. These included:

(a) All manufacturing processes were clearly defined and systematically reviewed, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that complies with their specifications
(b) Qualification and validation were performed

All necessary resources were provided, including:

1. Appropriately qualified and trained personnel
2. Adequate premises and space
3. (Suitable equipment and services
4. Appropriate materials, containers and labels
5. approved procedures and instructions
6. Suitable storage and transport
7. Adequate personnel, laboratories and equipment for in-process controls
8. Instructions and procedures were written in clear and unambiguous language, specifically applicable to the facilities provided
9. Operators were trained to carry out procedures correctly
10. Records were made during manufacture to show that all the steps required by the defined procedures and instructions had in fact been taken and that the quantity and quality of the products were as expected; any significant deviations were fully recorded and investigated;
11. Records covering manufacture and distribution, which enable the complete history of a
12. batch to be traced, were retained
13. The proper storage and distribution of the products
14. A system was available to recall any batch of product from sale or supply
15. Complaints about marketed products were examined, the causes of quality defects
16. Investigated, and appropriate measures taken in respect of the defective products to prevent Recurrence.

Batch number allocation

- SOP on Batch Numbering System reviewed. The allocation of batch numbering is as per SOP, starting with prefix code AA etc followed by year, product series as per the product category.
- **Recalls:** SOP and registers for 2009 and 2010, correlation with the last PQR and evaluation of selected examples.
- **Deviations:** SOP and registers for 2009 and 2010, correlation with the last PQR and evaluation of selected examples.
- **Change control:** SOP and registers for 2009 and 2010, correlation with the last PQR and evaluation of selected examples.
- **Variations:** SOP and list of variations with their approval dates.

Change control:

- Change in master BMR
- Changes in specifications:
- Change in LOD limits
- Change in related substance by HPLC
- Change in related substances by HPLC

SOP and registers for:

- Complaints
- Recalls
- Deviation control
- Change control
- Change control (P10/05/009)
- Reprocessing/reworking
- Utilization of recoveries

SOP was applied to:

- Systems
- Processes
- Materials
- Products and procedures associated with the manufacturing of pharmaceutical products
- There was one code transfer (in 2008) to the code used in the PQ product from BP to USP grade
- SOP "Supplier approval, qualification for reduced testing and monitoring including TSE requirements" was reviewed and found to be acceptable.

The suppliers were classified as:

- Approved
- Qualified
- Certified
- Disqualified
- Inspectors reviewed documents related to material and personnel flow, area classification

  Floor plans showing classification of each area, material movement, personnel movement, air pressure mapping for the ground floors, 1 and 2 floors of Unit IV

SOP for Product Quality Review

Job descriptions of key persons were available and the following were reviewed:

- Production Manager
- Manager QC
- Deputy General Manager – QA
- Manager – QA
- 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

There were 3 Types of USAGE LOGS:

A. Use
B. Cleaning
C. Maintenance Logs for each piece of equipment

- Each batch of FP was held in quarantine until it was tested and its production, packaging and testing records reviewed and found in compliance with GMP and regulatory requirements

There were written procedures and records to manage:

A. The receipt B. Quarantine C. Sampling
D. Labeling
E. Storage
F. Dispensing of materials
G. Cleaning of equipment and premises
H. Processing, packaging and distribution of products

Qualifications include:

- Definition of user requirements and specifications (URS)
- Design qualification
- Factory Acceptance Test
- Site Acceptance Test
- Installation Qualification
- Operation Qualification
- Performance Qualification

Re-qualification and re-validation:

- Critical equipment and systems were re-qualified every 3 years, non-critical every 5 Years. Production process was re-validated every 2 years (one batch), HVAC system was Re-validated every year.

- Cleaning process should be re-validated only if there will be changes in the cleaning process, method, formulation, SOP or storage conditions. Compressed air system was re-validated every year.

RISK ASSESSMENT:

- The inspectors then looked at risk assessment done for the production process of tablets (more specifically For coating) and the risk assessment done for the new coating machine installed. Some minor observations were made with regard to the ratings allocated and RPN calculated. For the new coating machine installed, the recent risk assessment was not addressing all possible failures of the equipment (in relation to temperature, rotation of the pan, spray rate / pressure etc)

The following risk assessment (RA) documents were reviewed:

- RA for Purified Water (PW) system: Chloride out of limits
- RA for Fluid Bed Drier (FBD): pre- and post-qualification stages.
- A RA SOP explaining the approach to HACCP was available

QUALITY RISK MANAGEMENT:

- The procedure had been implemented. Risk assessment and management protocol was available and was applicable to facilities, processing and product quality.
- In 2009 three products, based on the criticality of manufacturing process, sensitivity of drug product and the longest manufacturing process were selected to undergo this review.
- The Review considered if critical control points and **HACCP was used as the assessment tool**. Reviews were done by QA senior manager and production manager during the production of batches and the company was planning to perform such reviews annually, however this was not specified in the SOP.
- A quality risk management procedure had been implemented. SOP "Risk management (Failure mode effect analysis)" and flow chart were reviewed and found to be Satisfactory.
- WHAT ARE THE TOOLS FOR QUALITY RISK MANAGEMENT
- Change control (CC) SOP, Log books for Change Request 2010 - 2011 and reference matrix for impact analysis indicated selecting functions to do impact analysis and flow chart was reviewed
- Procedure had been implemented Quality risk management procedure had been implemented. Risk assessment and management protocol was available and was applicable to facilities, processing and product quality
- Products for study of QRM is selected based on criticality of manufacturing process, sensitivity of drug product and the longest manufacturing process were selected.
- QRM approach flow charts for process and equipment were available Organization charts.
- The deviation, change control and OOS logs plus the corresponding trends as applicable were reviewed

This was followed by a review of the following documents related to quality management system:

- Facilities
- Equipment and utilities

- Materials and management
- Processing
- Laboratory controls
- Stability testing
- Packaging and labelling
- Review of existing system
- Note: FMEA was applied as a risk assessment
- Self inspection once in 6 months for all departments according to written SOP and AUDIT schedule
- Audits were carried out by suitable trained personnel
  - Check list were used to carry out audits
  - Critical, Major and minor observations were identified Corrective Actions (CA were proposed after the audit and follow up was carried out by the QA
  - SOP risk management was reviewed
  - SOP is applicable to equipment, facilities and manufacturing operation which are likely to affect the product of process and for investigating the root causes of product complaints, OOS, and Deviations
  - Job descriptions of key personnel
  - SOP on Preparation of various lists, job responsibilities and Organization chart.
  - SOP on Control of Master Documents.
  - SOP on Creation, distribution, utilization, operation and destruction of SOPs.
  - Lists of SOPs.
  - SOP on Document and Data Control.
  - SOP on Generation and flow of BMRs and BPRs.
  - SOP on Batch numbering system (Formulations).
  - SOP on Batch split up.
  - SOP on Production Planning and Production Plan for March - May 2009.
  - SOP on Self inspection and Checklists.
  - SOP on Control on Logs, checklists and Formats.
  - SOP on Handling of Deviations. As an example, a major unplanned deviation occurred when Some in process tablets were accidentally spilled onto the floor. A shortfall of 8% of Theoretical yield was fully explained and the operator was retrained.
  - SOP on Change Control. Records for the several changes were reviewed.
  - SOP on Handing of Out-of-Specifications. A number of records for 2008 were selected for Scrutiny
  - SOP on Batch release system of formulations.
  - SOP on Excess material returns memo (EMRM).
  - SOP on Part batch release.
  - SOP on Reprocessing a batch

Quality Management:

- Product Quality Review
- Complaints
- Recalls
- Deviation control

- Change control
- Contract agreements
- Supplier approval / qualification
- Document Control
- Self inspection
- Batch document preparation, flow charts

A quality risk management procedure was approved in June 2008. Procedure was explained in the QRM Master Plan and was applied to:

- Equipment qualification
- Cleaning validation
- Failure and CAPA
- Tools listed in the ICH Q9 had been selected. Explanation was given for the application of the tools.

Quality risk management (QRM)

- There was a Quality Risk Policy for the site, and a corporate approach to risk management in the validation master plan.
- The FMEA SOP was applicable to equipment, facilities and manufacturing operations which were likely to affect the product of process and for investigating the root causes of product complaints, OOS, deviations or problems.
- QRM approach flow charts for process and equipment were available. QRM was found to be appropriately performed.
- SOP Risk management was reviewed and found to be acceptable.
- SOP was applicable to equipment, facilities and manufacturing operations which are likely to affect the product of process and for investigating the root causes of product complaints, OOS, deviations or problems.
- QRM approach flow charts for process and equipment were available
- Product quality review for the products under focus for that year were reviewed
- SOP and records for Product Quality Review (PQR), Complaints, deviations, change control,, OOS results
- Interim product quality review for particular year
- Batch Manufacture report for various batches (revalidation, validation, after change, batches selected from PQR
- SOP on Risk management (Failure mode and effect analysis and Root cause analysis).
- SOP on Analytical method transfer
- The presentation highlighted the capacities**, Quality Management System** and inspection history of the site. A copy of the presentation was obtained and will be filled in the company file.

Quality management review:

- SOP as well as Management review report July, 2010 to December, 2010. Was reviewed. SOP and report were found to be acceptable.

Product Quality Report (PQR):

- SOP Procedure for Product Quality Review (PQR)" was reviewed. According with SOP PQR should be carried out for each product manufactured in the plant.

The PQR evaluated:

- Process parameters (ammeter reading of RMG; mixing time in RMG; LOD after drying; LOD after final blend), FPP QC results (with statistical analysis including CpK for Assay),

PRODUCT QUALITY REVIEW:

The SOP on Annual product review and the PQR for the period January 2009 - December 2009 was reviewed:-

- There were no changes, deviations, OOS, complaints, recalls, validation done during the period, reprocess/rework.
- PQR of year 2008 was reviewed.
- There were 3 change controls but no deviations, OOS, complaints, recalls, validation done during the period and reprocess/rework.
- Annual Product Review Report for the period of Jan to Dec 2009 for Ethambutol Tablets BP 400mg reviewed. It covered LOD, DT, residual solvents (methanol, methylene chloride), dissolution, assay, yield among other parameters. The process capability index was calculated for some of the parameters (Residual Solvents, Assay, Dissolution and final yield).
- In Annual product review primary packaging materials were covered (compilation of batches received, suppliers name etc) but results of analytical tests were not trended and there was no conclusion or recommendation.
- Qualification status of relevant equipment was not covered in APR.
  Conclusion confirmed minimum and maximum values of all parameters were well within limits
- The product quality review report for 2009 was reviewed for the above mentioned product – Number of batches, complaints, recalls, deviations, changes, batch failures, variations, stability, validations (process) etc.. – Verified & found acceptable.
- The PQR stated that there was no complaint for this product, however, the complaint register showed that there was a complaint on the product destined for another market

QUALITY IMPROVEMENT STEPS:

- There was a system to ensure consistency and continuous quality and process improvement in form of regular internal audits, change control system, deviation management and regular quality review of all products manufactured.