Understanding the New Federal Framework for Oversight of Sterile Compounding

Presented as a Midday Symposium at the 49th ASHP Midyear Clinical Meeting and Exhibition

Monday, December 8, 2014
Anaheim, California

Planned and conducted by ASHP Advantage and supported by an educational grant from Baxter Healthcare Corporation.
Please be advised that this activity is being audio and/or video recorded for archival purposes and, in some cases, for repurposing of the content for enduring materials.
Understanding the New Federal Framework for Oversight of Sterile Compounding

Agenda

11:30 a.m. – 11:45 a.m.  Welcome and Introduction
How did you get here? Review of the compounding legislation and the previous contamination incidents that have occurred over the last 25 years
Eric Kastango, M.B.A., B.S.Pharm., FASHP

11:45 a.m. – 12:30 p.m.  Overview of the Legislation and Implementation Efforts to Date
Jane Axelrad, J.D.

12:30 p.m. – 12:45 p.m.  Key Factors to Consider when evaluating a FDA registered 503B Outsourcing Facility
Eric Kastango, M.B.A., B.S.Pharm., FASHP

12:45 p.m. – 1:00 p.m.  Panel Discussion: Questions and Answers

Food and beverage are no longer provided at Midday Symposia. This ASHP policy considers the varied internal policies of commercial supporters related to the Physician Payments Sunshine Act.

Faculty

Eric S. Kastango, M.B.A., B.S.Pharm., FASHP, Activity Chair
President/CEO
Clinical IQ, LLC and CriticalPoint, LLC
Madison, New Jersey

Jane Axelrad, J.D.
Associate Director for Policy
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, Maryland
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Activity Overview

This educational activity will examine the current status of FDA oversight of compounding pharmacies and explore strategies that pharmacists can implement to ensure patient safety. Implications of the Drug Quality and Security Act will be reviewed including the conditions necessary to qualify for the exemptions under sections 503A and 503B. Key factors to consider in deciding whether to purchase from an outsourcing facility will also be explained.

Learning Objectives

At the conclusion of this knowledge-based educational activity, participants should be able to

- Summarize the concepts in recent compounding legislation affecting federal oversight of sterile compounding.
- Describe the conditions under which facilities that compound sterile drugs can be exempt from the approval, adequate directions for use, and CGMP requirements under section 503A of the Federal Food, Drug, and Cosmetic Act (FFDCA) and the approval and adequate directions for use provisions under section 503B of the FFDCA.
- Describe key provisions of current good manufacturing practices (CGMPs) that are essential to compounding sterile drug products of high quality.
- Review the factors to consider when deciding where to purchase compounded drugs for your healthcare facility.

Your educational opportunities related to sterile compounding extend beyond today’s symposium...

- Available in 2015
  - On-demand activity based on today’s live symposium (1.5 hours of CPE, please note that individuals who claim CPE credit for the live symposium are ineligible to claim credit for the on-demand activity)

For more information and to sign up to receive e-mail updates about this educational series, visit

http://www.ashpadvantage.com/outsource
Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.5 hours (0.15 CEUs – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-14-712-L03-P for the live activity and ACPE activity #0204-0000-14-712-H03-P for the on-demand activity).

Complete instructions for receiving your statement of continuing pharmacy education credit online are on the next page.
Online CE Access: Conferences with Attendance Codes

Pharmacists and Technicians:
Per ACPE, CPE credit must be claimed **no later than 60 days** from the date of the live activity or completion of a home study activity. All ACPE accredited activities which are processed on the eLearning site will be reported directly to CPE Monitor. To claim pharmacy credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to www.MyCPENet.net for information and application. Please follow the instructions below to process your CPE credit for this activity.

Please follow these instructions to view your session material and claim CE:

1. The **ASHP eLearning** site allows participants to obtain statements of continuing education credit conveniently and immediately using any computer with an internet connection. Type the following link into your web browser to access the e-Learning site: [http://elearning.ashp.org/my-activities](http://elearning.ashp.org/my-activities)

2. If you already have an account registered with ASHP, log in using your username and password.

   **If you do not have an account with ASHP**, you will need to set up an account. Click on the Register link and follow the registration instructions. You do not have to be a member to create an account.

3. Once logged in, click on the name of the conference under **Your Conferences**.

4. At the top of the page is a field for redeeming Attendance Codes (formerly called ‘CE codes”). Enter the attendance code that was announced during the activity, and **click Submit**.

   Helpful Tip: If your code is not redeeming successfully, verify that you have clicked on the title of your conference in order to access the Attendance Code field, not the Enrollment Code field.

5. Each session will be listed under **Your Sessions**. Click **Claim Credit** for a particular session.

6. Complete any requirements for each session by clicking on the name of
that activity and following the instructions.

7. Click **Claim Credit**.

8. Review the information for the credit you are claiming. If all information appears to be correct, check the box at the bottom and click **Claim**. You will see a message if there are any problems claiming your credit.

9. After successfully claiming credit, you may print your statement of credit by clicking on **Print**. If you require a reprint of a statement of credit, you can return here at any time to print a duplicate. Please note that for CPE credit for pharmacists and technicians, printed statements may not be necessary because your credit is reported directly to CPE Monitor.

**NEED HELP? Contact eLearning@ashp.org**

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Understanding the New Federal Framework for Oversight of Sterile Compounding

Eric S. Kastango, M.B.A., B.S.Pharm., FASHP
President/CEO
Clinical IQ, LLC and CriticalPoint, LLC
Madison, New Jersey

Eric S. Kastango, M.B.A., B.S.Pharm., FASHP, is president of Clinical IQ LLC, a health care consulting firm and CriticalPoint, LLC, a web-based education company.

Mr. Kastango received his Bachelor of Science degree in pharmacy from the Massachusetts College of Pharmacy and Allied Health Sciences and his Master of Business Administration degree from the University of Phoenix. He is also the 2014 recipient of the NABP Henry Cade Memorial Award that recognized the efforts and assistance to the states and NABP to address the compounding tragedy that occurred in 2012.

Since 1980, he has practiced pharmacy in a number of practice settings, including hospitals, community, and home care, in a number of different roles, including the Corporate Vice President of Pharmacy Services for Coram Healthcare Corporation. He has also managed a FDA-registered cGMP manufacturing operation for Baxter Healthcare Corporation.

He is an active member and Fellow of the American Society of Healthcare Pharmacists and served on the USP Sterile Compounding Committee from 2005-2010 and 2010-2015 USP Council of Experts, Compounding Expert Committee until April 2013. He is currently an Expert Consultant to the USP and is actively working with NABP and state boards of pharmacy to provide training to their sterile compounding inspectors.

Eric is author of the 2004 ASHP Discussion Guide on Sterile Preparation: Summary and Implementation of USP Chapter 797, the ASHP Sterile Product Preparation CD-ROM: A Multimedia Learning Tool, the ASHP web-based 797 Compliance Advisor Gap Analysis Tool for USP Chapter 797 and the CriticalPoint web-based educational series on Sterile Compounding and the Annual National USP <797> Compliance Survey now in its fourth year. Eric has over 200 invited national and international professional presentations on various pharmacy practice topics such as pharmacy compounding and quality systems.
Jane Axelrad, J.D.
Associate Director for Policy
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, Maryland

Jane A. Axelrad, J.D., is the Associate Director for Policy in FDA’s Center for Drug Evaluation and Research (CDER) and the Agency’s Lead on Compounding. Ms. Axelrad manages the legislative, policy, surveillance and enforcement issues related to the oversight of drug compounding. From 1995 to 2013, she served as the Director, Office of Regulatory Policy, CDER, where she was responsible for managing the development of new regulations and policies applicable to the FDA’s regulation of human pharmaceuticals. Ms. Axelrad was instrumental in negotiating and implementing a number of key pieces of legislation including the FDA Modernization Act of 1997, the FDA Amendments Act of 2007, the Food and Drug Administration Safety and Innovation Act, and the Drug Quality and Security Act. Before Ms. Axelrad joined FDA in 1991, she held a series of legal and policy positions at the Nuclear Regulatory Commission and the Environmental Protection Agency. In 1997 and again in 2014, she received the HHS Secretary’s Award for Distinguished Service and she was named a Presidential Rank Meritorious Executive in 1998 and again in 2007. Ms. Axelrad received her BA in mathematics and sociology from the University of Michigan and her JD from the Columbus School of Law, Catholic University of America.
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Learning Objectives

After participating in this knowledge-based educational activity, attendees should be able to:
• Understand the concepts in recent compounding legislation affecting federal oversight of sterile compounding.
• Describe the conditions under which facilities that compound sterile drugs can be exempt from the approval, adequate directions for use, and CGMP requirements under section 503A of the Federal Food, Drug, and Cosmetic Act (FFDCA) and the approval and adequate directions for use provisions under section 503B of the FFDCA.
• Describe key provisions of current good manufacturing practices (CGMPs) that are essential to compounding sterile drug products of high quality.
• Review the factors to consider when deciding where to purchase compounded drugs for your healthcare facility.
How did you get here? Review of the compounding legislation and the previous contamination incidents that have occurred over the last 25 years

Eric S. Kastango, M.B.A., B.S.Pharm., FASHIP
President/CEO
Clinical IQ, LLC and CriticalPoint, LLC

“Study the past if you would define the future”
Confucius

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.
USP Compounding Standards

- Chapter <797>: Sterile Compounding
  - Official on January 1, 2004
  - Revised chapter official on June 1, 2008
  - Nationally enforceable
  - 24+ states require compliance
  - More states are modifying regulations
    - Codify USP <797>
    - Adopt portions
    - Develop own regulations
    - No action
- Chapter <795>: Nonsterile Compounding
- Proposed Chapter <800>: Hazardous Drugs

State Regulation of Pharmacy Compounding

- All states license pharmacists to compound
- Each state has varying degrees of regulations and oversight and enforcement of compounding practices
  - Only 24+ states require direct compliance with USP 797 after 10 years
- Until USP <797>, no consistent and enforceable compounding standard of practice existed

State Boards of Pharmacy

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<td>Wisconsin</td>
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Over 4 year period, overall compliance scores grouped by state regulatory status:

- Overall compliance improvement (all states) 7.4%
- Red states improved by 10.0%
- Yellow states improved by 8.4%
- Green states improved by 11.1%

Yesterday...
- NCC LVP
- FDA Alert Letter
- ASHP Urgent Attention Letter
- ASHP National Survey
- ASHP TAB
- USP <1206>
- ASHP National Survey
- FDAMA signed into law by President Clinton;Contained new section 503A regarding pharmacy compounding
- ASHP Guidelines revised
- Supreme Court held unconstitutional certain advertising restrictions in section 503A
- ASHP National Survey

Today...
- January 1, USP <797> first published
- November, NIOSH Alert published
- USP <797> released, new standard effective June 2008
- CDC and CMS recognizes USP <797>
- NECC tragedy
- 3rd CriticalPoint USP <797> Compliance Survey
- 3rd CriticalPoint USP <797> Compliance Study
- The Drug Quality and Security Act became law
- FDA published SEIA and SDE guidance
- 4th CriticalPoint USP <797> Compliance Study

See page 36 for enlarged view

See page 37 for enlarged view
Which of the following statements is not accurate?

a. A pharmacist must supervise compounding
b. All 50 states require compliance with USP Chapter <797>
c. Regulatory compliance with USP Chapter <797> is improving
d. The CDC and CMS recognize USP Chapter <797>

“Our patients have never had a problem”

Who’s been involved in compounding contaminated drugs?

- What do these entities have in common?
  - Retail/Community-based
  - Homecare/Home infusion
  - Hospital
  - Commercial outsourcer
- They all:
  - are licensed as pharmacies by their respective state boards of pharmacy
  - considered compounding pharmacies by the FDA
  - represent the full spectrum of practice settings run by pharmacists
What’s the damage?

Since 2001, over 25 pharmacy compounding incidents with 1,049 adverse events, including 89 deaths, have been reported.

- Contamination of sterile preparations was the most common compounding error, though others were the result of pharmacists’ and technicians’ miscalculations and mistakes in filling prescriptions.


### Brutal Facts

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<th>Year</th>
<th>State</th>
<th>Setting</th>
<th>Description</th>
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<tbody>
<tr>
<td>1990</td>
<td>Nebraska</td>
<td>Hospital</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>Community</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>Outsourcer</td>
<td>11 children became septic—10 tested positive for Enterobacter cloacae bloodstream infections associated with contaminated prefilled saline syringes. All patients were successfully treated and discharged.</td>
</tr>
<tr>
<td>2001</td>
<td>California</td>
<td>Community</td>
<td>13 patients were hospitalized and 22 received medical care following injections from Serratia marcescens contaminated betamethasone compounded at a community pharmacy. 3 patients died.</td>
</tr>
<tr>
<td>2001</td>
<td>Missouri</td>
<td>Hospital</td>
<td>4 children contracted Enterobacter cloacae infections from IV ranitidine compounded in a hospital pharmacy. All of the children survived the infection.</td>
</tr>
<tr>
<td>2002</td>
<td>North Carolina, South Carolina</td>
<td>Community</td>
<td>5 patients developed fungal meningitis resulting from Exophiala dermatitidis contaminated injectable methylprednisolone; 1 patient died 152 days after being injected.</td>
</tr>
<tr>
<td>2002</td>
<td>Michigan</td>
<td>Community</td>
<td>Pharmacy preparing injectable methylPREDNISolone and baclofen recalled the products because of contamination with Penicillium mold, Methylobacterium, and/or Mycobacterium chelonae. No adverse patient outcomes reported.</td>
</tr>
<tr>
<td>2003</td>
<td>Missouri</td>
<td>Community</td>
<td>Bacteria contamination with Burkholderia cepacia found in at least 2 batches of a compounded inhalant solution used by 19,000 patients with chronic lung diseases. One patient adverse outcome associated with the medication.</td>
</tr>
<tr>
<td>2004</td>
<td>Texas, New York, Michigan, Missouri</td>
<td>Homecare</td>
<td>80 patients developed Pseudomonas bloodstream infections after receiving heparin/saline flushes from multiple lots of preloaded syringes. By PFGE, clinical isolates from 50 (98%) of 51 patients were related to isolates cultured from unopened syringes.</td>
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### Brutal Facts (continued)

<table>
<thead>
<tr>
<th>Year</th>
<th>State</th>
<th>Setting</th>
<th>Description</th>
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<tbody>
<tr>
<td>2005</td>
<td>New Jersey,</td>
<td>Outsourcer</td>
<td>Up to 24 patients associated with Serratia marcescens infections due to contaminated magnesium sulfate mini-bags. No patient deaths associated with this event.</td>
</tr>
<tr>
<td>2005</td>
<td>California</td>
<td>Community</td>
<td>6 patients were blinded after receiving a compounded hyran blue ophthalmic injection contaminated with Pseudomonas aeruginosa and Burkholderia cepacia. There is an FDA-approved injectable product available.</td>
</tr>
<tr>
<td>2005</td>
<td>California</td>
<td>Outsourcer</td>
<td>Sterile tasc vials with unashed stoppers were not sterility tested before distribution from an outsourcing compounding pharmacy. No patients affected.</td>
</tr>
<tr>
<td>2005</td>
<td>Maryland</td>
<td>Outsourcer</td>
<td>3 patients died after exposure to cardioplegia solution from 2 lots contaminated with gram-negative rods.</td>
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<tr>
<td>2006</td>
<td>Nevada</td>
<td>Hospital</td>
<td>1 baby died from a 1,000-fold zinc overdose (mg and mg zinc sulfate confused) compounded in a hospital pharmacy.</td>
</tr>
<tr>
<td>2006</td>
<td>Ohio</td>
<td>Hospital</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>Maryland,</td>
<td>Outsourcer</td>
<td>5 patients in a Maryland hospital and 2 in a California hospital were diagnosed with Sphingomonas paucimobilis bloodstream infections after receiving fentanyl.</td>
</tr>
<tr>
<td>2007</td>
<td>Washington,</td>
<td>Community</td>
<td>3 patients died after receiving an intravenous corticosteroid product compounded at a concentration higher than standard (4 mg/mL vs. 0.5 mg/mL) in a compounding pharmacy.</td>
</tr>
<tr>
<td>2007</td>
<td>Oregon</td>
<td>Community</td>
<td>21 horses died after receiving a compounded substitute vitamin supplement containing vitamin B, sodium, magnesium, and selenium (product not approved in the US).</td>
</tr>
<tr>
<td>2010</td>
<td>Illinois</td>
<td>Hospital</td>
<td>1 child died after receiving more than 60 times the amount of sodium chloride prescribed due to a compounding error in a hospital pharmacy.</td>
</tr>
<tr>
<td>2011</td>
<td>California,</td>
<td>Homecare</td>
<td>16 patients being treated for wet macular degeneration developed severe eye infections due to contamination of bevacizumab during compounding; one patient blinded, another patient developed a brain infection.</td>
</tr>
<tr>
<td>2011</td>
<td>Tennessee</td>
<td>Homecare</td>
<td>9 patients among 19 died when PN solutions that were administered were contaminated with Serratia marcescens during compounding using non-sterile components to prepare amino acids.</td>
</tr>
<tr>
<td>2011</td>
<td>Alabama</td>
<td>Homecare</td>
<td>7 patients developed fungal endophthalmitis after use of the compounded product Brilliant Blue-G (BBG) or receiving injections of triamcinolone-containing products dispersed from the same compounding pharmacy. 39 patients lost vision.</td>
</tr>
<tr>
<td>2012</td>
<td>North Carolina</td>
<td>Hospital</td>
<td>7 patient outbreak with Burkholderia contaminans from contaminated fentanyl solution. No patients died.</td>
</tr>
</tbody>
</table>
New England Compounding Center (NECC) Meningitis Outbreak

**Date** September 21, 2012– October 23, 2013 (no further CDC updates expected)

**Location** USA (20 States)

**Cause** Fungal meningitis contamination of steroid medication

**Injuries**
- 751 total case count; 384 meningitis and spinal infection; 7 stroke; 325 paraspinal/spinal infection; 33 peripheral joint infection; 2 spinal and peripheral joint
- 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.

**Deaths** 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 U.S. rivaling other key drug safety issues in the past that have led to substantial drug safety legislation.

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Since 2012...

<table>
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<tr>
<th>Year</th>
<th>State</th>
<th>Setting</th>
<th>Description</th>
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<tbody>
<tr>
<td>2013</td>
<td>Connecticut</td>
<td>Outsourcer</td>
<td>FDA announced that a compounding pharmacy in New Jersey was voluntarily recalling all of its products after a Connecticut hospital reported that 5 bags of magnesium sulfate from the pharmacy were contaminated with mold. The pharmacy has since been closed by the NJ Division of Consumer Affairs. FDA issued a Consent Decree.</td>
</tr>
<tr>
<td>2013</td>
<td>Georgia, Louisiana, South Carolina &amp; Indiana Tennessee</td>
<td>Community</td>
<td>Five cases of eye infections in patients who received bevacizumab repackaged by a pharmacy in Georgia that was contaminated with bacteria.</td>
</tr>
<tr>
<td>2013</td>
<td>Tennessee</td>
<td>Community</td>
<td>96 facilities in 17 states received preservative-free methylPREDNISolone. 26 cases in 4 states met CDC “case definition” of skin and soft tissue abscesses from bacterial and fungal contamination associated with this medication. No life threatening infections reported.</td>
</tr>
<tr>
<td>2013</td>
<td>Texas</td>
<td>Compounding Pharmacy</td>
<td>A batch of compounded IV calcium gluconate found to be contaminated with Rhodococcus equi. 15 infected patients, 2 deaths (relationship to drug not known).</td>
</tr>
</tbody>
</table>

The brutal facts review of sterile compounding errors included all of the following **except:**

a. Overdoses of potassium chloride and zinc
b. Examples from the early 1990s ending in 2012
c. Eye infections and blindness from poor compounding practices of bevacizumab and BBG
d. Compounding errors have occurred in all types of entities (community, hospital, outsourcers)
FDA Actions

- FDA has inspected numerous compounding pharmacies and outsourcing facilities producing sterile drugs.
  - Since October 1, 2012, and as of September 30, 2014, FDA:
    - Conducted over 150 inspections of compounding pharmacies (123) and outsourcing facilities (27)
    - Issued 140 Form FDA-483s as a result of the inspections.
    - Issued 34 warning letters to compounding pharmacies (27) and outsourcing facilities (7), including one warning letter that addressed violations at four outsourcing facilities. Some of the warning letters were based on inspections conducted before the facility registered as an outsourcing facility.
    - One compounding pharmacy entered into a consent decree of permanent injunction.

A Form FDA-483 is a form issued at the end of an FDA inspection that lists observations made by FDA investigator(s) during an inspection of a facility. They are inspectional observations and do not represent a final Agency determination regarding compliance. FDA may determine that deviations listed on a form FDA-483 may or may not represent violations of the FD&C Act and may cite them in regulatory actions against the inspected facility.

See page 37 for enlarged view.
"Unfortunately, there are too many in health care who feel that if it hasn’t happened to them, the adverse experiences of others do not apply. “

Michael Cohen, MS, FASHP
Institute for Safe Medication Practices (ISMP)

Which of the following is not about FDA actions?

a. A “483” is a form issued at the end of an FDA inspection that lists observations made by the FDA investigator.

b. The smaller the hospital, the more likely they are to report they experienced compounding errors.

c. Since October 2012, the FDA has visited over 150 compounding pharmacies and outsourcers.

d. The FDA has issued almost as many “483s” as the number of pharmacies inspected.
Summary of Presentation

• Overview of 503A and 503B
• Implementation Efforts

Section 503A

• 503A describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA requiring:
  – FDA approval prior to marketing (section 505)
  – compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B)); and
  – labeling with adequate directions for use (section 502(f)(1))
• Pharmacies that qualify for the exemptions are primarily regulated by the states, although some Federal requirements still apply (e.g., no insanitary conditions)
Section 503A Requirements

• Compounding performed by licensed pharmacist in a licensed pharmacy or Federal facility, or by licensed physician
• Prescription for an identified individual patient; anticipatory compounding in limited quantities before receipt of prescription

Requirements for Bulk Drug Substances Used to Compound Under 503A

• Bulk drug substances (i.e., active ingredients) used to compound must be:
  – components of FDA-approved drugs;
  – the subject of a USP monograph; or
  – on a list of bulk drugs developed by FDA of bulk drug substances acceptable for compounding
• In addition:
  – bulk must be made at an FDA-registered facility; and
  – be accompanied by a Certificate of Analysis (COA)

Other Section 503A Requirements

• Cannot compound drugs that are on an FDA list of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective
• Cannot compound drugs that are on an FDA list of drugs that present demonstrable difficulties for compounding
Other Section 503A Requirements

• Cannot compound regularly or in inordinate amounts what are essentially copies of commercially available products
• Compounder cannot distribute or cause to be distributed interstate more than 5% of the total prescription orders dispensed or distributed by that pharmacy or physician unless they are located in a state that has entered into a Memorandum of Understanding that provides for appropriate investigation of complaints related to drugs distributed outside the state and addresses the distribution of inordinate amounts of compounded drug products interstate

Compounding Quality Act of the Drug Quality and Security Act

• Removes certain provisions from section 503A related to solicitation of prescriptions and advertising and promotion that were found to be unconstitutional by the U.S. Supreme Court in 2002
• Clarifies that section 503A is applicable to compounders nationwide
• Adds new section 503B: “Outsourcing Facilities”

A Registered Outsourcing Facility

• Must comply with CGMP requirements;
• Will be inspected by FDA according to a risk-based schedule; and
• Must meet certain conditions to be exempt from the new drug approval requirements, the requirements for adequate directions for use, and the track and trace requirements
Outsourcing Facility Conditions

- Registered outsourcing facilities must:
  - report to FDA twice a year information about the products they compounded during previous six months
  - report adverse events
  - label their products with certain information

Other Conditions Similar To Those In 503A

- Outsourcing facilities cannot compound drug products that appear on FDA lists
  - of drug products that have been withdrawn or removed from the market because the drug products or their components have been found to be unsafe or not effective,
  - of drug products that present demonstrable difficulties for compounding

Other Conditions for Outsourcing Facilities

- The outsourcing facility cannot compound a drug that is essentially a copy of one or more FDA-approved drugs
- The outsourcing facility cannot compound a drug that is subject to a REMS with elements to assure safe use or from a bulk drug substance that is a component of such drug unless the outsourcing facility demonstrates it will use controls comparable to the REMS
Outsourcing Facility Use of Bulk Drug Substances

• An outsourcing facility may not compound from bulk drug substances
  – unless the drug it is compounding appears on the FDA drug shortage list, or
  – the bulk drug substance appears on an FDA list identifying bulk drug substances for which there is a clinical need

Bulk Drug Substances Used by Outsourcing Facilities

• Bulk drug substances and other ingredients used to compound must comply with USP monographs, if they exist, and must come from facilities that have registered with FDA, and be accompanied by a certificate of analysis

Outsourcing Facility Fees

• A facility is not a registered outsourcing facility until it has paid the applicable annual establishment fee
• A facility could have registered as an outsourcing facility without paying a fee until September 30, 2014; entities registering after October 1, 2014 must pay fee
• Full establishment fee for FY15 is $16,442
• Statute also authorizes reinspection fees
An Outsourcing Facility

• Is defined as a facility that:
  – is engaged in the compounding of STERILE drugs
  – has elected to register as an outsourcing facility
  – complies with all of the requirements in section 503B

• In addition, an outsourcing facility:
  – is NOT required to be a licensed pharmacy, but
    compounding must be by or under the direct supervision of
    a licensed pharmacist
  – may or may not obtain prescriptions for identified individual
    patients

Compounders That Do Not Register as Outsourcing Facilities

• A compounder that
  – does not register as an outsourcing facility and
    comply with the conditions under section 503B, and
  – compounds drugs that do not qualify for the
    exemptions under section 503A

  is subject to all of the requirements in the FDCA
  applicable to conventional manufacturers

The New Law Leaves Some Issues Unresolved

• Compounders may seek to hide out in the
  traditional compounding category and escape
  detection

• The lack of clarity in section 503A over whether
  a state or FDA has primary responsibility over a
  particular pharmacy remains
FDA Moving Swiftly to Implement the Law

- Beginning just days after the legislation was signed, FDA began to issue policy documents to implement the new law.
- So far, in the past year, FDA has issued a proposed rule, five draft guidances, three final guidances, and one revised draft guidance.
- Many other documents are under development.

Withdrawn and Removed List

- FDA issued a proposed rule to update the list of drugs that have been withdrawn or removed from the market because the drug products or their components have been found to be unsafe or not effective.
- FDA proposed to add 25 drug products to the list that is codified at 21 CFR 216.24.
- Drugs on the list cannot be compounded under either section 503A or 503B.

FDA Solicited Nominations for Other Lists

- List of drugs that cannot be compounded under sections 503A or 503B because they are difficult to compound.
- List of bulk drug substances that may be used to compound under section 503A; nomination period later reopened.
- List of bulk drug substances that may be used to compound under section 503B (based on clinical need); nominations later reopened.
CGMP Requirements for Outsourcing Facilities

- In July, FDA issued a draft guidance, “Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities”
- The comment period closed September 2
- FDA is reviewing the comments and working on final guidance

Additional Recent Guidance for Outsourcing Facilities

- Final Guidance: Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act
- Final Guidance: Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744 K of the FD&C Act
- Revised Draft Guidance: Electronic Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

FDA Re-establishing Pharmacy Compounding Advisory Committee

- The committee will include 12 voting members, including a consumer representative and representatives of NABP and USP, and two non-voting industry members
- Nominations were solicited
  - More than 100 individuals were nominated
  - Nominees are being screened for conflicts of interest and evaluated to determine whether their qualifications match the required areas of expertise
  - The criteria for selection also include a diversity review for geographic, ethnic, and gender representation
Compounding Website

• Keep up to date on developments at:
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm
• Site contains a link to all policy documents, a list of registered outsourcing facilities, and other information about FDA’s oversight of compounding

FDA Continuing Surveillance of Compounding

• Since October 1, 2012, and as of September 30, 2014, FDA:
  – Conducted 150 inspections of compounding pharmacies (123) and outsourcing facilities (27)
  – Issued 140 Form FDA-483s as a result of the inspections.
  – Issued 34 warning letters to compounding pharmacies (27) and outsourcing facilities (7), including one warning letter that addressed violations at four outsourcing facilities. Some of the warning letters were based on inspections conducted before the facility registered as an outsourcing facility.
  – Two compounding pharmacies entered into consent decrees of permanent injunction, and a pharmacy and its co-owner each pled guilty to a criminal violation of the FD&C Act
Key Factors to Consider when evaluating a FDA registered 503B Outsourcing Facility

Eric S. Kastango, M.B.A., B.S.Pharm., FASHP
President/CEO
Clinical IQ, LLC and CriticalPoint, LLC

Reflection Point

“Doveryai, no proveryai”
“Trust but verify”
Former President Ronald Reagan

Evaluating Vendors of Compounded Products

• Use an assessment tool to verify the qualifications of the vendor such as Outsourcing Sterile Products Preparation: Contractor Assessment Tool
• The tool needs to be revised in light of the DQSA and the new guidance issued from the FDA for 503B Outsourcing Facilities
There are several elements that can guide your selection process when deciding whether to purchase compounded drugs from an outside vendor.

Do your research...Due Diligence
- Are they a 503B registered firm/entity?
- Have they been inspected by the FDA?
  - Were 483s issued?
  - Was a warning letter issued?
  - Did the firm respond to the FDA and was the response appropriate?
- Know what the 503B guidance expects of the vendor!

Key CGMP Concepts Desirable in a Vendor

1. CGMP mindset
   - A desired attitude and vigilant adherence to detail that is harmonized with a set of actions and behaviors in the manufacturing process

2. Autonomous Quality Unit
   - Decisions to accept or reject products are based upon a comprehensive set of predetermined specifications and independent from either financial or production pressures.

Key CGMP Concepts Desirable in a Vendor

3. Receipt and Release of Non-Sterile Ingredients, Materials, Supplies, and Packaging
   - Confirming the identity and quality of starting materials is fundamental to building quality into the manufacturing process.

4. Buildings/Facilities and Environmental Monitoring
   - Any quality manufactured medication must be produced in a suitable environment that controls the risk of contamination and error.

5. Standard Operating Procedures
   - In order to ensure process uniformity within an organization and maintain it consistently, standard operating procedures are critical.
### Key CGMP Concepts desirable in a vendor

#### 6. Personnel Training, Qualification, and Monitoring
- The qualitative and quantitative specificity and rigor of personnel working in an aseptic processing area is critical to ensuring quality

#### 7. Stability Program and Expiration Dating
- There must be a robust stability program that uses appropriate and validated methods and procedures to determine the stability characteristics of the manufactured product and to establish appropriate storage conditions and expiration dates.

### Key CGMP Concepts desirable in a vendor

#### 8. Cleaning and Disinfecting; Equipment Use Logs
- Facilities and equipment must be qualified, calibrated, cleaned and maintained to prevent contamination and mix-ups. Properly maintaining facilities and equipment is critical to ensure suitability and fitness of use.

### Key CGMP Concepts desirable in a vendor

#### 9. Process Validation
- Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.
- The effectiveness of any procedure used to sterilize or assure the quality / stability of a manufactured product must be established through process validation.
10. Equipment Calibration, Validation, and Preventative Maintenance System
   - A robust process validation system requires a clear understanding of how equipment will be used to achieve the quality, integrity, strength, and sterility of each batch.
   - Each piece of equipment or group of equipment requires a calibration log that specifies the frequency of calibration, points where calibration is checked and its acceptable operating range.

11. Operational Variances and Complaint System/Corrective and Preventive Action (CAPA)
   - A compliance system that tracks and trends feedback to improve the manufacturing process is a cornerstone of CGMP quality systems. A Corrective and Preventive Action (CAPA) system focuses on the systematic investigation of discrepancies (failures and/or deviations) in an attempt to prevent their reoccurrence (corrective action) as well as eliminate the cause of potential nonconforming product and other quality problems (preventive action).

12. Finished Product Release System
   - A finished product release system assures that each batch of product conforms to predetermined specifications. Written procedures for the release of finished products must include an established sampling plan for testing the completed batch of finished product.
All of the following are desirable characteristics in an outsource vendor except:

a. A quality unit comprised of key operations staff
b. Comprehensive and consistent process validation
c. Evidence of a suitable environment that controls the risk of contamination and error
d. A compliance system that tracks and trends feedback to improve the manufacturing process

Summary

• The world of compounding and outsourcing fundamentally changed with the passage of the DQSA in 2013
• Pharmacists engaged in sterile compounding need to understand Section 503A and importance of complying with USP chapters on compounding
  – Review of internal sterile and nonsterile compounding practices needs to be done against USP chapters for compounding
  – Know your state pharmacy law and ensure compliance

Summary

• Pharmacists purchasing from Vendors of Compounded Products need to know what is required of these firms by the FDA
  – Purchase from 503B registered firms when possible
  – Engage organizational senior leadership, risk management, and other key stakeholders in evaluating potential 503B vendors
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<tr>
<th>Resources</th>
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<tbody>
<tr>
<td>Pew Charitable Trust</td>
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<tr>
<td>- U.S. Illnesses and Deaths Associated With Compounded or Repackaged Medications, 2001-Present</td>
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<tr>
<td>- Ensuring the Safety of Compounded Drugs, Study highlights key quality standards – Paper written by Clinical IQ, LLC</td>
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<tr>
<td>FDA Website: Compounding</td>
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<td>- <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm">www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm</a></td>
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Overall Compliance Scores 2011 vs 2014 based on State Regulations

Over 4 year period, overall compliance scores grouped by state regulatory status:
• Overall compliance improvement (all states) 7.4%
• Red states improved by 10.0%
• Yellow states improved by 8.4%
• Green states improved by 11.1%

Yesterday...

1975
• NCC LVP

1990
• FDA Alert Letter
• ASHP Urgent Attention Letter

1991
• ASHP National Survey

1993
• ASHP TAB

1995
• USP <1206>
• ASHP National Survey

1997
• FDAMA signed into law by President Clinton; Contained new section 503A regarding pharmacy compounding

2000
• ASHP Guidelines revised

2002
• Supreme Court held unconstitutional certain advertising restrictions in section 503A
• ASHP National Survey
Today…

2004
• January 1, USP <797> first published
• November, NIOSH Alert published

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

2011
• 1st CriticalPoint National USP <797> Compliance Survey

2012
• CDC and CMS recognizes USP <797>
• NECC tragedy
• 2nd CriticalPoint USP <797> Compliance Survey

2013
• 3rd CriticalPoint USP <797> Compliance Study
• The Drug Quality and Security Act becomes law

2014
• FDA published 503A and 503B guidance
• 4th CriticalPoint USP <797> Compliance Study

Today…

**FDA Actions**

A Form FDA-483 is a form issued at the end of an FDA inspection that lists observations made by FDA investigator(s) during an inspection of a facility. They are inspectional observations and do not represent a final Agency determination regarding compliance. FDA may determine that deviations listed on a form FDA-483 may or may not represent violations of the FD&C Act and may cite them in regulatory actions against the inspected facility.
Self-Assessment Questions

1. 503A describes the conditions under which certain compounded human drug products are entitled to exemptions of the FDCA. Which section is NOT included in that exemption?
   a. FDA approval prior to marketing (section 505)
   b. Compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B))
   c. Labeling with adequate directions for use (section 502(f)(1))
   d. Adulteration (section 501(b))

2. Which USP standard describes the requirements for compounded sterile medications in the United States?
   a. USP Chapter <795>
   b. USP Chapter <1211>
   c. USP Chapter <797>
   d. USP Chapter <823>

3. All of the following are desirable characteristics in an outsource vendor except:
   a. A quality unit comprised of key operations staff
   b. Comprehensive and consistent process validation
   c. Evidence of a suitable environment that controls the risk of contamination and error
   d. A compliance system that tracks and trends feedback to improve the manufacturing process

4. Which of the following factors are important for pharmacists to consider when purchasing from vendors of compounded products?
   a. Purchase from 503B registered firms when possible
   b. Engage organizational senior leadership, risk management, and other key stakeholders in evaluating potential 503B vendors
   c. Understand the requirements of the FDA Compliance Guidance for 503B and audit the facility to ensure compliance
   d. All of the above

Answers

1. D
2. C
3. A
4. D