

A Compilation of WHO GMP Audit Points

Collected from WHOPIR of 28 companies

Part VI of VIII

Current article – Part VI – Materials
Management

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MATERIALS MANAGEMENT

Vendor approval:

- The vendor qualification procedures and several audit reports were reviewed. The SOP provided for periodic re-audit of suppliers at least after 3 years for APIs, 4 years for excipients / solvents/disinfectants, 4 years for packaging materials and 5 years for equipment.
- The list of the products manufactured by the vendor was not Attached to the questionnaires as required by the checklist and/or claimed by the responses therein
- Sampling, vendor qualification, reduced sampling and individual material specification and these were not adequately interlinked or cross-referenced
- A Pantone colour swatch was available for artwork colour assessment. Test records, where done, were satisfactory and the “accept/ reject” criteria well presented. However, the AQL testing of components was not applied with sufficient rigour
- These revisions plus AQLs and related adequate sampling plans (according to BS 6001 and ISO 2859) for packaging materials (Labels, cartons, bottles, cups, etc.) were included in the revised SOP
- Vendor requalification was done once every 3 years for APIs, once every 5 years for other raw materials and packaging materials. A supplier was disqualified following failure of 3 consignments or delivery of a contaminated consignment or failure to take adequate CAPAs
- Note: Vendors audit should be performed once per 3 years
- Vendor evaluation checklists
- In case of new vendor for API, the procedure involved evaluation of samples by R&D, evaluation of vendor using questionnaire and site audit before being placed on approved vendor list
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- List of qualified vendor list for API

Vendor Audit Programme

- There was programme for evaluation and approval of suppliers which was managed under an Approved SOP.
- The SOP allowed for the removal of any established supplier who subsequently fell short of requirements.
- The number of monitoring points was calculated by taking the square root of the warehouse volume.
- The performance of vendors was reviewed annually and there was a procedure for requalification once every three years for APIs and once every 4 years for excipients
- Suppliers of all materials (not just APIs and excipients) were subject to vendor audits. A typical Questionnaire was sent to all suppliers for basic information. It included requests for information on the buildings, the QC/QA and where applicable TSE free certification
- Audits had followed the SOP in force at the time and had been completed within ± 4 days of the scheduled date either by questionnaire or a site visit
- The one of the suppliers was marked 2 (acceptable) on an arbitrary scale of 0 to 3 and a SMF was provided.
- Some suppliers of the excipients was approved by questionnaire

- SOP "Quality audits", flow chart
- Vendor's audits in most cases were carried out by the corporate auditors. Approved vendors lists for APIs manufacturers and packaging material manufactures were available
- Starting materials, packing materials, and components receiving, quarantine, sampling and storage areas + SOP'S
- SOP on Receipt, Identification, storage and movement of raw materials and packing materials in the ware house + RELATED " Process Flow Chart" and material inward register
- Incoming goods and finished products were quarantined until tested and released by QA
- Damaged containers were informed to QC.
- Areas were provided for goods receipt, initial clean down using a vacuum cleaner and quarantine and finished goods
- Plain aluminum foil was stored in reels in a locked room, the booth used for dispensing foil operated under a positive P of 5" H₂O relative to the outer area
- Printed packing materials (Labels) were stored in locked pigeon holes
- There was a system for development, qualification, disqualification and requalification of vendors of RM and PM
- This procedure was generally well implemented and comprehensive list of approved vendors existed
- The system of vendor approval included a comprehensive questionnaire filled by the manufacture, testing of pre-shipment sample and, auditing of the facilities of the vendors
- The performance of vendors was reviewed annually and a procedure for requalification once every two years
- A vendor was disqualified if 3 consecutive batches supplied were found unsatisfactory
- Receipt of goods followed the standard routine according to an SOP
- A Purchase Order, Goods Received Note (GRN), and certificate of analysis (COA) had to be available before goods were unloaded
- When a shortfall in deliveries occurred a new purchase order was prepared which stated the quantity actually received
- A stock reconciliation of two of the APIs were reviewed. All transactions were satisfactorily recorded and the stock record balanced
- The Goods receiving SOP must have this instruction
- The storage conditions of all materials were defined and list was available at the receiving area to guide the staff to place the materials in the right area
- Each consignment was quarantined sampled and tested before release
- Goods were stacked in quality steel racking
- Location codes for each item were clearly displayed at the end of each lane
- All items were stored in containers with their status clearly displayed
- Cartons and leaflets (inserts) were stored in boxes with pharmacode, which were easily readable when inspected
- All packaging materials were transported to the packing hall in lockable mobile cages

- There were separate storage facilities in which rejected materials were securely stored until either they were disposed of by return to the supplier or destruction or they were reviewed and approved by QA for further testing and repacking
- Proper checks according the check list were carried out for incoming materials. Approved vendors list was Available in the warehouse. All incoming materials were de-dusted before placing to the quarantine area.
- Printed packaging materials were sampled following AQL
- Approved Suppliers List: with focus to APIs, Excipients and packaging materials for the products in focus
- Afterwards materials were moved to the quarantine area and GRN was prepared and initiation was sent to the QCL
- Sampling was done under RLAF. RLAF operational procedure was available.
- Line clearance was checked by QA officer before sampling operations.
- Sampling tools were stored and cleaned in QCL. Sampling tools cleaning procedure was validated. SS sampling tools were used.
- Item code transfer was not transfer for starting material
- Dispensing was done under RLAF. After dispensing materials were passed through material pass box and delivered to the production floor by the lift. Lift shaft was ventilated with filtered air.
- Dispensed materials were stored in double poly bags, placed in the SS containers. One label was placed between poly bags and other stacked to the outer bag
- Balance and operator location positions were identified during RLAF qualification studies
- If materials after dispensing were taken back to the store, those were properly identified with "loose" label
- Cleaned dispensing tools were wrapped in poly bags and stored in locked SS cabinet. All Cleaned tolls, drums or containers were properly labeled and "due to clean date" indicated.
- If the cleaned tools, drums or containers in stores or in production have not been used within the specified date (7 days) red color stamp "clean before used" were put on the labels.
- Sampling plan was drawn up in accordance with AQL.
- Printed packaging materials were securely stored in double locked mobile racks. One key was with store officer and one with QA officer
- Roll sticker labels were used for the labelling
- Labels indicting manufactures batch numbers and amount were stacked on the inside part of the roll
- Labels had Pharma code. Pharma code reader was not installed on the packaging line. Company was planning to install the reader in the future. Joints on the roll labels were indicated with red color. First and last label from the roll were stacked to the BPR as well as the label after the joints proper checks according the check list were carried out for incoming materials
- Printed packaging materials were sampled following AQL
- The process flow for the specific products under inspection was logical and followed a defined pattern From receipt of the raw material from the delivery vehicle into a closed unloading platform, through a qualified and maintained de-duster cabin, and into a quarantine and store where Quarantine and Release were controlled by status labeling and color coding and SAP system
- SOP "Reference substance - Creation, Handling and use" and register were reviewed by the inspectors

- Sampling Near infra red instrument was used for the identity tests (ID) tests of every container before sampling.
- Conditions of storage for different materials had been defined and were regularly monitored.
- Samples of APIs were taken from each container using a dedicated sampling room. Each sample was tested for identity and then pooled to make a composite for other tests and reserve sample. The maximum number of samples that could be pooled into a composite had not been determined
- WHO recommended sampling plans
- A sample inward register was used, allocating an individual number to every sample to be analysed. The register was used for all types of samples, covering raw materials, packaging materials, environmental, and stability samples
- Company representatives and operators were asked if different shipments were ever received at the same time and loaded on the same pallets at the same time. They replied that this was not the case, mainly because the plant was not producing at full capacity but that if this was ever to happen, a physical separation would be used to reduce the risk of any mix-up
- The cleanliness of the area was found to be acceptable and was maintained for 7 days. The pallets used inside as well as outside were initially said to be cleaned across the facility, which could pose a contamination risk as this would mean bringing the dirty/contaminated pallets across a corridor adjacent to other areas. It was later explained that pallets used outside were cleaned by "mopping" (not inside the facility). The SOP has been provided and found which is accepted after review
- Operators present described the procedure used for cleaning the room and for use/cleaning of the vacuum cleaner. The SOP and associated logbook (CQA86, version 09) were examined and found to be up to date, but the earliest record dated only from July 2010. The cleanliness status of the vacuum cleaner was clearly identified and was verified by opening and examining the filter and pipes
- Dispensing Area: The cleaning status was found to be maintained for 7 days, as cleaning was performed every 7 days on a regular basis
- Packing was accompanied by pre and post line clearance.
- The dispensing rooms were accessed through air locks. The pressure differentials were set between 1.8Pa and 2.4Pa

Sampling:

- All containers of API was sampled and tested for identity, while full testing was done on composite sample

A documentation system was in place to guide production and control of products. These included:

- Batch master formula, specifications of starting, packaging materials and packaging components, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and various standard operating procedures and protocols. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.
- 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

- There must be segregation according to quarantine and released materials
- APPROVED VENDOR LIST OF API AND PACKING IS AVAILABLE WITH STORES
- Temperature mapping in warehouse has been carried out
- Note: Two permanent monitoring positions were selected based on worst case results for high and low temperatures
- Product Master Files, codes, specifications for APIs and FPPs, plus List of approved vendors
- Material Transfer Records
- Vendor development and requalification of RM
- Report for API transfers
- Report of Stock transfer
- Verification of suppliers
- Manufactures of API
- Footwear cleaning
- Sampling tools cleaning
- Dispensing tools cleaning
- Recipes of products (Whether the recipes were ensuring that the only the correct API could be issued for use in products)
- Audit trail for transfers
- APIs sourced from all suppliers for selected APIs including the use in products by batch to verify in which batches these were used
- Verification of the use of batches of selected APIs in products prequalified to ensure that only APIs from approved sources were used
- Material document list
- Material inventory list
- Process orders
- List of approved external vendors for procurement
- Approved suppliers list (ASL)
- In the receiving area, containers were de-dusted, then labeled and logged into the ICS SYSTEM(Inventory control system) before being labeled as quarantined products were stored and distributed in traceable way

DISPENSING:

- Dispensing area separate for API & Actives
- Note: Before dispensing identity of the container has to be established
- Check-weighing of balances before dispensing
- Cleaning has to be conducted before proceeding to next dispensing
- Primary packing materials were sampled under RLAF and capsules were sampled in the excipients sampling room

General procedures regarding:

- Receipt

- Identification
- Quarantine
- Storage
- Handling
- Sampling
- Testing
- Approval / rejection of materials were available for inspection

PACKING MATERIAL:

- For testing pm the instruments like screw micrometer, steel rules, rub tester torque tester were used
- An illuminated screen was used to detect pinholes in foils
- Authorized reference samples were available for artwork and technical drawings
- A pantone colour swatch was reportedly held in the packaging development laboratory
- Samples were taken from deliveries using the normal sampling plan given in BS 6001

Testing of packaging materials:

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

Inventory Management System:

- A in house development computer system was used but only as a database for stock control.
- Status of goods was still controlled using a manual procedure involving status labels and QA / QC authorizing signatures.
- Goods were then dispatched to Baddi where a goods receiving procedure (SOP) was in force. Goods were checked against the purchase order (PO) before unloading. Certificates of analysis and TSE documentation must accompany the PO and challan. Records even included the delivery vehicle registration number. Variance in quantity delivered against that ordered was set at +10%.
- Outer packaging was cleaned and removed and goods placed in quarantine and a copy of the GRN was sent to QC as a notification that sampling was required. Materials were recorded as individual lots and each separate lot was stored on its own pallet(s).
- The Goods in officer printed a bin card which was kept with the goods throughout its life cycle in the factory. QC allotted a sequential analytical AR number and printed out a corresponding "under test" label, which was attached to each container before sampling.

- Upon completion of testing the appropriate status label (Approved/Rejected) was signed and attached to the container(s).
- The GRN was stamped "Passed" and given to goods in for their records.
- The QC workstation had the capability to move raw materials in the "under test" fields to the "free stock" fields. This in theory would only permit the warehouse to issue approved materials, FIFO being a standard procedure.
- It was noted that the dispensing procedure allowed for issue of materials pending final test results. This is considered a contravention of cGMP, even though it was documented as a deviation
- Stock close out followed the procedure in an SOP. The reconciliation limit was $\pm 2\%$ but the situation to invoke action had yet to occur. There was no investigational procedure available for guidance in the event of this happening.
- Monthly cycle counts were conducted for class A items (APIs, other raw materials and packing materials). Other items (Class B) were checked annually. The system was randomly interrogated for individual stock records.
- Monthly cycle counts were conducted for class A items (APIs, other raw materials and packing materials). Other items (Class B) were checked annually. The system was randomly interrogated for individual stock records. The total holding of each material was broken down into individual lot Nos. Each transaction or return to stores was ascribed a reference number. The usage of a batch of one of the APIs was trailed. The residual stock in the computer listings was 5Kg .This tallied with the actual weight in stock. (Weighing requested by the inspector).
- The system was automatically backed up every three hours and a daily record of transactions was placed on CD by the stores. The system satisfied the basic requirements of password protection, time out if unattended, and data entry verification. No problems were encountered throughout the Inspection whenever any information requiring a computer interrogation was requested
- The system of vendor approval included a comprehensive questionnaire filled by the manufacture, testing of a pre-shipment sample and, when found necessary, auditing of the facilities of the vendor and/or production of pilot batches
- The sampling plans used were consistent with those prescribed under British Standard BS 6001- 1and AQL were appropriately applied
- The materials in the intermediate store had been stored there within 1 - 5 days which was well within the validated holding time of 30 days
- Packaging material containers were sampled using BS 6001 requirements (SOP QC 061/R5). Observations related to this sampling have been addressed
- All deliveries were entered into a sample log. Any component was traceable using its code number, AR number and GRN. Specifications, drawings and authorized standard reference artwork samples were available for all the packaging components
- Procedure for sampling, inspection, checking/analysis and release of packaging materials was reviewed. Statistical sampling was applied, sampling plan was based on Acceptable Quality Limit (AQL). The procedure had been implemented recently and was partially still in a trial phase.
- The storage conditions of all materials were defined and a list was available at the receiving area, intermediate storage areas and finish goods store to guide the staff to place the material in the right area. Granules, uncoated tablets and coated tablets were stored in sealed SS Intermediate
- Bulk Containers (IBCs) and their holding time had been validated
- There was a system for development, qualification, dequalification and requalification of vendors of Raw Materials and Packaging Materials as described earlier
- The questionnaires (one for RM and another for PM) used plus the reports of evaluation of

selected vendors and the analytical reports for the first 3 batches analysed during evaluation of the vendor were reviewed

- Controlled temperature storage For controlled areas temperature, the limits were 15 - 25 °C with RH at 40-65%.
- API's were stored in a controlled temperature room. Aluminum foil and capsules were also stored in a controlled environment.
- In the receiving area, containers were de-dusted, then labeled and logged before being labeling as quarantined.
- RM/PM Receiving areas on the ground floor following the logical flow: Offloading bay, Dedusting area, change rooms to the warehouses, staging areas, weight checking areas, Quarantine areas, approved RM warehouse, solvent storage and dispensing area.
- Temperature was continuously controlled by data loggers in defined locations. Temperature mapping in the warehouse had been carried out. Two permanent monitoring positions were then selected based on the worse case results for high and low temperatures.
- The SOP on cleaning of the loading and off-loading bay
- The SOP for cleaning the dispensary and the records for routine zero check on pressure gauges were reviewed but the frequency for the zero check could be increased
- The use of equipment was traceable through equipment identification in the batch records.
- Stability study samples of two types yearly sample, validation batch samples
- The temperature profile was ascertained by following an approved protocol. The number of Monitoring points was calculated by taking the square root of the warehouse volume.
- Printed packaging materials, audit every two years
- Review of purchase and receiving records for two drums of a certain excipient which had been returned to the "under test area a" for retesting showed that, on receipt, the stores manager notified qa of a delivery of material from the unapproved supplier; QA then cleared the material to be received.
- Review of the sampling log book also revealed that several batches of two APIs had been received from sources not listed on the approved suppliers for the two APIS and had been sampled. These were traced back into the enterprise resource planning (ERP) computer Database. The materials were coded differently from those from authorized suppliers. A further "reverse trace" was conducted in the ERP to link the APIs to the FPPS in which they were used and their distribution
- The receiving area for packaging materials was also the dispatch area for finished goods, but administrative procedures had been put in place to avoid any mix-ups. The quarantine was on level 4. Selection of containers for sampling was according to BS 6001 or ISO2859.