A Compilation of WHO GMP Audit Points

Collected from WHOPIR of 28 companies

Part III of VIII

Current article – Part III – Production

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Production:

- Some production equipment was designed with plc control systems and the related software had been validated.
- Equipment was attached with calibration due dates.
- When the equipment has moved form on location to new location, the re-qualification protocol and reports has to be done.
- For controlled areas temperature, the limits are 15-25 degrees with RH at 40 – 65%
- The wash area has good flow of dirty and nylon brushes were discarded after use.
- The technology transfer process was reviewed for specific products and was considered comprehensive and covered batch formula, storage, test methods and stability. It also included a product development report an impact assessment on cleaning validation and method transfer for the analytical test methods.
- Sop on rework and reprocessing.
- Spot check on the use log for punches and dies showed that their issue and use were well recorded. And has to systematically rotate to ensure uniform wear and tear.
- On the reconciliation record, the number of tablets was changed from 2600 to 52000 without any written record of the reason for the change – Any changes in the record have to be explained why there was change.
- Hold time validation for cleaned and unclean equipment.
- Transfer technology was included in the change control programme (the transfer of one of the capsules products between filling machines was satisfactory recorded)
- **Note**: when ever changes in the machines, the operating instructions in the sop have to be correctly changed inspectors will check the old and new sop to check changes has been made satisfactorily or not.
- Sop for in-process control of tablet compression.
- Batch release procedure required checks of batch manufacturing and packaging Protocols and laboratory records.
- Re-qualification and/or re-validation were required in case of changes and this requirement was re-enforced by the corporate change control sop.
- There was a validation matrix for the key processes, systems and major equipment.
- Production practices were generally good except for concerns about labeling of “rejected Bulk” from the filling line as "recovered bulk" which suggested it was meant for reprocessing.
- Entrance to the sampling units was via airlocks.
- Recording three separate product potency calculations when making one virgin batch from three separate batches of API.
- Cleaned equipment hold time was specified holding times for intermediate products were specified.
- PW was used for final rinsing of the equipment. Equipment was dried using filtered compressed air.
- Holding time for materials from dispensing to bulk tablets was specified as maximum 30 days and the holding time for bulk tablets was 6 months.

- Limits for yield had been set at different stages of production and packaging and any results beyond the limits were investigated and documented.
- Other production tools as sieves, finger bags and engineering tools were also stored in the Locked rooms in SS cabinets.
- In the sifting room there was dynascan illuminator fixed to the wall.
- Metal sieves integrity was checked before and after sifting of each product.
- Materials after sifting and granulation were transferred to the next processing room via Double doors pass box.
- The wash areas were connected to the production rooms (sifting and granulation). To Avoid production room's contamination; air was 100% exhausted from the washing rooms.
- BMR in current use compared with that used in validation and submitted in the dossier.
- Materials were transported from warehouse to production departments in locked Stainless steel trolleys.
- Sop on reprocessing and rework was reviewed.
- Care has to take to prevent gaps between the filters in the tray dryers.
- Milled materials were collected in cloth bags.
- It was indicated that it was not a requirement for products meant for local market to go through a metal detector.
- Packing was accompanied by pre and post line clearance.
- Capsulation was done by tamping and dosing using automatic capsule filling machines.
- Tablet press Servicing followed an approved sop.
- Some granules and/or bulk tablets were transferred in sealed drums from workshop 1 to workshop 2 for compression or co-packaging.
- Bulk tablets were stored in in-process SS bins beyond the validated holding time (3 months) and could be retested and stored for another period.
- Such holding time would be included in the shelf life of the batch and such tablets would be subjected to extra concurrent Stability testing.

- **A compression machine equivalency report was reviewed as part of change control and this covered various factors such as**:

    1. Operating principle
    2. Operating principle
    3. Feed type
    4. Number of stations
    5. Rpm
    6. Dwell time and pre- compression.

  The evaluation was conducted in an appropriate manner and gave confidence that the product would be manufactured appropriately if it is transferred to another machine.

- Exhaust from the FBE was passed through cartridge filter, powder remains were collected, and water was added and mixture was discharged at Effluent Treatment Plant.
- Equipment calibration schedule was established and followed for each department. The system to verify and control the calibration status of critical equipment was in Place.

- The sequence of the dressing procedure was not clearly described in the SOP. The changing procedure for personnel entering the sampling and dispensing areas in the raw materials warehouse was not sufficiently described.
- Material and personnel flows were defined and allowed a logical order of goods processing.

Examples of validation reviewed were:

- All stages were validated following a protocol.
- The process was outlined in a flow diagram.
- Blend uniformity was determined after sampling predetermined layers after setting mixing times.
- The optimum blending time which yielded a blend with all active meeting specified level was determined.
- The compression cycle was validated using a protocol.
- Samples were taken at startup, middle and end of run at three speeds met tablet specification.

Punch and die management:

- The life cycle was governed by tablet type: 4x106 compressions for circular tablets; 2x106 for other shapes and double layer tablets; and 1x106 for effervescent tablets. the log usage for each set was kept in an individual register.
- Punches and dies were properly maintained and stored, turnover of punches and dies were measured and recorded in the **TABLET TOOLING LOG CARD.**
- Punches and dies were well controlled.
- Punches and dies were inspected for compliance with specifications, rotated at the time of Issue, checked for suitability before use according to and sop, cleaned and lubricated.
  There was a sop for polishing and records were in place.
- Punches cleaning and polishing procedures were in place. Punches drawings and certificates were available for inspectors. Punches were numbered and rotation was insured Punches usage was recorded in the punch stock card.
- Validation for cleaning punches and dies using kerosene.
- Whereas the objective was to demonstrate that there were no kerosene residues on the punches and dies following cleaning, the conclusion referred to absence of kerosene in the next batch.
- There was no study to demonstrate the effectiveness of the swabbing to recover kerosene from the surfaces of the punches and dies. (In any case, the use of kerosene should be discouraged).
- Pharmacopoeia grade liquid paraffin was used for punches and dies. Punches were Numbered and rotation was ensured.
- Punches and dies were cleaned and inspected for damage and return to the stores.
  They were oiled with specific brand of oil, The oil had COA and was CFR 178.3570 approved for use on product contact parts.

- The punches and dies were randomly selected from the (30 station press) BY SQUARE ROOT OF N +1 for measurable wear and tear as evidence that more than just a visual inspection was performed.

FBE:

- The sop for measuring air velocity in the FBE referred to the area of the duct when the area which was actually and rightly used was of the bowel.
- Qualification was conducted using a protocol. Inlet air and exhaust air temperature sensors were calibrated with certified equipment whose own calibration was traceable to the relevant national standard.
- Data for bed temperature uniformity and correct operation of the solid flow sensor was satisfactory.

Rotary 30 station tablet press:

- Initial hardness measurements were determined manually and the result obtained was used to set the PLC which monitored the cycle and prevented pressure overload.
- It was noted that the lubricant for machine parts, which came into contact with the tablets was food grade oil.

IPQC ROOM:

The usual equipment for controlling compression parameters where the calibration status of equipment was checked

- Disintegration (calibration was carried out every month)
- Weight (Balance verification was carried out every day)
- Friability (calibration was carried out every 6 months)
- Hardness & thickness & diameter (calibration was carried out every month)
- Granules could be kept up to 3 months which had been validated.

Packaging:

- The blister-packing machine was operated using a sop.
- Details of the clean down from the previous product and set up for the next were entered onto the packing record.
- Components and tablets had been issued and checked before packing commenced. Reels of foil were checked for splicing before and during packing.
- The purchasing specification reportedly controlled the number of splices per reel.
- Samples of foil, pre and post splice were included in the records when appropriate.
- Primary labels were monitored on line with bar code readers. All in process checks were up to date and endorsed with a QC signature.

- Cartons were corded offline using locally sourced stereos.
- Excess/unused /damaged stereos were destroyed at the conclusion of a packing run.
- The sop for batch release provided for the return of unused labels to store but there was no reference to any checks to ensure the absence of any overprinting (E.g. batch numbers) before returning.

Rework:

- The definition of reprocessing was to repeat the previous sub-batch process if the desired result was not achieved.
- Rework was the variation of an established process due to an unexpected Deviation.
- The definitions did not allow for the addition of acceptable residues of a previous batch to a virgin batch and reworking was not included in the standard BMR format
- Re-processing was defined as re-drying, re-sieving or milling.
- Reworking was defined as: blending, drying, opening the secondary / territory pack and repacking t h e m in different orientation.