"Lessons to be Learned from the NECC 483"

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Disclaimer

“Although I am an Expert Consultant to the USP, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative. The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP or any other organization I may be associated with, nor should they be construed as an official explanation or interpretation of <797>.”

Learning Objectives

The objectives for your presentation for pharmacists and technicians are as follows:
• Review the details of the New England Compounding Center meningitis outbreak.
• Describe the requirements for achieving a state of control such as training, environmental controls, cleaning, standard operating procedures and quality checks.
• Explain the role and responsibility of the pharmacist and pharmacy technician in preparing or securing sterile compounds.

Thoughts

“I can't go back to yesterday because I was a different person then.”

Lewis Carroll, *Alice in Wonderland*

Exserohilum rostratum

Image courtesy www.cdc.gov

New England Compounding Center (NECC) Meningitis Outbreak

<table>
<thead>
<tr>
<th>Date</th>
<th>September 21, 2012 (on-going) – August 5, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>USA (23 States)</td>
</tr>
<tr>
<td>Cause</td>
<td>Fungal meningitis contamination of steroid medication</td>
</tr>
<tr>
<td>Injuries</td>
<td>749 Total Case Count, 384 meningitis and Spinal Infection, 7 Stroke, 323 Paraplegia/Spinal infection, 35 Peripheral Joint Infection, some patients recovering from the meningitis are falling ill again. Sufferers of the new infection are now coping with epidural abscesses and infections near the injection site.</td>
</tr>
<tr>
<td>Death(s)</td>
<td>63</td>
</tr>
<tr>
<td>Litigation</td>
<td>More than 20 lawsuits filed against NECC.</td>
</tr>
</tbody>
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Source: [http://www.cdc.gov/hai/outbreaks/ meningitis-mapp-large.html](http://www.cdc.gov/hai/outbreaks/ meningitis-mapp-large.html)

The scale of the meningitis outbreak makes this event the worst among a series of fatal or harmful infections and overdoses linked to pharmacy compounding practices in the US rivaling other key drug safety issues in the past that have led to substantial drug safety legislation.
Persons with Fungal Infections Linked to Steroid Injections, by State

Source: http://www.cdc.gov/hai/outbreaks/meningitis‐map‐large.html

NECC Findings from FDA 483

On 10/06/2012, the firm’s third action, a completed AIR audit of this one of the firm’s three (AIR 12) was identifying the facility and received the audit. Obviously, once the firm’s fourth action, the audit was reviewed and found to be in compliance with the FDA’s Good Manufacturing Practices (GMP) and the company’s Quality System. The firm was in compliance with GMP and the company’s Quality System. The firm was in compliance with GMP and the company’s Quality System. The firm was in compliance with GMP and the company’s Quality System.

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There was no inspection carried out by the firm on the facility that was recorded in the firm’s Quality System. The firm was in compliance with GMP and the company’s Quality System. The firm was in compliance with GMP and the company’s Quality System. The firm was in compliance with GMP and the company’s Quality System.
USP <797> Elements

There are three broad areas that contribute to meeting the objectives of USP <797>:

- Contamination Control
- Training and Documentation
- CSP Checks and Tests

- Address sources - people, products, process
- Create a “clean” environment where aseptic compounding will take place
- Compounding personnel are skilled, educated and trained
- Operator testing for proficiency
- Written policies, procedures
- Document training
- Reduce occurrence of contamination
- Verify the process produced correct CSPs
- Use the same process each time
- If contamination or error happens, detect it and take action

Achieving a State of Control

- Hand Hygiene, Garbing, Aseptic technique
- Training
- Facility design, Environmental Control
- Environmental Sampling
- Cleaning
- Standard Operating Procedures
- Components
- Sterilization, Quality Release Checks

Hand Hygiene

- Hand washing is defined as the vigorous, brief (30 seconds) rubbing together of all surfaces of lathered hands, followed by rinsing under a stream of water.
- Hand washing suspends microorganisms and mechanically removes them by rinsing with water.
- Single most important way to reduce the risks of transmitting germs
- Even after using anti-microbial soap, there is still about 20,000 microbes per sq. mm

Compounding Personnel

- Hair net
- Beard cover and face mask
- Gown
  - Nonsterile
- Gloves
  - Sterile
- Shoe covers

Critical Factors in Aseptic Technique

Compounding Risk Assessment

• How are staff trained initially and what is the ongoing process to ensure staff competency?
• What methods are available to assess accuracy of compounded products?
  – Is validation with spectroscopy or other methodology used?
• What is the process for checking high alert/high risk medications?
  – Are pre-checks performed by the pharmacist?
  – When is independent double-checking performed?

Lack of Sterile Compounding Knowledge/Skill

• Pharmacists
  – Intravenous medication therapy does not appear to be an area of focus in pharmacy training
  • Recent survey regarding the extent of instruction on sterile preparations in U.S. pharmacy schools revealed only 13% of schools felt that students had “adequate training in compounding sterile preparations”

Ensure a Knowledgeable, Engaged Workforce

• Maximize the unique skills and qualities of each staff member.
• Comprehensive orientation
• Ongoing training related to job activities
• Continual competency verification
• Reward staff who identify “near misses” and make proactive suggestions for improvement.

Create a Quality Culture!

Environmental Controls

• Aimed at creating ISO 5, 7, and 8 environments
  • ISO 5 – LAFW, BSC, CAI, CACI are “Primary Engineering Controls”
  • Must maintain ISO 5 during dynamic (in use) working conditions
  • Unidirectional airflow required

Primary Engineering Controls

- ISO Class 5
- Direct Compounding Area (DCA)

Images courtesy ClinicalIQ™, LLC.
Environmental Sampling

- Environmental Sampling 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
- Personnel-related Environmental Sampling
  - Personnel fingertip sampling during initial training, with media fills and as a competency assessment tool
  - Surface sampling for viable microorganisms

Environmental Monitoring Trending

“Regardless of the number of cfu identified in the pharmacy, further corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden…”

USP Chapter <797> USP 34-NF 29

CFU Identification and Sources

<table>
<thead>
<tr>
<th>Microorganisms (gram stain/ morphology)</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>Staphylococci/ 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 barns, especially in late summer/ fall, possible human contaminant</td>
</tr>
<tr>
<td>Diptheroids/ Coryneforms</td>
<td>Poor air conditioning (leading to sweating and personal discharge from gowns)</td>
</tr>
</tbody>
</table>

Source: Azzur Labs (www.AzzurLabs.com)

Cleaning and Disinfection

Daily Cleaning/Disinfection:
- ISO Class 5 surfaces
- ISO Class 5 equipment
- Work surfaces near the ISO Class 5 area such as carts
- Floors
  - Cleanroom
  - Atrium
  - Must occur when compounding is NOT taking place

Images courtesy ClinicalIQ™ LLC.
Cleaning and Disinfection

- Routine cleaning & disinfection decreases the overall bioburden in the compounding area therefore reducing the risk of contamination to CSPs.
- It is one part of an overall quality management plan. Other components include:
  - Design/function of primary and secondary engineering controls
  - Material/component handling procedures
  - Personnel hand hygiene and garmenting
  - Environmental sampling/testing

Standard Operating Procedures

- Requires formalized policies, processes and procedures used in preparing CSPs
- One element of quality that may not be routinely performed in pharmacies is documentation, or written “proof” that compounding occurring properly

Stability Studies

- Review articles about proper conduct of stability and compatibility studies written by Lawrence Trissel.
- Evaluate the information for the following:
  - Materials, test conditions and methods are completely described
  - A Stability-Indicating Assay is used
  - An Analytical Determination is performed at the outset
  - A time-zero determination of drug concentration is essential
  - Replicate assays at adequate/appropriate intervals since single point assays are not robust and do not control for the effects of assay variability and human error
  - Make sure the conclusions drawn fit the results obtained

What is Pharmacy’s Responsibility?

Principle:
A pharmacist respects the covenantal relationship between the patient and pharmacist.

What does that mean?
- The pharmacist has moral obligations in response to the gift of trust received from society.
- In return, the pharmacist promises to help individuals achieve optimum benefit from their medications, to be committed to their welfare, and to maintain their trust.

Redacted Example of Inadequate Stability Study Data

Understanding all of the elements

ASSUMPTION!
CSP is stored at its optimal temperature at all times.

Due to the inherent low probability that a Sterility Test can detect low levels of contamination in a batch, sterility assurance must always be based on process design and control.
Excellence is an art won by training and habituation. We do not act rightly because we have virtue or excellence, but we rather have those because we have acted rightly. We are what we repeatedly do. Excellence, then, is not an act but a habit.

Aristotle

Self-Assessment Questions

True or False?
- The patient impact associated with the fungal contamination of the methylprednisolone acetate drug produced by NECC has been successfully halted.

Self-Assessment

Which of the following are components for achieving a “State of Control” in sterile compounding operations? (select all that apply)?
- Cleaning and disinfecting
- Receiving ordered components from vendors
- Personnel work practice controls such as handwashing and garbing
- Material/component handling procedures
- Environmental monitoring

Self-Assessment Questions

According to USP Chapter <797>, when should the identity of microorganisms (at the genus level) be determined
- A. When the number of CFUs exceed the alert level of the ISO classified area being tested
- B. When the number of CFUs exceed the action level of the ISO classified area being tested
- C. Anytime there is growth
- D. Annually

Self-Assessment Questions

True or False?
- A robust quality system ensures that critical processes are routinely monitored and that information gained is used to improve processes which include the revision written PnP and staff training.