Agenda

- “Risk” – Current Regulatory Background
- Elements of an Investigation Plan
- Key Investigation Points
- Root Cause Analysis
- Corrective/Preventive Action and Assessing Effectiveness
- Assesing Facility and Product Impact – “Risk”
“Risk” – Current Regulatory Background

Guidance for Industry
Quality Systems Approach to
Pharmaceutical CGMP Regulations

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

September 2006
Pharmaceutical CGMPs
“Risk” – Current Regulatory Background

Guidance for Industry

Q9 Quality Risk Management

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2006
ICH

Orlando FL, April 2013
“Risk” – Current Regulatory Background

Definition of Risk

• The probability of occurrence of harm
• The severity of that harm
“Risk” – Current Regulatory Background

PHARMACEUTICAL CGMPs FOR THE 21ST CENTURY—A RISK-BASED APPROACH

FINAL REPORT

Department of Health and Human Services
US Food and Drug Administration
September 2004
“Risk” – Current Regulatory Background

FY2006 cGMP Inspection Site Selection

Risk Factors and Model – Mathematical Model

- Size (Sales)
- Establishment Type
- Last 3 District Decisions
- Field Alert History

Facility Risk

Year of Last cGMP Inspection

Total Score

Product Risk

- RX/OTC Products
- Sterility/Non Sterile
- Therapeutic Category

Manufacturing Process Risk

- Process Control
- Contamination Potential

http://www.fda.gov/cder/present/DIA2006/Famulare.pdf

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Elements of an Investigation Plan

- Data Trend Analysis
- Equipment
- Media
- Microbial Identification
- Training
- Facility
- Cleaning
- Area Activity
- Personnel

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Key investigation points will depend upon whether or not the excursion is an Alert Level or an Action Level excursion…

• **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.*

• **Action Level**: An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.*

* US FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, September 2004

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Key Investigation Points

Adverse Trends and Sub-Alert Level Trends also warrant investigation…

- **Adverse Trend**: An Adverse Trend is typically based on multiple excursions. “One point does not a trend make”. It should be investigated to the same level of scrutiny as an Action Level excursion. “Remedial measures should be taken in response to unfavorable trends.”*

- **Sub-Alert Level Trend**: The “behavior” of results below the Alert Level signal the potential of a trend toward exceeding the Alert Level. This type of trend should be investigated to the same level of scrutiny as an Alert Level excursion.

* US FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, September 2004
Key Investigation Points

Sub-Alert Level Trend Example…

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Key Investigation Points

Alert Level Excursion

• Trend analysis – Is there an Adverse or Sub-Alert Level Trend?
• Number of individuals in the area/room at the time of sampling
• Area activity – Were there any non-routine activities in the area/room?
• Microbial identification of isolate(s) – Gram-negatives? Spore-formers? Possible source(s) (e.g., human)?
• Is there an increase (%) in the excursion rate from the current quarter to the previous quarter?
Key Investigation Points

Action Level Excursion

• Requires a cross-functional (i.e., multi-departmental) Team to provide information relating to the elements of the investigation plan
  > Quality Control
  > Engineering
  > Manufacturing
  > Quality Assurance
  > Validation

• The Team should meet on a routine basis (e.g., weekly) to discuss status of investigations
Key Investigation Points

Action Level Excursion
• Quality Control
  > Analyst
    + Was the analyst’s training current at the time of sampling?
    + Did the analyst follow the procedure correctly?
    + Did the analyst notice any deviation in the performance of the equipment or materials used?
    + Is there historical evidence of an excessive number of excursions associated with the analyst’s sampling?
Key Investigation Points

Action Level Excursion
• Quality Control
  > Materials
    + Was the medium brought to room temperature prior to use?
    + Was the medium stored appropriately?
    + Did the lot of medium pass QC testing (growth promotion, contamination check, pH)?
    + Was the medium’s integrity verified before use?
    + Did the medium vendor notify of any manufacturing or formulation changes?
Key Investigation Points

Action Level Excursion

• Quality Control
  > Equipment
    + Was the equipment within calibration?
    + Has the equipment been properly maintained?
    + Was the equipment set at the correct parameters?
  > Data
    + Were the raw data documented properly?
    + Were sample result calculations performed correctly?
Key Investigation Points

Action Level Excursion

• Manufacturing
  > Cleaning
    + Does a review of cleaning records indicate any non-routine activity?
    + Were disinfectants prepared properly?
    + Were cleaning supplies autoclaved correctly?
    + Were cleaning personnel training records current?
    + Did cleaning personnel follow procedures correctly?
    + Did cleaning personnel gown correctly?
Key Investigation Points

**Action Level Excursion**
- Manufacturing
  - Activities
    + What was the activity in the area during the 24 hours prior to the excursion?
    + What were the activities in the adjoining rooms?
    + Were there any non-routine activities in the area?
    + For personnel excursions, with what activities was the operator associated?
    + Were there any deviations in gowning, personnel flow or material flow?
Key Investigation Points

Action Level Excursion

- Facilities/Engineering
  > Equipment
    + Were the room temperature and relative humidity within specification?
    + Were differential pressures within specification/acceptable operating range?
    + Were the HEPA filters within certification?
    + Was the AHU operating within acceptable parameters?
    + Was there any maintenance performed in the area or on the clean utility within the 24 hours prior to the excursion?
Root Cause Analysis

• Deviations
  > What changed? What’s different?
  > Were there any deviations associated with training, equipment, cleaning, etc.?

• Historical Trend
  > Is this a repeat occurrence?
  > Is there a trend associated with facility activities?
  > Is there a seasonal trend?

• Ingress
  > Was there ingress into or from adjoining areas?

Be objective! Let the data and information obtained from the Key Investigation Points speak for themselves.

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Root Cause Analysis

EXAMPLE – Investigation of a floor Action Level excursion in a gowned vestibule

• Data trend analysis showed an adverse trend.
• Microbial ID’s showed a mix of human- and environmentally-sourced organisms.
• Review of area activity showed heightened personnel and material flow at a certain time of the day, typically just prior to EM.
• Key investigation points showed no deviations associated with training, equipment, media, etc., except…
Root Cause Analysis

EXAMPLE – Investigation of a floor Action Level excursion in a gowning vestibule

- Interview of personnel and review of cleaning records revealed an historical (sporadic) difference in the method of disinfectant preparation, depending upon the individual preparing the solution. These variations were based upon each individual’s interpretation of the SOP’s instructions.
EXAMPLE – Investigation of a floor Action Level excursion in a gowning vestibule

• Root Cause
  > Variations in the method of disinfectant preparation resulted in sporadic ineffectiveness in maintaining floor bioburden below Action Level during high activity periods.
Corrective/Preventive Action

• (Re)Training
• Modification of procedures/practices
  > Cleaning frequencies/disinfectants
  > Calibration/certification frequencies
  > Personnel/material flow
  > Manufacturing processes
  > Subject the organism(s) to disinfectant efficacy testing
  > Include the organism(s) in EM media growth promotion testing
• Equipment modification
  > Room air changes
  > Temperature/humidity
• Equipment repair
Corrective/Preventive Action

EXAMPLE – Investigation of a floor Action Level excursion in a gowning vestibule

- Re-train the operator on the proper method of preparing disinfectants
- Revise cleaning procedures to be more clear
- Subject the organism(s) to disinfectant efficacy testing
- Include the organism(s) in EM media growth promotion testing
- Increase the cleaning frequency subsequent to high-activity periods

Finished?
No… Assess Effectiveness
Assessing Effectiveness

EXAMPLE – Investigation of a floor Action Level excursion in a gowning vestibule

- Observations during re-training
- EM resampling
- Increased frequency of EM
- Additional monitoring sites
- Long-term data trending
Assessing Facility and Product Impact – “Risk”
Assessing Facility and Product Impact – “Risk”

Facility Impact Assessment

• Key investigation points such as differential pressures and area activity should be considered

• Historical trends:
  > Facility design – Has it been effective in containing infrequent excursions to individual rooms?
  > Cleaning/Disinfection program – Is sustained efficacy of the disinfecting agents and cleaning procedures evident?

• The assessment is typically based upon an analysis of contamination ingress/egress
Assessing Facility and Product Impact – “Risk”

EXAMPLE – Investigation of a floor Action Level excursion in a gowning vestibule

• From the Root Cause analysis…
  > Data trend analysis showed an adverse trend
  > Review of area activity showed heightened personnel and material flow at a certain time of the day
  > Root cause was that the disinfection program was flawed, resulting in sporadic ineffectiveness

• Ingress/Egress Analysis
  > DP’s have historically been maintained within operating limits
  > Historical EM data of adjoining areas, including those closely associated with excursion dates, have been below Alert Levels

Facility impact?
Assessing Facility and Product Impact – “Risk”

Product Impact Assessment

• To reject, or not to reject…
  > 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 a direct measure of product sterility

• Weigh the preponderance of evidence to judge the risk to the product
  > 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
Assessing Facility and Product Impact – “Risk”

Product Impact Assessment
• Is the excursion an isolated event?
• Were EM data before and after the event acceptable?
• Do EM data demonstrate an overall state of control of the aseptic manufacturing area and process?
• Do historical process and EM data trends demonstrate absence of process-related issues?
• Were there any mechanical or material issues associated with the aseptic process?
• For personnel excursions, do gown qualification and historical monitoring data support that the excursion is an atypical event?
Assessing Facility and Product Impact – “Risk”

Product Impact Assessment

• Do historically acceptable media fill process simulations provide supporting evidence that control of the process is consistently maintained?

• Can you statistically demonstrate the unlikelihood of product contamination? (e.g., Statistical Process Control [SPC], Failure Modes and Effects Analysis [FMEA])

• Do sterility test results meet acceptance criteria? (Caution! statistically insignificant)
EXAMPLE – Investigation of an air viable Action Level excursion in an ISO5 filling enclosure (#1)

- EM data (surface, air, personnel) before and after the event, as well as throughout the fill, were below Alert Levels
- There were no mechanical or material issues associated with the fill
- Process parameters (critical control points) have historically been within limits
- EM data trends show no evidence of a recurring or systemic issue
Assessing Facility and Product Impact – “Risk”

EXAMPLE – Investigation of an air viable Action Level excursion in an ISO5 filling enclosure (#1)

• Media fills for the past three years have resulted in zero positive units
• The manufacturing process design provides for a Sterility Assurance Level (SAL) of $10^{-6}$ (The average number of units per batch is 50,000)
• Sterility results of the batch are negative

Product impact?
Assessing Facility and Product Impact – “Risk”

EXAMPLE – Investigation of an air viable Action Level excursion in an ISO5 filling enclosure (#2)

- There were intermittent Non-Viable Air Alert Level excursions throughout the fill
- A small hole was discovered in the HEPA filter
- Process parameters (critical control points) have historically been within limits
- EM data trends show no evidence of a recurring or systemic issue
Assessing Facility and Product Impact – “Risk”

EXAMPLE – Investigation of an air viable Action Level excursion in an ISO5 filling enclosure (#2)

• One media fill last year resulted in two positive units
• The manufacturing process design provides for a Sterility Assurance Level (SAL) of $10^{-6}$ (The average number of units per batch is 50,000)
• Sterility results of the batch are negative

Product impact?
A Risk-Based Approach for Investigating Environmental Monitoring Excursions

Example of total annual EM excursions...

- 99% Cut-Off (Action Level)* = 1% expected excursion rate
- 20,000 EM samples taken annually
- \( (20,000) \times (0.01) = 200 \) investigations
  (almost one per day!)

A daunting task...

- “Chasing ghosts”? 
- No “smoking gun”? 
- **DUE DILIGENCE** is the key to mitigating the risk of recurrence!

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A Risk-Based Approach for Investigating Environmental Monitoring Excursions

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• Assessing Facility and Product Impact – “Risk”
References

• ISO 14644 – Cleanrooms and Associated Controlled Environments
References


• Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002, Annex 1 (European Union)

• Current U.S. Pharmacopeia <1116>

• 21 CFR 211.113, Control of Microbiological Contamination
References


References


A Risk-Based Approach for Investigating Environmental Monitoring Excursions

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A Risk-Based Approach for Investigating Environmental Monitoring Excursions

Q & A...

http://www.aschoonerofscience.com/just-for-fun/gift-ideas-for-a-microbiologist-or-pathologist/