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

Eric S. Kastango, MBA, RPh, FASHP
President/CEO of Clinical IQ, LLC and CriticalPoint, LLC
Madison, NJ and Gaithersburg, MD
eric.kastango@clinicaliq.com

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.

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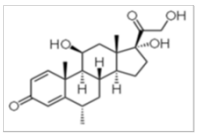
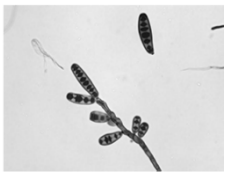
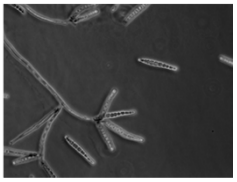


"Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions"

Exserohilum rostratum



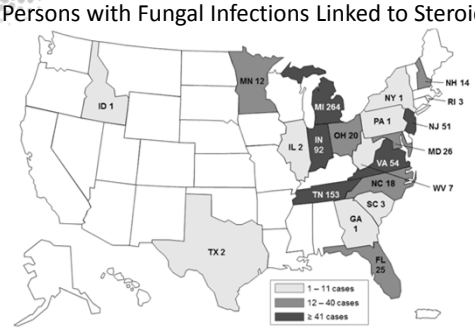


Images courtesy www.cdc.gov

CDC Case Count

New England Compounding Center (NECC) Meningitis Outbreak	
Date	September 21, 2012 (on-going) – September 6, 2013
Location	USA (23 States)
Drug/Lot	Methylprednisolone acetate PF, Lots 05212012@68, 06292012@26, 08102012@51.
Cause	Fungal meningitis contamination of steroid medication
Injuries	750 Total Case Count, 379 meningitis and Spinal Infection, 6 Stroke, 288 Paraspinal/Spinal infection, 30 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.
Death(s)	64
Litigation	More than 20 lawsuits filed against NECC

Persons with Fungal Infections Linked to Steroid



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

CDC Update

http://www.cdc.gov/HAI/outbreaks/meningitis.html

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

http://www.mass.gov/eohhs/docs/dph/quality/boards/necc/necc-preliminary-report-10-23-2012.pdf

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.

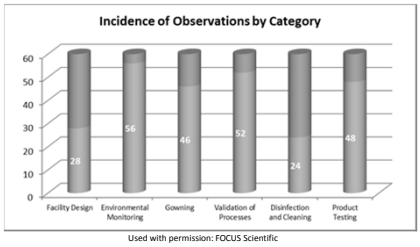
http://www.fda.gov/aboutfda/centersoffices/officeofglobalregulatoryoperationsandpolicy/ora/oraelectronicreadingroom/ucm325828.htm

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 *Rhondococcus equii*
  - 15 infected, 2 deaths
- Several compounding pharmacies have issued Voluntary Recalls of Medications Due to Concerns of Sterility Assurance at Testing Vendors

FDA Microbiology FOCUS

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



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FDA Issues: Garbing

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- 48 of the companies visited by FDA were cited for gowning 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?

1. http://www.nytimes.com/2012/06/14/health/human-microbiome-project-decodes-our-100-trillion-good-bacteria.html
2. Dr. Ken Goldstein Cleanroom Consultants, and Mike Fitzpatrick, Lockwood Greene, Cleanrooms East 99.

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 .

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FDA Issues: Facility Design

- Appropriate Workflow
  - Technician observed exiting the "ISO 5" area into adjacent "ISO 7" ante room 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 stoppered then carried on a tray to ISO 7 room where they are lyophilized.
  - Pens brought into ISO 5 area from outside
  - "Slow deliberate" motions not always noted

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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

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Brutal Facts – Since USP Chapter <797>

Year	State	Description	Type	483 Issued
2010	IL	1 child died after receiving more than 60 times the amount of sodium chloride prescribed due to a compounding error in a hospital pharmacy.	Hospital	N
2011	CA, FL, TN	16 patients being treated for wet macular degeneration developed severe eye infections due to contamination of AVASTIN (bevacizumab) during compounding; one patient blinded, another patient developed brain infection.	Hospital Compounder	Y
2011	AL	9 patients among 19 died when parenteral nutrition solutions that were administered were contaminated with Serratia marcescens during compounding using non-sterile components to prepare amino acids.	Homecare Compounder	Y
2012	CA	9 patients developed fungal endophthalmitis after use of the compounded product Brilliant Blue-G (BBG) or receiving injections of triamcinolone-containing products dispensed from the same compounding pharmacy.	Compounder	Y
2012	Nationwide	More than 700 patients contracted fungal meningitis after receiving methylPREDNISolone acetate injection prepared by a compounding pharmacy that was contaminated with Exserohilum rostratum (a brown-black mold) Aspergillus.	Compounder	Y

Brutal Facts – Since USP Chapter <797>

Year	State	Description	Type	483 Issued
2013	CT, NJ	A contaminated batch of magnesium sulfate minibags was identified in hospital. Several violations of state law. Pharmacy closed and PIC license was revoked.	Compounder	Y
2013	TX	A batch of compounded IV Calcium Gluconate found to be contaminated with Rhondococcus equii. 15 infected patients, 2 deaths (relationship to drug not known)	Compounder	Y
2013	TN	Testing of drug vials taken from a specialty pharmacy has shown bacterial and fungal contamination. Reports of skin abscesses in individuals in North Carolina and Illinois who received injections of the steroid methylprednisolone acetate prompted the investigation.	Compounder	Y
2013	Nationwide	Several compounded medications recalled out of the abundance of caution. Lack of sterility assurance. Testing procedures not in compliance with compendial standards.	Contract Lab	Y

Current Events

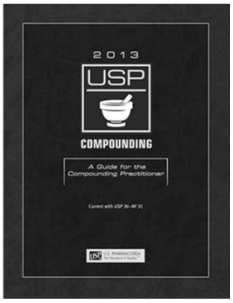
- Pending Federal Legislation-H.R. 3204, The Drug Quality and Security Act-2 Titles
- "Title I - Compounding Quality Act," establishes a clear boundary between traditional compounders and compounding manufacturers, which make sterile products without or in advance of a prescription and sell those products 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 503A 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)

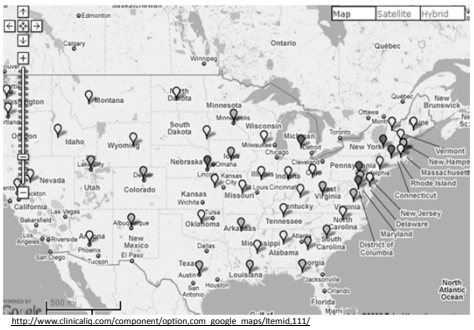
- Title II, "The Drug Supply Chain Security Act," provides a uniform, national drug tracing framework to track prescription drugs from the manufacturer to the pharmacy and raises the standards for prescription drug wholesalers across the U.S.
  - Create a new framework for securing our prescription drug 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>



http://www.clinicaliq.com/component/option,com_google_maps/Itemid,111/

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

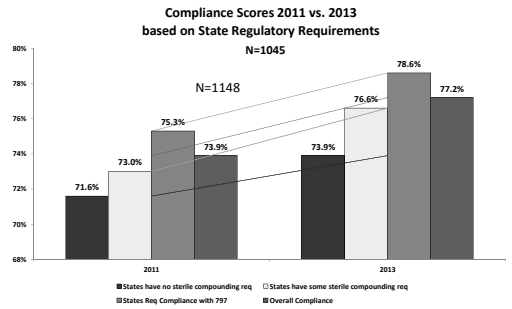
A Conduct a self-assessment/gap analysis

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



Source: Douglass K, Kastango E, Cantor P, et al. The 2013 USP <797> compliance study. *Pharm Purch Prod.* Oct 2013

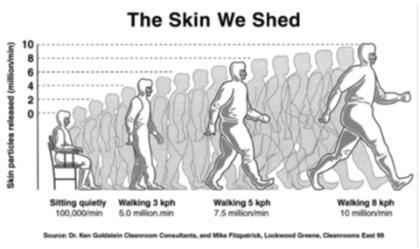
National Compliance Survey Scores

Year to Year Compliance Score Comparisons for Certain Domains

Domain	2011	2012	2013
Hand Washing and Garbing	76.7%	78.6%	78.5%
Initial and Ongoing Training and Competency Measurement	75.5%	79.2%	77.8%
Personnel Media-Fill Challenge Testing	82.9%	86.9%	85.2%

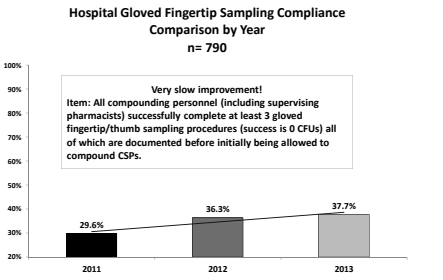
Source: Douglass K, Kastango E, Cantor P, et al. The 2013 USP <797> compliance study. *Pharm Purch Prod.* Oct 2013.

Importance of Garbing



Used with permission: Particle Measuring Systems

State of Compliance



Source: Douglass K, Kastango E, Cantor P, et al. The 2013 USP <797> compliance study. *Pharm Purch Prod.* Oct 2013.

Is this an example of USP 797 compliant garbing ?

A Yes

B No

National Survey Facility Scores

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

Source: Douglass K, Kastango E, Cantor P, et al. The 2013 USP <797> compliance study. *Pharm Purch Prod.* Oct 2013.

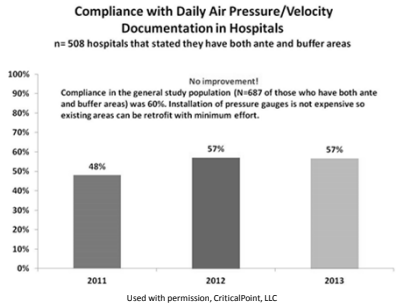
National Survey EM Scores

Compliance with USP Chapter <797> ES requirements

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

Source: Douglass K, Kastango E, Cantor P, et al. The 2013 USP <797> compliance study. *Pharm Purch Prod.* Oct 2013.

State of Compliance



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USP <797> is …

A A minimum standard for sterile compounding

B A Best Practice guideline

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 their state

The Way Forward

- USP Chapters on compounding will continue to be the gold standard
- Expect changes to the chapter:
  - Frequency of environmental monitoring
  - Clarification of cleaning and disinfection practices
  - Clarification of critical quality testing metrics
    - Extending BUD via Sterility Testing
    - Chemical Stability via Stability Indicating Methods

USP U.S. Pharmacopeial Convention
Global Expertise
Trusted Standards
Improved Health

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/ORA/ORAElectronicReadingRoom/ucm340853.htm

