Strategies for Managing Environmental Monitoring Investigations

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The discussion below includes strategies for managing EM investigations. Although not intended to be all-inclusive, these strategies provide a means by which a cGMP firm may implement or improve an EM program that will allow effective minimization and assessment of risk to the manufacturing environment, process, and product. Although the discussion's scope is mainly applicable to aseptic manufacturing processes, much of what is presented may be implemented by firms that manufacture non-sterile products (e.g., API's, solid dosage, etc.). The discussion includes:

- Elements of an investigation plan
- Key investigation points
- Root cause analysis
- Corrective/preventive action (CAPA) and assessing effectiveness
- Assessing facility and product impact

Much of the discussion of key investigation points includes specific areas of investigation pertaining to individual functional groups. Root cause analysis, CAPA, and impact assessment include high-level discussions leading to the investigation conclusion.

Elements of an Investigation Plan

The list below includes general elements, or areas, that comprise an investigation plan. Since the depth and scope of an investigation will be dependent upon the type of excursion (Alert Level or Action Level), not all of these elements may be included in the plan. In addition, not all elements are applicable to each functional group within a firm's organization.

- Data trend analysis
- Equipment
- Media
- Microbial Identification
- Training
- Facilities
- Cleaning/Sanitization
- Area Activity
- Personnel

Key Investigation Points

Key investigation points will depend upon whether the excursion is an Alert Level or Action Level excursion, or associated with an identified Adverse Trend. The FDA's guidance, "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice," provides definitions for Alert and Action Levels:

- Alert Level: An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are always lower than Action Levels.
- Action Level: An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective/preventive action based on the investigation.

Although the guidance does not provide a definition of "Adverse Trend," it does state the following: "Environmental monitoring methods do not always recover microorganisms present in the sampled area. In particular, low-level contamination can be particularly difficult to detect. Because false negatives can occur, consecutive growth results are only one type of adverse trend. Increased incidence of contamination over a given period is an equal or more significant trend to be tracked." Therefore, a firm's own EM program must define what constitutes an Adverse Trend. The author proposes the following definition: Results of environmental monitoring that may indicate a potential problem with the environmental control systems in place. It should also be noted that it is a regulatory expectation that an Adverse Trend be investigated to the same level of scrutiny as an Action Level excursion. The following are examples of data trends that may constitute an Adverse Trend. These may differ depending upon how conservatively a firm approaches trend analyses.

- Two or more excursions for a given sample type (e.g., viable air) in an area or room on the same day;
- Two or more consecutive excursions for a given sample type in an area or room from any sample site on different days;
- Three or more excursions for a given sample type in an area or room during a defined period (e.g., one month).

For most firms, an excursion may be quantitative (i.e., Alert or Action Level) or qualitative (e.g., objectionable organism). For the latter, the EM program should include a list of organisms considered

"objectionable," within the context of the type of manufacturing process(es) and potential impact of these organisms. Typically, these include spore-forming and/or endotoxin-producing organisms.

Since, by definition, Alert Level excursions are an "early warning of potential drift from normal operating conditions," key investigation points are narrower in scope than those for Action Level excursions. Quality Control (QC) should address the key investigation points below.

- How many individuals were in the area or room at the time of sampling?
- Were there any non-routine activities prior to or at the time of sampling?
- Based upon microbial identification of the isolate(s), what is/are the potential sources (e.g., human, water-borne, etc.) of the organism(s)?
- Is there an unacceptable increase in the excursion rate (e.g., percentage) from the previous quarter to the current quarter? For example, a reasonable cut-off may be a greater than five percent increase. This may indicate that environmental controls are drifting from normal operating conditions.
- Is there an Adverse Trend?

Investigation of Action Level excursions requires a cross-functional Team to provide information relating to the elements of the investigation plan. Typically, the Team is comprised of such functional groups as QC, Manufacturing, Engineering, Validation, and Quality Assurance (QA).

The Team should meet on a routine basis (e.g., weekly) to discuss the status of investigations, and minutes of these meetings should be recorded. Investigations of Action Level excursions should be complete within the regulatory expectation of 30 (calendar) days. For excursions in general, data for the area and its adjacencies should be reviewed, including data below the Alert Level, to determine if low-level contamination is prevalent beyond the site in question. Particular attention should be focused on critical processing areas and personnel monitoring results.

QC provides essential information to support the accuracy and validity of the Action Level excursion result. Below are summarized questions that the investigation should ask, in addition to those covered by investigation of an Alert Limit excursion. Much of this information can be obtained during an analyst interview. Implementation of an "event log" for recording atypical activities as part of the EM program is extremely useful, as this can eliminate having to rely on analysts' memories.

- Was the analyst's training current at the time of sampling?
- Were sampling procedures correctly followed?
- Were there any deviations in the performance of the equipment or materials used?
- Were there any atypical activities in the room or area at the time of sampling?
- Has the analyst obtained out-of-limit results for this or any other EM during a defined period prior to the excursion date? Although this is not in itself cause for invalidating the result, excursions that are consistently associated with a single analyst should prompt an evaluation of his/her training.

Information relating to the suitability of the medium includes:

- Was the medium brought to room temperature prior to use?
- Was the medium properly stored before use?
- Was the medium capable of recovering a low-level microbial challenge, and was its sterility or absence of contamination confirmed? Firms should have a robust system of receiving and qualifying media, by which these properties are challenged (e.g., growth promotion testing).
- Did the medium vendor notify of any manufacturing or formulation changes? A strong quality agreement with media vendors, including well-defined requirements for reporting changes, will help ensure timely notification of changes that might impact a firm's EM program.
- Were there issues with the medium's integrity before use, such as cracked plates, torn bags, loose bottle or tube caps, etc? The analyst may have noticed this for a different set of medium from the same lot (even if used on a different sample date), but the information is still relevant.

A review of QC equipment used at the time of sampling should be performed.

- Was the equipment within its defined calibration interval? Sampling procedures typically include a requirement that analysts verify calibration of an instrument before using it.
- Was the equipment properly maintained prior to the sample date? A review of equipment maintenance records should provide this information.
- Was the equipment set at the correct parameters (e.g., total volume of air sampled) at the time of sampling?
- Are result calculations accurate? Raw data associated with viable air sampling typically requires manual calculations to determine the number of colony-forming units (cfu) per unit volume of air.

A firm's Manufacturing department also provides information critical to investigation of an Action Level excursion. Key investigation points regarding area cleaning/sanitization include:

- Does a review of cleaning records reveal any non-routine activities?
- Were disinfectants prepared properly?
- Were cleaning supplies correctly sterilized?
- Was the training of cleaning personnel current at the time of the excursion?
- Were cleaning procedures correctly followed? If it is determined that a cleaning procedure lacks clarity, revision of the procedure and subsequent training should be effected as soon as possible.
- Were the cleaning personnel gowned properly? One may not consider this critical, since cleaning is a labor-intensive process. However, an improperly gowned cleaner may shed organisms into the environment subsequent to its disinfection, thereby defeating the purpose.

Manufacturing area activities frequently have a direct impact on the facility's environment, as personnel are generally considered the primary source of contamination.

- Did area activity during the 24 hours prior to the excursion, including those activities in adjoining areas, include atypical events or non-routine activities? Manufacturing area activity logs are an invaluable investigative tool for this investigation point.
- Were there were any deviations in gowning, personnel flow, or material flow? A review of records and interview with manufacturing personnel should be performed to determine this.
- For Action Level excursions associated with personnel monitoring, what were the activities with which the operator was associated?

The Facilities Engineering department also provides key supporting information for investigation of an Action Level excursion. The investigation should include information from the following key points.

- Were the temperature and relative humidity of the area, including adjoining areas, within specification at the time of and prior to the excursion date?
- Were differential pressures between the area in which the excursion occurred and the surrounding areas operating within specification at the time of and prior to the excursion?
- Were HEPA filters associated with supply air within certification?
- Was the air-handler unit (AHU) operating within acceptable parameters at the time of the excursion?
- Was there any maintenance performed in the area or on clean utilities within the 24 hours prior to the excursion?

Root Cause Analysis

The key investigation points described above will assist in arriving at the goal of the excursion investigation: probable root cause. Determination of a deviation can be critical to establishing probable root cause. Deviations associated with training, equipment, cleaning, area activity, etc., each suggest a probable root cause requiring its own corrective/preventive action. Historical data trends should be reviewed to determine if the excursion is a repeat occurrence. Repeated deviations may be apparent upon further investigation. These trends may also show if facility activities or seasonal variations are associated with repeated excursions. In addition, ingress analysis should be performed to determine if there was egress into or ingress from adjoining areas.

The author proposes the following example of root cause analysis. An Action Level excursion occurred at a floor site in a gowning vestibule. Data trend analyses showed presence of an adverse trend. Microbial identification results showed a mix of human and environmentally sourced organisms. This was not unexpected, given the level and type of activity for this type of area. A review of area activity showed heightened personnel and material flow at a certain time of day, typically just prior to monitoring. Key investigation points showed no deviations associated with training, equipment, or media. However, interviews with cleaning personnel and a review of cleaning records revealed a historical (sporadic) difference in the method of disinfectant preparation, depending upon the individual preparing the solution. These minor variations in preparation of disinfectant solutions were based upon each person's interpretation of the procedure's instructions. The investigation concluded with the following probable root cause: variations in the method of disinfectant preparation have resulted in sporadic ineffectiveness in maintaining floor bioburden below the Action Level during high activity periods.

Corrective/Preventive Action and Assessing Effectiveness

Determination of a probable root cause should lead to corrective/preventive action. A firm's Corrective Action/Preventive Action (CAPA) system should be used to document this action. For deviations associated with training issues, retraining may be appropriate. However, caution should be exercised to avoid excessive use of retraining in response to excursions, as this may implicate the effectiveness of the training program. Modification of procedures and/or practices may correct a probable root cause, such as changes to cleaning frequencies or disinfectants, calibration or certification frequencies, personnel or material flow, or manufacturing

flow, or manufacturing processes. In the example of the floor excursion above, the Team may have identified such corrective actions as retraining of the operator on proper method of preparing disinfectants, revision of cleaning procedures to provide clearer instructions, and/or an increase in cleaning frequency subsequent to high-activity periods. Equipment or facility modification may be implemented as corrective action, such as room air change rates and temperature or humidity. Equipment repair may also be identified to correct the probable root cause. The goal of effective corrective action is to ensure that the excursion remains an isolated incident.

A firm's CAPA system should be robust, to allow not just assignment, tracking, and closure of corrective actions, but to ensure that effectiveness assessment is performed. Often, the Team is gratified to not only determine a probable root cause for an excursion, but also to assign appropriate corrective action. However, it is a regulatory expectation that effectiveness be assessed. The FDA's "Guide to Inspection of Quality Systems" requires that inspectors, "determine the effectiveness of...corrective or preventive actions," and, "determine if there are any similar...quality problems after the implementation of the corrective or preventive actions." In the example above, effectiveness assessment may have included observations during retraining, resampling of the excursion site, increased frequency of EM, monitoring of additional proximal sites, and/or long-term data trending.

Assessing Facility and Product Impact

Assessment of product impact should be of greater focus subsequent to an investigation if the excursion site is located in a critical area, typically of low classification (e.g., ISO 5). Since, by design, greater classifications are associated with areas peripheral to the critical areas, assessment of product impact becomes less a focus, and facility impact assessment becomes a greater consideration. The key investigation points and root cause analysis provide the information necessary to arrive at an assessment.

For aseptic process operations, excursions in critical zones very often lead to difficulties in the disposition of a product batch. The Team may approach assessment of product impact in much the same manner as it would an out-of-specification test result. However, Action Levels should not be considered as extensions of product specifications. EM data are used only as inferential evaluation for batch release, and are not considered as a direct measure of product sterility. Even an Action Level excursion at a site very close to a product-exposure point during aseptic processing is not by itself justification for rejecting a batch. The batch acceptance or rejection depends upon the significance of the outcome of the comprehensive investigation of the excursion. Batch acceptance may be justified if the excursion was an isolated event, EM data before and after the event are acceptable, and EM data demonstrate an overall state of control of the aseptic manufacturing area and process. Historical process and EM data trends should be reviewed to confirm absence of process-related issues and frequent or multiple EM excursions. Absence of mechanical or material issues associated with the aseptic process lends support that the excursion did not impact the process. For personnel excursions, gown qualification and historical monitoring data should be reviewed to ensure the excursion is an atypical event, minimizing the potential impact to the process and product. Historically, accept-

able media fill process simulations, within the context of the aseptic processing guidance, provide supporting evidence that control of the process is consistently maintained. Although statistically less significant, acceptable sterility test results provide further justification for release of the product batch.

Facility impact assessment is typically associated with ingress analysis. As described above, key investigation points should be considered, such as differential pressures and area activity. If no ingress was observed, or the ingress was isolated to a short period, the impact to the facility was likely minimal. As described for batch-related excursions, historical trends are key to ensuring that the facility design, as well as the sustained efficacy of the disinfecting agents and cleaning procedures, are effective in isolating infrequent viable and non-viable particulate excursions to individual rooms over a short period of time.

Summary

During the investigation of an excursion, a large amount of multi-departmental Team effort can be expended in an attempt to find the "smoking gun." However, often no probable root cause can be identified. This is not unexpected by industry or regulatory agencies. For example, if a firm has established an Alert Level at the "95% Cut-Off" of historical data, per Parenteral Drug Association (PDA) Technical Report No. 13, one would expect a five percent excursion rate. If an EM program generates 20,000 samples annually, one would expect five percent of the results, or 1,000 results, to be above Alert Limits but within normal facility operating conditions (and thus unlikely to have an assignable root cause).

The Food and Drug Administration (FDA) is in a new era characterized by the concepts of risk management, risk mitigation and risk assessment, as exemplified by its initiative, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach." Issuance of the recent FDA aseptic processing guidance has prompted cGMP firms to reevaluate their environmental monitoring (EM) programs within the context of the FDA's expectations. Not surprisingly, minimization and assessment of risk is a key concept of this guidance. The strategies for managing environmental monitoring investigations discussed above will not only assist in arriving at an assessment of risk to the product or facility as a result of an excursion, but will also mitigate the risk of recurrence. Investigation of 1,000 excursions per year may seem a daunting task, but due diligence is the key to compliance with regulatory expectations.

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