"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	
Date	September 21, 2012 (on-going) – August 5, 2013
Location	USA (23 States)
Cause	Fungal meningitis contamination of steroid medication
Injuries	749 Total Case Count, 384 meningitis and Spinal Infection, 7 Stroke, 323 Paraspinal/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.
Death(s)	63
Litigation	More than 20 lawsuits filed against NECC

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

The sterility sample taken by the firm consisting of one 5ml vial of bulk formulated methylprednisolone acetate (preservative free) from lot 08102012@51 resulted in a sterile result (lab analysis started 8/14/12 and reported 8/28/12). However, the FDA analysis of FDA Sample #693965, consisting of methylprednisolone acetate (preservative free) 80mg/mL, 1mL filled vials, from Lot #08102012@51 collected from the firm, confirmed the presence of viable microbial growth in 50/50 vials tested. One vial examined microscopically showed fungal morphological features.

3. The firm's environmental monitoring program yielded the following microbial isolates (bacteria and mold) within Clean Room 1 and Clean Room 2, used for the production of sterile drug products, between January 2012 and September 2012. Firm personnel stated that the firm shuts off the air conditioning from 8:00 pm to 5:30 am nightly in the Clean Room.

There was no investigation conducted by the firm when levels exceeded their action limits and there was no identification of the isolates. No documented corrective actions were taken to remove the microbial contamination (bacteria and mold) from the facility.

NECC Findings from FDA 483

On 10/04/2012, a boiler installed within approximately 30 feet of the entrance to the Prep Room (ISO 8) was observed to be leaking water into puddles. Moreover, wet floor surfaces around the boiler appeared to be soiled with thick white debris and thick black, granular material. Gaps were observed between sliding doors, located at the transition between the Prep Room (ISO 8) and the warehouse, despite being fully closed. This room is used for the preparation of equipment and includes the (b) (4)

On 10/04/2012, we observed what appeared to be dark, hair-like discoloration along the gasket and crevices located at the bottom edge of the closed pass through installed within the wall of the ISO 6 Clean Room. The firm utilizes the ISO 6 Clean Room to formulate and fill sterile preparations, including methylprednisolone.

On 10/04/2012, we observed what appeared to be dark particulate and white, filamentous substances covering the louvers of an HVAC return located behind the "(b) (4) autoclave", located in the firm's Middle Room (ISO 7). This autoclave is used for the steam sterilization of formulated bulk drug suspensions, including preservative free formulations of methylprednisolone and triamcinolone, which are intended for injection.

Table #5: Air Sampling of ISO 7 (Class 10,000) Rooms
Alert: 5 CFU Action: 8+ CFU

Location	Result Bacteria	Result Mold	Date
Gown Room (Clean Room 1)			
Gown room	29*	1*	5/31/12
Gown room	11*	1*	6/28/12
Middle Room (Clean Room 1)			
Crimp Station	3	1	2/23/12
Prep Room (Clean Room 2)			
Prep room	0	1	5/2/12
Gown Room (Clean Room 2)			
Gown room	7*	3*	8/9/12

Note: (*) indicates result over action level

Table #6: Surface and Air Sampling of ISO 5 (Class 100) Clean Room 2
No Action/Alert Levels specified by firm for ISO 5 (Class 100) areas.

Location	Sample Type	Result Bacteria	Result Mold	Date
Table 1 (near Horiz L & R hoods)	Surface	0	3	1/26/12
Table 1 (near Horiz L & R hoods)	Surface	1	1	5/2/12
Between Horiz L & Horiz R	Air	1	1	7/25/12

Table #2: Surface Samples of ISO 7 (Class 10,000) Rooms
Alert: 5 CFU Action: 7+ CFU

Location	Result Bacteria	Result Mold	Date
GRmisc2 (floor under barrel against wall)	11*	0	3/29/12
8 FLR (gown room/near hooks)	10*	0	4/5/12
7 FLR (gown room/entrance)	0	1	4/5/12
GRmisc1 (rubber flap over wheel of rack)	9*	0	4/12/12
WallGR1 (window sill side to middle room)	9*	0	4/13/12
GRmisc1 (top of rack with bouffants)	12*	0	5/10/12
7 FLR (GR/entrance)	2	1	5/31/12
8 FLR (GR/near hooks)	19*	0	5/31/12
8 FLR (GR/near hooks)	0	13*	6/28/12
7 FLR (GR entrance)	3	3	6/28/12
GRmisc1 (bottom of bootie bin)	¾ of plate OG*	1*	7/26/12
GRmisc2 (bottom of mask bin)	plate ¾ overgrown*	0	7/26/12
8 FLR (GR/near hooks)	9*	0	7/26/12
GRmisc2 (front of 7-7.7 glove bin)	OG*	1*	8/2/12
GRmisc2 (loose bootie bin)	0	Plate ½ mold*	8/23/12
Middle Room (Clean Room 1)			
5 FLR (near crimp bench)	0	1	2/23/12
6 FLR (near sink bench)	0	1	2/23/12
6 FLR (near sink bench)	2*	11*	3/15/12
MRmisc1 (dh20 gallon)	1	1	5/10/12
Gown Room (Clean Room 2)			
Gown Room Flr	OG*	0	1/26/12
Gown Room Flr	0	1	3/1/12
Gown Room Flr	9*	0	8/9/12
Prep Room (Clean Room 2)			
Prep Room Flr	1	1	2/2/12
Misc #2 Flr (top of radio)	0	1	2/7/12
Misc Flr (Calcium chloride bin)	1	1	4/4/12
Prep Room Flr	15*	2*	6/13/12

Note: (*) indicates result over action level, OG indicates over growth

4. The environmental monitoring procedure requires sampling via personnel touch plates taken upon completion of sterile compounding and prior to cleaning. Records from January thru September 2012 for Clean Room 1 and Clean Room 2 showed the following results inside production hoods:

Table #1: Clean Room 1 and Clean Room 2 Facility Personnel Touch Plates

Date	Isolates	Location	Product
1/3/12	OG with bacteria	Horizontal 1 (Clean Room 1)	Avastin
4/12/12	OG with bacteria	IT/Hood 3 (Clean Room 1)	Product not documented
6/15/12	1 bacteria, 1 mold	Horizontal 2A (Clean Room 1)	Rapivi/Keter/Epi
6/21/12	2 bacteria	Horizontal R (Clean Room 2)	Product not documented
7/2/12	½ plate OG with bacteria	Horizontal L (Clean Room 2)	Product not documented
7/19/12	1 bacteria, 2 molds	Horizontal 2C (Clean Room 1)	Mafenide Acetate
7/31/12	2 bacteria	Horizontal 2A (Clean Room 1)	KCl/Lido/D5W
8/10/12	2 bacteria	Hood 3 (glovebox) (Clean Room 1)	Acc 20%, Ped Atropine

Note: OG indicates over growth

These results were not investigated and there was no identification of the isolates. There were no product impact assessments performed for any sterile products that were made in the hoods or gloveboxes on the days the samples were taken. In addition, the firm has no evidence that any corrective actions were taken to prevent contamination of the sterile drug products.

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 particulate 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

Effect of two work practice changes on the microbial contamination rates of pharmacy-compounded sterile preparations. Trissel et al."

Objective: To determine if simple work practice changes could effectively reduce the potential contamination occurrence

Results:

Group	Contamination	Type of Gloves			70% Isopropyl Alcohol (IPA)	
		None	Non-sterile	Sterile	Initial	Initial + Repeated
A (Years 1 and 2)	28/539 (5.2%)	X	X		X	
B (Year 3)	3/311 (0.96%)		X			X
C (Year 4)	1/296 (0.34%)			X		X

- Significant reduction in contamination:
  - Groups B + C compared to Group A (p=0.000018)
  - Group B compared to Group A (p=0.0029)
  - Group C compared to Group A (p=0.0005)
- Non-significant reduction in contamination:
  - Group C compared to Group B (p=0.3367)

Conclusions: The use of protective chemotherapy gloves that were repeatedly disinfected with IPA decreased the contamination rate of pharmacy-compounded sterile preparations

Trissel LA, Gumtompo JA, Sucnc LM, Woodard MY, Angelus CH. Effect of two work practice changes on the microbial contamination rates of pharmacy-compounded sterile preparations. Am J Health-Syst Pharm 2007 64:837-41.

Synder SL, Van Scoik S, et al. Assessing Contamination Rates of Medium-Risk Compounding With Sterile vs. Non-sterile Gloves in a community Hospital-2011 ASHP MCM Poster-NOLA

Critical Factors in Aseptic Technique

Table 1. Data Results

Agar Fingertip Testing	Bacterial Growth		P-value
	Yes	No	
Hand			0.735
Right (n = 78)	13	65	
Left (n = 78)	15	63	
Time of Testing			0.21
Before Compounding (n = 77)	17	60	
After Compounding (n = 77)	11	66	
Type of Glove			<0.001
Sterile (n = 80)	5	75	
Non-Sterile (n = 164)	25	79	

Mini bag testing	Bacterial Growth		P-value
	Yes	No	
Time of Testing			0.563
Before Compounding (n = 39)	3	36	
After Compounding (n = 40)	1	39	
Type of Glove			0.688
Sterile (n = 38)	2	36	
Non-Sterile (n = 45)	2	43	

- No significant difference in bacterial growth for the use of sterile versus non-sterile gloves in TSB mini-bags (p= 0.855)
- No significant difference in contamination risk based on if the test was completed with new gloves or gloves used for at least 1 hour of compounding in TSB mini-bags (p=0.293) or TSA plates (p=0.21)
- Significant difference between bacterial growth and type of glove used in TSA plates (p<0.001); Odds ratio of 3.3 times more likely to have bacterial growth with use of non-sterile versus sterile gloves
- No significant difference in contamination risk based on which hand was used during compounding (p=0.732)

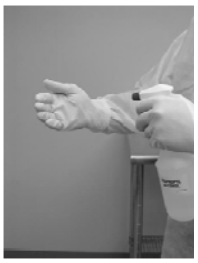
Synder SL, Van Scoik S, et al. Assessing Contamination Rates of Medium-Risk Compounding With Sterile vs. Non-sterile Gloves in a community Hospital-2011 ASHP MCM Poster-NOLA

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[1]
    - 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"



1 Hellums M, et al. Instruction on compounded sterile preparations at U.S. schools of pharmacy. *Am J Health Syst Pharm.* Nov 1 2007;64(21):2267-2274.

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!

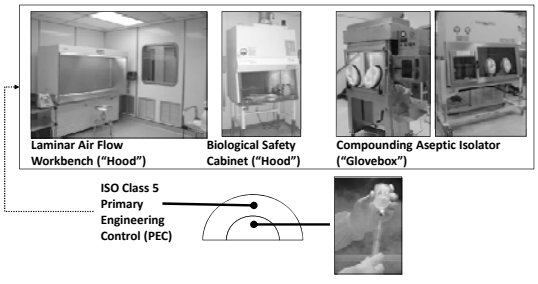
Environmental Controls

- 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

Environmental Controls

- ISO 7 buffer area and ISO 8 ante area – are "Secondary engineering controls"
- Must maintain ISO 7 or 8 during dynamic (in use) working conditions
- Airflow and balance testing required at the installation site
- Only personnel and materials essential for compounding and cleaning are permitted

Primary Engineering Controls



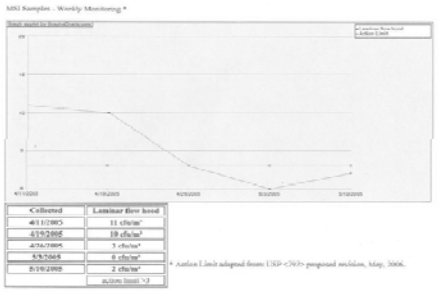
Environmental Sampling

- 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 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

Environmental Monitoring Trending

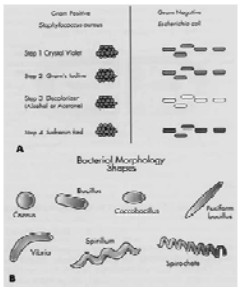


Courtesy of msi®

Environmental Sampling

- "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



CFU Identification and Sources

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

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
  - Anteroom
  - 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 garbing
  - Environmental sampling/testing

Images courtesy ClinicalIQ™, LLC.

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

Redacted Example of Inadequate Stability Study Data

SAMPLE INFORMATION

Customer:
Received:
Description: AMIODARONE 900MG IN 500ML D5W
Lot Number:
Sample #:
Cmpd Date:
Storage*: Room Temperature
Amount / Device: 900mg amiodarone in D5W 500ml

RESULTS

Test	Days	Specification	Result	Comment
Potency/Purity[1]	1	90.0 - 110.0 %	99.02% (891.21 mg/container)	Amiodarone HCl
Potency/Purity[1]	14	90.0 - 110.0 %	97.85% (880.63 mg/container)	Amiodarone HCl
Potency/Purity[1]	33	90.0 - 110.0 %	96.43% (867.86 mg/container)	Amiodarone HCl
Potency/Purity[1]	61	90.0 - 110.0 %	99.39% (894.51 mg/container)	Amiodarone HCl
Potency/Purity[1]	90	90.0 - 110.0 %	91.90% (827.02 mg/container)	Amiodarone HCl
Endotoxin[2]	1	≤ 10.51 EU/mL	<0.50 EU/mL	
Sterility (Bacteria/Fungi)[3]	1	Negative at 14 days	Negative at 14 days	
Sterility (Bacteria/Fungi)[3]	33	Negative at 14 days	Negative at 14 days	
Sterility (Bacteria/Fungi)[3]	90	Negative at 14 days	Negative at 14 days	
Particulate Matter[4]	1	≥10µm: ≤25/mL ≥25µm: ≤3/mL	Meets Requirements	≥10µm: ≤8.3/mL ≥25µm: ≤0.1/mL
Particulate Matter[4]	33	≥10µm: ≤25/mL ≥25µm: ≤3/mL	Meets Requirements	≥10µm: ≤16.4/mL ≥25µm: ≤1.1/mL
Particulate Matter[4]	90	≥10µm: ≤25/mL ≥25µm: ≤3/mL	Fails Requirements	>10µm: 44.9/mL >25µm: 1.8/mL

What is Pharmacy's Responsibility?

Principle:

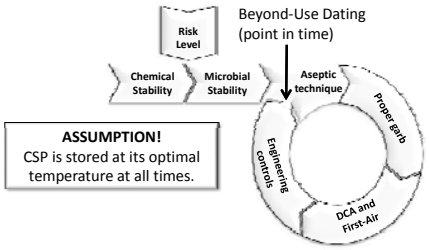
A pharmacist respects the covenantal relationship between the patient and pharmacist.

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.

From the Code of Ethics for Pharmacists (ASHP, 2007)

Understanding all of the elements



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

Thank you

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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.

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Self-Assessment

Which of the following are components for achieving a "State of Control" in sterile compounding operations? (select all that apply)?

a) Cleaning and disinfecting
b) Receiving ordered components from vendors
c) Personnel work practice controls such as handwashing and garbing
d) Material/component handling procedures
e) Environmental monitoring

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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

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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.

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