What's Bugging You About USP 797 Environmental Sampling

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Disclaimer

"Although Eric Kastango is a member of the 2010-2015 USP Compounding Expert Committee, he is speaking today in his own individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely his own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>."
Program Objectives

- Review of relevant patient incidents involving CSP contamination
- Review the 797 requirements for environmental sampling
- Case Study
For in much wisdom [is] much grief: and he that increaseth knowledge increaseth sorrow.

Ecclesiastes 1:18, King James Bible
March 2001, Missouri


- **Scenario**
  - Received IV ranitidine compounded with ACD while in the hospital.
  - Multidose source vial hung for 48 hours on ACD

- **Action/Results**
  - 4 patients developed an infection, 1 case of bacterial meningitis and transferred to another hospital

- **Root Cause**
  - Poor employee hand hygiene and garbing practices
  - Failure to comply with compounding practices
May 2001, California

- Outbreak of *Serratia marcescens* Infections following Injection of Betamethasone Compounded at a Community Pharmacy. CID 2006;43:831-7.

- Scenario
  - 11 patients with culture-confirmed *S. marcescens* following injection of compounded betamethasone from 25 May through 31 May 2001. Case patients had meningitis (5 patients, with 3 deaths), epidural abscesses (5 patients), or an infected hip (1 patient).
  - *S. marcescens* was isolated from 35 (69%) of 51 betamethasone vials recovered, from pharmacy surfaces, and from multiple parenteral materials used at the ambulatory surgery.

- Root Cause
  - Untrained and garbed compounding personnel
  - Failure to achieve sterility
Brutal Facts

September 2002, South Carolina

- *Exophiala* Infection from Contaminated Injectable Steroids Prepared by a Compounding Pharmacy --- United States, July--November 2002. MMWR December 13, 2002 / 51(49);1109-1112

- Scenario
  - Five cases of *Exophiala* infection associated with injectable medication had occurred, one patient dies
  - Cases occurred up to 152 days following injection of contaminated CSP.

- Root Cause
  - Untrained compounding personnel
  - Failure to achieve sterility
    - Improper use of autoclave
Brutal Facts

February 2004, Texas


- Scenario
  - Home infusion pharmacy prefilling syringes of heparin and saline
  - Was not registered as a medical device manufacturer with the FDA
  - 36 *Pseudomonas fluorescens* (*P. fluorescens*) infections in four states
  - FDA issues nationwide recall
Brutal Facts

December 2004, Maryland


- **Scenario**
  - Sixteen (16) patients from three (3) clinics develop HCV infection after administration of Tc 99m radioisotope used in cardiac stress tests
  - Contamination implicated to be a cross-contamination between a blood-labeling procedure and the preparation of the radioisotope
  - Sixteen patients contract Hepatitis C
    - Several patients adversely affected (death and disease)

- **Root Cause**
  - Breaks in aseptic technique were identified at the pharmacy. Nuclear pharmacies that handle biological products should follow appropriate aseptic technique to prevent contamination of sterile radiopharmaceuticals.
Brutal Facts

March 2005, Texas

- A Multi-state Outbreak of *Serratia marcescens* Bloodstream Infection Associated with Contaminated Intravenous Magnesium Sulfate from a Compounding Pharmacy.

- Scenario
  - Outsourcing (pharmacy) operation preparing Magnesium Sulfate minibags
  - Registered as a manufacturer with the FDA
  - *Serratia marcescens infections*
  - FDA issues nationwide recall
Brutal Facts

September 2005, Maryland

- **Scenario**
  - Outsourcing (pharmacy) operation preparing several different CSPs
  - Registered as a manufacturer with the FDA
  - *Discovery of gram-negative rods in two lots of cardioplegia solution*

- **Results/Outcome**
  - FDA issues recall in several states
  - At least ten patient deaths from contaminated solutions
  - FDA issues company a Warning Letter citing several locations

- Available online: [http://www.fda.gov/foi/warning_letters/archive/g5817d.htm](http://www.fda.gov/foi/warning_letters/archive/g5817d.htm).
Brutal Facts

March 2011, Alabama

- *Serratia marcescens* associated infections and deaths associated with contaminated parenteral nutrition prepared by a compounding pharmacy

Scenario

- At least sixteen case of infection, 9 deaths from *Serratia* infection associated with parenteral nutrition (PN).
- Pharmacy used nonsterile components to prepare the PN-amino acids.
- The environmental contamination (sink, mixing tank, stirrer) that was found (genotype/phenotype) was the same found in the infected patients.

Root Cause

- Untrained compounding personnel
- Failure to achieve sterility
  - Improper use of filter

Serratia marcescens
Better reporting or a growing problem?

Trends in Patient Incidents Involving Compounding Errors

- 30% in 2009
- 33% in 2010
- 34% in 2011

▲ 34% of all hospitals recognize that they have had a patient incident(s) involving a compounding error over the past five years.

N=413

USP <797>: Pharmaceutical Compounding-Sterile Preparations

- The intent of the chapter is “to prevent patient harm and fatality from microbial contamination (nonsterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients in CSPs.”

- Chapter formerly known as <1206>: Sterile Drugs for Home Use

- Effective January 1, 2004

- Revised and effective June 1, 2008
Environmental Sampling – Why Is It Important

- Can allow for early detection of contamination and its source.
  - **Sources**
    - Personnel
    - Work surfaces
    - Supplies
    - Equipment
    - Failure of engineering controls
Environmental Sampling

- Designed to demonstrate that the primary and secondary engineering controls, disinfecting procedures, and work practices result in a suitable environment for aseptic compounding.
- Utilizes several approaches to assess and evaluate:
  - Total particle counts
  - Air viable organism cfu
  - Surface viable organism cfu
  - Finger touch plates
Newly revised chapter ties viable and nonviable testing to certain conditions as a minimum standard for compliance.

This approach was in response to the recommendations made by the IC Advisory Panel, which had members from the CDC, APIC, SHEA, ASM, and a hospital based pharmacist.¹

¹ Arjun Srinivasan, Judene Bartley, William Rutala, Alice Weissfeld, and Kathleen Gura
Keith St. John was Chair of this Advisory Panel, appointed by CEO of USP, Roger Williams, MD
Environmental Sampling

- ES section has been separated into a facility-related performance metric and a personnel-related performance metric

- Facility-related Environmental Sampling
  - Viable air sampling via volumetric method (impaction) to occur at least every 6 months, linked with re-certification activities

- Personnel-related Environmental Sampling
  - Personnel fingertip sampling during initial training, with media fills utilized as a competency assessment tool
  - Surface sampling for viable microorganisms to assess the effectiveness of disinfection – another competency assessment
Environmental sampling conditions:

- As part of the commissioning and certification of new facilities and equipment.
- Following any servicing of facilities and equipment.
- As part of the re-certification of facilities and equipment (i.e., every 6 months).
Environmental sampling conditions:

- In response to identified problems with end products or staff technique
- 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.)
Growth Media

- Soybean Casein Digest Media (Trypticase Soy Broth/Agar) to support the growth of bacteria.
- Malt Extract Agar or other media that supports the growth of fungi.
- Added neutralizing agents such as lecithin and polysorbate 80 when appropriate.
  - Surface sampling
  - Personnel glove sampling
Sampling for Air Viable Organisms

- Volumetric air sampling is required.
- Settling Plates cannot be sole method of evaluating air viable organisms.
  - They are not qualitative
  - Settling of particles by gravity influenced by size of particle and by air movement

Courtesy of MSI, Inc. Houston, TX  (www.microbiologyspecialists.com)
Volumetric Air Sampling

- Shall be performed at locations that are prone to contamination during compounding or staging of supplies, labeling, gowning and cleaning.

- Required frequency
  - Low, medium and high-risk level compounding – at least semi-annually

- More frequent sampling will provide earlier detection of loss of environmental control.

- Base frequency of sampling on:
  - Criticality of compounding occurring in area.
  - Number of excursions over assigned action level.
Viable Air Sampling

- Sampling plan to include:
  - Method of collection (e.g., Impaction sampling)
  - Frequency of testing
  - Volume of air sampled (400-1000L)
  - Time of day and activity of compounding
  - CFUs action levels

- Minimum frequency of testing
  - Initial facility commissioning
  - At least every six months during recertification of facility and engineering controls of all sterile compounding areas

Reference: USP <1116>: Microbiological Evaluation of Clean Rooms and Other Controlled Environments
Volumetric Air Sampling Equipment

Merck MAS100

BioScience SAS180

SKC, Inc.

ThermoElectron

Biotest RCS Isolator

Biotest RCS
Surface Sampling

Surface Cleaning and Disinfection Sampling and Assessment

- Surface sampling is an important component of the maintenance of a suitable microbially controlled environment
  - *Transfer of microbial contamination from improperly disinfected work surfaces via inadvertent touch contact by compounding personnel can be a potential source of contamination of CSPs*
- It is useful for evaluating facility and work surface cleaning and disinfecting procedures and employee competency in work practices such as disinfection of component/vial surface cleaning.
Surface Sampling

- Contact Plates (plate size 24-30 cm²)
  - Media plate which has a convex surface.
  - A general growth medium such as Trypticase Soy Agar along with neutralizing agents such as lecithin and polysorbate 80 is usually used.
  - Used to sample only smooth, flat, and nonporous surfaces.

- How to use
  - Gently roll the plate over the surface to be sampled.
  - Media residue will be left behind.
  - Clean and disinfect sampled area thoroughly.
Surface Sampling

- Often done at the end of the shift or end of the work day.
- Can be performed in all ISO classified areas.
- Performed using contact plates or swabs.
- Sampling areas should be defined in the sampling plan.
Surface Sampling

Images courtesy Dr. Laura Thoma
Surface Sampling

Images courtesy Dr. Laura Thoma
Surface Sampling
Gloved Fingertip Sampling

- Initial training assessment with audit tool
- Successful gloving with three-time fingertip sampling with ZERO CFUs
- Annually re-assessment for low and medium-risk compounding operations
- Semi-annual re-assessment for high-risk compounding operations
- During any media fills
Gloved Fingertip Sampling

Images courtesy ClinicalIQ™, LLC.
### Microbiological Action Sampling Levels

<table>
<thead>
<tr>
<th>Classification</th>
<th>Volumetric Air Sample Required*</th>
<th>Finger Tip Sample</th>
<th>Surface Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt; 1</td>
<td>Zero x 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>&gt; 10</td>
<td></td>
<td>&gt; 5</td>
</tr>
<tr>
<td>ISO Class 8</td>
<td>&gt; 100</td>
<td></td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

CFUs per cubic meter of air or per plate.

*A sufficient volume of air (400-1,000 L) should be sampled to detect excursions specified in the levels above.*
Environmental Sampling

- Total particles counts
  - Initial facility commissioning
  - At least every six months during recertification of facility and engineering controls of all sterile compounding areas
- Volumetric Air Sampling—every six months
- Glove fingertip sampling occurs annually for Low and Medium Risk and semi-annually for High Risk Level to assess staff competency of maintaining aseptic practices
- Surface sampling used to evaluate the effectiveness of cleaning/disinfecting procedures and work practices and occurs annually for Low and Medium Risk and semi-annually for High Risk Level sterile compounding
“Regardless of the number of cfu identified in the pharmacy, further corrective actions will be dictated by the identification of micro-organisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden…”

*USP Chapter <797> USP 34-NF 29*
Environmental Sampling

- When action levels are exceeded, an investigation into the source of the contamination shall be conducted.

- Sources to check:
  - HVAC systems
  - Damaged HEPA filters
  - Changes in personnel garbing habits
  - Changes in work practices
# CFU Identification and Sources

<table>
<thead>
<tr>
<th>Microorganisms (gram stain/ morphology)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Staphylococcus/ Micrococcus</td>
<td>• Personnel habits or gowning problems</td>
</tr>
<tr>
<td>• Gram negative rods</td>
<td>• Water condensation, leaking, aerosols</td>
</tr>
<tr>
<td>• Bacillus species</td>
<td>• Dust, dirt, floor traffic, possible air handling</td>
</tr>
<tr>
<td>• Molds</td>
<td>• Influx of unfiltered air, mold from street clothing or mold-contaminated cardboard, water reservoir, i.e. incubator humidification system</td>
</tr>
<tr>
<td>• Yeast</td>
<td>• Possible outdoor air influx; clothing-borne, especially in late summer/ fall; possible human contaminant</td>
</tr>
<tr>
<td>• Diptheroids/ coryneforms</td>
<td>• Poor air conditioning (leading to sweating and personnel discharge from gowns)</td>
</tr>
</tbody>
</table>

Source: *Microbiological Environments* (www.microbioenv.com)
Case study

- A microbial contaminant, *Brevibacillus brevis* was recovered from both a CSP and the pharmacy buffer area.

- Is there a relationship between sporadic outbreaks of *Bacillus* bacteremia and contamination introduced while compounding or administration?

- *Bacillus cereus* was implicated in the TRIAD alcohol pad recall.
Case study

Figure 1: rep PCR dendrogram and virtual gel image of *Bacillus* strains 3031450 (lane 1) and 3031454 (lane 2). The dendrogram demonstrates 99.6% similarity.
Patient Safety remains Priority #1!

- Patient Safety is a partnership involving multiple disciplines and is not achieved in “isolation.”

- It takes all of us working together to achieve the goal of “zero tolerance” for preventable healthcare-associated infections, whether at the patient’s bedside or in the pharmacy.
Any Questions?

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