Compounding Sterile Drugs: A Regulatory Update

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March 21, 2017
Objectives

• Review incidents surrounding sterile compounded products in the United States

• Summarize historical, current and proposed sterile compounding standards

• Review key resources
Five pharmacy regulations health execs must keep on their radars in 2017

March 19, 2017  By Kenneth Maxik

1. USP <797> Pharmaceutical Compounding – Sterile Compounds
2. USP <800> Hazardous Drug - Handling in Healthcare Settings
3. MM.09.01.01 Antibiotic Stewardship Standard
4. 503A & 503B Compounding
5. 340B Mega-Guidance Withdrawn
The Cost of Waiting

Introduction of a bill to amend the Federal Food, Drug, and Cosmetic Act to provide for safe and appropriate compounding of drugs by licensed pharmacists and physicians.

Proposed in 2007

The Drug Quality and Security Act approved in 2013 to amend the Federal Food, Drug, and Cosmetic Act to provide for safe and appropriate compounding of drugs by licensed pharmacists and physicians.

Approved in 2013
PEW Summary of Events

- Summary of incidents 2001 to November 2015
- 25 compounding errors or potential errors
- 1,076 adverse events
- Including 90 deaths
What really is the problem?

- Fungal infections outbreak linked to contaminated steroid injections
- Reported in 20 states
- 64 individuals died and 751 people were sickened
Jurors wrap up first day of deliberations in meningitis trial

Walter F. Roche J., For USA TODAY NETWORK-Tennessee 3:38 p.m. CT March 17, 2017
Drug Quality and Security Act 2013

• The Drug Quality and Security Act (DQSA) signed into law on November 27, 2013
  - Public Law 113-54
  - New Law Consists of Two Sections

• Title I: Compounding Quality Act
• Title II: Drug Supply Chain Security Act
  - Drug pedigree through distribution channel
  - Manufacturer to the pharmacy
Compounding Quality Act FDA

**Hospitals and Clinics**

- Pharmacy Compounding of Human Drug Products under Section 503A of the Federal Food, Drug, and Cosmetic Act
- State Boards of Pharmacy
- CMS
- Food & Drug Administration
  - USP 797 + 503A + State Regulations + FDA Guidance

**Outsourcing Manufacturers Voluntary**

- Guidance for Industry
  - Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act
- Food & Drug Administration
- State Boards of Pharmacy
  - Current Good Manufacturing Practices; section 211 + FDA Guidance

3. 2016 GAO report: Drug Compounding: FDA has taken steps to implement compounding law, but some states/stakeholders reported challenges
Differences between cGMP & USP <797>

- Crosswalk of USP Chapter <797> and cGMP (21 CFR 211):
  - 187 individual cGMP requirements specifically examine
  - 20 are fully covered in USP Chapter <797>
  - 127 requirements of cGMP are not covered by USP Chapter <797>
**Good Manufacturing Practice**
Quality standards that drug manufacturers and “outsourcing facilities” must follow when making sterile drugs

Personnel must be **completely covered with sterile gowning** (no exposed skin).

**U.S.P. 797**
Quality standards that traditional compounding pharmacies must follow when making sterile drugs

Gowning required, but **only gloves must be sterile**. Neck and face may be uncovered.

Manufacturers **must test** non-sterile ingredients to be used in sterile drugs for pre-existing contamination.

Compounding pharmacies are **not required to test** for contaminants in non-sterile ingredients.

**Daily monitoring** for contamination is required in the manufacturing space, including during or immediately after production.

**Monitoring** for contamination is **less frequent**. Air particulate levels checked twice yearly.

FDA Report Card

• “Increased its inspections of facilities … regulatory actions in response to violations of the law that put patients at risk;

• Issued numerous policy documents

• Convened advisory committee

• Obtained input from stakeholders and;

• Worked closely with states to share information and coordinate efforts.”

Source: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm535968.htm
nationwide in late 2012, federal inspections of such facilities climbed sharply, as did safety citations.

- **INSPECTIONS WHERE “OBJECTIONABLE” SAFETY CONDITIONS DOCUMENTED**
- **COMPLETED FDA INSPECTIONS COMPOUNDING PHARMACIES**

1 – Figures DO NOT include pharmacies dedicated to producing veterinary drugs

Source: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm535968.htm
CMS Conditions Of Participation

CMS Memorandum Summary
Revised Hospital Guidance for Pharmaceutical Services and Expanded Guidance Related to Compounding of Medications

“hospital must have pharmaceutical services administered in accordance with accepted professional principles,

… U.S. Pharmacopeia/National Formulary (USP/NF)”
Surveying Bodies for Compounding

- State Boards of Pharmacy
- FDA: Food and Drug Administration
- CMS: Centers for Medicare/Medicaid Services
- TJC: The Joint Commission
- DNV Healthcare
- HFAP: AOA’s Healthcare Facilities Accreditation Program
- ACHC: Accreditation Commission for Healthcare
- PCAB: Pharmacy Compounding Accreditation Board
The Joint Commission

Source: https://www.jointcommission.org/certification/mdccert.aspx
FDA Guidance Documents

Sterile compounding

New FDA Sterile Compounding Draft Guidance documents released this year:

2. “Insanitary conditions at Compounding facilities” - 08/2016
3. “Prescription requirement under Section 503A of FDC Act” - 04/2016
4. “Hospital and health-system compounding under the FDC Act” - 04/2016
5. “Facility definition under Section 503B of FDC Act” - 04/2016
6. “Compounded drug products that are essentially copies of a commercially available drug product under Section 503A of FDC Act” - 07/2016
7. “Compounded drug products that are essentially copies of approved drug products under Section 503B of the Federal Food, Drug, and Cosmetic Act” - 07/2016

Source: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm
FDA Guidance Documents

Sterile compounding

1. **12/28/16**: Compounding and Repackaging of Radiopharmaceuticals By Outsourcing Facilities Guidance for Industry


Source: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm
Pharmacy compounding of human drug products

**FDC Act Guidance, June 2016**

- 503A exemptions
  - Drug is compounded for an identified individual
  - Drug is compounded by a licensed pharmacist in limited quantities
  - Drug is compounded in compliance with USP chapters
  - May not distribute >5% of their total compounded products interstate
- 503A does not exempt drugs from entire FDC act
- FDA may still act against the pharmacy
Insanitary Conditions at Compounding Facilities

August 2016

Adulterated - if prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.

- **Vermin** (insects or rodents in production area or nearby)

- **Visible microbial contamination** (bacteria, mold) in production area

- **Non-microbial contamination** (rust, glass shaving, hair)

- **Handling beta-lactam, hazardous or highly potent drugs without adequate containment**
  - Lack of cleaning equipment and personnel to prevent *cross-contamination*

- **Production of drugs while construction is underway**

Examples of Insanitary conditions

Sterile Operations

- Putting on gowning material improperly—gown touching floor, putting on sterile gloves and touching outside with bare hands
- Failing to disinfect or change gloves frequently enough
- **Wearing non-sterile gloves in aseptic area**
- Engaging in aseptic activities with exposed hands, wrists, legs, hair, or mouth
- Aseptic manipulations outside an ISO 5 area
- Exposing unprotected sterile product (including stock solution) to lower than ISO 5 quality air
- **Engaging in aseptic processing after leaving cleanroom and re-entering from non-classified area and not replacing apparel (gowns, gloves, masks, foot covers)**
- Touching equipment or other surfaces (telephone) located outside ISO 5 area with gloved hand and not changing gloves
- **Unsealed loose ceiling tiles**
- **Visibly dirty or rusty equipment or surfaces such as shelves**
- Presence of sinks or drains in ISO 5 area,
- **Non-sterile disinfecting agents and cleaning pads used in ISO 5 area**

Hospital and health-system compounding

FDC Act, April 2016

For all 503a Facilities

• Limits to 1 mile the distance between compounding pharmacy and health-care facility

• Pharmacy compounding (503A) and outsourcing (503B) should not occur near each other

• If a hospital pharmacy location is 503B for any drugs
  – FDA would require that all drug products made at the hospital address, including in the satellite and operating room pharmacies, meet the requirements for outsourcing facilities

Copied Compounded Drug Products

FDC Act, July 2016

- **Section 503A**
- "Compounded drugs pose a higher risk to patients versus FDA-approved drugs"
- "Restrictions on making drugs that are essentially copies"
  - Same active pharmaceutical ingredient (API);
  - API has the same, similar or easily substitutable dosage strength;
  - Commercially available drug product can be used by the same route of administration as prescribed for compounded drug
- Exceptions include documented allergies of incipient or unique route

The FDA has identified this as a Class I recall, the most serious type of recall. Use of these devices may cause serious injuries or death.

Recalled Product:
- Product Name: Normal Saline Flush
- Product description: 12ml IV Flush syringe with a 3 mL, 5 mL, or 10 mL fill volume
- Product Codes: All lots of product codes: 1203, 1205, 1210 and 1210-BP
- Manufacturing Dates: September 24, 2015 to August 1, 2018
- Distribution Dates: February 16, 2016 to September 30, 2016
- Devices Recalled in the U.S.: 386, 175 syringes nationwide

Source: http://www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm535293.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
Seeing the Unseen

Glass

Precipitant

Filaments

Coring

National Sterile Compounding USP <797>

Posting Date: September 25, 2015

Comment Deadline: January 31, 2016

Revision Announcement: January 27, 2017

Goal Publish Date: ???

Polling Question

How compliant is your site with USP <797>?  

A. Meets or exceeds USP <797>  
B. Meets most of USP <797>  
C. Meets some of USP <797>  
D. Planning to formally address USP <797>  
E. No plans for compliance
Hospital Compliance ... 36%

2016 STATE OF PHARMACY COMPOUNDING

<797> Compliance

Self-Reported Compliance with USP <797> Requirements

- 36% Meets/exceeds all requirements
- 51% Meets most requirements
- 9% Meets some requirements
- 3% Planning
- 1% No plan

With the coming update to <797>, those facilities that have yet to achieve full compliance likely will need to invest significant time and resources to meet the new standards.

State of Pharmacy Compounding, Pharm Purch Prod. 2016; 4: S1-S45.
Key Revisions to USP 797

Proposed revision to USP 797 is a complete re-write of 2008 chapter

• Compounded Sterile Products Categories nomenclature
  – **OLD**: Immediate use; Low-risk; Medium-risk; High-risk
  – **NEW**: Urgent use; Category 1; Category 2
  – **REMOVAL** of hazardous drugs section= USP 800
  – **In-Use-Time** = time a CSP must be used after it has been opened or punctured

• Sterility testing sampling for batching <40 (Test 10% of the batch size)

• Allergens and radiopharmaceuticals no longer exempted

Source: [http://www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision](http://www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision)
Key Revisions to USP 797

Proposed revision to USP 797 is a complete re-write of 2008 chapter

<table>
<thead>
<tr>
<th>Monthly viable air sampling</th>
<th>Was every 6 months</th>
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</thead>
<tbody>
<tr>
<td>Monthly viable surface sampling</td>
<td>Was periodic</td>
</tr>
<tr>
<td>Quarterly media fill test</td>
<td>Was annually</td>
</tr>
<tr>
<td>Quarterly finger glove tip test</td>
<td>Was annually</td>
</tr>
<tr>
<td>Room temperature</td>
<td>20° C or cooler</td>
</tr>
<tr>
<td>Humidity</td>
<td>Below 60% at all times</td>
</tr>
</tbody>
</table>

- Personal Protective Equipment and Cleaning
  - Sterile gloves and sterile sleeves or gowns
  - Sterile wipes and cleaning equipment

Source: http://www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision
Hazardous Drug Compounding USP <800>
Polling Question

How compliant is your site with USP <800>?

A. Meets or exceeds USP <800>
B. Meets most of USP <800>
C. Meets some of USP <800>
D. Planning to address USP <800> prior to July 1, 2018
E. No plans for compliance by July 1, 2018
Las Vegas – Some health systems pharmacies do not effectively protect their staff from exposure to cytotoxic agents, according to survey findings presented at the ASHP 2016 Midyear Clinical Meeting.

The survey of almost 900 facilities found that roughly two-thirds of workers handling hazardous drugs complied with U.S. Pharmacopeia (USP) Chapter <800> requirements.

Source: Pharmacy Practice News 2017;44(2):13
What Options Are Available for Safe Patient Care?
Choices for Sterile Products

- FDA registered pharmaceutical manufacturer premade
- Point of care activated devices
- Outsource compounding pharmacy
  - 503B
- Insourcing by hospital pharmacy
  - 503A
- Compounding/mixing at bedside
Evaluating Product Safety

2nd Consensus Development Conference

• Safety of Intravenous Drug Delivery System

• Participants ranked products based on safety
  – (highest=7 lowest=1):
  – Manufacturer ready-to-use (6.0)
  – Point-of-care activated (4.6)
  – Outsourced ready-to-use (4.5)
  – Pharmacy compounded (4.2)
  – Non-pharmacy compounded at point of care (1.8)

Following a prolonged dip from 2013-2015, the number of facilities utilizing outsourced vendors came roaring back this year. Nearly 7 out of 10 health systems rely on outsourced vendors to meet at least some of their compounding needs.
Looking forward, most facilities expect to continue outsourcing much of the same product mix that they currently rely on their vendors to supply.

Outsourcing Assessment

From a legal and The Joint Commission perspective Hospitals are responsible for the services provided to patients from an outsourced vendor.
## Checking Outsourcing Compliance

### Registered Outsourcing Facilities

Firms Registered As Human Drug Compounding Outsourcing Facilities Under Section 803B of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Updated as of 10/24/14

### Information Concerning Outsourcing Facility Registration

<table>
<thead>
<tr>
<th>Firm Name</th>
<th>Date of Registration as an Outsourcing Facility</th>
<th>End Date of Last FDA Inspection Related to Compounding</th>
<th>Was a Form FDA-483 Issued?</th>
<th>Other FDA Action, If Any, Based on Last Inspection?</th>
<th>Compounds Sterile Drugs From Duck Drug Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Pharmacy, Lutz, FL</td>
<td>6/3/2014</td>
<td>Not yet inspected</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Advanced Pharma, Inc., Houston, TX</td>
<td>1/22/2014</td>
<td>2/17/2014</td>
<td>Yes</td>
<td>Open</td>
<td>No</td>
</tr>
<tr>
<td>Alexander Infusion, LLC d/b/a Avant Health Care, New Hyde Park, NY</td>
<td>4/21/2014</td>
<td>7/8/2014</td>
<td>Yes</td>
<td>Open</td>
<td>Yes</td>
</tr>
<tr>
<td>AmeriLab LLC, Edmond, OK</td>
<td>5/23/2014</td>
<td>Not yet inspected</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Anacor Pharmaceuticals Corporation, Las Vegas, NV</td>
<td>9/23/2014</td>
<td>Not yet inspected</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Astra Health, Chandler, AZ</td>
<td>12/25/2013</td>
<td>9/5/2014 (Incomplete)</td>
<td>No</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>California Pharmacy and Compounding Center, Newport Beach, CA</td>
<td>4/30/2014</td>
<td>8/23/2014</td>
<td>Yes</td>
<td>Open</td>
<td>Yes</td>
</tr>
<tr>
<td>Central Drug Company,</td>
<td>12/16/2013</td>
<td>11/1/2013</td>
<td>Yes</td>
<td>Open</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Source: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm389118.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm389118.htm)
Accessed May 15, 2015
## Understanding Outsourcing Issues

### Frequency of FDA 483 Observation Topics

<table>
<thead>
<tr>
<th>483 Issue</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate/Improper Environmental Monitoring</td>
<td>81.9%</td>
</tr>
<tr>
<td>Validation of Sterilization: Media Fills</td>
<td>78.7%</td>
</tr>
<tr>
<td>Lab Procedures: Testing/Contract Lab Control</td>
<td>76.6%</td>
</tr>
<tr>
<td>Inadequate Gowning</td>
<td>76.6%</td>
</tr>
<tr>
<td>SOPs to Prevent Microbial Contamination</td>
<td>74.5%</td>
</tr>
<tr>
<td>Non-existent or Not Followed</td>
<td>66.4%</td>
</tr>
<tr>
<td>Stability Program</td>
<td>68.1%</td>
</tr>
<tr>
<td>Batch Release</td>
<td>61.7%</td>
</tr>
<tr>
<td>Control of Equipment</td>
<td>60.6%</td>
</tr>
<tr>
<td>Inadequate Facility/Smoke Studies</td>
<td>60.6%</td>
</tr>
<tr>
<td>Inadequate Cleaning/Disinfection</td>
<td>58.5%</td>
</tr>
<tr>
<td>Control of Pyrogenic Contamination</td>
<td>51.5%</td>
</tr>
<tr>
<td>Investigation</td>
<td>51.1%</td>
</tr>
<tr>
<td>Quality Assurance Unit Not Effective/Production SOPs Not Followed/Effective</td>
<td>36.2%</td>
</tr>
<tr>
<td>Separation of Clean and Dirty Operations/Storage of Materials</td>
<td>29.8%</td>
</tr>
<tr>
<td>Inadequate Raw Material Control</td>
<td>24.5%</td>
</tr>
<tr>
<td>Container Preparation</td>
<td>22.3%</td>
</tr>
<tr>
<td>SOP/Control of Production</td>
<td>16.0%</td>
</tr>
<tr>
<td>Safeguard Against Penicillin/Cephalosporin Cross-Contamination</td>
<td>12.8%</td>
</tr>
<tr>
<td>Labeling Issues</td>
<td>12.8%</td>
</tr>
<tr>
<td>Records Not Available</td>
<td>12.8%</td>
</tr>
<tr>
<td>Personnel Not Trained/Inadequately Trained</td>
<td>11.7%</td>
</tr>
<tr>
<td>Obvious Product Contamination (Micro/Particulate)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Change Control</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

*Frequency indicates the percentage of pharmacy 483 reports that reference this topic of the 94 present on the FDA Web site. Interpretation of the 483 findings and assignment to a particular category were performed solely by the author.*
ISMP Sterile Compounding Summit

• ISMP Summit 2011
  – When available
    • commercially manufactured
    • premixed IV products
  – Use over manually compounded sterile products

Drug Supply Chain Security Act, FDA, CMS, Joint Commission

- “Track & Traceability Act”
- “Pedigree Act”
- Transaction History (TH)  
  - Owners
- Transaction Information (TI)  
  - identifies the product  
    - (NDC, Lot Number, Date of Transaction, etc.)
- Transaction Statement (TS)  
  - attests that the TI and TH information is accurate
• Eliminate all 1,000 mL bags of sterile water (labeled for “injection,” “irrigation,” or “inhalation”) from all areas outside of the pharmacy.

• When compounding sterile preparations:
  – Preform verification to ensure proper ingredients are added
  – Confirm proper amount (volume) of each ingredient prior to adding
  – NO Syringe Pull-Back Method!!!

• Highly Recommended: Implementation of IV Efficiency (safety tracking) Software

Overall, one-third of health systems acknowledge having had a patient event involving a compounding error over the past 5 years. It is probable that the higher rates reported in the largest facilities are a result of stronger reporting systems.

“relying on fallible and microbial contaminated humans to perform flawlessly and with perfection is a doomed strategy that will inevitably lead to aseptic failures and contaminated doses”

Lawrence A. Trissel, B.S. Pharm., FASHP

Am J Health-Syst Pharm. 2007; 64:837-41
Questions/Discussion