USP 797 and USP 795: The “Why” behind the USP compounding chapters

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Learning and Performance Objectives
At the end of this session, learners will be able to:
Summarize the evolution of the practice of sterile compounding including misadventures that shaped pharmacy regulation.
Explain current and upcoming national and state laws and standards as it pertains to compounding.
Describe essential elements of performance described in USP Chapters <795> and <797> respectively as they relate to non sterile and sterile compounding.
List the performance elements required of healthcare personnel performing limited sterile compounding outside of a controlled pharmacy compounding environment.
Define the importance of achieving and maintaining a state of control as it relates to sterile compounding.

Brutal Facts

<table>
<thead>
<tr>
<th>Year</th>
<th>State/State(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Nebraska</td>
<td>4 patients died of a bacterial infection from non-sterile cardioplegia solution compounded in a hospital.</td>
</tr>
<tr>
<td>1990</td>
<td>Pennsylvania</td>
<td>2 patients lost their vision after becoming infected by Pseudomonas aeruginosa found in indomethacin eye drops compounded in a drug store even though commercial non-steroidal drops were available at the time.</td>
</tr>
<tr>
<td>1998</td>
<td>California</td>
<td>11 children became septic—10 tested positive for Enterobacter cloacae bloodstream infections associated with contaminated prefilled saline syringes.</td>
</tr>
<tr>
<td>2001</td>
<td>California</td>
<td>11 patients contracted Serratia marcescens infections following the injection of betamethasone compounded at a community pharmacy.</td>
</tr>
<tr>
<td>2001</td>
<td>Missouri</td>
<td>4 children contracted Enterobacter cloacae infections from IV ranitidine compounded in a hospital pharmacy.</td>
</tr>
<tr>
<td>2002</td>
<td>North Carolina, South Carolina</td>
<td>5 patients developed Exophiala infections from contaminated injectable methylPREDNISolone that was prepared by a compounding pharmacy; one patient died.</td>
</tr>
<tr>
<td>2002</td>
<td>Michigan</td>
<td>Pharmacy preparing injectable methylPREDNISolone and baclofen recalled the products because of contamination with Penicillium mold, Methylobacterium, and/or Mycobacterium chelonae.</td>
</tr>
<tr>
<td>2003</td>
<td>Missouri</td>
<td>2 patients were blinded after receiving a compounded ciprofloxacin injection contaminated with Pseudomonas aeruginosa and Burkholderia cepacia; the injectable product is a commercially available product.</td>
</tr>
<tr>
<td>2005</td>
<td>California</td>
<td>12 patients developed Exophiala infections after receiving heparin/saline flushes from multiple lots of prefilled syringes.</td>
</tr>
<tr>
<td>2005</td>
<td>Minnesota</td>
<td>2 patients were blinded after receiving an unspecified contaminated product compounded as a concentration higher than standard (4 mg/mL vs. 0.5 mg/mL) in a compounding pharmacy.</td>
</tr>
<tr>
<td>2005</td>
<td>California</td>
<td>Sterile kit used with unsterilized stoppers were not sterility tested before distribution from an outsourcing compounding pharmacy.</td>
</tr>
<tr>
<td>2005</td>
<td>Maryland</td>
<td>10 patients died after exposure to cardioplegia solution from a loss contaminated with gram-negative rod.</td>
</tr>
<tr>
<td>2006</td>
<td>Ohio</td>
<td>1 child died after a compounding error led to administration of chemotherapy in 23.4% sodium chloride injection instead of 0.9% sodium chloride.</td>
</tr>
<tr>
<td>2007</td>
<td>Washington, Oregon</td>
<td>2 possibly 3 patients died after receiving an intravenous combination product compounded at a concentration higher than standard (4 mg/mL vs. 0.5 mg/mL) in a compounding pharmacy.</td>
</tr>
<tr>
<td>2009</td>
<td>Florida</td>
<td>2 horses died after receiving a compounded antibiotic ointment containing vitamins B, potassium, magnesium, and selenium (product not approved in the US).</td>
</tr>
<tr>
<td>2010</td>
<td>Illinois</td>
<td>1 child died after receiving more than 4 times the amount of sodium chloride prescribed due to a compounding error in a hospital pharmacy.</td>
</tr>
</tbody>
</table>
### Brutal Facts

<table>
<thead>
<tr>
<th>Year</th>
<th>State</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>California, Florida, Tennessee</td>
<td>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.</td>
</tr>
<tr>
<td>2011</td>
<td>Alabama</td>
<td>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.</td>
</tr>
<tr>
<td>2012</td>
<td>California</td>
<td>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.</td>
</tr>
<tr>
<td>2012</td>
<td>Nationwide</td>
<td>More than 750 patients contracted fungal meningitis after receiving methylPREDNISolone acetate injection prepared by a compounding pharmacy that was contaminated with Exserohilum rostratum &amp; Aspergillus.</td>
</tr>
</tbody>
</table>

### 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

### Brutal Facts

The compounded drug at the center of the NECC contamination case was Methylprednisolone.

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

### Exserohilum rostratum

- Image courtesy: www.cdc.gov

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

Date: September 21, 2012 (on-going) – October 23, 2013

Location: USA (23 States)

Cause: Fungal meningitis contamination of steroid medication

Injuries: 751 Total Case Count, 379 meningitis and Spinal Infection, 6 Stroke, 288 Perisospinal/Spinal infection, 90 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

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

4/5/2014
Pharmacy compounding is simply the art and science of preparing customized medications that are not otherwise commercially available.

Only 1 in 6 graduates are prepared for sterile compounding work*

The federal government, through the FDA, is arguing that patient safety is in jeopardy

All states license pharmacists to compound

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.

History of Sterile Compounding

Despite the chapter’s uniform sterile compounding standards, schools of pharmacy may not always include sterile compounding

Only 1 in 6 graduates are prepared for sterile compounding work*

History of Compounding

All states license pharmacists to compound

States laws vs. Federal laws (FDA)

The federal government, through the FDA, is arguing that patient safety is in jeopardy

Each state has varying degrees of regulations and oversight and enforcement of compounding practices

22 states require direct compliance with USP 797 after 10 years

Until USP <797>, no consistent and enforceable compounding standard of practice existed

History of Sterile Compounding

Yesterday…

• CDC and CMS recognizes USP Chapter <797>
• NECC tragedy
• 2

• USP Chapter <797> revised, new standard effective June 2008

2011

Today…

• January 1, USP <797> first published

2002

• ASHP National Survey

• NCC LVP

• FDA Alert Letter

• ASHP Urgent Attention Letter

• ASHP National Survey

• ASHP TAB

• ASHP National Survey

• ASHP TAB

• ASHP National Survey

• ASHP Guidelines revised

2015

• ASHP National Survey
How Compliant Are We?

Three national surveys:
- ASHP: every 3 years
- CriticalPoint’s online USP <797> Compliance Study (annually since 2011)
- Pharmacy Purchasing & Products every year

State of Compliance

<table>
<thead>
<tr>
<th>State Regulatory Requirements</th>
<th>Compliance Scores 2011</th>
<th>Compliance Scores 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>States have no sterile compounding req</td>
<td>71.6%</td>
<td>73.9%</td>
</tr>
<tr>
<td>States have some sterile compounding req</td>
<td>73.0%</td>
<td>75.3%</td>
</tr>
<tr>
<td>States require compliance with 797</td>
<td>76.6%</td>
<td>78.6%</td>
</tr>
</tbody>
</table>

Compliance Scores 2011 vs. 2013 based on State Regulatory Requirements


State Board of Pharmacy Position on USP 797

The Drug Quality and Security Act (DQSA)

Drug Quality and Security Act (DQSA)
- Current status: signed into law by President Obama on November 27, 2013
- Divided into 2 major sections called Titles

The Drug Quality and Security Act (DQSA)

Title I – Compounding Quality Act
- Eliminates the unconstitutional provisions of 503A that “…created uncertainty regarding the laws governing compounding.”
- Requires FDA to engage in two-way communication with state regulators – identified as a major deficiency in FDA’s response to the meningitis outbreak.
- Preserve and protect the practice of Traditional Pharmacy compounding in community pharmacies.

The Drug Quality and Security Act (DQSA)

Title I: Compounding Quality Act: 503B - Outsourcing Facilities.
- Permit entities engaged in compounding of sterile drugs to register as “Outsourcing Facilities.”
- Under Section 503B, pharmacy outsourcing facilities to voluntarily register as “outsourcing facilities,” making them subject to good manufacturing practices, risk-based inspection and other standards.
The Drug Quality and Security Act (DQSA)

Title 2: Drug Supply Chain Security Act
- Track and Trace Program
  - The development of the system will be phased in with new requirements over a 10-year period.
  - These requirements will include placing unique product identifiers on individual drug packages and providing product and transaction information at each sale with lot level information, in paper or electronic format.

Source: [http://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/default.htm](http://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/default.htm)

The Drug Quality and Security Act (DQSA)
- Section 503A (21USC353a) - Traditional compounding
  - State-based regulations – State Boards of Pharmacy
  - Traditional, individualized prescriptions
- Section 503B (21USC353b) - Outsourcing facilities
  - FDA jurisdiction; registration; reporting; cGMPs
  - Manufacture and interstate shipment of larger quantities of compounded drugs without prescriptions
  - Under direct supervision on a pharmacist

Source: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm)

Section 503A
- Health-systems are exempt from registration with the FDA
- Insourcing/regionalizing is possible in some states

<table>
<thead>
<tr>
<th>Health System Regionalization</th>
<th>Permitted by SBOP</th>
<th>Prohibited by SBOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia</td>
<td>New Jersey</td>
<td>Massachusetts</td>
</tr>
<tr>
<td>Ohio</td>
<td>California</td>
<td>Wisconsin</td>
</tr>
</tbody>
</table>

Source: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm)

503A standards (continued)
- Use bulk from FDA registered facility only
- May not compound those on list of drugs removed from the market
- No inordinate amounts of what are “essentially copies of commercially available drug products”
- Not a product identified as presenting demonstrable compounding difficulties
- Measured dose inhalers
- Transdermal systems, others?
- Subject to inspection by FDA if not in compliance with USP chapters on compounding

Source: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm)

Registered Outsourcing Facilities
- Firms Registered As Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Thirty-eight (38) registered establishments As 503B
- [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm)

Source: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm)

The Drug Quality and Security Act (DQSA) - The “Risk based system” for FDA inspections –
- Compliance History of the Outsourcing Facility
- Record, History, and Nature of the recalls linked to the Facility
- The “inherent risk” of the drugs compounded at the facility.
- Inspection frequency within the last 4 years by FDA.
- Whether the facility intends to compound a drug under section 506 E (drug shortage item).

Source: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm)
The Drug Quality and Security Act (DQSA)

- **Prohibited Acts –**
  - Wholesaling -
  - There is a carve-out for “drugs used in a healthcare setting.”
  - Intentional Falsification of Prescriptions
  - Failure to report ADRs
  - Misbranding of Drugs

The “Missing Parts” –
- A complete list of FDA approved API suppliers.
- The FDA’s Bulk Drug Substance list
- The FDA’s Drug Shortage list (506 E).
- The list of “Drugs presenting demonstrable difficulties for compounding”
- A complete FDA DO NOT Compound list.

FDA Information
- **Outsourcing Registration List**
  - [http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm](http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm)
- **Inspections; Recalls; other Actions**
  - [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm)
- **Regulatory Policy Information**
  - [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm)
- **Compounding FDA Web page**
  - [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm)

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
  - Cuddy USP <797>
  - Adopt portions
  - Develop one regulations
  - No action
  - Shall vs. Should: Appendix I

- **USP Chapter <795>: Nonsterile Compounding**

Who Compounds Sterile Preparations?

**USP <797>** applies to all personnel who compound sterile preparations

- Pharmacists
- Pharmacy Technicians
- Nurses
- Physicians
- Anesthesia Personnel
- Other hospital clinicians
- Veterinarians
- Veterinary Technicians
Where are CSPs Compounded?

- Pharmacies
- Hospitals
- Home Care
- Nuclear
- Community
- Hospital departments
- Long-term care and rehab facilities
- Ambulatory offices and clinics
- Imaging
- Allergy
- Oncology
- Surgical centers

Types of CSPs

- Large volume parenterals
- Small volume parenterals
- Piggyback bags
- Syringes
- Irrigations
- Ophthalmics
- Parenteral nutrition (PN)
- Infusions
- Allergen extracts
- Radiopharmaceuticals

Not in Scope of USP <797>

- Manufactured products
- FDA labeling
- Administration of medications
- <797> applies up to the points of administration
- CDC provides guidance on “hang time”

CSP Microbial Risk Levels

- True emergency situations
- Compounded outside of a hood
- Aseptic technique is followed
- Administration begins within 1 hour of start of preparation
- Appropriately labeled

Manufactured Products

- Premixed IVs
- Vial and Bag Systems

CSP Microbial Risk Levels (continued)

- Segregated Compounding Area
- CSPs made in a hood that is not placed in a cleanroom
- Cannot be used for hazardous drugs
- Expectations still include
  - Hand hygiene and garbing
  - Daily & monthly cleaning
  - Environmental sampling

Examples:
- Initial dose of norepinephrine drip in ICU after pharmacy hours
- Initial dose of norepinephrine compounded in satellite pharmacy in the ER
CSP Microbial Risk Levels (continued)

High Risk
- Net > 3 sterile drug packages used (including diluent)
- Using sterile equipment
- Compounded in an ISO Class 5 device usually in an ISO Class 7 environment
- Limited, basic, closed-system aseptic transfers and manipulations
- Expectations: all QA components with annual aseptic media fill and GFS

Medium Risk
- Using 4 or more sterile ingredients, complex aseptic manipulations
- No bacteriostatic additive and administered over several days
- For multiple patients (anticipatory batch compounding) OR
- For 1 patient on multiple occasions (patient-specific batch)

Low Risk
- Prepared from sterile ingredients but exposed to < ISO Class 5 air
- > 6 hour delay from compounding to sterilization
- Purity of components is assumed but cannot be verified by documentation

Immediate Use
- Made with non-sterile ingredients and/or using non-sterile containers, devices or equipment
- Prepared from sterile ingredients but exposed to < ISO Class 5 air
- > 6 hour delay from compounding to sterilization
- Purity of components is assumed but cannot be verified by documentation

Definitions of SDV and MDV are in the USP General Notices and Requirements

Single dose vials:
- Opened or punctured in ISO 5 environment may be used for up to 6 hours.
- Opened or punctured in worse than ISO 5 must be used within 1 hour or discarded.
- Single dose ampules must be discarded after opening and not stored for any time period

Multiple dose vials – Contain antimicrobial preservative(s)
- Designed for entry on multiple occasions.
- BUD: 28 days after initial entry unless specified otherwise by the manufacturer.
- Based on USP <51> Antimicrobial Preservative Testing
- Expiration date on vial is based on an unopened, properly stored vial.

Pharmacy Bulk Package (PBP)
- USP <1> Injections
- Sterile preparation for parenteral use that contains many single doses
- Restricted to the preparation of admixtures for infusion or filling empty sterile syringes
- Closure penetrated only once
- Used in a suitable work area such as a laminar flow hood
- Includes a statement limiting the time frame in which the container may be used once it has been entered

Example: 1 dose of 1000 mL DSW with 30 mEq potassium chloride added
Example: Parenteral Nutrition or Batch of IV minibags/syringes
Example: Morphine sulfate from nonsterile powder for PCA
Beyond-Use Dating (BUD)

Recognizes the probability of contamination even under best conditions:
- Optimal employee performance
  - 0.1% (1 contaminated dose out of 1,000)
- Contamination rates published in the literature
  - 0.1% – 16%
- Patient Safety: Protect patients from dangerous or even fatal overgrowths of microorganisms that may have been accidentally introduced
- Storage time needs to be greater than zero but less than positive infinity*

* Personal conversation with Dr. David W. Newton, September 30, 2009

Parameters for Establishing BUD

- Hand Hygiene - USP <797>
  - Hand washing is defined as the vigorous, rubbing together of all surfaces of soap lathered hands (30 sec.), followed by rinsing under a stream of water.
  - The process of hand washing mechanically removes microorganisms of the hands.
  - The single most important way to reduce the risk of transmitting microorganisms causing infections.
  - Even after using antimicrobial soap, there is still about 20,000 microbes per sq mm left on the hands.¹

¹ Adapted from: Hospital Infection Control Practice, 2nd Edition, 1996
K1 Add reference on where this data is from.
Keith, 3/16/2014
Compounding Personnel
- Hair net
- Beard cover and face mask
- Gown
- Nonslips
- Gloves
- Sterile
- Shoe covers

Critical Factors in Aseptic Technique

<table>
<thead>
<tr>
<th>Group</th>
<th>Contamination</th>
<th>Type of Gloves</th>
<th>Initial</th>
<th>Betadine + Repeated</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Non</td>
<td>0/0 (0.00%)</td>
<td>Nonslips</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>B Non</td>
<td>0/0 (0.00%)</td>
<td>Nonslips</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Significant reduction in contamination:
- Group B compared to Group A (p<0.0001)
- Significant reduction to Group A (p<0.0001)

Conclusion: The use of prototype chemistries was significantly reduced with the decrease in contamination levels.


Importance of Garbing

Is this an example of USP 797 compliant garbing?
- Yes
- No

Appearance of Personnel
- Neat, clean
- In good health
- No visible piercing
- No makeup
- No long or artificial nails
- Properly garbed
  - Cleanroom vs. other areas

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### Compounding Personnel
- Hair net
- Beard cover and face mask
- Gown
- Nonsterile gloves
- Shoe covers

### Personnel
- Compounding supervisor
- Compounding personnel
- Orientation
- Training
  - Didactic
  - Hands-on
- Tests
  - Written
  - Related to compounding practices
  - Skills assessment

### Personnel Monitoring
- Aseptic Media Fill Testing
- Gloved Fingertip Testing
- Surface Sampling

### Media Fill
- Demonstrates the ability to aseptically mix a CSP
- Must reflect the most complex process performed

### Gloved Fingertip Test
- Demonstrates the ability to garb aseptically
- USP <797> Appendix III
- Requires
  - Appropriate agar plates
  - Personnel garbed, including sterile gloves
  - Control plate
  - Performed in cleanroom or anteroom immediately after donning sterile gloves but before cleansing them with sterile 70% IPA

### Facilities & Environmental Control
- Image: Courtesy CriticalPoint, LLC
- Image: Courtesy CriticalPoint, LLC
- Image: Courtesy CriticalPoint, LLC
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

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

Air Cleanliness

- ISO classification
  - The smaller the number, the cleaner the air
  - Refers to number of particles allowed per volume of air
  - PEC = ISO 5
  - Buffer area = ISO 7
  - Anteroom ISO 7 if it opens into a positive pressure cleanroom
  - ISO 7 if it opens into a negative pressure cleanroom

Cleanliness Classification Comparison

- Class limits for sterile compounding based on the number of particles ≥ 0.5µm per m³ (ISO) or per ft³ (former Federal Standard 209E)
- Count locations are determined based on room size and classification and are measured under dynamic operating conditions.

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>US FS 209E</th>
<th>ISO mt</th>
<th>FS 209e (ft³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Class 1</td>
<td>35.3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Class 10</td>
<td>352</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Class 100</td>
<td>3500</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Class 100</td>
<td>35,200</td>
<td>1000</td>
</tr>
<tr>
<td>7</td>
<td>Class 10,000</td>
<td>352,000</td>
<td>10,000</td>
</tr>
<tr>
<td>8</td>
<td>Class 100,000</td>
<td>3,520,000</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Cleanliness Classification Comparison

- Class limits for sterile compounding based on the number of particles ≥ 0.5µm per m³ (ISO) or per ft³ (former Federal Standard 209E)
- Count locations are determined based on room size and classification and are measured under dynamic operating conditions.

Facility Design

- If differential pressure design, then pressure gauges installed and monitored at least daily:
  - Buffer ± 0.02” w.c. positive or 0.01” negative
  - Anteroom ± 0.02” w.c. positive
- If open concept (air displacement design):
  - Velocity across entire opening maintains 40 feet/minute and verified by smoke
  - Not allowed if HD compounding
- Air Cleanliness
  - Buffer ISO Class 7
  - Anteroom ISO Class 7/8
- Air Exchanges
  - Buffer rate at least 30 ACH with 15 of those from HEPA filtered or supplied air
  - Anteroom no requirement but at least 30 ACH recommended
Surround the DCA with layers of protection

Primary Engineering Controls (PECs)

Compounding Aseptic Isolator (CAI)

Compounding Aseptic Containment Isolator (CACI)

Maximum allowable leakage is 0.01% of the upstream aerosol concentration.

Certification within the last six months

- All PECs must be ISO 5
- Buffer area must be ISO 7
- Ante area can be ISO 8 if it opens only into a positive pressure ISO 7 room
- Ante area must be ISO 7 if it opens into a negative pressure cleanroom
- HEPA-filtered air
- Air changes must be 30 ACH
- Up to 15 ACH can come from LAFW
- Rooms and devices used for hazardous drug preparation must be negative pressure and should be vented to the outside

One configuration allowed for "low volume"

Certification Report

Adapted from CETA Compounding Isolator Testing Guide. CAG-002-2006 and reviewed by Jim Wagner in March 2014.
Environmental Sampling Dilemma:
- One of the most contentious sections of USP Chapter <797>
- Since the 1980's, the US Centers for Disease Control (CDC) has not advocated routine microbial environmental culturing (sampling) of inanimate surfaces in the absence of an outbreak situation
- The US Food and Drug Administration requires sterile processing operations in manufacturing facilities to perform daily monitoring of viable air, surface and personnel glove fingertip samples

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
  - Surface sampling for viable microorganisms
- Personnel-related Environmental Sampling
  - Personnel fingertip sampling during initial training, with media fills and as a competency assessment tool
  - Surface sampling for viable microorganisms

General Environmental Sampling “Shalls”
- Detailed written PnP on all aspects of environmental sampling
- Sampling occurs in all ISO areas from cleanest to dirtiest ISO 5 > ISO 7 > ISO 8
- CFU Action Levels established
- Evidence of logical plan of action in the event sampling exceeds Action Levels

<table>
<thead>
<tr>
<th>Classification</th>
<th>Air Sample Size (CFU/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>ISO Class 8</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

Growth Media
- Soybean Casein Digest Media (Trypticase Soy Broth/Agar) to support the growth of bacteria
- Malt Extract Agar or other media that supports the growth of fungi
- Must use plates with lecithin and polysorbate 80 which are chemicals that neutralize cleaning agents when performing:
  - Surface sampling
  - Personnel glove sampling associated with MFUs

Sampling for Air Viable Organisms
- Volumetric air sampling is required
- Predefined amounts of air
- Settling plates cannot be the only method of evaluating air viable organisms
- Not quantitative
- Settling of particles influenced by size of particle and air movement
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

"Regardless of the number of cfu identified in the pharmacy, further corrective actions will be dictated by the identification of microorganisms 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

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Gram stain/ morphology</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci/Micrococci</td>
<td></td>
<td>Persistent hobbies or growing problems</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td></td>
<td>Water condensation, leaking, sanitation</td>
</tr>
<tr>
<td>Bacillus species</td>
<td></td>
<td>Dust, dirt, floor traffic, possibly human handling</td>
</tr>
<tr>
<td>Molds</td>
<td></td>
<td>Humidity, condensation, moist environment, possibly water contaminated cardboard, water reservoir, i.e. incubator humidification system</td>
</tr>
<tr>
<td>Yeasts</td>
<td></td>
<td>Influx of unfiltered air, mold from street clothing, mold-contaminated cardboard, i.e. incubator humidification system</td>
</tr>
<tr>
<td>Diptheroids/coryneforms</td>
<td></td>
<td>Poor air conditioning, leading to sweating and personnel discharge from gowns</td>
</tr>
</tbody>
</table>

Source: Microbiological Environments (www.microbioenv.com)

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 and function of primary and secondary engineering controls
  - Material/component handling procedures
  - Personnel hand hygiene and gowns
  - Environmental sampling/testing

Cleaning

- Cleaning is the removal of visible soil (e.g., organic and inorganic material) from objects and surfaces normally accomplished manually or mechanically using water with detergents or enzymatic products.

Sanitizing

- Chemical process of reducing the number of disease-causing agents on cleaned surfaces to a safe level.

Disinfecting

- Disinfection describes a process that eliminates many or all pathogenic microorganisms, except bacterial spores, on inanimate objects.

What is the difference between cleaning, sanitization and disinfection?

- Cleaning
- Sanitizing
- Disinfecting
Use of Disinfectants
- Must be germicidal detergent
- Dilution of agent is critical to its efficacy
- Contact time
- Storage conditions: light or temperature sensitive
- Follow manufacturer instructions

What cleaning supplies do you recommend using?
- Cleaning & disinfecting agents
- Mop(s) and, if necessary, bucket(s)
- Non-shedding, non-linting wipes
  - Pre-saturated and dry
  - Polyester knit fabrics
  - Nylon fabrics
- Isolator cleaning tools
- Equipment should be dedicated!!

Cleaning and Disinfection

<table>
<thead>
<tr>
<th>More than Daily*</th>
<th>Daily</th>
<th>Monthly</th>
</tr>
</thead>
</table>
| ISO Class 5 PEC & work surfaces | Cleaning & disinfecting agents | Empty trash ISO Class 5 PEC
  - Beginning of day/shift
  - Prior to each batch
  - Every 30 min
  - When visibly soiled
  - As spills occur
  - Next to contamination
  - Empty trash as needed
| Empty trash | Empty trash | Cleaning:
  - Walls, pass-throughs
  - Every surface
  - Outside of PECs
  - All cases (top, bottom, wheels, etc.)
  - Supply bins
  - Doors, handles, vents
  - ISO Class 5 PEC
  - Restock supply cart
  - Floors (same as daily)
  - Clean refrigerators, freezers, incubators, etc.

* Clean PEC with sterile 70% IPA
** Clean with germicidal detergent diluted with SWf Irrigation followed by sterile 70% IPA; use decontamination first agent if HD PEC

For 42 years, I made small, regular deposits of education, training and experience ... and the experience balance was sufficient that on January 15th I could make a sudden, large withdrawal”

Chesley Sullenberger
### Testing Required

**Sterility Testing**
- High risk level CSPs prepared in groups > 25 identical individual SDCs or in MDC for administration to multiple patients
- High risk level CSPs prepared and exposed for > 12 hours to temperatures of 2–8°C or > 6 hours at temperatures > 8°C before they are sterilized.
- When assigned BUDs exceed the storage times published in USP Chapter 797 (regardless of compounding risk level)

**Endotoxin (pyrogen)**
- Required for all above except inhalation and ophthalmic dosage forms

---

### Storage – Hazardous Drugs

**NIOSH Hazardous**
- Not EPA hazardous
- Separate area
- Negative pressure
- 12 ACPH

**Can be inside negative pressure buffer area**

---

### Understanding all of the elements

**Beyond-Use Dating (point in time)**

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.

**Assumption!**
CSP is stored at its optimal temperature at all times.

---

### Major Differences between USP <797> and Proposed <800>

<table>
<thead>
<tr>
<th><strong>USP &lt;797&gt;</strong></th>
<th><strong>Proposed New Chapter USP &lt;800&gt;</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical Compounding</strong></td>
<td><strong>Hazardous Drugs</strong></td>
</tr>
<tr>
<td>Sterile Preparations</td>
<td>Handling in Healthcare Settings</td>
</tr>
<tr>
<td>Applies to sterile compounding only</td>
<td>Applies to sterile and nonsterile compounding</td>
</tr>
<tr>
<td>Applies from receipt of inventory up to drug administration</td>
<td>Applies from receipt of inventory through drug administration</td>
</tr>
<tr>
<td>All HDs must be stored separately in area with 12 ACPH and 0.01&quot; negative to adjacent space</td>
<td>Antineoplastic HDs must be stored separately from non-HDs in an area with 12 ACPH and 0.01&quot; negative to adjacent space unless coated, final-manufactured dosage forms are clearly labeled as HDs and safety strategies are detailed in PhRs</td>
</tr>
<tr>
<td>Exemption for low volume compounding</td>
<td>No low volume exemption</td>
</tr>
</tbody>
</table>

---

### Major Differences between USP <797> and Proposed <800>

<table>
<thead>
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<tr>
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<td><strong>Hazardous Drugs</strong></td>
</tr>
<tr>
<td>Sterile Preparations</td>
<td>Handling in Healthcare Settings</td>
</tr>
<tr>
<td>CSTD use is a &quot;should&quot;</td>
<td>CSTD use is a &quot;shall&quot;</td>
</tr>
<tr>
<td>Defines PECs for HD sterile compounding</td>
<td>Defines PECs for nonsterile and sterile HD compounding, allowing for manipulation of HDs that do not produce aerosols (e.g. coated tablets or capsules) outside of a C-PAC</td>
</tr>
<tr>
<td>Prohibits SCA for HD compounding; Requires SBC to be housed in ISO class 7 room that is 0.01&quot; w/c negative</td>
<td>Permits SCA for HDs provided CAC/IBSC in area that has 12 ACPH and 0.01&quot; w/c negative; Maximum BUD 12 hours</td>
</tr>
<tr>
<td>Does not require environmental and medical surveillance</td>
<td>Requires environmental and medical surveillance</td>
</tr>
</tbody>
</table>
Review of USP <795>
Pharmaceutical Compounding - Nonsterile Preparations

Eric S. Kastango, MBA, RPh, FASHP

Non-Sterile Compounding
- USP <795> Pharmaceutical Compounding - Nonsterile Preparations
- Other USP Chapters related to compounding
- State regulations concerning compounding

USP <795> is a minimum standard – not a guideline

Who Compounds Nonsterile Preparations?
- USP <795> defines compounder as a professional authorized by the appropriate jurisdiction to perform compounding pursuant to a prescription or medication order by a licensed prescriber
- Pharmacists
- Pharmacy Technicians
- Physicians
- Veterinarians
- Veterinary Technicians
- Nurses

Status of USP <795>
- Revised Chapter official as of June 2011
- USP Compounding Expert Committee
  - Revision process for all new and revised USP chapters
  - Published in Pharmacopeial Forum for public comment
- Other related Chapters
  - Chapter <800> Hazardous Drugs – Handling in Patient Care Settings – Published for comment on March 28, 2014
  - Chapter <1168> Compounding for Investigational Studies – to be proposed in PF 39(5) Sept/Oct 2013

Sections of USP <795> ...
- Introduction
- Definitions
- Categories of Compounding
- Responsibilities of the Compounder
- Compounding Processes
- Compounding Facilities
- Compounding Equipment
- Component Selection, Handling, and Storage

... Sections of USP <795>
- Stability Criteria and Beyond-Use Dating
- Packaging and Drug Preparation Containers
- Compounding Documentation
- Quality Control
- Patient Counseling
- Training
- Compounding for Animal Patients
**Categories of Compounding**

**Simple Compounding**
- Reconstituting or manipulating a commercial product that may require the addition of one or more ingredients as directed by the manufacturer
- A preparation that has a USP compounding monograph or appears in a peer-reviewed article that contains:
  - Specific quantities for all components
  - Compounding procedures and equipment
  - Stability data for that formulation with beyond-use date (BUD)

**USP Compounding Monographs**

**Moderate Compounding**
- Making a preparation that requires special calculations or procedures to determine quantities of components per preparation or per individualized dosage units
- Making a preparation for which stability data for that specific formulation is not available
- Example: mixing two or more manufactured creams when the stability of the mixture is not known
Complex Compounding

Making a preparation that requires special training, environment, facilities, equipment, and procedures

Examples
- Transdermal dosage forms
- Modified-release preparations

Responsibilities of the Compounder

- The compounder must be proficient in compounding
- The compounder must prepare compounds
  - with acceptable strength, quality, and purity
  - in accordance with the prescription or medication order
  - the finished preparation with appropriate packaging and labeling
  - in compliance with established state agencies, state boards of pharmacy, federal law, and other regulatory agencies

It's Not Just USP <795>

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Prescription Container Labeling</td>
</tr>
<tr>
<td>659</td>
<td>Packaging and Storage Requirements</td>
</tr>
<tr>
<td>797</td>
<td>Pharmaceutical Compounding - Sterile Preparations</td>
</tr>
<tr>
<td>1066</td>
<td>Physical Environments that Promote Safe Medication Use</td>
</tr>
<tr>
<td>1151</td>
<td>Pharmaceutical Dosage Forms</td>
</tr>
<tr>
<td>1160</td>
<td>Pharmaceutical Calculations in Prescription Compounding</td>
</tr>
<tr>
<td>1163</td>
<td>Quality Assurance in Pharmaceutical Compounding</td>
</tr>
<tr>
<td>1178</td>
<td>Prescription Balances and Volumetric Apparatus</td>
</tr>
<tr>
<td>1191</td>
<td>Stability Considerations in Dispensing Practice</td>
</tr>
<tr>
<td>1265</td>
<td>Written Prescription Drug Information - Guidelines</td>
</tr>
</tbody>
</table>

General Principles of Compounding

- Training and documentation of competence
- Compounding ingredients
- Equipment
- Facilities
- Quality control and assurance
- Error prevention
- Documentation

Personnel Training
Orientation and Training

- USP <795>
- Other applicable USP Chapters
- Safety Data Sheets (SDS, formerly MSDS)
- Hazardous Drug safety
- Facility policies and procedures
- Oversight by skilled compounder
- Demonstration of verbal and functional knowledge
- Review and approval by compounding supervisor
- Documentation of competence
- Annual review of skills

Policies and Procedures

- Available to staff
- Evidence of review
- Reflects current practice and regulatory requirements

Definitions

- API: Active Pharmaceutical Ingredient
  - The active ingredient
- Added Substances
  - Inactive ingredients, excipients, pharmaceutical ingredients
- Vehicle
  - Carrier or diluent in which liquids, semisolids, or solids are dissolved or suspended

API and Other Bulk Substances

- Best option: USP, NF or FCC (Food Chemical Codex) substances manufactured in an FDA registered facility
- If ingredients from a non-FDA registered facility are required, use professional judgment and obtain a Certificate of Analysis
- Caution with components not of “compendial quality”
- Standards of American Chemical Society (ACS) grade materials are not tested for impurities that might raise patient safety concerns

Certificate of Analysis
Dietary and Nutritional Supplements

- Must comply with any federal or state regulations.
- Generally, dietary supplements are prepared from ingredients that meet USP, NF, or FCC standards.
- If not, must have acceptable food-grade quality.

Expiration Date of Bulk Components

- If there is no expiration date:
  - Label with the date of receipt.
  - Assign a conservative expiration date.
  - Cannot exceed three years from date of receipt.

Water

- Potable water
- Hand washing
- Equipment washing
- Purified Water
  - Is a “shall” requirement for compounding.
  - Is a “should” requirement for rinsing equipment and supplies.
  - Methods of purification include: deionization, distillation, ion exchange, reverse osmosis, filtration, etc.

Storage

- Must be stored as directed by the manufacturer or according to USP, NF, or FCC monograph requirements.
- Appropriate temperature and humidity.
- Labeled appropriately.
- Off the floor.
- Handled and stored to prevent contamination.
- Rotated so that oldest stock is used first.

USP Temperature Ranges

<table>
<thead>
<tr>
<th>Storage Temperatures</th>
<th>Degrees Fahrenheit</th>
<th>Degrees Centigrade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Room Temperature</td>
<td>68 to 77</td>
<td>20 to 25</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>36 to 46</td>
<td>2 to 8</td>
</tr>
<tr>
<td>Freezer</td>
<td>-13 to 14</td>
<td>-25 to -10</td>
</tr>
</tbody>
</table>
Facilities
- Adequate space specifically designed for compounding
- Separate and distinct from sterile preparation area
- Clean, orderly, sanitary and in good state of repair
- Orderly placement of equipment and materials
- Designed, arranged, and used to prevent cross-contamination
- Well-lighted
- Appropriate heating, ventilation, air conditioning

Facilities
- Hand and equipment washing facilities
- Hot and cold water
- Soap or detergent
- Air-dryer or single-use towels
- Plumbing system

Stock
- Component, container, and closure stock stored off the floor
- Rotated so oldest stock used first

Waste
- Waste held and disposed of in sanitary and timely manner
- In accordance with local, state, and federal guidelines

Equipment and Utensils
- Appropriately designed
- Adequate capacity
- Surfaces that contact components are not reactive, additive, nor sorptive
- Are maintained as directed by the manufacturer
- Refer to USP <1176> Prescription Balances and Volumetric Apparatus
- Routinely inspected
- Calibrated, if necessary
Equipment for Special Compounds
- When possible, equipment should be dedicated for specific uses
- Antibiotics
- Cytotoxics
- If not dedicated equipment, the equipment and utensils used are meticulously cleaned
- If possible, disposable items are used to reduce chance of bioburden and cross-contamination

Containers and Closures
- Suitable, clean material
- Non-reactive
- Cannot alter quality, strength, or purity

USP Standards: Containers and Packaging

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Notices and Requirements</td>
<td>Compounding Monographs</td>
</tr>
<tr>
<td>659 Packaging and Storage Requirements</td>
<td></td>
</tr>
<tr>
<td>660 Containers - Glass</td>
<td></td>
</tr>
<tr>
<td>661 Containers - Plastic</td>
<td></td>
</tr>
<tr>
<td>671 Performance Testing</td>
<td></td>
</tr>
<tr>
<td>681 Repackaging into Single-Use Containers and Unit Dose Containers for Nonsterile Solid and Liquid Dosage Forms</td>
<td></td>
</tr>
<tr>
<td>1136 Repackaging - Unit-of-Dose</td>
<td></td>
</tr>
</tbody>
</table>

Beyond-Use Dates

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical stability of the drug</td>
<td>Chemical stability of the compounded preparation</td>
</tr>
<tr>
<td>Based on drug-specific &amp; general stability documentation/literature to reduce potential of falling outside required USP strength (+/- 10% of labeled content)</td>
<td></td>
</tr>
<tr>
<td>Stability in Container</td>
<td></td>
</tr>
<tr>
<td>Expected Storage conditions</td>
<td></td>
</tr>
<tr>
<td>Competent Personnel</td>
<td></td>
</tr>
</tbody>
</table>
Stability of Compounded Nonsterile Preparations

- Manufacturer's information
- Package insert
- USP
  - Compounding monographs
  - All applicable USP General Notices and Chapters
- Peer-reviewed literature

BUD by Type of Formulation

- The BUD cannot exceed the expiration date of the API or any other component

<table>
<thead>
<tr>
<th>Type of Formulation</th>
<th>Maximum BUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-aqueous formulation</td>
<td>6 months</td>
</tr>
<tr>
<td>Water-containing oral formulations</td>
<td>14 days under refrigeration</td>
</tr>
<tr>
<td>Water-containing topical/dermal and mucosal liquid and semisolid formulations</td>
<td>30 days</td>
</tr>
</tbody>
</table>

Labeling

- The labeling should indicate that “this is a compounded preparation”

Documentation

- Master Formulation Record
- Compounding Record
- Standard Operating Procedures
- Safety Data Sheets (SDSs, previously MSDSs)
Documentation

- Written or electronic
- Comply with record-keeping requirements of State Board of Pharmacy
- Documentation is not required when preparing a compound according to the manufacturer’s labeled instructions
- All other compounds require
  - Master Formulation Record
  - Compounding Record

Master Formulation Record

- Official or assigned name, strength, dosage form
- Calculations and doses
- Ingredients and quantities
- Compatibility and stability info and references
- Equipment needed
- Mixing instructions
- Label information
- Container used
- Packaging and storage requirements
- Description of the final preparation
- Quality control procedures and expected results

Compounding Record

- Official or assigned name, strength, and dosage
- Reference to Master Formulation Record
- Names and quantities of all components
- Sources, lot numbers, and expiration dates of components
- Total quantity compounded
- Names of persons who prepared, performed QC, and approved the preparation

... Compounding Record

- Date of preparation
- Assigned control or prescription number
- Assigned BUD
- Copy of label
- Description of final preparation
- Results of QC (weight of capsule, pH of liquid)
- Documentation of any QC issues and any ADRs reported by patient

Standard Operating Procedures

- SOPs should include
  - Facilities for preparation
  - Equipment for packaging
  - Personnel
  - Storage
- SOPs should ensure
  - Accuracy
  - Quality
  - Safety
  - Uniformity in compounding
  - Accountability

Quality Control
Quality Assurance Plan

- Quality Control
- Personnel orientation and training
- Variances
- Trends

<1163> Quality Assurance in Pharmaceutical Compounding

- Training
- SOPs
- Documentation
- Verification
- Testing
- Cleaning and disinfection
- Containers, packaging, repackaging, labeling, and storage
- Outsourcing
- Responsible Personnel

Patient Counseling

Shall Statements: Patient Counseling

- The patient or patient's agent shall be counseled about proper use and instructed to report any adverse event

Critique of North Dakota Rules and Regulations

- North Dakota Board of Pharmacy Rules
  - 61-02-01-03. Pharmaceutical compounding standards.
    - All compounders of sterile and nonsterile products must be in compliance with this rule by January 1, 2015.
    - Abbreviated version of USP Chapters <797> and <795>
    - Compounding personnel must be familiar with USP standards and North Dakota regulations: what is the expectation of this statement?
    - No guidance on the specific facility requirements except for CACIs used for hazardous drugs
      - No air changes per hours
      - No pressure differentials (except for HDs)
    - No guidance on environment monitoring and acceptance criteria

Image copyright Bellingham, 2013

Critique of North Dakota Rules and Regulations

- North Dakota Board of Pharmacy Rules
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      - No pressure differentials (except for HDs)
    - No guidance on environment monitoring and acceptance criteria
North Dakota Board of Pharmacy Rules

- 61-02-01-03. Pharmaceutical compounding standards.
- No requirement to do air, surface or gloved fingertip except for high-risk level compounding
- Only air sampling (volumetric or gravimetric)
- No requirement for sterile gloves and sterile IPA
- Lacks specificity making compliance difficult and will make enforcement challenging.
  - How will the pharmacists know when their operation and facility is operating under a state of control they?
  - ... was built correctly?
  - How will the Board inspectors know when a pharmacy that is compounding is not complying with the regulation?

Thank you

- Eric S. Kastango, MBA, RPh, FASHP
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- eric.kastango@clinicaliq.com