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Environmental Monitoring and Contamination Control
September 11, 2015

Featured Speaker: **Scott Sutton, Ph.D.**
The Microbiology Network
N. Chili, New York

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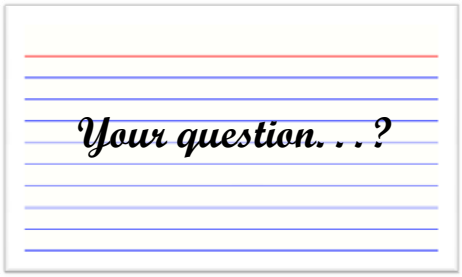

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Resources

- Visit www.ProCE.com/PharMEDiumRx to access:
  - Handouts
  - Activity information
  - Upcoming live webinar dates
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Webinar Information

Questions? Email us at info@proce.com or call our office at 630.540.2848.

Section 503B of the Food, Drug and Cosmetic Act: What does it mean?
Live webinar date: March 14, 2014 - 11:30am - 12:30pm CT

Activity Information	Download Handout	Live Webinar CE: Post-Test/Evaluation
	Coming Soon	*Coming Soon*
		On-Demand Webinar CE: Post-Test/Evaluation
		Coming Soon

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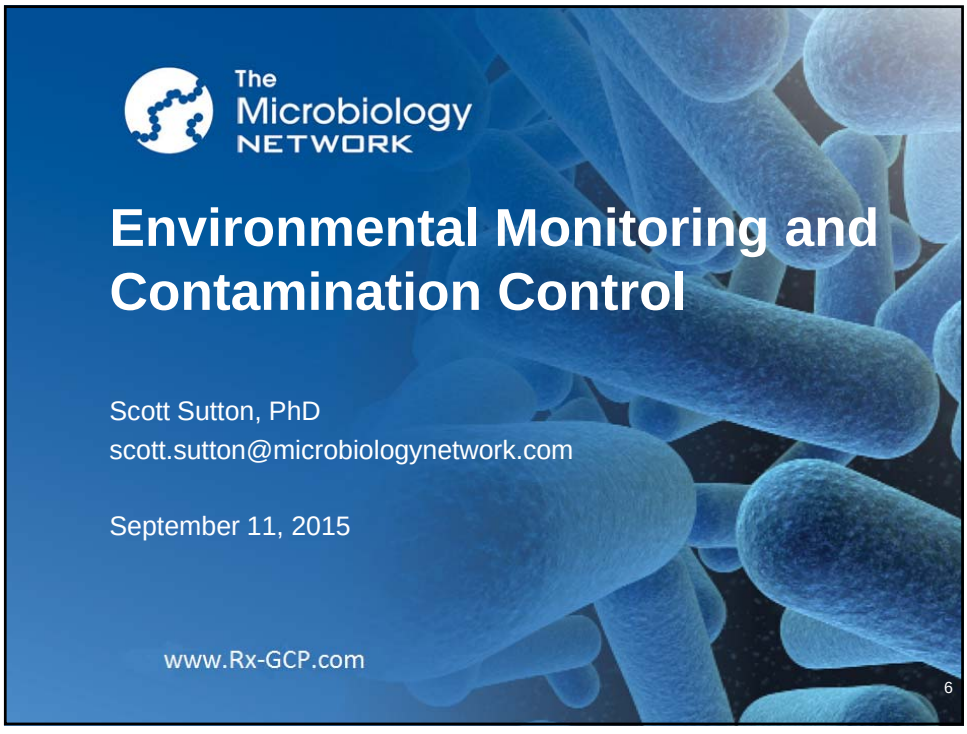

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- I am an independent consultant.
- I have been involved with USP for many years.
- I do not represent USP or any other organization.
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Presentation Overview

- What's the Point of the Program?
- Components of the Program
- Appropriate Sites for Monitoring
- What Are We Supposed to Do With All the Data?

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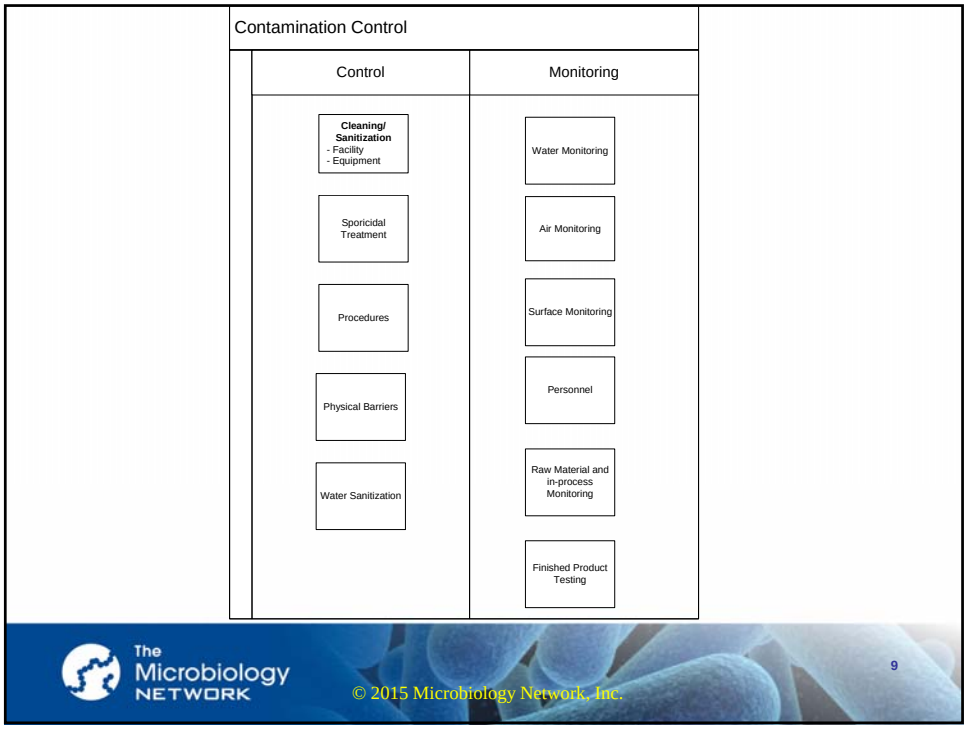
Contamination Control
Control
Monitoring
Cleaning/ Sanitization
- Facility
- Equipment
Sporicidal Treatment
Procedures
Physical Barriers
Water Sanitization
Water Monitoring
Air Monitoring
Surface Monitoring
Personnel
Raw Material and in-process Monitoring
Finished Product Testing
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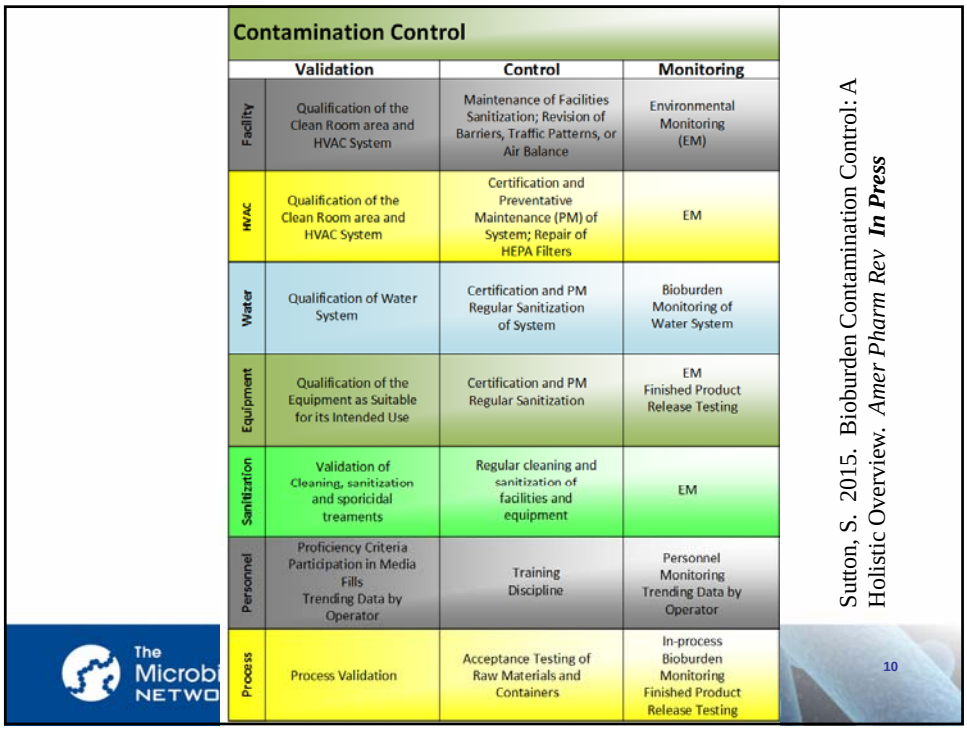
Contamination Control
Validation
Control
Monitoring
Facility
Qualification of the Clean Room area and HVAC System
Maintenance of Facilities Sanitization; Revision of Barriers, Traffic Patterns, or Air Balance
Environmental Monitoring (EM)
HVAC
Qualification of the Clean Room area and HVAC System
Certification and Preventative Maintenance (PM) of System; Repair of HEPA Filters
EM
Water
Qualification of Water System
Certification and PM Regular Sanitization of System
Bioburden Monitoring of Water System
Equipment
Qualification of the Equipment as Suitable for its Intended Use
Certification and PM Regular Sanitization
EM
Finished Product Release Testing
Sanitization
Validation of Cleaning, sanitization and sporicidal treaments
Regular cleaning and sanitization of facilities and equipment
EM
Personnel
Proficiency Criteria
Participation in Media Fills
Trending Data by Operator
Training
Discipline
Personnel Monitoring
Trending Data by Operator
Process
Process Validation
Acceptance Testing of Raw Materials and Containers
In-process Bioburden Monitoring
Finished Product Release Testing
Sutton, S. 2015. Bioburden Contamination Control: A Holistic Overview. *Amer Pharm Rev* ***In Press***
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What is the Point of the Program?

USP <797>

"The ES program should provide information to staff and leadership to demonstrate that the PEC is maintaining an environment within the compounding area that consistently ensures acceptably low viable and nonviable particle levels."

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What is the Point of the Program?

USP <797>

"Environmental sampling shall occur as part of a comprehensive quality management program and shall occur minimally under any of the following conditions:

- as part of the commissioning and certification of new facilities and equipment;
- following any
- as part (i.e.,
- every 6
- in response or staff
- technique; or
- in response to issues with CSPs, observed compounding personnel work practices, or patient-related infections (where the CSP is being considered as a potential source of the infection)."

This section of <797> is commonly interpreted as "every six months"

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What's the Point?

Demonstration of Microbial Control

- Sanitization Studies
- Contamination control planning
- Equipment Hold time Studies (establishment of clean and dirty hold times - process hold times are process-specific)
- Selection of sample sites for environmental monitoring.
- Establishment of pharmacy-relevant alert and action levels for controlled environments
- Ongoing Monitoring Program

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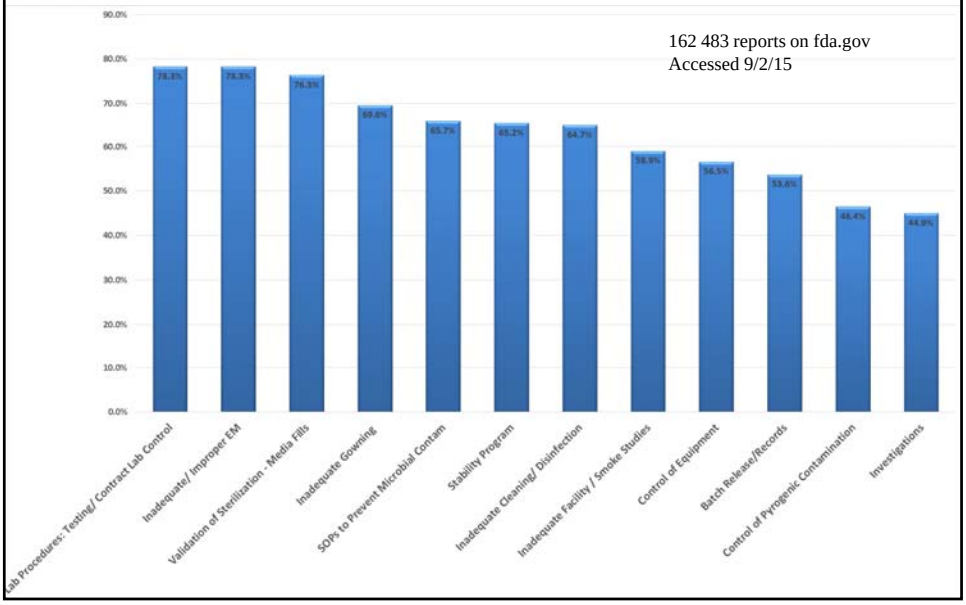
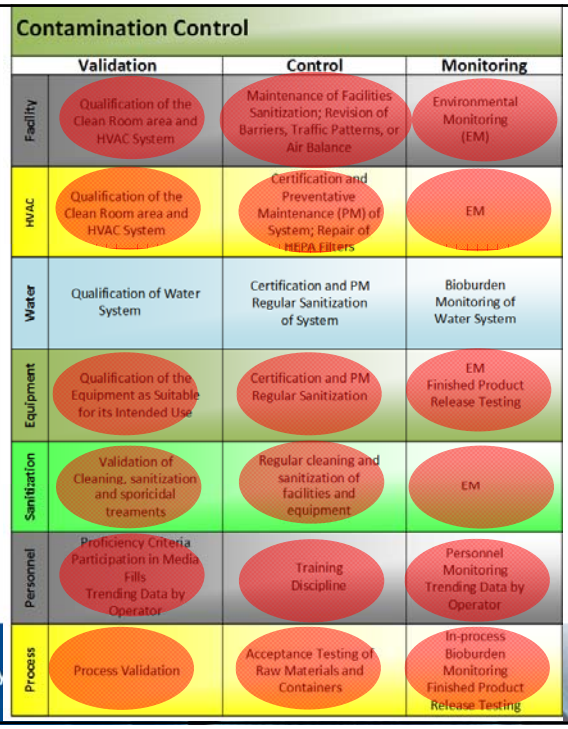
FDA 483 Observations



Topics of FDA Pharmacy 483 Observations

Environmental Monitoring



EM – Documentation of Pharmacy Environment "State of Control"

"In aseptic processing, one of the most important laboratory controls is the environmental monitoring program. This program provides meaningful information on the quality of the aseptic processing environment (e.g., when a given batch is being manufactured) as well as environmental trends of ancillary clean areas. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs (211.42 and 211.113)."

FDA. 2004. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice. Section X.A.1.

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EM – Documentation of Facility State of Control

"Environmental monitoring data will provide information on the quality of the manufacturing environment." FDA. 2004. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice. Section X.A.2.

USP <797>
"The ES program should provide information to staff and leadership to demonstrate that the PEC is maintaining an environment within the compounding area that consistently ensures acceptably low viable and nonviable particle levels."

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FDA 503B CGMP Draft Guidance

- "Sterile drugs should be produced only in ISO 5 or better air quality."
- "The air cleanliness classification of the area surrounding the ISO 5 zone immediately adjacent to the aseptic processing line should meet, at a minimum, ISO 7 (Class 10,000) standards."

Guidance for Industry: Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act July, 2014
Section III.A. Facility Design

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FDA 503B CGMP Draft Guidance

- Cites 21 CFR 211.42(c)(10)(iv) for EM program
- Expectations:
  - Cover all production shifts and include monitoring during normal production conditions
  - Include at least daily monitoring of the ISO 5 zone during operations
  - Establish alert and action limits and appropriate responses to each
  - Describe use of sampling devices, alert and action limits, and testing methods (e.g., media, plate exposure times, incubation times and temperatures) that are designed to detect environmental contaminants, including changes in microflora type and amount
  - Be supported by an evaluation of the choice of the sampling locations and sampling methods

Guidance for Industry: Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act July, 2014
Section III.C. Environmental and Personnel Monitoring

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FDA 503B CGMP Draft Guidance

- Cites 21 211.113(b) and 211.28(a) for Personnel Monitoring
- Expectations:
  - Includes a routine program for daily/shift monitoring of operators' gloves and an appropriate schedule for monitoring gowns during operations
  - Establishes limits that are based on the criticality of the operation relative to the contamination risk to the product
  - Calls for an investigation of results that exceed the established levels or demonstrate an adverse trend, a determination of the impact on the sterility assurance of finished products intended to be sterile, and the development and execution of appropriate corrective actions

Guidance for Industry: Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act July, 2014
Section III.C. Environmental and Personnel Monitoring

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FDA 503B CGMP Draft Guidance

Finally, the draft guidance recommends laboratory QC measures:

"Procedures should include establishing the validity of the microbiological media, including the preparation, sterilization, and growth potential of the media used in performing tests, including environmental and personnel monitoring."

Guidance for Industry: Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act July, 2014
Section III.C. Environmental and Personnel Monitoring

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Presentation Overview

- What's the Point of the Program?
- Components of the Program
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Monitoring Program Components

- Written procedures
- Training of personnel
- Surface monitoring
- Microbial air monitoring
- Non-viable particulate air monitoring
- Personnel monitoring
- Critical utilities-water, compressed gasses

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Monitoring Program Components

- Surfaces
  - Using sterile materials is appropriate, written procedure should include sanitization procedures for all items taken into the aseptic areas
  - Monitor surfaces in critical and non-critical areas
  - Select sites that indicate effectiveness of sanitization programs and appropriate personnel practices

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Monitoring Program Components

- Typical surfaces monitored include:
  - Floors, walls and ceilings
  - Control panel surfaces
  - Doors, especially push plates
  - Equipment surfaces, both non-product contact and product contact surfaces

Contact plates
Flat Paddle Samplers
Swabs

Monitoring Program Components

- Microbial air
  - Sterile materials
  - Disinfection of equipment
- Typical areas to monitor include:
  - In the critical zones (ISO 5), near product exposure areas
  - In the support/non-critical areas (ISO 7) based on area usage

Active Air Samplers
Passive Sampling

Monitoring Program Components

- Non-viable particulate
  - Disinfection of equipment
  - Monitor in critical and non-critical areas
- Typical areas to monitor include:
  - Same sites as microbial monitoring
  - Additional sites in critical zones (ISO 5)

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Utilities

- Water-usually limited number of sites in aseptic areas
- Compressed gasses
  - Product contact (purging or overlay)
  - Equipment operation (exhausts into room)

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Presentation Overview

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Sites
Established by Qualification Study

- Viable air monitoring - passive — Near open product, critical work areas
- Viable air monitoring - active — Same as non-viable sites
- Surface Monitoring (room)
- Surface Monitoring (equipment)
- Utilities

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Passive viable air monitoring

- 4 hours exposure (EU 2008)
- Not disruptive to the immediate environment (Whyte, 1996)
- Not as prone to variation among different vendors as are active samplers (Yao and Mainelis 2006).

EU. 2008. EudraLex: The Rules Governing Medicinal Products in the European Union Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use: Annex 1 Manufacture of Sterile Medicinal Products

Whyte, W. 1996. In Support of Settle Plates. *PDA J Pharm Sci Tech*. 50(4):201-204.

Yao, M. and Mainelis, G. 2006. Investigation of Cut-Off Sizes and Collection Efficiencies of Portable Microbial Samplers. *Aerosol Sci Technol*. 40:595 – 606.

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Location of Sites for Qualification Study

- At which sites would microbial contamination most likely have an adverse effect on product quality?
- What sites would most likely demonstrate heaviest microbial proliferation during actual production?
- What sites would represent the most inaccessible or difficult areas to clean, sanitize, or disinfect?
- What activities in the area contribute to the spread of contamination?
- Would the act of sampling at a given site disturb the environment sufficiently to cause erroneous data to be collected or contaminate product?"

PDA. 2014. PDA Tech Report #13 (Revised): Fundamentals of an Environmental Monitoring Program

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Recommendations on Sample Sites

- Contamination vectors (handles, control panels, doors, etc).
- High traffic areas
- Personnel flow
- Material flow
- Waste Flow
- Surfaces that are difficult to disinfect
- HVAC returns
- Product risk
- Extent of product exposure
- The type of activity performed near that site
- Interventions and manipulations
- Surfaces that are difficult to disinfect

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Selection of Routine Sites

- Sites are selected for ability to give useful information on the state of control for the pharmacy as a compounding facility
- Number of sites determined by risk analysis
- Location of sites must carry data justification
- Routine EM protocol must unambiguously identify site

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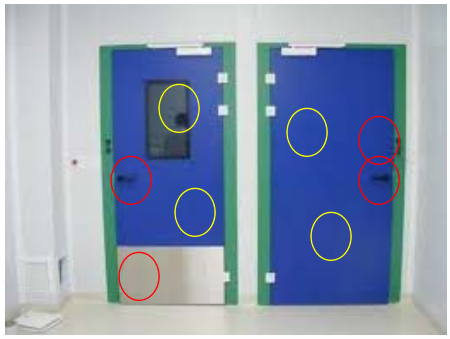
Specific Sample Sites



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FDA - Trending

Trend reports should look at many different factors

QAU to use trend reports in EM investigations

SOPs describe how management is informed of trends and investigations

FDA. Section IX.A.2. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. 2004

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Trending vs Alert and Action Levels

- Can arbitrary numbers be set?
- Trending critical –
  - By Location
  - By Product
  - By Date
  - By Month
  - By Season
- Trend Numbers
- Trend genus/species

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Establishing Alert and Action Levels

- Alert levels are typically based on analysis of historical data for the facility/area. In new facilities they can be based on experience or other guidance and followed by regular evaluation of the data collected.
- Action levels can be derived from historical data or based on guidance such as USP <1116>.

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Presentation Review

- What's the Point of the Program?
- Components of the Program
- Appropriate Sites for Monitoring
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Thank you for your attention
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