The Changing Sterile Compounding Regulations

Willis C. Triplett, Pharm.D.
2015 OSHP Annual Meeting
April 23, 2015
Learning Objectives (RPh & CPhT)

- Explain USP <797>
- Describe the timetable and requirements of Proposed USP <800>
- Discuss the differences between 503A and 503B entities
- List the implications of Continuous Quality Improvement in managing sterile product compounding
Part 1 - The Historical Context and the Impact of the Fungal Meningitis Outbreak of 2012
Clear lines of differentiation
Clear lines of differentiation

Pharmacies
- State Regulations/USP
- State Boards
- Filled Prescriptions
- Face-to-Face
- Specific Patient
- Lived Nearby

Manufacturers
- cGMP
- FDA
- Made Huge Batches
- Drug Supply Chain
- Never met specific patients
- Lived Around the World
Lines Began to Blur

- **Chain Drug Stores**
  - Acquired independent pharmacies in great numbers, resulted in
  - Increasing numbers of prescriptions-per-hour
  - Decreasing time spent-per-patient

- **Advent of PBM Mail Order**
  - Prescriptions began to cross state lines
  - Utter loss of face-to-face relationship between pharmacist and patient

- **Independent Pharmacies (those remaining)**
  - Turned to compounding - cash business - no middle man - increased face-to-face contact between pharmacist and patient
  - Retail pharmacists who succeeded in nonsterile compounding, added sterile
Lines Began to Blur

- **Drug Shortages**
  - Vital staple drugs, including sterile ones (Potassium Chloride, etc.)
  - Large Scale sterile compounding pharmacies stepped in:
    - Prepared large batches
    - Never knew individual patients
    - Shipped over large geography - across state borders
  - Felt no bounds - did not limit to IM, SC, IV, but ventured on to epidural & intrathecal routes
  - Nearly no compounder adhered to cGMP - some did not even follow USP <797>
  - Predictable disaster waiting to happen
10 Bonus Points
Tennesseans of the Year - 2012

April Pettit, M.D., MPH
Infectious Disease Specialist
Vanderbilt Medical Center

Marion Kainer, M.D., MPH
Director – Healthcare-Associate
Infections and Antimicrobial Resistance
Tennessee Department of Health
September, 2012

- In 9/2012, 78-year old male patient was REadmitted to Vanderbilt University Hospital, suffering from agitation, headache, and low back pain
- Previously seen and treated for presumed bacterial meningitis
- Dr. April Pettit ordered another LP and asked the lab to culture not just for bacteria, but also for tuberculosis and fungi
- The next day - September 18, 2012 - the lab reported growth of aspergillus! (a form of fungus)
- Given that aspergillus meningitis is extremely rare, Dr. Pettit began to probe the family about how he could have contracted it
September, 2012

- Dr. Pettit learned he had received an epidural injection at St. Thomas Outpatient Clinic in Nashville four weeks earlier
- Dr. Pettit alerted the Tennessee Department of Health and Dr. Kainer began to investigate immediately and contacted CDC, where she had previously worked for two years as an epidemic intelligence officer
- Kainer established that the medicine had come from a Framingham Massachusetts compounding pharmacy, called New England Compounding Center (NECC) but NECC denied any known safety problems with the drug
- Kainer identified two more possible cases from St. Thomas by 9/21
Another case was identified on Monday 9/24 and CDC called Massachusetts health officials to learn more about NECC.

CDC notified FDA on 9/25 - FDA conducted an inspection on 10/1-2, 10/4-5, 10/9, and 10/15.

NECC announced a voluntary nationwide recall on 10/6.

FDA raided NECC on 10/16 and seized product.

FDA issued a 483 report regarding NECC - 50 out of 50 vials yielded microbial growth - filthy tacky mats - leaking boiler caused puddle on the floor just 30 feet from the clean room.
The Aftermath

- Outrage by public and congress as mainstream media presents the facts of the case
- On 10/28/2012, Governor Patrick (MA) asked Sophia Paredis to resign from Massachusetts Board of Pharmacy Regulation - V.P. for Compliance at NECC sister company, Ameridose
- Congressional hearings - 11/14/12 - House Energy & Commerce Committee; 11/15/12 Senate HELP Committee
- On 12/13/2012, FDA issued a 483 Inspection Report regarding Custom Compounding Center in Los Alamitos, CA, marking the first of many dozens of FDA inspections of pharmacies
The Aftermath

- Drug Quality and Security Act (DQSA) passed - 11/21/2013 - modified the Food Drug and Cosmetic Act of 1938 (FDCA) to better define 503A pharmacies and created “Outsourcing Facilities” under 503B
- President Obama signed DQSA on 11/27/2013
- July 2014 - FDA publishes:
  - Guidance entitled “Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act”; and
The Aftermath - Indictments

• December 14, 2014 - Indictments
  ▫ Barry Cadden, RPh, NECC owner - 25 counts of Second-Degree Murder
  ▫ Glen Chin - 25 counts of Second-Degree Murder
  ▫ Pharmacists
    • Christopher Leary - Joseph Evanosky - Cathy Chin - Michelle Thomas - Gene Svirsky - Alla Stepanets
  ▫ Technicians
    • Scott Connolly - Sharon Carter
  ▫ All ten pharmacy personnel charged with various racketeering, mail fraud, wire fraud, adulteration, and misbranding offenses.
Polling Question

- Regarding the Fungal Meningitis Outbreak of 2012:
  1. 751 people were infected;
  2. 64 people died from infection;
  3. 20 states suffered cases, but Michigan, Tennessee, and Indiana were hardest hit, accounting for more than 2/3 of the cases;
  4. Massachusetts accounted for zero cases (0).
  5. 1 through 4 are all true.
 Polling Question

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Part 2 - DQSA - 503A and 503B
Because NECC (and perhaps many companies) were de facto manufacturers masquerading as pharmacies, Congress hoped to sharpen the definitions of “pharmacy” and “manufacturer”

503A

- Provides exemption to the requirements of 3 sections of the FDCA for licensed pharmacists and licensed physicians:
  - 501(a)(2)(B) - Current good manufacturing practices
  - 502(f)(1) - Labeling and Directions for Use (Misbranding)
  - 505 - NDA or ANDA

- Provided all 503A conditions are met
Conditions required for 503A exemptions

Compounded drug products qualify for the exemptions IF:

1. The drug product is compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient.
Conditions required for 503A status

Compounded drug products qualify for the exemptions IF:

2. The compounding of the drug product is performed:
   • By a licensed pharmacist in a state licensed pharmacy or a Federal facility, or by a licensed physician on the prescription order for an individual patient made by a licensed physician or other licensed practitioner authorized by state law to prescribe drugs; or
   • By a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient and:
     • is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the human drug product; and
     • those orders have been generated solely within an established relationship between the licensed pharmacist or licensed physician and either such patient for whom the prescription order will be provided or the physician or other licensed practitioner who will write such prescription order (sections 503A(a)(1) and (2) of the FD&C Act).
Conditions required for 503A status

Compounded drug products qualify for the exemptions IF:

3. The drug product is compounded in compliance with the United States Pharmacopoeia (USP) chapters on pharmacy compounding using bulk drug substances, as defined in 21 CFR 207.3(a)(4), that comply with the standards of an applicable USP or National Formulary (NF) monograph, if one exists.

If such a monograph does not exist, the drug substance(s) must be a component of an FDA-approved human drug product. If a monograph does not exist and the drug substance is not a component of an FDA-approved human drug product, it must appear on a list of bulk drug substances for use in compounding developed by FDA through regulation (section 503A(b)(1)(A)(i) of the FD&C Act).
Conditions required for 503A status

Compounded drug products qualify for the exemptions IF:

4. The drug product is compounded using bulk drug substances that are manufactured by an establishment that is registered under section 510 of the FD&C Act (including a foreign establishment that is registered under section 510(i) of the FD&C Act) (section 503A(b)(1)(A)(ii) of the FD&C Act).

5. The drug product is compounded using bulk drug substances that are accompanied by valid certificates of analysis for each bulk drug substance (section 503A(b)(1)(A)(iii) of the FD&C Act).

6. The drug product is compounded using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapters on pharmacy compounding (section 503A(b)(1)(B) of the FD&C Act).
Conditions required for 503A status

Compounded drug products qualify for the exemptions IF:

7. The drug product does not appear on the list, published at 21 CFR 216.24, that includes drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (section 503A(b)(1)(C) of the FD&C Act).

8. The licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products (section 503A(b)(1)(D) of the FD&C Act).

9. The drug product is not a drug product identified by FDA by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product (section 503A(b)(3)(A) of the FD&C Act).
Conditions required for 503A status

Compounded drug products qualify for the exemptions IF:

10. The drug product is compounded in a state that has entered into a memorandum of understanding (MOU) with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside such state; or, in states that have not entered into such an MOU with FDA, the licensed pharmacist, licensed pharmacy, or licensed physician does not distribute, or cause to be distributed, compounded drug products out of the state in which they are compounded, more than 5% of the total prescription orders dispensed or distributed by such pharmacy or physician (sections 503A(b)(3)(B)(i) & (ii) of the FD&C Act).
Requirements Applicable to Drug Products that Meet the Conditions of Section 503A

Individuals and firms may be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of other requirements of the FD&C Act. Such violations may include, but are not limited to, the following:

1. The drug product must not consist in whole or in part of any filthy, putrid, or decomposed substance, or be 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. (Sections 501(a)(1) and (a)(2)(A) of the FD&C Act)

2. If the drug product purports to be a drug that is recognized in an official compendium, its strength must not differ from, and its quality or purity must not fall below, the standards set forth in the compendium, unless the difference is plainly stated on its label. (Section 501(b) of the FD&C Act)
Requirements Applicable to Drug Products that Meet the Conditions of Section 503A

Individuals and firms may be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of other requirements of the FD&C Act. Such violations may include, but are not limited to, the following:

3. For a drug product not subject to section 501(b) of the FD&C Act, the drug’s strength must not differ from, and its quality or purity must not fall below, that which it purports to have. (Section 501(c) of the FD&C Act)

4. If the drug product purports to be a drug that is recognized in an official compendium, it must be packaged and labeled as prescribed in the compendium. (Section 502(g) of the FD&C Act)

5. The drug product’s labeling, advertising, and promotion must not be false or misleading. (Sections 502(a), 502(bb), 10 and 201(n) of the FD&C Act)
FDA Published Enforcement Approach

“Generally, FDA expects to employ a risk-based enforcement approach with respect to violative compounded drugs, giving the highest enforcement priority to compounded drugs and violations of the FD&C Act and FDA regulations that pose the greatest public health risks. However, FDA emphasizes that it need not identify a particular safety problem before pursuing enforcement action.”
FDA 503A Guidance said “USP Standards” - but their Inspections imply cGMP

When FDA inspectors hit the streets visiting pharmacies they issued 483s against pharmacies as though the pharmacies should be following cGMP
503A Conditions by my interpretation

- Traditional pharmacy practice...
- compounding a valid prescription...
- From a valid, licensed, authorized prescriber...
- For a patient that you both know and are legitimately acting in the care of - and who lives in within your state borders...
- Even if it’s a sterile product compounded from non-sterile ingredients...
- And it’s not identical to a marketed product...
- And it does not include any forbidden components...
- You have nothing to worry about
503B Outsourcing Facilities

- Under the 503B provision the DQSA created a new category of medication supplier called, “Outsourcing Facility.”
- “503B pharmacy” = “503B entity” = “Outsourcing Facility”
- The intent of the 503B was to give pharmacies that do large-scale non-patient-specific sterile compounding a means to self-identify to FDA
- They would pay a significant fee to become inspected by FDA and would, by enrolling, agree to operate in accordance with cGMP
- If there were any complaints or problem reports, FDA would re-inspect and the 503B entity would pay the cost of subsequent re-inspection
503 Exemptions

- **503B**
  - A human drug product compounded by or under the direct supervision of a licensed pharmacist in a registered outsourcing facility can qualify for exemptions from the drug approval requirements in section 505.
    - 502(f)(1) - Labeling and Adequate Directions for Use (Misbranding)
    - 505 - NDA or ANDA
    - 582 - Track and Trace
  - However to qualify, certain conditions must be met
Conditions required for 503B exemptions

Outsourcing Facilities qualify for the exemptions IF:

1. The outsourcing facility must be in compliance with the registration and reporting requirements of section 503B(b). This includes submitting twice yearly reports regarding the drugs compounded by the outsourcing facility and submitting adverse event reports in accordance with section 503B(b)(5).

2. The outsourcing facility compounds drugs using one or more bulk drug substances, the bulk drug substances must meet certain requirements.

3. The outsourcing facility compounds using ingredients other than bulk drug substances, those ingredients must meet certain requirements.
Conditions required for 503B exemptions

Compounded drug products qualify for the exemptions IF:

4. The outsourcing facility must not compound drugs that appear on a list published by FDA of drugs that have been withdrawn or removed from the market because the drugs or components of such drugs have been found to be unsafe or not effective.

5. The outsourcing facility must not compound drugs that are essentially a copy of one or more approved drugs.

6. The outsourcing facility must not compound drugs that appear on a list published by FDA of drugs that present demonstrable difficulties for compounding.
Conditions required for 503B exemptions

Compounded drug products qualify for the exemptions IF:

7. If the outsourcing facility compounds from a drug that is the subject of a risk evaluation and mitigation strategy (REMS) approved with elements to assure safe use pursuant to section 505-1, or from a bulk drug substance that is a component of such drug, the outsourcing facility must demonstrate to FDA before beginning to compound that it will use controls comparable to the controls applicable under the REMS.

8. The outsourcing facility’s compounded drugs will not be sold or transferred by an entity other than that outsourcing facility.
Conditions required for 503B exemptions

Compounded drug products qualify for the exemptions IF:

9. The outsourcing facility has paid all applicable establishment and re-inspection fees owed under section 744(k)

10. The outsourcing facility must include on the labels and labeling of its compounded drug products the information required under section 503B(a)(10)
To Qualify for the Exemptions:

- **ALL** of the facility’s compounded drugs are compounded in accordance with section 503B (i.e. to the standard of cGMP)
- The facility must be engaged in compounding **STERILE HUMAN** drugs
- The definition of compounding does not include repackaging
- A “drug” does **NOT** include a **BIOLOGICAL** product (under section 351 of PHS Act) or an **ANIMAL** drug (under section 512 FDCA)
- Drugs compounded at an outsourcing facility are **NOT** eligible for the exemptions provided in section 503A, even if the conditions in that section are met with respect to the particular drug.
Polling Question:

- Most hospital pharmacies qualify for what exemption to the FDCA?
  - 340B
  - 510(k)
  - 503A
  - 503B
  - All of the Above
  - None of the Above
Polling Question:

- Most hospital pharmacies qualify for what exemption to the FDCA?
  - 340B
  - 510(k)
  - 503A
  - 503B
  - All of the Above
  - None of the Above
Polling Question:

• In response to the drug shortages, some hospital systems might create a centralized compounding pharmacy to meet their own internal needs for sterile products. They might prepare large batches well in advance of a prescription. Which designation would they need to seek?

  ▫ 340B
  ▫ 510(k)
  ▫ 503A
  ▫ 503B
  ▫ All of the Above
  ▫ None of the Above
Polling Question:

- In response to the drug shortages, some hospital systems might create a centralized compounding pharmacy to meet their own internal needs for sterile products. They might prepare large batches well in advance of a prescription. Which designation would they need to seek?
  - 340B
  - 510(k)
  - 503A
  - **503B**
  - All of the Above
  - None of the Above
USP - The official compendium of the USA
USP stands for United States Pharmacopoeia, a product of the U.S. Pharmacopeial Convention
Formed January 1, 1820
Recognized as the official compendium of the USA by the FDCA of 1938
USP Standards subsequently have been adopted in whole or in part by 140 nations
Sets standards for adulteration and misbranding for USA, et al
Scientific, voluntary, and not-for-profit
No enforcement apparatus
• Merged with the National Formulary and now published together as USP-NF
• Publishes its book on an Annual Basis ($850.00 USD)
• Can purchase Compounding Compendium only ($150.00 USD)
• Book has Chapters - 3-digit chapters (e.g. <797>) are binding national standards; 4-digit chapters (e.g.<1206>) are recommendations
• FDA can enforce any binding national standard at its discretion
• USP is organized as committees and panels of volunteer experts
Compounding Compendium:

- Complete, up-to-date text of all five essential compounding General Chapters from USP-NF
  - <795> Pharmaceutical Compounding—Nonsterile Preparations
  - <797> Pharmaceutical Compounding—Sterile Preparations
  - <1160> Pharmaceutical Calculations in Prescription Compounding
  - <1163> Quality Assurance in Pharmaceutical Compounding
  - <1176> Prescription Balances and Volumetric Apparatus

- All supporting general chapters are referenced and hyperlinked from the compounding chapters; more than 40 in all;
  Examples of supporting general chapters include:
  - <71> Sterility Tests
  - <85> Bacterial Endotoxins Test
  - <1151> Pharmaceutical Dosage Forms

- General Notices and Requirements, providing definitions and important information necessary to correctly interpret and apply compounding standards

- More than 170 USP-NF monographs for compounded preparations. Example monographs include:
  - Baclofen Oral Suspension
  - Lisinopril Oral Suspension
  - Metoprolol Tartrate Oral Suspension
Part 3 - USP <797>
USP General Chapter <797> - Pharmaceutical Compounding - Sterile Preparations

• Introduced in 2004; Revised in 2008; Another revision coming soon
• Chapter <795> pertains to Nonsterile Compounding
• Proposed <800> does not replace any chapter - it will be a new addition; Non-pharmacists often assume that higher numbered chapters replace lower numbered chapters
• When next revision of <797> is published it is expected to be harmonized with <800>
• When <797> was introduced to pharmacy leaders at the 2003 Midyear, a lot of faces looked like this...
<797> is coming!
Presentation at MYCM
By Phil Schneider, Clyde Buchanan, & Doug Lang
December 6, 2003
The primary concern was, how would enforcement look in January 2004?
January 1, 2004 came and went quietly

- And there was much rejoicing among practicing pharmacists
- No sudden State Board drop-ins; No announcements of big fines
- Many state boards of pharmacy did not specifically recognize, adopt, acknowledge or comment on <797>
- Few state boards inspectors got training in <797>
- Many pharmacy leaders did embrace it and demonstrated best practices
- But many considered it complicated, difficult, and internally contradictory, and - it was ignored by many pharmacy organizations
- ...which set the stage for the Fungal Meningitis Outbreak
USP <797>

What does it really cover?

- It’s actually only 38 pages total - only 26 before Appendices
- It’s organized like this:

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Suggested Standard Operating Procedures (SOPs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsibility of Compounding Personnel</td>
<td>Elements of Quality Control</td>
</tr>
<tr>
<td>CSP Microbial Contamination Risk Levels</td>
<td>Verification of Automated Compounding Devices (ACDs) for Parenteral Nutrition Compounding</td>
</tr>
<tr>
<td>Personnel Training and Evaluation in Aseptic Manipulation Skills</td>
<td>Finished Preparation Release Checks and Tests</td>
</tr>
<tr>
<td>Immediate-Use CSPs</td>
<td>Storage and Beyond-Use Dating</td>
</tr>
<tr>
<td>Single-Dose and Multiple-Dose Containers</td>
<td>Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs</td>
</tr>
<tr>
<td>Hazardous Drugs as CSPs</td>
<td>Patient or Caregiver Training</td>
</tr>
<tr>
<td>Radiopharmaceuticals as CSPs</td>
<td>Patient Monitoring and Adverse Events Reporting</td>
</tr>
<tr>
<td>Allergen Extracts as CSPs</td>
<td>Quality Assurance (QA) Program</td>
</tr>
<tr>
<td>Verification of Compounding Accuracy and Sterility</td>
<td>Abbreviations and Acronyms</td>
</tr>
<tr>
<td>Environmental Quality and Control</td>
<td></td>
</tr>
</tbody>
</table>
USP <797>

- If you compound sterile products and are not familiar with <797>, you should peruse it as soon as possible
- National Standard
- Even if not explicitly specified in state law, it’s in the FDA Guidance for 503A
- If you follow it diligently, patients will be safe
USP <797> -stated purpose - to describe conditions and practices to prevent harm, including death, to patients that could result from:

1. Microbial Contamination
2. Excessive Bacterial Endotoxins
3. Variability in the intended strength of correct ingredients that exceeds either:
   ▫ Monograph Levels for Official Articles, or
   ▫ 10% for Nonofficial Articles
4. Unintended chemical and physical contaminants
5. Ingredients of inappropriate quality

...in Compounded Sterile Preparations
USP Terminology

- Product vs. Preparation
- CSP = “Compounded Sterile Preparation”
- BUD = “Beyond-Use Date”
- SCA = “Segregated Compounding Area”
- SEC = “Secondary Engineering Control”
- cfu = “Colony Forming Unit”
- ISO
- Unidirectional Flow

- Risk Level
  - Low
  - Medium
  - High
- Buffer Area
- Clean Room
- Positive Pressure
- Negative Pressure
USP <797> - Terminology

PEC (Primary Engineering Control)

Positive Pressure
- LAFW
- Open

Negative Pressure
- CAI
- Closed
- BSC
- CACI
USP <797>

- HEPA = High Efficiency Particulate Air
- ACPH = Air Changes per Hour
- psi = pounds per square inch
- SOP = Standard Operating Procedure
- CTSD = Closed System Transfer Device
- PPE = Personal Protective Equipment
- ACD = Automated Compounding Device
- ALARA = As Low As Reasonably Achievable

- First Air
- Critical Site
- Critical Area
- Disinfectant
- Media-Fill Test
USP <797>

- Needs to remain the standard for health care
- USA cannot afford to provide health care by cGMP
- USP <797> did not fail us - NECC et al failed <797>!
- State Board Inspectors need to “know it cold” & “write tickets”
USP <797> - if FDA drops by

- Cooperate politely - Do not leave them sitting in your lobby
- Receptionist should be courteous, but businesslike
- Ask to review their credentials and really peruse them - keep your copy of the 482
- Escort the Inspector(s) to the room you will devote to his/her use - cancel all conflicting activities
- Set up your own “War Room” and designate your records couriers
- Don’t wait to be asked for your Org Chart, SOP Manual, CAPA logs - just produce them
- With every question, state and keep restating that you are a 503A pharmacy, operating to the standard of USP <797> - this will form the basis for your organization’s response to your 483
- Have a team member inform your corporate governance/risk management
- If State Board representative is not present, consider calling them (per risk mgt)
- Photograph everything the inspector photographs from the same angles
- Accompany the inspector every time he/she moves around the facility
- If they enter your clean rooms, insist that they gown and garb per SOP
USP <797>

Revolves around:
• Physical Conditions of the “clean” areas
• Our own policies and procedures - words matter
• Training our personnel (in our own policies and procedures, national standards, risks and benefits, best practices...)
• Sense of MISSION - LIVES DEPEND ON OUR DOING THIS RIGHT!
• Culture of Quality - Jidoka - “Stop the Line” - Call them on it - Keep coworkers and bosses honest - Never look the other way
• Fully Functional Quality Management Program
USP <797>

The environment is very important, but...
• “...direct touch contamination is the most likely source of introducing microorganisms into CSPs prepared by humans.”
USP <797>

- Train, Train, Train - Quiz Continuously on SOPs
- One Way - not Bob’s way or Betty’s way - ONE WAY - and everybody knows it
- The ONE WAY is clearly documented in SOPs and all staff know all SOPs
- Collect and record all required data without fail - and if we fail, record the fact of the failure and address it - every single time
- If you did not document it, you did not do it
- Once collected, you must TREND your data and establish controls to be able to spot “special causes”
- Ensure that your outside testing is done correctly and right on time
- YOU are responsible for vetting your certifier and ensuring that the certification performed satisfies every requirement of <797> and SOPs
USP <797>

- Media-Fill Test Procedure
- USP <797> provided an “Example of Test Procedure” for each risk level in the 2008 revision
- These were examples to be used as a guide, not one-size-fits-all recipes
- <797> states for each risk level that the Media-Fill is performed, “under conditions that closely simulate the most challenging and stressful conditions encountered during compounding.”
- This means the compounding that your staff perform
- Appropriately designing your Media-Fill Challenge is entirely on you!
Polling Question

It is vitally important to ensure that your Policies and Procedures are in harmony with every requirement of both USP General Chapter <797> and governing state and federal regulations?

• True
• False
Polling Question

It is vitally important to ensure that your Policies and Procedures are in harmony with every requirement of both USP General Chapter <797> and governing state and federal regulations?

• True
• False
Polling Question

Every operator must understand and be able to explain correctly and in detail every sterile compounding SOP as it applies to their work. Is this statement:

• True
• False
Polling Question

Every operator must understand and be able to explain correctly and in detail every sterile compounding SOP as it applies to their work. Is this statement:

• True
• False
Polling Question

If we hire a certifier who fails to appropriately perform a smoke test or viable airborne particle sampling, who is responsible for this failure?

- The Certifier
- We are
Polling Question

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- The Certifier
- We are
Polling Question

If we hire a certifier who enters our Buffer Room without washing, gowning, and garbing:

• That’s okay because he/she is just in there to verify the equipment
• We must never allow this to happen
Polling Question

If we hire a certifier who enters our Buffer Room without washing, gowning, and garbing:

• That’s okay because he/she is just in there to verify the equipment
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Part 4 - Proposed USP <800>
General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings

<table>
<thead>
<tr>
<th>&lt;797&gt;</th>
<th>Proposed &lt;800&gt;</th>
</tr>
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<tbody>
<tr>
<td>Meant to protect patients from faulty sterile preparations that healthcare workers compound</td>
<td>Meant to protect healthcare workers from the hazardous drugs we handle</td>
</tr>
<tr>
<td>Scope relatively narrow - focused on compounding steps</td>
<td>Scope much broader - covers everyone who might come in contact with HD from receipt at healthcare facility all the way through administration and disposal from patient homes.</td>
</tr>
</tbody>
</table>
Timeline - Proposed General Chapter <800>

• Originally published for comment in PF 40(3)[May-Jun 2014]
• Due to massive number of comments, USP posted “Notice of Intent to Revise” on 13-Oct-2014
• Revision posted to website on 01-Dec-2014 for early comments
• Revision was republished in PF 41(2)[Mar-Apr 2014]
• Comments to the Revision will be accepted until 31-May 2015
Timeline - Proposed General Chapter <800>

- Originally published for comment in PF 40(3)[May-Jun 2014]
- Due to massive number of comments, USP posted “Notice of Intent to Revise” on 13-Oct-2014
- Revision posted to website on 01-Dec-2014 for early comments
- Revision was republished in PF 41(2)[Mar-Apr 2014]
- Comments to the Revision will be accepted until 31-May 2015
Proposed General Chapter <800>

- Defines HD as those set forth in the most current NIOSH List
- NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2014 (September, 2014)
- 2014 NIOSH List was enhanced to include 3 categories:
  - Group 1: Antineoplastic Drugs
  - Group 2: Non-antineoplastic Drugs that meet one or more NIOSH criteria for “hazardous”
  - Group 3: Drugs that primarily pose a reproductive risk to men and women actively trying to conceive and women who are pregnant or breast feeding
Defined as “hazardous” drugs that exhibit one or more of six characteristics in humans or animals:

- Carcinogenicity
- Teratogenicity (or other developmental toxicity)
- Reproductive Toxicity
- Organ Toxicity at low doses
- Genotoxicity
- Structure and toxicity profiles that mimic existing drugs determined hazardous by the five criteria above
OSHA Hazard Communication Standard

Requires employers to develop a hazard communication program appropriate for their unique workplaces, which must include the identification of all hazardous drugs the worker may encounter on the job. The employer must:

• Evaluate whether these drugs meet the criteria for defining hazardous drugs, and
• Post a list of the hazardous drugs to ensure worker safety
The subtle implication is that each organization must evaluate each newly-added drug to determine whether it should be included on the organization’s unique list.

Also note that the Communication Standard applies not just to health care professionals, but also to others who participate in product acquisition, storage, transportation, housekeeping, and waste disposal.
Informal Poll

Which best describes your hospital’s HD list as of today:
1. Ours meets all requirements and is up to date
2. Ours meets all requirements but has not been updated to reflect the 2014 changes
3. We have one but it’s out of date and does not meet all requirements
4. We have never had a list that I know of
Core Principle of <800> - Containment

• Must contain the HD and keep it apart from everyone except the patient
• How do we maintain containment?
  ▫ Engineering Controls (Secondary and Primary)
  ▫ Garb
  ▫ Thoughtful SOPs, well deployed
  ▫ Disciplined, Consistent Work Practices
• We verify containment by
  ▫ Rigorous and Regular Environmental Sampling
Containment Requirements

• Any antineoplastic HD requiring manipulation and HD Active Pharmaceutical Ingredients (API) on the NIOSH list MUST follow the requirements of <800>
  ▫ Final antineoplastic dosage forms that do not require any further manipulation other than counting final dosage forms may be dispensed without any further requirements for containment unless required by the manufacturer’s labelling

• For dosage forms of other HDs on the NIOSH List, the entity may perform an assessment of risk to determine alternative containment strategies and work practices
Containment Requirements

The Assessment of Risk must consider at least:

- The category of HD
  - Antineoplastic
  - Non-Antineoplastic
  - Reproductive Risk
- Risk of Exposure
- Packaging
- Manipulation
Types of Unintentional Exposure

Compounding
- Crushing tablets or opening capsules
- Transferring oral or topical liquids between containers
- Constituting or reconstituting powdered/lyophilized HDs
- Withdrawing or diluting injectable HDs
- Expelling air from syringes containing HD
- HD residue on PPE/garb
- Deactivating, decontaminating, cleaning, disinfecting surfaces
- Maintenance of contaminated equipment or devices

Spills
Receipt
Types of Unintentional Exposure

Dispensing
- Counting tablets/capsules from bulk containers

Administration
- Generation of aerosols of HD given by any route
- Performing specialized procedures
  - Injection
  - Irrigation
  - Inhalation
  - Topical administration
  - Oral administration

- Patient-care activities
  - Handling of body fluids
  - Handling items contaminated with body fluids
Requirement for a “Lead Person”

86 Each entity must have a designated person who is qualified and trained to be
87 responsible for developing and implementing appropriate procedures; overseeing entity
88 compliance with this chapter and other applicable laws, regulations, and standards;
89 ensuring competency of personnel; and ensuring environmental control of the storage
90 and compounding areas. The designated individual must thoroughly understand the
91 rationale for risk-prevention policies, risks to themselves and others, risks of non-
92 compliance that may compromise safety, and the responsibility to report potentially
93 hazardous situations to the management team. The designated individual must also be
94 responsible for the continuous monitoring of the facility and maintaining reports of
95 testing/sampling performed in facilities.
Physical Facility Requirements

Must have DESIGNATED AREAS for HD:
- Receipt and unpacking
- Storage
- Compounding (both sterile and nonsterile)
- Dispensing
Designated Area Requirements

- Receipt and unpacking
  - Can be in negative pressure
  - Can be in neither positive, nor negative pressure
  - Must never be in positive pressure

- Storage
  - Store to prevent spills or breakage
  - Never on the floor
  - Can store with other inventory:
    - Non-antineoplastic HD
    - Reproductive risk-only HD
    - Final dosage form antineoplastic HD
  - Must be stored separate from other inventory in a room with negative pressure and >= 12 ACPH:
    - Antineoplastic HD requiring manipulation other than counting final forms
    - Any HD API
  - Refrigerated antineoplastic HD
    - Dedicated Refrigerator
    - Negative Pressure Room
    - >= 12 ACPH
    - If placed in Buffer Room, should place exhaust adjacent to refrigerator’s compressor
Designated Area Requirements

• Compounding
  ▫ Engineering controls are required to protect from both cross-contamination and microbiological contamination during all phases of the compounding process
  ▫ Engineering Controls for HD:
    • C-PEC - ventilated device designed to minimize worker exposure to HD
    • C-SEC - the room where the C-PEC resides
    • Supplemental engineering controls - CSTDs, etc.
C-PECs for HD must:

• Be externally vented through HEPA filtration
• Be physically separated from other preparation areas
• Have a negative pressure of 0.01 to 0.03 inches of water column
• Operate continuously
  ▫ Should operation stop, compounding must be suspended immediately and C-PEC should be covered per manufacturer recommendations
  ▫ On power-on, C-PEC interior surfaces must be decontaminated, cleaned, and disinfected and compounding resumed only after recommended recovery time
Nearby availability from C-PEC for HD

- Sink
- Eyewash station
- Must be placed in areas where their presence does not interfere with ISO air classifications
Compounding Both Sterile and Nonsterile HD

• Respective C-PECs must be in separate rooms, unless
• The C-SEC can be maintained at ISO 7 throughout nonsterile compounding, in which case:
  ▫ The sterile and nonsterile C-SECs must be placed >= 1 m apart and
  ▫ Particle-generating activity cannot take place with sterile compounding is in progress
Nonsterile HD Compounding

• C-PEC not required if only handling non-generating final forms
• C-PECs used for nonsterile HD must:
  ▫ Be vented to the outside, or
  ▫ Exhaust must be redundant HEPA filtered in series
  ▫ May include:
    • BSC - Class I or Class II
    • CACI
    • Containment Ventilated Enclosure (CVE or “Powder Hood”)
  ▫ For occasional HD use, can use sterile compounding C-PEC if decontaminated, cleaned, and disinfected before resuming sterile
Nonsterile HD Compounding

- C-PEC must be placed in a C-SEC that provides $\geq 12$ ACPH and is vented to the outside.
- C-PEC internal surfaces must be:
  - Smooth
  - Seamless
  - Impervious
Sterile HD Compounding

- All of <797> must be faithfully followed
- All C-PECs must be externally vented
- Sterile HD must be compounded in ISO 5 air quality or better
  - BSC Class II (A2, B1, B2) or III, or
  - CACI
  - LAFW and CAI must never be used to compound antineoplastic HD
  - BSC or CACI used for HD must not be used for non-HD compounding unless:
    - Placed into protective outer wrapper AND
    - Labelled to require PPE for administration
Sterile HD Compounding

- C-PEC must be located within a C-SEC
- The C-SEC that contains the C-PEC is either
  - An ISO 7 Buffer Room (preferred) or
  - An unclassified C-SCA (Maximum BUD of HD CSP is 12 hr)
  - If an ISO 7 Buffer Room
    - Externally Vented
    - Negative Pressure between 0.01 and 0.03 inches of water column
    - $\geq 30$ ACPH
  - If an unclassified C-SCA
    - Externally Vented
    - Negative Pressure between 0.01 and 0.03 inches of water column
    - $\geq 12$ ACPH
    - Hand washing sink at least 1.0 meter from C-PEC
    - Low- and Medium-Risk HD compounding only - NO HIGH RISK
Sterile HD Compounding

Containment Supplemental Engineering Controls (e.g. CSTD)

- Users must evaluate performance claims
- A CSTD is never an acceptable substitute for a C-PEC in compounding
- CSTDs MUST be used in the administration of HDs when the dosage form allows
Recommendation for Environmental Surveillance

- Environmental wipe sampling should be performed initially (to establish the baseline) and ever six months or more often.
- Purpose is to verify that containment has been achieved.
- Surface wipe sampling should include:
  - Interior surfaces of C-PEC, plus any equipment contained therein.
  - Staging areas near the C-PEC.
  - Areas adjacent to the C-PEC (floors under staging area).
  - Patient administration areas.
- Measurable contamination should trigger CQI.
Personal Protective Equipment

- PPE provides worker protection to reduce exposure to HD aerosols and residues
- When working outside the C-PEC, PPE is our only protection
- SOPs must describe PPE to be worn, based on risk exposure
- Appropriate PPE must be worn when handling HDs including:
  - Receipt
  - Storage
  - Transportation
  - Compounding (Sterile and Nonsterile)
  - Administration
  - Deactivation - Decontamination - Cleaning - Disinfection
  - Spill recovery
Gloves

• **Chemotherapy gloves**
  - must be tested for ASTM standard D6978
  - must be powder-free
  - must be inspected for physical defects prior to use (no pin holes)
  - must be changed no less often than every 30 minutes
  - must be changed when torn, punctured, or contaminated
When required, disposable gowns must be tested and proven resistant to permeability by HDs.

Disposable gowns made of polyethylene-coated polypropylene or other laminate are superior to uncoated gowns.

Must close in the back and have long sleeves.

Cuffs must be elastic or knit.

Unless permeation information is available, should be changed no less often than every 3 hours or immediately after splash or spill.

HD gowns must never be worn into other areas.
Other coverings

- Head and hair covers must be worn
- Shoe covers must be worn in compounding any HD
- When compounding sterile HD, second shoe covers are donned on entering the buffer room and doffed on departing the buffer room
- Coated sleeve covers may be used - when used must be carefully removed and disposed of when task is complete
Eye and Face Covering

- Appropriate eye and face protection must be work when there is a risk for spills or splashes of HDs when working outside a C-PEC (this includes nurses hanging HD above eye level).
- Full-faceplate respirators provide adequate eye and face protection.
- Goggles must be used when eye protection is required.
- Face shields + goggles provide full range protection.
- Face shields alone, eyeglasses, and safety glasses are not adequate protection.
Respiratory Protection

- Fit-tested NIOSH N95 respirators are adequate to protect against airborne particles, but NOT vapors
- Surgical masks are not adequate
- Surgical N95 respirators may be adequate for most situations
- For unpacking unknown HD, an elastomeric half-mask with a multi-gas cartridge and P100 filter should be used
- For attending to HD spills or airborne exposures, a full-faceplate chemical cartridge respirator must be worn
Personnel Training

- All personnel must be trained on all aspects of HD as they pertain to their job functions
- Training must occur prior to handling HD
- Effectiveness of training must be demonstrated before handling HD
- Competency reassessed:
  - At least annually
  - With every newly added HD
  - With any newly added equipment or material change in process or SOP
Personnel Training

- **Must include:**
  - Overview of the entity’s list of HD and their risks
  - Review of entity’s SOPs relating to the handling of HD
  - Proper use of PPE
  - Proper use of equipment and devices
  - Management of spills
  - Response to known/suspected HD exposure
Receiving

- Entity must establish SOPs for receiving HD
- HDs must be delivered to the HD storage area immediately upon arrival
- PPD must be used in unpacking HD and a spill kit must be easily accessible
- Damaged packages should be sealed without opening when possible, marked as “Hazardous” and returned when possible
- When a potentially damaged package must be opened, opening should be done within a C-PEC and the damaged form should be sealed, labeled “Hazardous” and properly disposed of
- C-PEC should be deactivated - decontaminated - cleaned - disinfected
Labeling, Packaging, and Transportation

- Entity must establish SOPs for labeling, packaging, and transporting HD
- SOPs must address:
  - Prevention of accidental exposure
  - Response to exposure
  - Use of a spill kit
- Labeling - HD as identified by entity must be clearly labeled at all times during transport
- Packaging
  - Containers/materials must be selected that will maintain physical integrity, stability, and sterility of HD as well as protection from damage, leakage, contamination, and degradation
  - SOPs must specify appropriate shipping containers and insulation
- Transport
  - Labeled, stored, and handled per all pertinent regulation during transportation
  - Pneumatic tubes must never be used to transport HDs
  - Transportation must be in accordance with SDS
Dispensing and Compounding

- All compounding of HD must be compliant with <795> and <797>
- When preparations are compounded within a C-PEC, a plastic-backed mat must be used to shield the work surface
- Mat should be changed regularly and whenever a spill is noted
- HD compounding equipment must be dedicated to HD use
Administering

• All HD should be administered via closed systems
• HD tubings should be dispensed primed when appropriate
• PPE must be worn while administering
• CTSDs MUST be used to administer HDs unless the dosage form precludes their use
Deactivation - Decontamination - Cleaning - Disinfection

- Deactivation - Render the compound inert or inactive
- Decontamination - Removed the inert residue
- Cleaning - Germicidal detergent + sterile water
- Disinfection - Destroy microorganisms
Spills

• Any personnel required to clean up an HD spill must have first received training in spill management, PPE, and NIOSH-certified respirators
• Spill kits and trained personnel must be readily available
• Spill materials must be disposed of as hazardous waste
• Circumstances and management of spills must be documented
• Medical evaluation must follow up any exposures during spills
Medical Surveillance

• Medical surveillance is meant to be a part of a comprehensive exposure control program
• Healthcare workers who handle HD should be enrolled in a medical surveillance program
• Medical surveillance is meant to provide a means of early detection of health problems among personnel
• It helps evaluate the effectiveness of the protection offered by engineering controls
Part 5 - Statistical Quality Management
The word, “Quality” has many meanings to many people

USP <797> states that “A provider of CSPs shall have in place a formal Quality Assurance program intended to provide a mechanism for monitoring, evaluating, correcting, and improving the activities and processes described in this chapter.”

No matter how good our operation is, we should be constantly striving to improve our results

CQI provides the methods and tools to continuously improve our operation
Quality Management (CQI)

- We generally sense how our operation is doing - we know what a “normal” week or a “normal” month feels like.
- We generally sense how “well cared for” our customers are feeling - hopefully we survey them and ask/beg/plead for criticism - we can only fix problems we know we have.
- We track many important pieces of data without even trying to because our enterprise software does it for us automatically.
- Quality Management means we move away from our general intuition about how things are going and move toward scientific study of statistical trends of accurate data.
Quality Management (CQI)-How it works

• How do we pick what activity to improve?
  ▫ Look at recent or frequent “sentinel events” first
    • Determine what went horribly wrong (“special cause”), why it went wrong (root cause analysis), and how to stop the gap, pending a permanent fix
  ▫ None? Good. Things seem to be running along “normally”-and have for a while? Good.
    • We are in a state of statistical control - only common causes of variation are in play - we’re having the “usual” problems about as “often as usual”
  ▫ Let’s make a list of the activities our operation is worst at
  ▫ We review the list and rank each item by (1) importance and (2) how hard it would seem to fix
  ▫ Important things that are easy to fix always outrank trivial things that are difficult to fix - ranking things in between is senior management’s call
Quality Management (CQI)-How it works

• Once we have chosen what to improve
  ▫ We look back over our records to measure our past performance
  ▫ No records? Start recording today and mark you calendar to revisit quality when you’ve got enough records
  ▫ We’ve got records? (“control chart”) Start measuring variability in performance, looking for patterns
  ▫ Spot a pattern - start asking why? What went wrong?
  ▫ First “why” will likely be trivial - ask why again - and again - and again - and again - the “fifth why” usually begins to bring truth into (“root cause”)
  ▫ Never forget, always be alert - Root Cause(s) can be plural
Quality Management (CQI)-How it works

• We’ve asked “why” enough times (iterations) to have identified what really went wrong, which will be a process that is either broken or never existed. The fix will be improving the faulty process or creating/training/implementing a good one. How do we determine what process to revise/create?

• We PLAN
  ▫ Assemble representative stakeholder(s) from ALL teams touched
  ▫ Determine how each team’s perspective interacts with the process
  ▫ Engage in dialogue* to determine the optimally feasible, most efficient, and least onerous solution
  ▫ * - there can be NO DEFENSENESS OR BLAME in dialogue
Quality Management (CQI)-How it works

• Okay, we’ve chosen a weakness - drilled with “whys” to its root cause - we’ve made our PLAN - so now we DO - DO means test in an experimental way
  ▫ We train all affected DO staff in the “new way” of doing work
  ▫ We test them, confirm understanding, “hover” nearby being available for questions and guidance
  ▫ We ensure data capture by which to measure outcome of the DO
  ▫ We let the “new way” run/operate/function
  ▫ We allow ample time for “new way” to prove itself, checking our captured data occasionally
Quality Management (CQI)-How it works

- After we’ve done our PLAN and our DO - it’s time to CHECK
  - We examine the results from our “new way” experiment
  - Did our “new way” work? What did we LEARN from our DO
  - Has our target deficiency been resolved?
  - If YES, we ACT
    - ACT means we permanently/formally incorporate the “new way” into our SOPs and training for all future hires
  - If NO, we do not return to “square one” - reexamine our “whys” - set stage for new PLAN
  - We determine whether we had the right teams represented
  - We assemble another stakeholder group, create fault-free dialogue
  - We formulate a PLAN, et cetera
Quality Management (CQI)

- PLAN-DO-CHECK-ACT
- Abbreviated PDCA
- Shewhart Cycle or Deming Cycle
- How many iterations do we do?
  - Until we find an improvement that works
- Why PDCA?
  - It’s scientific trial-and-fail or succeed
  - It’s how all progress is ever made
  - It’s how all learning is ever achieved
CQI for a Human Start-Up Entity (baby)

- Every advancement is by trial-and-failure until we achieve trial-and-success
- Every failure must be followed by “back to the drawing board”
- Every ACT (incorporation of new process into SOPs) must be MAINTAINED. It’s inconceivable that a child who can run could forget how to sit up.
- Expectation of easy success is absurd – what week-old infant ever ran?
- Blame? - find a place for blame if you can
Quality Management for Sterile Compounding Pharmacies

- For Quality Management to succeed, it MUST have unmitigated support from all levels of management.
- Quality Management always depends on input from stakeholders from all pertinent teams and its stated goals must remain a top priority - make every effort to never cancel or postpone Quality Oversight Committee.
- Do not limit membership on Quality Oversight just to managers - Quality is every employee’s business.
- The fuel that drives QM is accurate, compiled, updated and trended data.
Part 6 - Discussion, Questions, Dialogue, Debate