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Investigations For Production Areas


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Audit Forum

Audit Forum provides readers an opportunity to discuss information, experiences, and practices within the broad topic scope of audits. Discussion topics may include external and internal audits, best practices, problem situations, and other areas of concern. Traditional audit activities as well as virtual audit topics may be discussed.

Audits are a part of daily life in pharma, med devices, and other regulated industries. Audits used to be relatively limited and generally routine in performance. In the “old” days, audits were conducted face-to-face at the manufacturing site. Some audits began with facility tours and emphasized review of documented procedures; others were more process oriented as opposed to document reviews. Interactions were direct – without PPE masks. Since then, we have evolved to virtual audits with Zoom technology with auditors and company personnel offsite. Manufacturing facilities provide video technology for facility tours. Audits now require new and different considerations, skill sets, training, and preparation; more changes are a certainty.

Topics previously addressed in Audit Forum include the following:

1. Invitation to Participate. JGXP, V25, #3, May 2021
2. Lessons From Previous FDA Observations – Drugs. V25, #4, July 2021
3. A Control Strategy Gone Wrong. JGXP, V25, #3, Sept 2021
4. Audit Trails. JGXP V25, #6, Nov 2021

Journal submissions for publication in the Journal of Validation Technology and Journal of GXP Compliance are most welcome. Blog discussions posted on the IVT Network are more informal and are also very welcome. IVT “Voices in Validation” podcasts provide visual and verbal discussion by individuals and groups. This Forum will succeed by contributions from the Quality and Compliance community. Please respond in the comments section below with ideas, suggestions, or topics for discussion.

ABSTRACT

Many deviations and investigations occur due to issues in the production system in pharmaceutical facilities, e.g., presence of particulate matter in product, equipment malfunctions, failure to meet operational parameters, failure to meet control parameters, and the like. According to European Compliance Academy (ECA, 2019), there were 21 Warning Letters issued relative to issues with review of Production Batch Records. Depending upon your point of view, these may be either production issues or quality issues, or both. This paper describes considerations for conducting investigations relative to deviations that occur in the production system, although deviations may have been issued to the laboratory, utility, or quality system (Moldenhauer, 2020).

Examples of Deviations in The Production System

Some examples of deviations that can occur in or related to production systems are:

- Filling machine fill volumes out of specification
- Glass breakage at unacceptable levels in glass washer
- Presence of brown-black particulate matter in product
- Water present in vials after depyrogenation in a tunnel
- Pump failure in a sterilizer or a filling machine
- Exceptionally high reject or scraps rates from a piece of equipment
- Sterilization control parameters not met
- Sterilization or depyrogenation temperatures not within established limits
- Use of the wrong sterilization or depyrogenation cycle.
- Control panel printer fails to print
- Non-sterilized product found in sterile product hold area
- Failure to meet rotation requirements in blenders or compounding equipment

CONDUCTING A STRONG INVESTIGATION

Deviations can often happen in production facilities. Unfortunately, when working in regulated industries, it is important to minimize the severity and frequency of unexpected events. There are also occurrences that are**not** outside of established parameters but are unusual from what is typically seen. Unexpected results or conditions can also trigger deviations. When these types of events occur, it is important to investigate to aid in the understanding of what was the root cause of the event. After determining the root cause (or most probable root cause), appropriate corrective and preventative actions (CAPAs) should be developed. In addition, the investigation and CAPAs should have a system established to ensure that the effectiveness of the CAPAs is assessed. Once the CAPA is deemed effective, the investigation can be closed.
Miller (2013) developed a three-step system for investigating deviations. This is an overview of the system described by Miller.

1. **Obtaining All The Initial Information**
   The very first step of the investigation is determining the total scope of the event. One must understand what occurred, when it occurred, who was involved, the identification of the product, components, equipment (par numbers and lot numbers) involved, and what was occurring when the event occurred. One must also identify the SOPs that are used/followed during this process, and whether any corrections or actions were taken immediately. Determine and document whether any product was segregated or discarded as part of the event. Include information on any testing performed immediately. An initial impact assessment should be conducted regarding the event to assess the potential impact to product. All this information provides the background or basis for the investigation to be conducted. Many find it useful to develop a checklist of the initial information needed. The checklist can then be used to document the information following the checklist. The following is an example of the kinds of information that could be included in the checklist. (Miller, 2013)

	Deviation Investigation Checklist
1.	Create a listing (form or checklist) to describe the details assc should either be generated as a timeline, or a timeline should
2.	Description of the procedure used by quality to identify and se should include documentation that shows that these procedur
3.	Identification of the personnel interviewed regarding the devia
4.	Description of samples taken for testing, the type of testing re available).
5.	Listing of the applicable SOPs and product/material specificat
6.	Identification of the equipment maintenance records and copi associated usage and/or equipment logbooks.
7.	Copies of the associated batch records and associated docur segregation records.

8.	Validation and requalification information for the product, proc the deviation event.

Table 1: Example of a Deviation Investigation Checklist, obtaining the initial information
(adapted from Miller, 2013 and Moldenhauer, 2020)

1. **Interviewing All Affected (Necessary) Personnel**
   Interviewing the affected personnel is useful in understanding exactly what happened. They can describe what they saw and did. Sometimes, an individual may not write down every detail that occurred, but when talking it will be described. More often than not, few details are included in deviation write ups. This may be due to a rush to complete the paperwork, lack of time, or other reasons. In most cases, reviewers of these documents have questions that were not answered in the writeup. As such, the interviews can be critical to the success of the investigation. Additionally, it can aid in the development of relationships between co-workers and management. This type of discourse is also useful, as questions can be asked when they come up during the discussion. It is also useful to gain information on potential causes and CAPAs from those individuals that work with a process all the time. Many times, this step is considered one of the most valuable in the investigation process. (Miller, 2013 and Moldenhauer, 2020)
2. **Reading and Understanding the Applicable Standard Operating Procedures** (SOPs).
   To really understand a deviation and how to assess the root causes and the appropriate CAPAs, it is useful to carefully read and understand the affected SOPs associated with the deviation. Part of this information will aid in the understanding of the process being conducted. Often companies with poor quality systems, rush to blame the personnel rather than finding the appropriate root cause of the event. This is a convenient response, as the so-called CAPA is retraining the employee. A good investigation understands what should have happened as well as what did happen. The inherent problem is responding to the need to retrain employees. When this is a frequent CAPA response, one should consider the need to reassess or restructure the training process. (Miller, 2013 and Moldenhauer, 2020)

Commonalities to All Production Related Investigations

Investigating a production-related deviation requires**detailed information** on exactly what went wrong, when it happened, why you think it happened, who was working on it when it happened, what corrective actions you took immediately, whether product was segregated or discarded, and identification of all the pertinent information on the equipment, process, product, materials, and testing used. It is always important to**get feedback** from the operators in the area when the deviation occurred and immediately preceding the deviation occurring. It is common to think of this process as if you are a reporter, ask questions like Who? What? When? Where? How?

It is important to thoroughly understand the normal production process used. One should question whether this type of deviation could occur on all similar equipment, e.g., across all filling machines, or across all moist heat sterilizers. Be sure that you document the rationale of why you assumed this to be a global issue versus a localized issue, or vice-versa. You also need to look to see if the parameters related to the deviation are evaluated in the validation process. If so, how is this data different from the previous validation?

Understanding the process may require that you work with the process development group to assess what impact this deviation may have on the product being produced. Often, new personnel may not understand all the potential impacts on the process. Training of personnel and familiarity with the products manufactured is critical for those who are responding to deviations and conducting the investigations.

For production deviations, it is always useful to utilize a subject matter expert (SME) as part of the investigation team. The SMEs typically have a better understanding of critical aspects of the process. It is also useful to include engineering personnel in the assessment of the equipment's performance and required operational parameters. When your facility does not have a SME for the assigned topic, consultants can be used to fulfill this need.

Completed and outstanding work orders and change requests for the equipment used in the production of material with the deviation should always be reviewed. It is not sufficient to just review what orders are outstanding or performed, but one must also consider why the changes or work was requested and could this work cause the deviation or contribute to why you have a deviation to review.

It is useful to do a complete inspection of any production equipment utilized in the process being investigated. A cross-functional team is useful in this process. Some companies choose to go through Installation Qualification (IQ) checklists to see if the equipment is still “as installed.” Depending upon the type of equipment, it may be useful to run an engineering run to verify that the equipment is operating as intended, e.g., a temperature distribution study may be useful for a controlled temperature piece of equipment, a sterilizer, or an oven.

In evaluating the specific deviation, it is useful to look at the whole process, i.e., how the material flow, production process, and personnel flow work together. The affected utilities in the area should also be considered for their potential impact on the process.

Calibration of equipment can play a key role in equipment performance. It is useful to review the most recent calibration documents to see whether calibration was needed, was performed, and whether issues occurred during the calibration. Check to verify if the calibration was conducted with standards calibrated to national standards organizations.

Commonalities to Non-Sterile Processes

For non-sterile processes, many of the deviations are related to a specific piece of equipment malfunctioning or operating outside of its specified control parameters. This type of deviation is addressed in the same way across all types of processes.

A common type of deviation in non-sterile processes is the presence of particulate matter. This can occur in processes that have dedicated equipment as well as ones without dedicated equipment. We tend to think that validated cleaning processes are not needed for dedicated equipment. While that may be true from a regulatory perspective, one needs to be sure there is no long-term build-up of either product residuals or other materials within the equipment. Another typical cause of particulate in non-sterile processes is damage to inside of equipment, e.g., compounding and blending equipment. It is important to examine the inside of the equipment physically and visually. It is useful to use a camera system to visually inspect the inside, as you can enlarge the vision area or get a closer view.

For non-dedicated equipment, the same types of examinations are performed on the equipment, but it is also supplemented by reviewing and assessing the appropriate product specific cleaning validation studies. In some cases, using non-specific tests like total organic carbon (TOC), may not provide sufficient data to assess for all types of residues and biofilms. (Moldenhauer, 2020) It is also useful to use camera systems to evaluate the condition of the internal piping.

Piping and tubing between different pieces of equipment may also contribute particulate matter. One should also carefully examine the gaskets and connections between different pieces of equipment. Many gasket materials can break down over time and exposure to various cleaning and sanitizing agents. (Moldenhauer, 2020)

Presence of black and brown particulate frequently leads regulatory investigators to think there might be fungal contamination in these areas. Taking preventative actions to ensure that the gaskets and connections are maintained in good condition can prevent possible contamination of the product. (Moldenhauer, 2020) Today, there are many antifungal products that can be used to remediate or prevent these types of occurrences.

Another source of contamination in non-sterile areas is the environment around the process. Look for places where the equipment is open to the environment. This can be a source of contamination if appropriate precautions are not taken.

It is also useful to look at places where wipes or cloths are used in the process. Some particulates can be generated from shedding of these types of materials, as well as from paper products like packaging. Often these types of materials leave fibers or other whitish types of particulates.

Commonalities to Terminally Sterilized Processes

There are a variety of types of deviations that can happen for terminally sterilized processes. It is important to recognize if “aseptic processing” is in your submissions for terminally sterilized products. If so, the steps prior to terminal sterilization should be investigated as an aseptic process. This is due to the regulatory expectation for aseptic processing. Additionally, one should review whether the “aseptic” portion of the process is used for some products that are only submitted to aseptic processing. If so, one must assess the impact of the deviation on those types of products also. For example, if you have an aseptic process followed by moist heat sterilization, presence of a low level of bioburden in the aseptic section of the process may not be as significant because the moist heat sterilization cycle would likely kill this level and type of contamination. Alternatively, if some products on this line are only subjected to the aseptic process, this may require a more stringent investigation and require performance of media fills to provide data on whether the contamination would be present in the finished aseptically processed products. If you have a regulatory submission that “requires” aseptic processing prior to terminal sterilization, then the process steps must**meet** the requirements for aseptic processing. When in doubt, you should consult the regulatory department to review the submission requirements.

Moist Heat Sterilization. There are many different types of deviations that can occur in moist heat sterilization processes. Additionally, there are variations in the type of moist heat sterilization cycles. The PDA has issued several technical reports on moist heat sterilization. In these reports there are examples of different types of deviations and issues associated with these types of deviations. Since many regulators use PDA Technical Reports, it is useful to know the recommendations for the deviations in these reports. Furthermore, if you don't follow the stated recommendations, you should have or know a justification for the methodology/ resolution you used instead of the recommendations in the technical reports. (Moldenhauer, 2020)
An abbreviated list of deviations is provided with some guidance for these deviations.

- **Chambers heat up time outside of established limit.**This time period may either be too short or too long. A key consideration for this parameter is the temperature of the product being sterilized at exposure start. This is important, as this product temperature will affect the total heat delivered to the product during exposure. A shorter heat up time may result in non-sterile product, or product that does not have the desired sterility assurance level. A longer time period could be due to equipment malfunction. Again, the temperature at exposure start affects the product temperature at exposure start, which in turn affects the lethality to the product. Too much heat may provide a lethality that exceeds the limits for which stability data exists. This may necessitate a sublot being placed upon stability evaluation.
- **Exposure time too short or too long.**Exposure time too short is an issue if it is less than the validated exposure time. It can result in insufficient sterility assurance levels being achieved. Exposure time too long is not a sterility assurance issue but is rather an issue on product stability. Too much heat may provide a lethality that exceeds the limits for which stability data exists. This may necessitate a sublot being placed upon stability evaluation.
- **Cooling time too short or too long.**A shorter than validated cooling time can be a safety issue to individuals handling the product post sterilization. If the cooling time is too long, the product remains hot longer than intended. This can result in additional lethality in the product. Too much heat may provide a lethality that exceeds the limits for which stability data exists. This may necessitate a sublot being placed upon stability evaluation.
- **Fan not operating or fan speed out of limits, or Water Spray not operating or parameters out of limits.**Both the fan and water spray are used in different types of moist heat sterilization cycles to provide a uniform distribution of temperature (heat) inside the sterilizer chamber. If either is not working or not working correctly, this can result in hot and cold spots within the sterilizer. Depending upon whether it is a hot or cold spot, the product may not achieve the desired sterility assurance levels or may have experienced too much lethality and may be a stability issue.
- **Incorrect sterilization cycle used for the load.**This type of deviation cannot be accepted unless the cycle used is subsequently validated and meets the intended requirements. Note: This should be reviewed with the regulatory department as depending upon how it was submitted in the regulatory approval, you may not be able to change the cycle parameters without a submission to the appropriate regulatory agency.
- **Wrong loading pattern used for the sterilization cycle.**This type of deviation cannot be accepted unless the cycle used is subsequently validated and meets the intended requirements. Note: This should be reviewed with the regulatory department as depending upon how it was submitted in the regulatory approval, you may not be able to change the cycle parameters without a submission to the appropriate regulatory agency.

Dry Heat Sterilization. Some of the types of deviations common to dry heat sterilization include:

- Out of exposure time limits, too short or too long (batch processes)
- Belt speed out of limits, too fast or too slow (continuous processes)
- Exposure temperature out of limits, too short or too long
- Wrong loading pattern (batch processes)

Deviations for exposure time (too short or too long) for batch processes and belt speed out of limits (too fast or too slow) are both deviations in exposure time. Failure to have the minimum required exposure time can result in a batch of product that does not meet the requirements for sterility assurance of the product. A key component of this investigation is verification that the cycle is or is not within the validated sterilization parameters. If it is too short, it may be necessary to run validation studies at the conditions used in the cycle with the deviation to assess whether the appropriate level of sterility assurance is achieved in the cycle. However, even validation of the cycle after the fact may not be sufficient for batch release depending upon how the cycle parameters are included in the regulatory submission. (Moldenhauer, 2020)

If the exposure time is too long, this is typically an issue of stability. If this exposure time is not within the times currently on stability, it may be necessary to sublot the material and place the sublot on stability evaluation. It is important again to check with the regulatory submission to see how the parameters are specified in the submission. If a maximum exposure time is specified, you may not be able to accept the batch even with supporting stability data unless you submit a change to the submission.

Use of the wrong loading pattern, may require validation of the loading pattern, if the loading pattern used is not within the minimum and maximum loading patterns qualified.

Radiation Sterilization. There are at least two types of radiation sterilization processes common to pharmaceuticals, gamma sterilization and E-beam sterilization. The majority, if not all, gamma sterilization is conducted at contract sterilization facilities. E-beam sterilizers can be at contract sterilization facilities or be installed at the manufacturer's site.

Contract sterilization facilities are commonly used. There are ISO documents and AAMI documents that govern the methods to use to develop, validate and implement radiation sterilization methods. In many cases, the contract facility has designed and performed the qualification of the sterilization method. Within gamma sterilization, there are different sterilization models available. It is important to understand the sterilization model used as there are different levels of risk dependent upon whether an "overkill" type of approach is used or a "bioburden based" approach is used. Understanding this level of risk aids in determining the disposition of the product when a deviation occurs. (Moldenhauer, 2020)

Gas Sterilization. There are several different sterilization media that may be used as part of gas sterilization. The most used gases in pharmaceutical processes include ethylene oxide (EtO), chlorine dioxide, nitrogen dioxide, and ozone gas. In recent years, there have been papers advocating the use of xenon gas, predominantly for decontamination of areas.

Each different gas must be investigated for material compatibility. There are materials which are not compatible with the various gas types. If functional or physical defects are found, they must be assessed for the possibility of incompatible materials.

Another concern with gas sterilization is whether the sterilant can penetrate to all areas of the product. Recently, a company planned to use EtO sterilization for glass vials. However, the penetration ability of EtO does not allow for sterilization of the solution within a glass vial. In fact, each of the gas types provided in this section have different levels of penetration. Additionally, they have differences in efficiency based upon the sterilization temperatures, humidity, and pressures. Changing from one gas type to another must carefully consider the limitations of each type of sterilant. The material compatibility, loading and density of the product should also be considered. When reviewing deviations, it is important to assess the limitations of each type of gas as unique for that type of gas only, unless there are specific references to say it is applicable to other gas types.

Considering resterilization to address a deviation should be based upon having significant data to show that the item being sterilized can withstand the additional sterilization cycle from a material compatibility, sterilant residuals, physical and functional viewpoint. Stability data should also be available to support the resterilization process.

Deviations in packaging materials, loading, product density, temperature, humidity (humidification), and placement of biological indicators should be carefully checked against the validation parameters to assess whether validation must be conducted.

For some gases like ethylene oxide, deviations in the aeration time could cause a significant risk to employee safety. For these types of deviations, it is important to gain input from health and safety officers.

Commonalities to Aseptic Processes

Aseptic processes are carefully scrutinized by regulatory investigators. One reason for this is that it is easy for a contaminated container to be assessed as negative, when it is actually contaminated. Additionally, the sensitivity of the sterility testing in the compendia is not able to detect single cell contaminants.

When investigating contamination in an aseptic process, it is important to look back to the last successful media fill conducted on that product line. When all products are qualified individually via media fills, one must look at the product in question as well as the most recent media fill of any product on the same line. Unfortunately, it is important to be able to justify why any of the product since the acceptable media fill is not at risk of contamination. In many cases, heroics are involved in resolving aseptic processes with a deviation. Every different step of the production process and supporting processes need to be investigated, e.g., review of environmental monitoring, sampling procedures, material transfer, the preparation and sterilization of the materials and components, transfer processes and the like. As such, these investigations are typically very complicated. Many companies choose to use outside consultants to review these types of investigations and to provide and expert opinion on the adequacy and accuracy of the investigation.

ASSESSING OTHER AFFECTED PRODUCTS

Deviations with production and utility systems can be difficult to resolve when it comes to assessing other affected products. For example, when starting an investigation with a tube and cap issue, initially one would have to assess whether the deviation affects all tubes and caps. After some level of investigation, it may be determined it only happens with specific sizes of tubes and caps. Further investigation may show that the problem is related to a specific cap size. The final assessment of the investigation may show that the deviation is a result of a torquing device for one specific cap size. As such, the “other affected products” may change at various steps of the investigation.

Quite often during a regulatory investigation, a common question is how you identified what should or should not be affected. It is very important to document this decision-making process either in the deviation report or in a white paper supporting the deviation. It can be useful to discuss this assessment with a multi-functional team.

ESTABLISHING CORRECTIVE AND PREVENTATIVE ACTIONS

One should be sure to incorporate effectiveness checks to verify that the actions taken actually “fixed” the cause of the deviation. Failure to follow up is likely to result in more deviations occurring.

CONCLUSION

Deviations in the production and/or utility systems often cause concerns for internal and external auditors and regulatory investigators. Common issues are associated with how one determined the other affected products or failure to adequately determine other affected products. Most often this is tied to a failure to properly document how and why you determined that product was affected or excluded. Another common issue is whether resolution of the deviation addressed the impact of the deviation upon the validated status of the equipment, for example in an aseptic process, one might question why a media fill study was not conducted to show that the process is still operating in a state of compliance. Another common concern is the impact of the deviation of the stability of the product. Questions often asked relative to this issue include – do you have data to show that this type of deviation will not or does not affect product stability. A simple way to address this is to consider placing a sub-lot of a batch of product with a deviation on stability evaluation.

There are additional concerns when an API or finished product is contract manufactured for a different company. This could lead to questions on how the owner of the product (for whom it was contract manufactured) was notified of the deviation and whether it affects the stability or product claims of the material.

Failure to thoroughly investigate deviations for the production and utility systems can result in adverse findings (FDA-483s) or warning letter observations in multiple areas all for the same one problem. For example, a failure to evaluate a production deviation for its impact on the equipment validation and stability of the product could result in observations for the production system, the quality system not carefully reviewing and approving the deviation (i.e., they did not evaluate these impacts), and the laboratory system for not having stability data to support the deviation.

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