Deciphering Quality Assurance Procedures and Results from Your Outsourced Sterile Compounding Vendor

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Sterile Preparation Compounding
"Each problem that I solved became a rule which served afterwards to solve other problems."

- Rene Descartes
(1596-1650),
"Discours de la Methode"
## CDC Meningitis Outbreak Statistics

### New England Compounding Center (NECC) Meningitis Outbreak

<table>
<thead>
<tr>
<th>Date</th>
<th>September 21, 2012 (on-going) – October 23, 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>751 Total Case Count, 386 meningitis and Spinal Infection, 7 Stroke, 325 Paraspinal/Spinal infection, 33 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>64</td>
</tr>
<tr>
<td>Litigation</td>
<td>More than 20 lawsuits filed against NECC</td>
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</table>
Most Recent 2013 events

- **FDA Actions**
  - FDA cGMP inspections of 67 pharmacies, contract testing labs (5)
  - Seventy (70) “483s” (list of inspectional observations) published on FDA website [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm340853.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm340853.htm)
  - Closure/remediation against 483s

- **Medprep Consulting – New Jersey**
  - Cease and desist issued; pharmacy closed

- **Specialty Compounding – Texas**
  - Contaminated IV Calcium Gluconate with *Rhondococcus equii*, 15 infected, 2 deaths

- **Clinical Specialties – Georgia**
  - Voluntarily recalled 79 lots of bevacizumab-filled syringes (Avastin, Genentech) intended for retinal injections because of the risk for eye infection

- **Several compounding pharmacies have issued Voluntary Recalls of Medications Due to Concerns of Sterility Assurance at Testing Vendors**
History of Compounding

- Pharmacy compounding is simply the art and science of preparing customized medications that are not otherwise commercially available.

- Compounding is performed by or under the supervision of a pharmacist pursuant to an order from a licensed prescriber for an individual patient.

- Compounding is an essential element of pharmacy.
“Compounding” means the preparation of Components into a Drug product

1. as the result of a Practitioner’s Prescription Drug Order or initiative based on the Practitioner/patient/Pharmacist relationship in the course of professional practice, or

2. for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or Dispensing.

Compounding includes the preparation of Drugs or Devices in anticipation of receiving Prescription Drug Orders based on routine, regularly observed prescribing patterns.

Drug Quality and Security Act

- Current status: passed House & Senate; signed by President Obama on November 27, 2013
- Title 1: Compounding Quality Act
  - protects traditional pharmacies but clarifies the FDA’s authority over the compounding and requires coordination between the FDA and the states to ensure that drug compounding occurs safely
  - eliminates the unconstitutional provision of Section 503A of the Federal Food, Drug, and Cosmetic Act (FFDCA) which created the uncertainty surrounding compounding laws
  - requires the FDA to engage in two-way communications with state regulators
  - Under Section 503B, pharmacy outsourcers to voluntarily register as “outsourcing facilities,” making them subject to good manufacturing practices, risk-based inspection and other standards
Pharmacy Compounding Minimum Standards

- **Non Sterile Compounding**
  - USP Chapter <795>
    Pharmaceutical Compounding-Nonsterile Preparations
    - Minimum standard
    - Last revised June 2011

- **Sterile Compounding**
  - USP Chapter <797>
    Pharmaceutical Compounding-Sterile Preparations
    - Minimum standard
    - Last revised June 2008
    - USP Compounding Expert Committee working on revision
    - USP Chapter <800> Compounding Hazardous Drugs is in development
    - To be published in Spring 2014 PF
The Use of Outsourced Vendors

- 70.9% of hospitals outsource sterile compounding (fully or partially) according to a 2011 ASHP survey\textsuperscript{22}
- From legal and Joint Commission perspective, the hospital is responsible for the services provided to its patients under contract

Joint Commission Requirements for Contracted Providers

- Contracted services must adhere to all applicable TJC standards
  - “The same level of care should be delivered to patients regardless of whether services are provided directly by the hospital or through contractual agreement.”
  - For Example:
    - MM.05.01.09 – Medication labels – standard format/content
    - HR.01.06.01 – Staff competencies assessed
- Contracted providers can be evaluated for compliance during the hospital survey
  - can include a site visit

Care, treatment, and services provided through contractual agreement are provided safely and effectively.

- **EP 1:** Clinical leaders and medical staff provide advice on sources of contracted services.

- **EP 2:** Hospital describes, in writing, the nature and scope of services provided under contract.

- **EP 3:** Designated leaders approve contracts

- **EP 4:** Establish performance expectations for the contracted service

EP 5: Communicate the expectations in writing to the provider of the contracted services.

- Need not be in contract, can be addendum or separate document

EP 6: Evaluate these services in relation to the established expectations.

EP 7: Take steps to improve these services when the expectations are not met.

EP 8: Maintains continuity of care/services when contract terminated/renegotiated.

CMS: Governing body is responsible for oversight and monitoring of these requirements.

Summary of Joint Commission Requirements for Contracted Providers

- Contracted services must adhere to all applicable TJC standards
- Selected with clinical leader/medical staff input
- Contract approved by governing body
- Development, communication, and on-going evaluation of written performance expectations
  - Governing body must review and approve ongoing evaluation

Selection of an Outsourced Vendor

- Initial review (if not done yet, do so!) and ongoing evaluation.
  - Outsourcing assessment tools or use of consultants
- Components:
  - Document review
  - Due diligence
  - On-site visit
  - Evaluation
  - Contract
  - On-going monitoring ← Focus of webinar
Outsource Providers
- FDA registered outsourcing facilities
- Local compounding pharmacies – not registered with agency
  - Does the state require compliance with USP chapters on compounding and have they been inspected?
  - Subject to future Compliance Policy Guidance (CPG)
    - Currently out for public comment

The Food and Drug Administration is encouraging healthcare providers to make sure the compounded drugs they buy are mixed in facilities that are registered with the federal agency and are subject to inspections.
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
Keys Elements of Quality

**Personnel Training**
- Are licenses, registrations and CE current?
- How many hours of didactic training for compounders?
  - Evaluate training curriculum, training logs, rosters
- Aseptic media fills
  - What is the design of the media fill process
    - FDA cited several providers for not mimicking most challenging compounding methods practiced
  - How many and how often?
  - What happens in the event of contamination?
- Gloved fingertip sampling
  - Frequency (how often), media used
  - All fingers?
  - What happens in the event of CFU growth?
Facility and Primary Engineering Control (PEC) Certification

- What procedure is used to certify facility and PECs?
  - Are CETA Guidelines, CAG-003, current version used?
  - How often does testing occur?
  - At rest or under dynamic conditions?
- Non-viable particle counts?
  - How often (every six months plus additional sampling)
  - What does it mean the results mean?
  - What happens if the count is too high?
- In-situ smoke studies
  - FDA cited several providers for not having done a smoke study
Key Elements of Quality

Environmental Monitoring - Air Sampling

- Methods used to sample (volumetric vs. gravimetric)
- Locations sampled
- Media used (TSB/A, MEA or SAB)
- Media incubation temperatures
- CFU alert/action levels
  - What happens if excursions are identified
  - Speciation of microorganisms
    - Human pathogens vs. pathogenic microorganism
      - Gram negative rods, coagulase-positive staphylococcus, molds, yeast
Key Elements of Quality

Environmental Monitoring – Surface Sampling

- Methods used to sample (plates vs. swab)
- Locations sampled
  - Are personnel garb sampled?
- Media used (TSB/A, MEA or SAB)
- Media incubation temperatures
- CFU alert/action levels
  - What happens if excursions are identified
  - Speciation of microorganisms
    - Human pathogens vs. pathogenic microorganism
      - Gram negative rods, coagulase-positive staphylococcus, molds, yeast
Key Elements of Quality

Other Facility Performance Criteria

- Pressure Differentials
  - How are excursions handled and documented
- Temperature Monitoring
  - How are excursions handled and documented

Components used

- FDA approved, commercially available products
- Bulk stock solutions prepared from non-sterile API
  - Once a high-risk, always a high-risk
  - Low and medium-risk CSPs are made from FDA approved, commercially available product.
Methods of Sterilization

- Are sterilization methods used in manufacturer of CSPs?
  - Aseptic technique
  - Filtration
  - Form of Terminal Sterilization
    - Autoclaves or other methods
    - The use of biological indicators with every cycle
Key Elements of Quality

Chemical Stability

- Data is critical to evaluating performance of outsourcing pharmacy
- Processes, procedures and drug stability-indicating methods need to be evaluated and understood by customer
  - Since FDA has not approved the drugs prepared at these facilities, you need to do your best to determine applicability
- FDA registered pharmacy outsourcer facilities are required to validate their methods so claims of proprietary should not be hindrance
- If outsourcer refuses to provide, amend contract that holds outsourcer accountable to quality in a lawsuit
Key Elements of Quality

Sterility Testing

- In absence of sterility testing (according to USP 71 or another validated method), the default BUDs apply
  - What method is used, when and why
    - USP 71-Membrane Filtration vs. Rapid Micro Method
  - Are batches released “at risk”?
- If process validation/verification is used, what does that mean?
  - Since humans are fallible and prone to error, how does this method meet the USP standards?
## Sterility Testing Quick Reference

<table>
<thead>
<tr>
<th>Key Element</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Correct # units</strong></td>
<td>Per USP Chapter &lt;71&gt;, Table 3</td>
</tr>
<tr>
<td><strong>Correct volume/unit</strong></td>
<td>Per USP Chapter &lt;71&gt;, Table 2</td>
</tr>
<tr>
<td><strong>Correct method</strong></td>
<td>• Membrane filtration: pool all samples and run through single filter</td>
</tr>
<tr>
<td></td>
<td>• Must have justification if using direct inoculation: 1:1 (unit tested and broth used)</td>
</tr>
<tr>
<td></td>
<td>• Other methods (not in USP Chapter &lt;71&gt;) IF verification demonstrates equivalence to USP Chapter &lt;71&gt;</td>
</tr>
<tr>
<td><strong>Method Suitability Testing performed</strong></td>
<td>Determines if the sterility testing method is valid for a particular type of CSP and that the drug does not interfere with the sterility test method</td>
</tr>
<tr>
<td><strong>Correct Media Used</strong></td>
<td>• Fluid thioglycollate media (FTM) Incubated for 14 days (20-25°C) anaerobic and aerobic bacteria</td>
</tr>
<tr>
<td></td>
<td>• Soybean casein digest media (SCDM) Incubated for 14 days (30-35°C) for both aerobic bacteria and fungi</td>
</tr>
</tbody>
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Rapid Microbiological Methods

- Need to validated to be equivalent to USP Chapter <71>
  - Limit of Detection? 1-10 CFU*/mL
- These methods can be validated as alternative methods to the compendial sterility testing using the validation of alternative microbiological criteria outlined in USP Chapter <1223>

*CFU = colony-forming unit
Rapid Microbiological Methods

- **RMM Technologies**
  - Adenosine triphosphate (ATP) bioluminescence technology
  - Solid-phase cytometry (fluorescent cell labeling and laser scanning)
  - CO₂ sensing (BacT/ALERT®)
  - Polymerase chain reaction (PCR)
Elements of Quality

• Customers Complaints and Recalls
  • How many complaints have been filed with vendor?
    ▪ Percentage per total doses – Is this a good indicator
    ▪ Classification/Nature of complaints
  • Has the vendor had to do a recall of any product during the quarterly reporting period?

• CAPA-Corrective and Preventative Action
  • Does the vendor have this program and what were the findings?
Closing Thoughts

“Doveryai, no proveryai”
“Trust but verify”
Former President Ronald Reagan
Thank you

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