Gowning is required in a sealed product processing area

Risk Management in Pharmaceutical HVAC Operations

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Introduction

Risk Management has become a topic of broad societal interest in view of the current economic turbulence, and is now an essential component of organizational planning. As a society, we are viewing risk not as something to be avoided, but something to be anticipated and managed by minimising the probability and severity of its adverse impact. Risk Management has become so much a part of organizational culture, that it has spawned a new perspective. This has happened in most spheres of pharmaceutical manufacturing too.

Quality Risk Management (QRM) may be treated as a part of the broader discipline of Risk Management. This process provides a rationale to understand risk and mitigate it via appropriate and robust controls.

Risks in Pharma Manufacturing

In pharmaceutical manufacturing, risk to the product and consequently to the patient has been most closely related to issues of cross-contamination and contamination. The former is related to oral solid dosage, and the latter to aseptic operations. The manufacturing environment and its support systems including HVAC contribute significantly to cross-contamination and contamination. Both are to be kept under a state of control all the time.

The *ISPE Baseline Guide* of International Society for Pharmaceutical Engineering mentions the level of risk to product quality based on scientific knowledge, which leads to patient protection. The level of effort in QRM should reflect the level of risk. Product and process information should relate to patient safety, and this information should be the basis of science and risk based decisions to ensure that the manufacturing systems

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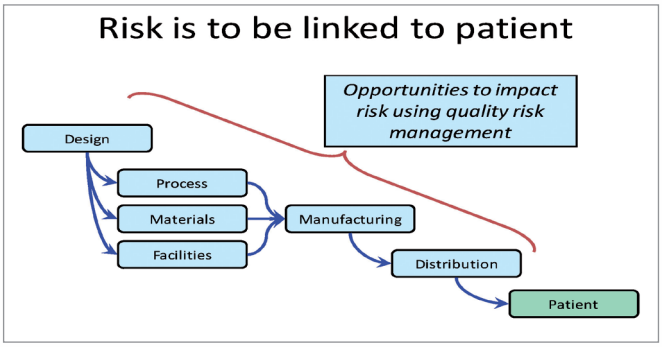

Figure 1: The patient risk chain

are designed and verified to meet the requirement. *Figure 1* shows the patient risk chain.

These considerations should include Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), process control strategy and prior production experience. As the process understanding increases, the risk to the patient can be controlled. *Figure 2* explains this idea.

Quality by Design (QbD) concept should be applied for a lifecycle approach. Continual improvement can happen as information is gained from operations. Constant review of energy optimization is quite routine. Improvement in HVAC based on such reviews should be encouraged, though current change management programs do not encourage this.

Some of these issues are discussed below.

Controlling Cross-contamination

It is well-known that multi-product sites in India are increasing in number, and items from these sites constitute a major part of pharma exports. These multi product sites may possess marketing authorization to produce 200 to 300 items without a distinction between Oral Solid Dosage (OSD) formulations that are "highly potent" (0.125 mg per tablet) or "not so potent" (500 mg per tablet). The HVAC system for production areas has to demonstrate that cross-contamination of any active substance is completely controlled and avoided. Besides working in dedicated manufacturing areas, these premises are designed as completely closed, are artificially

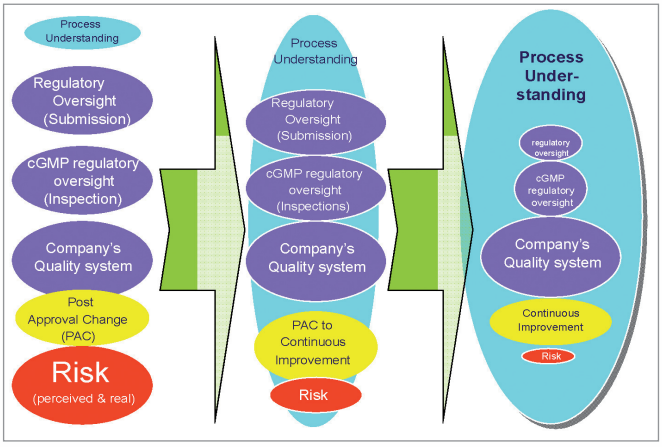

Figure 2: Increase in process understanding reduces risk

lighted, and ventilated through HVAC systems. Such systems are therefore to be inspected for ensuring that cross-contamination is avoided. These systems are tailor made and thus vary in type and content from site to site. The approach followed is therefore based on assessment of risk to the product, patient and operator. Based on my experience of inspections, a few points to demonstrate cross-contamination avoidance are mentioned below.

Not So Potent Products

- OSD facilities handling "not so potent" active substances do not require areas with assigned cleanliness classification.
- AHU filtration progression generally is: minimum 30%, followed by 85% pre-filtration and 95% final filtration.
- In exposed OSDs and dry bulk product areas, terminal HEPA filters with 95% pre-filters may be more practical. HEPA filtration may be considered to prevent cross-contamination and limit operator exposure in all recirculation systems.
- Non-recirculation systems do not require HEPA filtration for cross-contamination control.
- All return or exhaust air grills should be equipped with 30% "dust stop" filters.
- Recirculation systems may be applied in multi-product areas where solvents are not present.
- Recirculation of room air is not recommended when solvents are present. Recirculation of room air is not allowed when solvents may be present above 25% of the Lower Explosion Limit (LEL). Where solvents are occasional and in small volume, the return air duct should be equipped with hydrocarbon sensors to switch the system to 100% outside air in the event of a spill.
- Recirculation of return air from production areas to non production areas without treatment is not acceptable.
- Cleanliness of the open processing area should be maintained via control of air flow between the product handling area, or air lock and surrounding areas.
- Monitoring and alarming of the direction of air flow (through differential pressure or flow pattern) to surrounding rooms is strongly recommended, through Building Management System (BMS) or System Control and Data Acquisition (SCADA).
- Air flow pattern should be such that it flows from the operator's breathing zone and the room entrance toward the source of airborne dust.
- Recirculation of LEV (Local Exhaust Vent) within a production area with a dedicated AHU requires supply through HEPA filtration.
- Recirculation of LEV exhaust to the AHU is not acceptable.
- Filtration of LEV through HEPA filters, scrubbers or other equivalent treatment methods is required prior to release in the atmosphere.
- Dehumidification should be considered for low humidity room control of facilities with limited cooling capacity – say a room with 27°C temperature and 45-50% RH.

Potent Products

- Closed containment is the primary means of control for this class of material. If processes are proven closed, recirculated air should include HEPA filtration.
- LEV should be provided at points where containment is broken.
- Where LEV is used with any possibility of duct contamination, HEPA filters should be installed near the room before AHU.
- Audio and visual alert on loss of air flow containment should be transmitted to the controlled area.
- Room airlocks/ anterooms are recommended for powder handling areas to provide a barrier that maintains a positive air flow differential with respect to the corridor and the processing room (this may also serve as gowning area).
- Air flow into de-gowning area should be negative with respect to the corridor and processing to contain particles shed from clothing.
- As the items being handled are potent, a secondary control to prevent the spreading of active materials is unidirectional air flow within the room. The air grills should be positioned in such a way that supply air is directed to flow across the operator breathing zone before crossing any source of dust. Return points should be mounted on the far walls.
- It is strongly recommended that any air leaving the processing room boundary NOT be recirculated. Design the main air system for 100% exhaust and once through supply. However, if air recirculation within the room is required, HEPA filters should be installed in the supply and return (known as double HEPA filtration), and should be checked at least once in six months.
- These return/ exhaust HEPA filters should not be located within the room or where airborne powders are expected, should be easy-and-safe-change type with bag-in bag-out (BI/BO) housing and bubble tight dampers.
- Terminal HEPA filters are required for protection against backflow if product containment should fail during an AHU failure.

In order to avoid cross- contamination, independent AHUs for each area provide the answer. In this situation, the number of AHUs in any average size unit will be 20-25. Alternatively, compliance may be demonstrated by providing a few AHUs (5-6), maintaining proper pressure differentials and installing a BMS. Further, being a multi product facility, after verification that all the above points are taken care of, the manufacturer should maintain a use log of the room using the same set of equipments and handling different products. The auditors can look for the sequence in which the products are handled in that room, and verify that room conditions were met, premises and equipment were cleaned using a validated cleaning procedure and deviations did not take place.

The US FDA recently gave a citation to a unit in the USA owned by one of the pharma giants in India when they noticed from the room use log of the preceding one month that no procedures were in place to demonstrate avoidance of cross-contamination of one potent item with another. Though it had been noticed by Quality Assurance (QA) and reported, no measures were taken to correct the situation and production continued.

It may be worthwhile to add here that Indian regulation does not have any requirements for items of "immunosuppressant" (anti-retroviral) category, and they are processed without adequate segregation and precautions. This is treated as a critical observation by overseas inspectors.

Environment Monitoring

Another criterion of a safe product is that its manufacturing environment is under control, which may be demonstrated through a program. The purpose of an environmental control program is to keep the microbes out. This concept was enforced through Good Manufacturing Practices (GMPs) of EU and USFDA in early 2005, and is treated as current. It is expected by regulators that ingress of microbes would be controlled through "sealed product processing areas", maintaining pressure differentials, checking HEPA filter integrity at regular intervals, control of temperature and RH at all the times and provision of air locks for sealing product processing areas. Air-lock protocol should be such that one door is opened at a time. Secondary/ tertiary gowning is also required, materials under process have low count and product contact surfaces are sanitized through an established contact time of sanitizer in use. Premises maintenance program should be very good, otherwise microbes will settle in cracks, crevices, broken light fixtures and poorly sealed holes, etc. A double cleaning exercise in hours of crises (when a higher count is noticed) can be very effective. In brief, they should not be allowed to settle.

If, during the environment monitoring program, the count noticed is high, it is indicative of a problem in the production area and should not be treated as a sampling or sampler error. As no standard values of temperature and RH are specified anywhere in the text, these are to be decided for process and operator comfort requirements. The pressure differential between two different cleanliness grade areas should be at least 15 pascals. While gathering information, data on non-viable counts should not be ignored. Though this count does not have one to one relationship with microbes, if it jumps higher than the baseline particle level, an incident can be recorded. In short, the environment monitoring program should be designed to demonstrate, day after day, that predefined cleanroom conditions, as defined in the Standard Operating Procedure (SOP), are met.

Aseptic Manufacturing

In aseptic manufacturing a critical factor is the state of environment under which the product is being produced. This is both a regulatory and a practical concern. Unlike terminal sterilised products, aseptic manufacturing mandates that the various components be sterilized separately and then assembled in predefined aseptic conditions. Here micro-organisms are prevented from entering (aseptic) or are killed

continued on page 54

continued from page 52

in the container (terminally sterilized). Aseptic manufacturing is the most technically challenging method of producing sterile products.

Environment conditions are composed of viable and non-viable particulates as well as general cleanliness in manufacturing and storage areas. A significant lapse in any of these areas may render the product contaminated. As per US FDA guidelines, such product will be treated as adulterated and may have to be recalled from the market. No manufacturer would want to distribute a product that could potentially harm the user.

Environmental contaminants do not result in a uniform pattern of contamination, and the probability of environmental contaminants entering the product is extremely limited. In addition, the demonstrated presence of a viable particle in a particular environment does not automatically mean that the product is contaminated. It is to be understood that an aseptic environment is not a sterile environment. The food industry has coined the term "commercial sterility", which means that the material or area does not contain organism of a kind or number likely to cause harm under conditions of anticipated use.

In all such cases, the risk is to be assessed and mitigated. This approach uses scientific data and principles to assess the relative risk benefit value of specific control measures. For example, if a terminal HEPA filter gets damaged, this may permit contamination from the air supply (AHU) and duct to enter the room. The probability in this case will be low, risk impact will be high in non sterile area and low in sterile area (as the product is being handled in sterile atmosphere under laminar air flow), ability to detect will also be low (room environmental counts may increase) and the environment management person, if not trained adequately, may miss this. A risk reduction measure could be the installation of a primary HEPA filter.

Another situation could be low air flow due to increase in filter pressure drop. The probability here will be high as filters get dirty often; the impact will also be high as low air flow means low room pressure and reduced air changes. The ability to detect will be high as the differential pressure indicator will show it. Risk reduction here may be achieved by providing an air flow monitoring device at the AHU fan to compensate for air flow changes. In case alarms are used, an alarm may be placed here.

Conclusion

By implementing QRM principles as a lifecycle approach for evaluation, selection and routine running of HVAC, a good and safe environment for production of pharmaceuticals can be realized.

References

1. *WHO TRS 961* Annex – 5
2. *WHO TRS 957* Annex – (Sterile Preparations)
3. *WHO TRS 957* Annex – 3 (Hazardous Substances)
4. *WHO TRS 937* Annex – 2
5. *ISPE Good Practice Guide*
6. *Pharmatimes Journal*