USP <797> Shock and Awe: What is it going to take?

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Learning Objectives

- Discuss current NECC fungal meningitis case count, USP <797> National Compliance Survey results and the shortcomings that occurred during the sterile preparation contamination tragedies since 2012.
- Identify issues discussed by congressional hearings and pharmacy state boards on contaminated sterile preparations.
- List the risks of failing to apply appropriate quality assurance to compounding or buying sterile preparations.

Thought

“’You can avoid reality, but you cannot avoid the consequences of avoiding reality.’”

Ayn Rand (1905-1982)

The compounded drug at the center of the NECC contamination case was which of the following?

A. Betamethasone
B. 17-α hydroxyprogesterone (17-P)
C. Methylprednisolone
D. Potassium chloride

Methylprednisolone

- A synthetic glucocorticoid or corticosteroid drug.
- All injectable dosage forms have preservatives which is contraindicated intrathecally.

Exserohilum rostratum

*Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions*

Images courtesy www.cdc.gov
FDA Inspection Findings After Deaths

- Ingredients used in manufacture were not sterile
- Autoclave cycle for the sterilization of suspensions not validated
- Action and Alert Limits were consistently exceeded in surface and air samples, no action taken
- Environmental sampling results of the air, surfaces and personnel gloved fingertip sampling plates consistently showed bacteria and mold, yet no investigation occurred
- Inappropriate facilities for sterile compounding, dirty pass through boxes, HVAC louvers, etc.

Mass DPH Inspection Findings After Deaths

- Violations of 247 CMR 9.01(3) or 247 CMR 6.01(5)(a)
- NECC distributed large batches of compounded sterile products directly to facilities apparently for general use rather than requiring a prescription for an individual patient.
- Product was not autoclaved properly
- Products was shipped before sterility test results were received
- Did not validate autoclaves
- Dirty powder hoods
- Hoods, tacky mats, facility was dirty
- Boiler was leaking, adjacent to the ante area

Current Events

- FDA Actions
  - FDA cGMP inspections of 64 pharmacies, contract testing labs (5)
  - 67 “483s” (list of inspectional observations) published on FDA website
- Medprep Consulting – New Jersey
  - Cease and desist issued; pharmacy closed
- Specialty Compounding-Texas
  - Contaminated IV Calcium Gluconate with Rhodococcus equi
  - 15 infected, 2 deaths
- Several compounding pharmacies have issued Voluntary Recalls of Medications Due to Concerns of Sterility Assurance at Testing Vendors

CDC Case Count

<table>
<thead>
<tr>
<th>New England Compounding Center (NECC) Meningitis Outbreak</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date</strong></td>
</tr>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td><strong>Drug/Lot</strong></td>
</tr>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td><strong>Injuries</strong></td>
</tr>
<tr>
<td><strong>Death(s)</strong></td>
</tr>
<tr>
<td><strong>Litigation</strong></td>
</tr>
</tbody>
</table>

Persons with Fungal Infections Linked to Steroid

Source: [CDC](http://www.cdc.gov/hai/outbreaks/meningitis.html)
FDA Microbiology FOCUS

- Facility Design
- Environmental Monitoring
- Gowning of Staff
- Disinfection and Cleaning
- Testing of Product
- Validation of Processes

FDA Issues: Garbing

- 48 of the companies visited by FDA were cited for gowned deficiencies:
  - Each human being harbors 1,000,000,000,000 microbes\(^1\)
  - Shed 100,000 particles per minute which increases with any movement\(^2\)
  - How do we wrap a person up so they are not bringing microbes into the aseptic environment?

FDA Issues: Environmental Monitoring

- 56 of the FDA 483 Audits had some issue with ES
- How do we trend non-viable particles, bacteria, yeast and mold counts?
- On surfaces, in the air and on people?
- Over changing seasons?
- During the course of compounding?

The minimum sampling frequency of twice a year is NOT adequate to evaluate the microbial control of the pharmacy compounding.

FDA Issues: Facility Design

- Qualification
  - No airflow studies (smoke studies)
  - No HEPA filter integrity testing
  - Electrical cord hanging in the back right of aseptic processing area. In situ air pattern analysis has not been performed to ensure the cord does not obstruct air flow
- Cleanliness
  - Cracked walls
  - Dirty hoods, debris on louvers, vents, lights, filters
  - Broken lights
  - Rust

FDA Issues: Facility Design

- Appropriate Workflow
  - Technician observed exiting the “ISO 5” area into adjacent “ISO 7” area on 3 or more occasions while exposed product is mixing.
  - Incubator to store plates for ES is in clean room where sterile drug product is produced, does it add particulates?
  - Sterile drug product filled into vials in ISO 5 hood and partially stopped then carried on a tray to ISO 7 room where they are hypophorized.
  - Pens brought into ISO 5 area from outside
  - “Slow deliberate” motions not always noted

Brutal Facts – Since USP Chapter <797>

<table>
<thead>
<tr>
<th>Year</th>
<th>State</th>
<th>Description</th>
<th>Type</th>
<th>ISIs Issued</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>AL</td>
<td>1 child died after receiving more than 10 times the amount of sodium chloride prescribed due to a compounding error in a hospital pharmacy.</td>
<td>Hospital</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>CA, FL, TN</td>
<td>16 patients being treated for wet muscle degeneration developed severe eye infections due to contamination of ANISTROPHOS® (benoxinate) during compounding, one patient blinded, further patient developed aseptic meningitis.</td>
<td>Hospital, Compounder</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>AL</td>
<td>9 patients among 18 died when parenteral nutrition solutions that were administered were contaminated with Stachybotrys. Maintenance during compounding using non-sterile components to prepare aseptic sols.</td>
<td>Hospital</td>
<td>1</td>
</tr>
<tr>
<td>2012</td>
<td>CA</td>
<td>9 patients developed fungal endophthalmitis after use of the compounded product Brilliant Blue (GB3) in reconstituting injections of lamotrigine containing products dispensed from the same compounding pharmacy.</td>
<td>Compounder</td>
<td>1</td>
</tr>
<tr>
<td>2012</td>
<td>Nationwide</td>
<td>More than 700 patients contracted fungal meningitis after receiving methylprednisolone sucralfate solution prepared by a compounding pharmacy that was contaminated with Exserohilum rostratum (brown mold) A3438A.</td>
<td>Compounder</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^1\) https://www.nytimes.com/2012/06/14/health/human-mold.html
\(^2\) 11542 https://www.fda.gov/ScienceResearch/SurveillanceMonitoring/StandardizedCleanroomMonitoring/ucm330980.htm

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Brutal Facts – Since USP Chapter <797>

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<thead>
<tr>
<th>Year</th>
<th>State</th>
<th>Description</th>
<th>Type</th>
<th>Rec Issued</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>CS Nc</td>
<td>A contaminated batch of magnesium sulfate (used as a preservative) was identified in a hospital. Several isolations of Staph. aureus were found. Pharmacy closed and PIC license was revoked.</td>
<td>Compounder Y</td>
<td>F</td>
</tr>
<tr>
<td>2013</td>
<td>TX</td>
<td>A batch of compounded Fadroxol 100 mg/200mL was contaminated with Lanosin. One death was reported.</td>
<td>Compounder Y</td>
<td>F</td>
</tr>
<tr>
<td>2013</td>
<td>TN</td>
<td>Testing of drug vials taken from a specialty pharmacy has shown bacterial and fungal contamination. Reports of six adverse events in North Carolina and Illinois who received injections of the steroidal/benzoic acid-containing products prompted FDA investigation.</td>
<td>Compounder Y</td>
<td>F</td>
</tr>
<tr>
<td>2013</td>
<td>Nationwide</td>
<td>Several compounded medications recalled out of the abundance of caution. Lack of sterility assurance. Testing procedures not in compliance with USP standards.</td>
<td>Contract Lab</td>
<td>F</td>
</tr>
</tbody>
</table>

Current Events

  - "Title I - Compounding Quality Act," establishes a clear boundary between traditional compounders and compounding manufacturers, which make sterile products without or in advance of a prescription and sell those products across state lines.
  - "Preserve and protect the practice of traditional pharmacy compounding occurring in community pharmacies regulated by state boards of pharmacy.
- Eliminate the unconstitutional provisions of Section 505A of the Federal Food, Drug, and Cosmetic Act (FFDCA) that created uncertainty regarding the laws governing compounding and require FDA to engage in two-way communication with state regulators – a major deficiency in FDA’s response to the meningitis outbreak.
- Permit entities engaged in the compounding of sterile drugs to register as “outsourcing facilities.”

Current Events (continued)

- Title II, "The Drug Supply Chain Security Act," provides a uniform, national drug tracing framework to track prescription drugs from the manufacturer to the pharmacy and raises the standards for prescription drug wholesalers across the U.S.
- Create a new framework for securing our prescription drug supply chain. The bill also would establish a 10-year transition to a unit level tracking system for enhanced security.
- Eliminate the patchwork of red tape, like California’s pedigree law, on drug manufacturers, wholesale distributors, pharmacies, repackagers, and third-party logistic providers (3PLs). These changes would help alleviate drug shortages and reduce government-imposed costs on prescription drugs.
- Create floor and ceiling licensure standards for wholesale distributors and 3PLs while preserving state authority for licensure issuance and fee collection.

USP Compounding Standards

- USP Chapter <797>: Sterile Compounding became official on January 1, 2004
- Revised chapter official on June 1, 2008
- Nationally enforceable
- 23 states require compliance, more states are modifying regulations
- Shall vs. Should: Appendix I
- USP Chapter <795>: Nonsterile Compounding

State Board of Pharmacy Position USP <797>

What is the best way (and value for $) to access USP chapter <797>compliance?

A. Conduct a self-assessment/gap analysis
B. Hire a consultant
C. Wait for DPH to find a negative finding
D. Wait for state board of pharmacy to find a negative finding
State of Compliance

Compliance Scores 2011 vs. 2013 based on State Regulatory Requirements

<table>
<thead>
<tr>
<th>Domain</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand Washing and Garbing</td>
<td>76.7%</td>
<td>76.8%</td>
<td>78.8%</td>
</tr>
<tr>
<td>Initial and Ongoing Training and Competency Measurement</td>
<td>75.5%</td>
<td>79.2%</td>
<td>77.8%</td>
</tr>
<tr>
<td>Personnel Media-Fill Challenge Testing</td>
<td>82.9%</td>
<td>86.9%</td>
<td>85.2%</td>
</tr>
</tbody>
</table>


National Survey Facility Scores

<table>
<thead>
<tr>
<th>Domain</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounding Facility Mgt (CFM): Airflows</td>
<td>60.5%</td>
<td>60.5%</td>
<td>59.0%</td>
</tr>
<tr>
<td>Pressure Differential Monitoring</td>
<td>50.6%</td>
<td>56.3%</td>
<td>59.0%</td>
</tr>
<tr>
<td>CFM: Cleaning and Disinfecting</td>
<td>73.9%</td>
<td>79.1%</td>
<td>76.8%</td>
</tr>
<tr>
<td>CFM: Equipment Calibration</td>
<td>70.3%</td>
<td>74.3%</td>
<td>73.3%</td>
</tr>
<tr>
<td>CFM: Temperature and Humidity Monitoring</td>
<td>84.4%</td>
<td>87.6%</td>
<td>85.4%</td>
</tr>
<tr>
<td>General Facility Design</td>
<td>75.8%</td>
<td>76.5%</td>
<td>76.2%</td>
</tr>
<tr>
<td>Primary/Secondary Engineering Controls</td>
<td>77.8%</td>
<td>80.0%</td>
<td>82.2%</td>
</tr>
</tbody>
</table>

National Survey EM Scores
Compliance with USP Chapter <797> ES requirements:

<table>
<thead>
<tr>
<th>Domain</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gloved Fingertip Sampling</td>
<td>45.4</td>
<td>53.3</td>
<td>51.4</td>
</tr>
<tr>
<td>Quality Management (QM): ES Program</td>
<td>64.7</td>
<td>66.4</td>
<td>67.7</td>
</tr>
<tr>
<td>QM: General Viable Air and Surface Sampling Considerations</td>
<td>59.1</td>
<td>62.0</td>
<td>61.1</td>
</tr>
<tr>
<td>QM: Incubation</td>
<td>59.8</td>
<td>68.3</td>
<td>65.4</td>
</tr>
<tr>
<td>QM: Non-Viable Particle Testing</td>
<td>90.8</td>
<td>93.2</td>
<td>91.6</td>
</tr>
<tr>
<td>QM: Surface Sampling - A personnel metric</td>
<td>59.1</td>
<td>63.0</td>
<td>61.3</td>
</tr>
<tr>
<td>QM: Viable Air Sampling - A facility metric</td>
<td>59.6</td>
<td>67.0</td>
<td>68.4</td>
</tr>
</tbody>
</table>


State of Compliance
Compliance with Daily Air Pressure/Velocity Documentation in Hospitals

![Graph showing compliance in hospitals over time.]

The Way Forward
- Legislation will be passed and it may or may not address the fundamental issues re: compounding vs. manufacturing
- State Boards of Pharmacy are actively and aggressively determining the risk of a similar event occurring in their state

Closing Thought
Pedantry and mastery are opposite attitudes toward rules.
To apply a rule to the letter, rigidly, unquestioningly, in cases where it fits and in cases where it does not fit, is pedantry...
To apply a rule with natural ease, with judgment, noticing the cases where it fits, and without ever letting the words of the rule obscure the purpose of the action or the opportunities of the situation, is mastery.

George Polya, mathematician (1887-1985)
Resources

- United States Pharmacopeia Chapter <797> Pharmaceutical Compounding—Sterile Preparations (USP 36 – NF 31)
- FDA 2013 Pharmacy Inspections and Related Records website, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAOnteractiveReadingRoom/ucm340853.htm