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A Contamination Control Strategy Gone Wrong

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ABSTRACT

Warning letters and regulatory inspection observation reports (e.g., FDA 483) often provide useful information for assessing risks in your facility and preparing for upcoming inspections. Starting with the updates to the European Union's Annex 1 for the Manufacture of Sterile Drugs there has been an increased focus on contamination control strategies in facilities. A contamination control strategy is an integral part of pharmaceutical manufacturing, whether sterile or non-sterile. For this article we are going to look at a series of observations for a vaccine production facility and how we might learn from these observations. Highlighted are some of the contamination control issues. The FDA 483 Report was published in redacted form. (FDA, 2021)

Deviation for Potential Cross Contamination Was Not Adequately Conducted

When conducting investigations at facilities, we often make many assumptions that are not documented or that are not adequately investigated. Some examples of the types of comments made are:

- Failure to consider the operator who weighed and dispensed raw materials for the batch record implicated in the cross-contaminated batch.
- Operator who entered both manufacturing areas where the affected batches in the cross-contamination were manufactured.
- Under video surveillance, the operator was observed wearing protective gowning and foot protection in the controlled not classified room, before entering into the hallway outside [REDACTED].
- The deviation did not include consideration of the potential impact of the continued use of [REDACTED] to store raw material for the manufacture of [PRODUCT NAME] viral vaccine drug substance. These were identified in the deviation as not being designed to allow for proper decontamination.
- It is not known how long the client [REDACTED] virus will remain viable on a surface. There was no additional cleaning other than routine cleaning in response to the deviation.
- There is no assurance that other batches have not been subject to cross-contamination.

Looking at this deviation, the regulatory inspection is looking for much more detail than the typical, general comments, on operator performance and behavior. Furthermore, many activities that are routinely performed in pharmaceutical/vaccine manufacture may not have been adequately documented, e.g., all additional cleaning. We also need to consider adding routine review of camera systems if they are present.

A Leak was Observed, Recipe Aborted, and a New Recipe Started

The problem associated with this observation was that no allowances were present in the procedure that provided for aborting a recipe nor was this procedure in the Master Batch Record. The investigation was insufficient as it did not describe how the operators were trained to perform this procedure, nor to investigate the product impact on the filling process.

This deviation is troubling because we do not always know in advance what we need to so. Perhaps, we need to clearly define how to handle unplanned deviations/issues. This could be put into the procedure in a larger picture, e.g., immediately notify Quality Assurance, keep track of all the instructions in what to do, oversight or training to perform the procedures, and so forth. It would be difficult to have advance knowledge of every type of deviation and remediation that could occur.

LOGBOOK ENTRIES

There were logbook entries that something was fixed and repaired at a specific time in the batch production. However, no investigation was generated to identify the impact on the product being manufactured at the same time as the logbook entries. No corrective actions taken were documented.

For a deviation of this type, it is critical to understand across the manufacturing facility, that when you make changes, corrective actions, repairs and the like it should always result in a deviation to study the impact of the change on the product being produced. One cannot just assume that a repair has no effect on the production. You need to be able to document your thought process and rationale for the changes and how you decided that there was no impact. Most often, when called in as a consultant to resolve long-term issues, one finds that it was something that was discredited by the reviewers very early in the investigation process. Be sure you know why potential causes are being discredited. If you can't find a root cause, go back and re-evaluate those items eliminated early in the process. It is also important to ensure that you may the decision to discredit a root cause based upon good science. Often one hears commentary about something that can or cannot happen that is not what the literature says is true. For example, assuming that there is no biofilm present in a line because a chemical treatment was performed, without other testing and evaluation.

The Manufacturing Site Was Not Maintained in a Clean and Sanitary Condition

Some examples that were provided in the Inspection report included information like the following:

- Waste generated during the manufacture of the product was not decontaminated using a validated/qualified method.
- Manufacturing rooms and hallways were not cleaned with [REDACTED]
- Peeling paint was observed over several days. These rough surfaces make it difficult or impossible to adequately clean and disinfect the affected areas.
- Paint was observed peeling on walls and paint peels were found on the floors and in the hallways.
- In addition to paint peelings, there was evidence of brown and black residues.

In the present environment, there is no excuse for not have validated or qualified methods for decontamination of all items taken into or out of clean rooms. Understanding the risks associated biological materials generated as waste is critical in the design and implementation of quality systems for contamination control. Many vaccine manufacturers work with viruses that have significant health risks to the personnel working with the viruses. As such, strict controls and procedures should be established for how wastes are handled and ensuring that appropriate decontamination occurs. Even when waste control services are used, one can be fined for failure to ensure that the waste is handled properly and does not produce a risk to the associated workers.

Many warning letters in the last five years were related to failure to properly maintain facilities. Today, it is critical to have a system to ensure that the facilities are maintained and kept in good condition. In some cases, rust or damage was treated as mold contamination, others highlighted issues with particulate matter, and so forth. These are easy observations to prevent. Part of the daily routine of both workers and management should be to look at the facility and identify whether something needs to be fixed or repaired. When you see something, do something applies in pharmaceutical companies also!

The Building Used to Manufacture Product was not of Suitable Size, Design, and Location

Some examples of FDA concerns included the following:

- Inadequate number of decontamination [REDACTED] used to decontaminated waste to ensure that the waste is decontaminated in a timely fashion.
- The Inadequacy of waste management was further underscored by a planned deviation to change the path for wastewater in the facility and the ways the waste samples are decontaminated.

- Reviewing security camera data, the hallways were shown to be overcrowded with materials to be staged into other manufacturing areas and QC sampling.
- The doorways are too small for personnel using a pallet jack to get through the door. As such, personnel had to push and pull the material through several areas to get into the warehouse.

It is important to really evaluate whether sufficient room is provided to carry out assigned tasks. In many cases, employees complain about how spaces are not adequate, and a standard management response is something like, “we can’t do anything about it.” As management, we need to look at these concerns. Perhaps we need to evaluate continuous improvement changes to either change how we do the task, change the task itself, or change the facility to accommodate the task. We need to be proactive and make things better!

This observation is also an example of how one issue can trigger numerous observations. When waste decontamination was an observed observation, this triggered more review on other areas for the same kind of concerns in other areas.

Written Procedures for Preventing Cross-Contamination are not Followed

Some examples of what triggered this regulatory observation include the following:

- Security camera footage was observed and showed that employees were not handling the special medical waste was not followed for non-disinfected medical and non-decontaminated special medical waste.
- Employees were seen throwing unsealed bags of medical waste onto a service elevator for warehouse.
- Employees were observed carrying unsealed medical waste through the hallways. The unsealed containers made contact with containers of staged materials, walls, and fence barriers in the [REDACTED] corridor of the warehouse.
- Employees were observed removing their outer protective garments on the floor where raw materials were staged for manufacturing….

It is important to note increased focus on looking at security camera data and taking the time to evaluate what actually happened during the production process. Granted, this type of review may take hours, but the trend in regulatory observations, is that it is an expected activity. We need to conduct thorough investigations and really evaluate potential root causes. Problem solving tools like those used in many quality and engineering organizations, can aid in improving how we perform investigations. The usefulness improves when we use structured approaches to problem-solving.

In previous articles we have discussed that inadequate investigations and following SOPs have been among the highest causes of warning letters in companies. It is sad that companies are not taking to heart that we need to change what we are doing and critically evaluate compliance activities and investigations. This is one of the areas where we have great potential to reduce the risk of FDA 483s and Warning Letters.

CONCLUSION

Whether you are an auditor, or someone being audited, we need to continually improve what we do and why we do it. The regulatory observations discussed here also highlight the need for real training, i.e., training that results in employees doing things the right way every time. Supervisors and managers should be reviewing compliance to SOPs every time they walk through the area. We need to hold personnel accountable for following the rules. Failure to take on this type of mindset will continue to result in supply chain delays and failures to provide the necessary medicines in a timely fashion.

Quality is not just a word. It should be how we do our work!

LITERATURE CITED

1. FDA (2021) FDA-483 Inspection Report. Department of Health and Human Services. Food and Drug Administration. Downloaded from:https://www.fda.gov/media/147762/download on September 24, 2021.
