A Compilation of WHO GMP Audit Findings

Collected from WHOPIR of 28 companies
Part I of VIII

Current article – Part I Utilities

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INTRODUCTION

"*Knowing the enemy enables you to take the offensive, knowing yourself enables you to Stand on the defensive*"; (The Art of War Chinese Military general, Sun Tzu)

Similarly, if a company knows and understands what are the GMP expectations and compares itself, with the current status and prepares accordingly, then such a company can be well prepared for any type of inspections / audits. The story below supplements the above need.

Two sailors wanted to cross an ocean in two different boats. One sailor believed that he could cross the ocean to reach the other side with a belief that his previous experience would be helpful in accomplishing this goal. Though he had never crossed any ocean before single handedly (he had always sailed under the command of an experienced captain during his previous journeys); this time he did not take any expert help; and still ventured into the ocean.

The other sailor realized that, it would always be better to take advice of some experienced captain to lead him into the ocean. He therefore took the expert advice of an experienced captain and then went into the ocean. Let's now guess as to who reached other side of the ocean, quickly and safely and also lets think about the fate the other sailor who could not do so. The sailor who believed and relied on his own expertise only could not achieve the desired goal. This clearly tells that no matter, how well experienced you are, if the job is new to you, the experience you gained all these years is of little help. In such case, you need to take benefit of the expertise or study of someone who already has done the job previously. This habit not only saves valuable time, but it helps us prevent the repeat of costlier mistakes, which were previously done by someone.

To Achieve quality objectives of the organization, TEAM WORK is a must. Is there any such thing called "one-man show ? We need to think about this ? If an army commander, fought in the frontline (Hand to Hand combat with the enemy) in the battlefield, along with his soldiers, ignoring his actual role and responsibilities, can such a battle be won by this commander ?. A commander's role is to lead, guide, coach, counsell and command his soldiers towards victory in the battle. By planning, strategising, allotting, encouraging his team of soldiers according to their roles and expertise, the leader has to identify the strengths and weaknesses of his soldiers, as well of his enemies, and plan accordingly.

By ignoring all this, if he involves directly in an arm to arm fight with his enemy in front line battle, do

you think, such a battle could be won by this commander ?. In the real-life situation/s, an army commander will be securely situated in some place from frontline and would guide, lead, motivate and command his soldiers. He would make his soldiers to realize that team work alone will help them to win the battle.

> *"A war will only be won when every solider shares the same vision, it will not be won, if the commander alone had the vision to win the war. So, it's the duty of the commander to make his soldiers to realize the vision, and he has to guide them, lead them on how to win the vision of winning the war" – Art of War.*

Real Fact: An army commander carries an automatic pistol, which holds only 12 rounds of ammunition and spare of around 100 – 120 rounds. Whereas the team that he commands (the frontline soldiers) carry automatic Kalashnikovs, which carry more than 3000 rounds along with other ammunition. This clearly tells that a commander is there to lead his soldiers. To tell them,

What to do?
How to do?
When to do?

Make a team of them, and lead them towards victory in the battle.

A manager therefore is like a commander, who leads his team like his soldiers. If a company has to be prepared for audit, it's only possible by a well co-ordinated, guided, motivated and led team work. An elaborate plan is very essential to win the audit. Everyone has to see the vision of clearing the audit without any noncompliance.

This "Compendium of WHO Audit points" is hence prepared as an effort towards finding a way for an elaborate plan of what to do? How to do? And when to do? If our efforts help the company to realize its goal, I think that our efforts are rewarded. This would serve as a light house to the organisations who wish to seek sustainable compliance and implementation.

This article is divided into several parts and shall be published in eight parts from now. The first part shall be on utilities.

Utilities:

HVAC SYSTEM:

- HVAC SYSTEM requalification was contracted out
- Periodic revalidation was carried out on filters of HVAC system
- WHO Supplementary guidelines on good manufacturing practices for heating, Ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms has to implemented

The following tests are necessary for AHU:

- Qualification Protocol / report and data for specific AHU
- airborne particle count – once every year
- Airborne particle count - once per year
- Air flow test (feet³/min) - once per year
- Air velocity feet³/min
- Air changes per hour
- Air pressured difference test - once per year
- Installed filter leakage test - once per year
- Air flow visualization test - once per 2 years
- Temperature - once per year
- RH - once per year
- Recovery test - once per 2 years
- Containment test - 1 per 2 years
- Particle counts - every 6 months
- Air change rate - every 12 months
- UDAF velocity - every 12 months
- Particulate monitoring (at rest)
- Air balancing was checked with AHU – ON / OFF
- Measuring UDAF air velocities
- Check return air velocities for air flow patterns
- Check qualification documents and drawings
- The supply and return air ducts of AHU has to show the direction of air flow
- HVAC Primary filters cleaning SOP
- Review of AHU INTERLOCK VERIFICATION
- Production areas were ventilated with supply air grills located higher than return air grills, such that there was a downward flow of clean air from above and exhausted lower down.
- Pressure across the filter was monitored regularly through potable magnehelic gauges while pressure differentials between adjacent areas was monitored using fixed magnahelic gauges.

- The pressure differential in the LAF was recorded but the limits were not marked on the gauges and there was no record to show that the "clean up" or "recovery time" was being monitored.
- HVAC systems were designed to supply a minimum of 20 air changes per hour thereby targeting Grade D (Class 100,000) conditions in the production areas.
- The system was re-circulated with maximum of 10% fresh air and 90% used/re-circulated air but filtered with G4.
- Air was exhausted through a double HEPA filtration system, and pre-filters were maintained
- Each manufacturing area had a dedicated AHU with temperature controls and 0.3µ H13 terminal HEPA filters and there were dedicated dust extraction system. The exhaust from coating areas passed through a water scrubber.
- Aspects qualified included non-viable particle counts, Air velocity, air changes per hour, air flow Visualization test (DVDs for Smoke test), viable counts, settle plates exposed for 2 hours and active air sampling, recovery test, containment and leak test.
- HVAC system was designed in a way that production corridors were in positive pressure with respect to production rooms. HVAC system was controlled and monitored by the BMS system.
- The HVAC and dust collection systems were interlinked so avoid cross-contamination in case of utility failure means of a bag-in-bag-out system.
- The team reviewed and inspected in detail AHU 17 for manufacturing area and AHU 18 for the mixing area. Both had 10µ pre-filters, 10µ return filters, 3µ supply filters and 0.3µ final plenum filters.
- Damper positions were marked for every AHU
- Final filtration of air is through HEPA in all areas. Production areas are classified as class 100000. Non-viable particle count as well as microbiological monitoring of production areas is carried out at regular intervals.
- Filters were properly labeled, dampers positions were fixed and DOP ports were specified
- Conducted airflow visualization test to confirm effectiveness of the dust collecting system design.
- Prepare the DVD of the airflow patterns in rooms served by AHU
- AHU distribution and pressure differentials drawings for both Block A and B, revalidation
- Schedule for the AHUs, daily _P monitoring records.
- Incoming air was filtered via several pre-filters and dried. 0.01 µm filters were installed at the used points.
- The exhaust gases from the standby power generator were near and at the same level with floor where the inlets of the AHUs were located but they were channelled away as corrective action.
- Mark all the positions of the levers For air regulation fixed during qualification and pressure balancing.
- The HVAC and the dust extraction system in the sifting area were coupled so avoid Cross-contamination in case of utility failure.
- Review of the change control for coupling AHU 11 and the dust extractor showed that the impact on the parameters of the HVAC system had not been assessed.

- AHUs were fitted with an alarm system in case of failure and there was an SOP
- SOP on Duct leakage measurement
- The new AHUs that were installed were qualified (IQ, OQ and PQ). The schematic drawing and selected tests and results were reviewed. This included for IQ, OQ and PQ installation of various filters, temperature and relative humidity control, cleaning of filters, installed filter Leakage testing, temperature distribution, air exchange rate, recovery rate and pressure Differentials.
- Most doors were designed to open on the low pressure side and not the high pressure side.
- The qualification reports of the FBE were inspected. This included the schematic drawing, IQ (and selected component verification) such as the blower, blower capacity, air volume, filters, Temperature sensors for inlet and outlet and product temperature
- Filter integrity test certificates, HEPA and EU filters certificates and instrument calibration Certificates were available
- The HVAC system was provided with an alarm for T and RH. Filters' cleaning was properly documented. Preventive Maintenance schedule and check lists were presented to inspectors
- Training records of the staff that was cleaning the HVAC pre-filters
- The SOP on preventive maintenance of motors showed that AHU motors were serviced every 6 months
- The HVAC systems in each unit generally consist of many separate and independent units.
- Prepare the environmental conditions, cleanliness zones, pressure cascades as well as the general concept of the HVAC system
- PM schedules and logs were available for each individual AHU. Check list for planned
- PM of AHU 12 was checked and found to be satisfactory
- Ducts were cleaned following SOP "AHU duct cleaning". Ducts were dismantled and Cleaned once per year
- In the main building water was circulated continuously at 80 °C. PW system was sanitized regularly; filters were changed every 6 months
- Production areas (open processes) were classified as ISO-8. Secondary air-locks separated "Other areas" from ISO-8. Air-locks were also classified as ISO-8.
- The company monitored Δp-s between the corridor and rooms within the ISO-8 area (magnahelic gauges).
- The air-flow direction had been checked during qualification of the building at the doors leading from the air-locks to the ISO-8 corridor.
- The air-locks in the production area were designed to have an overpressure compared to the ISO-8 area corridors and ISO-8 area rooms.
- The ISO-8 area as a whole was designed to have an overpressure compared to surrounding areas and outside environment. The Δp limits were uniformly defined as 5 to30 Pa.
- HVAC system in Unit IV: AHU-37 was examined. All of the filters that were described in the diagrams were verified to be present. Measuring of the pressure drop was performed only over the 1st set of filters, not the second s
- The procedure for restarting the AHU's, which were stopped during cleaning of filters was requested

- DOP testing of HEPA filter.
- Measurement of air velocity and calculation of air changes per hour.
- Air handling unit with variable frequency drive.
- Clean up time in classified area.
- HVAC re-qualification was carried out every three years or if there were major breakdowns, replacement of critical components or major modifications. AHU requalification report has to prepare accordingly.
- There was an HVAC system fitted with a series of filters in the plenum (20µ, 10µ, 5µ, and 0.3µ) and designed with 90% - 95% re-circulated air and 5% - 10 % fresh air.
- Pressure differentials from the corridors to the processing rooms were monitored and recorded two times per day. Pressure differentials from the corridors to the processing rooms were set up from 10 to 40 PA. Corridors were maintained positive to the Processing rooms.
- Minimal pressure differences between adjacent rooms were between 2 and 4 Pascal, which is lower than the WHO recommendation for manufacture of finished products (5 to 15 Pascal).
- A written rationale for choosing the pressure cascade pattern could not be provided. For monitoring of pressure cascades each room was measured individually against atmosphere. Due to this system, differential pressures between adjacent rooms were cumbersome to calculate individually in practice.
- It was not clear in the AHU Qualification protocol whether the limit of ±20% variation of the air velocity across filters given as the acceptance criteria was with respect to the actual average velocity or design average velocity
- There was a "walk able ceiling" in between the service floor and processing rooms. HEPA Filters and lights were changed from this floor
- The wet/dry bulb thermometers were evenly distributed throughout the warehouse and measurements taken with the AHU's in operation. The temperature range was set between 150C and 250C with the RH limit of NMT 60%
- A visual assessment of the data showed the temperatures throughout to be of the order of 250C with no hot or cold spots. Corresponding wet bulb temperatures were not recorded but calculated RH values for each site reported. Without the wet bulb readings being entered it is impossible to confirm the RH values were in fact those stated.
- It was noted that the pressure gauge to indicate the pressure difference between Granulation Suite III and the corridor was not working while granulation was going on
- In many cases, the pressure differentials were not monitored. When asked why, the company stated that this is because manometers simply had not been installed. Company representatives claimed that adequate studies were performed using smoke tests. This was not an acceptable explanation because it only insures air flow direction.
- The company was asked how ingress was prevented and if any pressure gage was showing the pressure of the facility relative to the atmosphere. No clear answer could be provided at the time (It was later explained that this was monitored on the service.
- Requalification was required every 1 year ± 1 week.
- Production areas were ventilated with supply air grills located higher than return air grills, such that there was a downward flow of clean air from above and exhausted lower down.

The following tests were carried out during the AHUs re-qualification:

- AHU's re-qualification reports and available raw data have to be maintained for all the rooms fitted with AHU.
- Re-qualification was carried out every 6 months for all tests following ISO 14644

The following tests were carried out during the AHUs every day:

- Recovery rate - every 24 months
- DOP - every 24 months
- Pressure differentials and T&RH were monitored and recorded every day

Special care has to be taken for the following area AHU in detail:

- AHU serving compression
- Blending room and blend store in manufacturing
- AHU serving compression
- AHU serving pellet coating

Preventive Maintenance Program:

- Preventive maintenance for AHU AC-7 for Granulation I was also reviewed
- A planned preventive maintenance program (PM) of equipment and systems was in Place.
- Critical equipment was identified.
- PM SOPs were available for all equipment and Systems.
- PM was carried out following check lists.
- Preventive maintenance labels have to be maintained.
- SOP Preventive Maintenance (PM) + schedule was available for inspections. This SOP was also applicable to production equipment
- PM performance SOPs and checklists were available for all equipment
- Maintenance of all equipment was carried out according to a set schedule specifying weekly, monthly and quarterly service requirements. The schedule and service reports for the several equipment (Tablet press, FBD, Mixer Granulator, Metal detector, etc) were assessed.
- An SOP was in place to ensure PPM was being done. A "planner" was used to plan PPM each Year and checklists were used for individual equipment as per SOP.
- Details of the work to be carried out were given e.g. lubrication of parts, roller condition and hydraulic system checks.
- Originally, the weekly routine involved a brief clean up with a hydraulic pressure check. This schedule has now been upgraded to a more extensive programme. All time deadlines had been met and no matters of concern were noted.
- The vacuum cleaner was serviced in house following an SOP.

- The Preventive Maintenance program was managed using a SOP with annexure which defined the annual plan for equipment and utilities.
- The frequency of servicing (Fortnightly, quarterly, annually).
- The SOP details the action to take; the summary sheets recorded the date and work done
- In all the cases reviewed, the SOP and service report for breakdown in service has to be matched.
- Breakdown in Service was managed with an SOP
- The PPM program and monthly records for particular year, for the water system, has to be prepared.
- Generally, the equipment was well maintained. A preventive maintenance program was in place and was followed. Preventive Maintenance performed was recorded in check lists.

Periodic revalidation of HVAC systems / UAF systems and HEPA filters were performed in accordance with protocol and the following tests were performed:

The relevant SOP provided that

Temperature	**Monthly Once**
DPHEPA	
DPRoom	
ACPH	
Smoke Test	

Noise	**Checked every 3 Months**
V-Belt	
Pulley / Motor	
Dust	
Coil	
Drain	
Electrical	
Leakage of panles	

The validation report of AHU should contain:

1. Air velocity,
2. Air changes,
3. Flow patterns,
4. Particle counts,
5. Microbial counts,
6. Pressure differentials
7. Recovery time validated.

- It demonstrated that ISO 8 (Class 100,000) conditions with a recovery time of 20 minutes were achieved at rest and in operation.
- AHU's recovery time was established during validation studies. Recovery time was 20 minutes.

Compressed Air:

- SOP of compressed Air Systems and reports.
- SOP for cleaning filters of air compressor, to clean filters only filtered air is used.
- Compressed Air Sampling Check-list.
- A separate room was provided for the air filter washing and cleaning. An adequate number of spare filters were stored in a separate room.
- Confirmation that the air compressors were oil-free (by looking at the engineering drawings), the quality of the compressed air as well as the certificate from the manufacturers of the air compressors.
- Confirmation that the air compressors were oil-free (by looking at the engineering drawings), the quality of the compressed air as well as the certificate from the manufacturers of the air compressors.
- Compressed air after receiving tank was transferred to the service floor and was passed through 25 µm, 1 µm and 0.01 µm filters.
- The quality of compressed air was tested at the point of use in the micronizing area. Condensate drains were cleaned by the compressed air every month during the preventive maintenance.
- Two new compressed air generation systems were located in the plant. Oil-free compressors were used and 0.01 µm filters were installed at the user points.

Compressed Air system validation:

- Compressed air validation was performed in accordance with validation protocol/report "Compressed air validation repot". Samples were collected during 7 days. Re-validation was performed once per year, all above mentioned tests were carried out.