Compounding Pharmacies and Personnel Control

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Disclaimer

• I am making this presentation as an independent agent
• I am not making this presentation as a representative of USP, PDA, PMF, SCA, PSSNY or any other organization with which I am currently associated.
• The views expressed in this presentation are offered as mine alone.
Overview of Webinar

• Introduction
• Responsibility of Compounding Personnel
• Training of Compounding Personnel
• Expectations of "Quality Assurance in Pharmaceutical Compounding"
• Expectations of FDA under cGMP
• Summary

Personnel - <797>

“It is generally acknowledged that direct or physical contact of critical sites of CSPs with contaminants, especially microbial sources, poses the greatest probability of risk to patients. Therefore, compounding personnel must be meticulously conscientious in precluding contact contamination of CSPs both within and outside ISO Class 5 (see Table 1) areas.”
Personnel - <797>

“Some differences between standards for sterile compounding in this chapter and those for nonsterile compounding in Pharmaceutical Compounding - Nonsterile Preparations <795> include, but are not limited to, ISO-classified air environments (see Table 1); personnel garbing and gloving; personnel training and testing in principles and practices of aseptic manipulations and Sterilization; environmental quality specifications and monitoring; and disinfection of gloves and surfaces of ISO Class 5 (see Table 1) sources.”

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- <797> Responsibility of Compounding Personnel
- <797> Training of Compounding Personnel
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Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed. These performance responsibilities include maintaining appropriate cleanliness conditions…

SUPERVISORS SHALL ENSURE

1. Compounding personnel are adequately skilled, educated, instructed, and trained to correctly perform and document the following activities in their sterile compounding duties:
   a. perform antiseptic hand cleansing and disinfection of nonsterile compounding surfaces;
   b. select and appropriately don protective garb;
   c. maintain or achieve sterility of CSPs in ISO Class 5 (see Table 1) PEC devices and protect personnel and compounding environments from contamination by radioactive, cytotoxic, and chemotoxic drugs (see Hazardous Drugs as CSPs and Radiopharmaceuticals as CSPs);
   d. identify, weigh, and measure ingredients; and
   e. manipulate sterile products aseptically, sterilize high-risk level CSPs, and label and quality inspect CSPs.
<797> - Responsibility of Compounding Personnel  SUPERVISORS SHALL ENSURE

2. "Ingredients have their correct identity, quality, and purity.

3. Opened or partially used packages of ingredients for subsequent use in CSPs are properly stored under restricted access conditions in the compounding facility. Such packages cannot be used when visual inspection detects unauthorized breaks in the container, closure, and seal; when the contents do not possess the expected appearance, aroma, and texture; when the contents do not pass identification tests specified by the compounding facility; and when either the BUD or expiration date has been exceeded."

4. Water-containing CSPs that are nonsterile during any phase of the compounding procedure are sterilized within 6 hours after completing the preparation in order to minimize the generation of bacterial endotoxins.

5. Sterilization methods achieve sterility of CSPs while maintaining the labeled strength of active ingredients and the physical integrity of packaging.

6. Measuring, mixing, sterilizing, and purifying devices are clean, appropriately accurate, and effective for their intended use. when either the BUD or expiration date has been exceeded."
Eight more expectations for CSP quality and labeling expectations are listed in this section.

**Personal Hygiene/Gowning**

- Avoid contact with all unnecessary surfaces.
- Consciously avoid nervous mannerisms such as scratching or touching other body parts.
- Reduce excessive and unnecessary movement in order to minimize particulate contributions.
- Minimize working or moving gloved hands below the first primary work surface.
- Keep gloved hands above waist level.
Important Consideration

First Air

Gowning/Hygiene

- Goal is to contain the main source of contamination in the cleanroom
  - Minimize challenge to gown by minimizing bacterial shedding potential
  - Make sure that gown is complete
  - Endure that procedure to gown is designed to encourage aseptic exterior of gown
Methods of Spread

- Dispersion
  - Generate particulate matter
  - Viable microorganisms attached to particles (dead skin, hair, fibers)
- Touch Contamination
- Aerosols

Personnel Shedding – Particles per Minute by Activity

### Table III: Performance of cleanroom clothing systems after various numbers of washing and sterilization cycles.*

<table>
<thead>
<tr>
<th>Clothing</th>
<th>Contaminant</th>
<th>After 1 wash and sterilization cycle</th>
<th>After 25 wash and sterilization cycles</th>
<th>After 50 wash and sterilization cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-quality cleanroom clothing</td>
<td>Particles &gt;0.5 µm</td>
<td>585</td>
<td>3950</td>
<td>2860</td>
</tr>
<tr>
<td></td>
<td>Particles &gt;5 µm</td>
<td>9</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Colony-forming units</td>
<td>0.38</td>
<td>0.49</td>
<td>1.14</td>
</tr>
</tbody>
</table>

*Comparison of data (mean values) of the source strength (generated particles and colony-forming units [cfu] per second). People were dressed in various clothing systems washed and sterilized once, 25 times, or 50 times, respectively.


### Table IV: Source strengths (cfu/s) for high-quality cleanroom clothing and the estimated maximum number of operators allowed in an aseptic filling room with a maximum level of 10 cfu/m³.

<table>
<thead>
<tr>
<th>Number of washing and sterilizing cycles</th>
<th>Source strength (cfu/s)</th>
<th>Concentration (cfu/m³)</th>
<th>Maximum number of operators</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.38</td>
<td>0.76</td>
<td>13</td>
</tr>
<tr>
<td>25</td>
<td>0.49</td>
<td>0.98</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>1.14</td>
<td>2.28</td>
<td>3</td>
</tr>
</tbody>
</table>

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Training of Personnel

“Personnel who prepare CSPs shall be trained conscientiously and skillfully by expert personnel and through audio-video instructional sources and professional publications in the theoretical principles and practical skills of aseptic manipulations and in achieving and maintaining ISO Class 5 (see Table 1) environmental conditions before they begin to prepare CSPs.”
**Competency**

“Compounding personnel shall perform didactic review and pass written and media-fill testing of aseptic manipulative skills initially, at least annually thereafter for low- and medium-risk level compounding, and semiannually for high-risk level compounding. Compounding personnel who fail written tests or whose media-fill test vials result in gross microbial colonization shall be immediately re-instructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.”

**Media-Fill Challenge Testing**

- “The skill of personnel to aseptically prepare CSPs may be evaluated using sterile fluid bacterial culture media-fill verification…”
- “Media-fill testing is used to assess the quality of the aseptic skill of compounding personnel”
- “Media-fill challenge tests that simulate high-risk level compounding are also used to verify the capability of the compounding environment and process to produce a sterile preparation.”
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- Introduction
- Competency Evaluation of Garbing and Aseptic Work Practice
- Surface Cleaning and Disinfection Sampling and Assessment

- Introduction is a review of previous training session, with less emphasis on media-fills
- Describes using contractors for cleaning/disinfection. These need training (and demonstrate competence) in:
  - Proper hand hygiene
  - Garbing
  - Cleaning and disinfection procedures

Competency Evaluation of Garbing and Aseptic Work Practice

Competency check shall be done initially and at every media-fill using form similar to “Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding Personnel (see Appendix III)” and fingertip sampling.
Garbing And Gloving Competency Evaluation

• Visual observation
• Document results

Gloved Fingertip Sampling

• “All compounding personnel shall successfully complete an initial competency evaluation and gloved fingertip/thumb sampling procedure (zero cfu) no less than three times before initially being allowed to compound CSPs for human use.”
• Procedure provided:
  • TSA w/lecithin + polysorbate
  • Incubate 30°-35° for 48-72 hours
Aseptic Manipulation Competency Evaluation

- This section is about how the media-fill is an evaluation of the skill of personnel to aseptically prepare CSP.
- This is an error – the media fill should be used to document the capability of the facility, equipment, process and personnel to aseptically formulate. It should be performed on all compound process “families” at a minimum.
- Incubate media-fill vials for 14 days.

Aseptic Work Practice Assessment and Evaluation via Personnel Glove Fingertip Sampling

Use contact plates – recommended levels:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Fingertip Sample</th>
<th>Surface Sample (Contact Plate) (cfu per plate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>N/A</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>ISO Class 8 or worse</td>
<td>N/A</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>


- Introduction
- Competency Evaluation of Garbing and Aseptic Work Practice
- Surface Cleaning and Disinfection Sampling and Assessment

Surface Cleaning and Disinfection Sampling And Assessment

- Introduction
- Cleaning and Disinfecting Competency Evaluation
- Surface Collection Methods
- Action Levels, Documentation, and Data Evaluation
Competency Evaluation of Garbing and Aseptic Work Practice

- Surface sampling is useful for evaluating facility and work surface cleaning and disinfecting procedures and employee competency in disinfection
- Surface sampling shall be performed in all ISO classified areas on a periodic basis.
- Done at end of compounding
- Sample sites are constant, and defined
- Use solid agar or swabs for sampling

Surface Cleaning and Disinfection Sampling And Assessment

- Introduction
- Cleaning and Disinfecting Competency Evaluation
  - Visual observation – document results
- Surface Collection Methods
  - Brief instruction on sampling methodology
- Action Levels, Documentation, and Data Evaluation
Action Levels, Documentation, and Data Evaluation

- Excursions should be investigated
- Areas to investigate:
  - HVAC systems
  - Damaged HEPA filters
  - Changes in personnel garbing or working practices.
- The source of the problem eliminated
- The affected area cleaned
- Resampling performed

Analysis of Microorganisms Recovered

- CFU are an approximate measure of environmental microbial bioburden
- “Action levels are determined on the basis of cfu data gathered at each sampling location and trended over time.”
- All active air sampling recovery to be identified.
- “Highly pathogenic microorganisms”
  - Gram-negative Rods
  - Coagulase positive Staphylococcus aureus
  - Molds and Yeasts
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Quality Assurance

“The responsibility and authority for a quality assurance program should be clearly defined and implemented. Personnel responsible for the quality assurance program should have the education, training, and experience necessary to perform the assigned functions. Quality assurance personnel should assure that documentation, verification, and testing are performed in accordance with written policies and procedures. If deviations from approved policies and procedures occur, it is the responsibility of the quality assurance personnel to investigate and to implement appropriate corrective action. Documentation of any investigations and corrective actions is the responsibility of the quality assurance personnel. Responsible personnel in the quality assurance program are essential in assuring the safety, identity, strength, quality, and purity of compounded drug preparations.”
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Frequent 483 Citations - Current

84 Reports
9/25/14
### Frequency of Issue Cited

<table>
<thead>
<tr>
<th>Issue</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate/Improper EM</td>
<td>81.90%</td>
</tr>
<tr>
<td>Validation of Sterilization: Media Fills</td>
<td>78.70%</td>
</tr>
<tr>
<td>Lab Procedures: Testing</td>
<td>76.60%</td>
</tr>
<tr>
<td>Inadequate Gowning</td>
<td>76.60%</td>
</tr>
<tr>
<td>SOPs to Prevent Microbial Contamin</td>
<td>74.50%</td>
</tr>
<tr>
<td>Stability Program</td>
<td>68.10%</td>
</tr>
<tr>
<td>Batch Release</td>
<td>61.70%</td>
</tr>
<tr>
<td>Control of Equipment</td>
<td>60.60%</td>
</tr>
<tr>
<td>Inadequate Facility/Smoke Studies</td>
<td>60.60%</td>
</tr>
<tr>
<td>Inadequate Cleaning/Disinfection</td>
<td>58.50%</td>
</tr>
<tr>
<td>Control of Pyrogenic Contamination</td>
<td>51.50%</td>
</tr>
<tr>
<td>Investigations</td>
<td>51.10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Issue</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>QAU/Production SOPs Not followed/effective</td>
<td>36.20%</td>
</tr>
<tr>
<td>Separation of Clean &amp; Dirty Ops/Storage of Materials</td>
<td>29.80%</td>
</tr>
<tr>
<td>Inadequate Raw Material Control</td>
<td>24.50%</td>
</tr>
<tr>
<td>Container Preparation</td>
<td>22.30%</td>
</tr>
<tr>
<td>SOP/Control of Production</td>
<td>16.00%</td>
</tr>
<tr>
<td>Safeguard Against Penicillin/Cephalosporin Cross Contamination</td>
<td>12.80%</td>
</tr>
<tr>
<td>Labeling Issues</td>
<td>12.80%</td>
</tr>
<tr>
<td>Records Not Available</td>
<td>12.80%</td>
</tr>
<tr>
<td>Personnel Not Trained/Inadequately Trained</td>
<td>11.70%</td>
</tr>
<tr>
<td>Obvious Product Contamination (Micro/Particulate)</td>
<td>3.20%</td>
</tr>
<tr>
<td>Change Control</td>
<td>3.20%</td>
</tr>
</tbody>
</table>
Observation 4

Employees engaged in the processing of a drug product lack the training required to perform their assigned functions. Specifically, your firm does not have documentation to show that all employees involved in the preparation of sterile drug products have been trained. Employee [BLANK] has no documented training for the preparation of sterile drug products.

Employee [BLANK] attended a U.S. "Aseptic Compounding Training" course in July 2005 but has no written documented training related to aseptic processing of drug products. During this inspection on 3/4/13 & 3/5/13, we observed Employee [BLANK] preparing sterile drug products (lot #CBADAF25 of Pyrilamine Maleate USP 25mg/mL injectable, lot #CBADAF25 of Amikacin (745) Buffered 50mg/mL injectable, and lot #CBADAF25 of Ketamine 200mg/mL injectables) without properly gowning, including preparing sterile drug products in an ISO 5 laminar flow hood with the sleeves of her gown rolled up to the elbow exposing bare arms.

Observation 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process. Specifically,

a. Your firm's SOP 2.030, entitled Sterile Compounding Personnel Qualification, Version 1.0, dated, effective date of 03/01/09, requires each employee shall be evaluated on his or her designated aseptic process a minimum of every [BLANK]. During the review of your firm's media fill personnel qualification for the [BLANK] operation, one operator has not been qualified for the [BLANK] operation. Brilliant Blue G 0.032%, lot #[BLANK], indicates a total of [BLANK] (1.2ml) vials were filled or "punched out" by this operator.

b. Your firm's SOP 9.200, entitled Media Fills (Aseptic Process Validation), dated, effective date of 04/13/13, requires media fills to be conducted in the same manner and same quantity as product would be with the [BLANK] media fill qualification records do not document the identification of the hood used for the non-dedicated. The media fill qualification records do not document the identification of the hood used for the non-dedicated hood that can moved and used in any of the ISO 5 hoods that are stationed in the Cleanroom and none of the records documented the number of operators that worked in the Cleanroom at the time of the media fill. According to your management, [BLANK] operators are allowed in the Cleanroom at the same time.
483 Issued 2/4/14

OBSERVATION 3

Employees engaged in the processing and packing of a drug product lack the education, training, and experience required to perform their assigned functions.

Specifically, you could not provide any training or qualification of your aseptic technique or gowning practices other than your verbal declarations of [REDACTED] and that your last media fill was completed in 2002 at a previous employer.

Review of Webinar

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• <797> Training of Compounding Personnel
• <797> Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices, and Cleaning/Disinfection Procedures
• Expectations of <1163> “Quality Assurance in Pharmaceutical Compounding”
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QUESTIONS?

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Training
• In-house Training
• Distance (web-based) training
  • Next Compounding Webinar – Oct 16 - Compounding Pharmacies and Investigations
  • Custom webinar training
Thank you for your attention

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