Compounding Quality Act, Title I of the Drug Quality and Security Act of 2013: Understanding its impact on compounding and outsourcing

Eric S. Kastango, MBA, RPh, FASHP
Clinical IQ, LLC
Madison, NJ
Disclaimer

Eric S. Kastango, MBA, RPh, FASHP is Principal/CEO Clinical IQ, LLC and CriticalPoint, LLC.

I am also an Expert Consultant to the USP but am speaking today in my individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP or any other organization I may be associated with, nor should they be construed as an official explanation or interpretation of <797>.
“You can avoid reality, but you cannot avoid the consequences of avoiding reality.”

Ayn Rand (1905-1982)
# CDC Meningitis Outbreak Statistics

## New England Compounding Center (NECC) Meningitis Outbreak

<table>
<thead>
<tr>
<th>Date</th>
<th>September 21, 2012 (on-going) – October 23, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>USA (23 States)</td>
</tr>
<tr>
<td>Cause</td>
<td>Fungal meningitis contamination of steroid medication</td>
</tr>
</tbody>
</table>

**Injuries**

- 751 Total Case Count, 386 meningitis and Spinal Infection, 7 Stroke, 325 Paraspinal/Spinal infection, 33 Peripheral Joint Infection,
- Some patients recovering from the meningitis are falling ill again. Sufferers of the new infection are now coping with epidural abscesses and infections near the injection site.

**Death(s)**

- 64

**Litigation**

- More than 20 lawsuits filed against NECC
Between January 2000 and before the 2012 national fungal meningitis outbreak from the contaminated methylprednisolone, 11 outbreaks were identified, involving 207 infected patients and 17 deaths after exposure to contaminated compounded drugs.

Most Recent 2013 events

- New Jersey Pharmacy
  - Cease and desist issued; pharmacy closed on the order of NJ AG
  - JAMA article detailing the hospital contamination/recall

Most Recent 2013 events

Table 2. Hospital System Costs Associated With Fungal Contamination of Magnesium Sulfate

<table>
<thead>
<tr>
<th>Activity</th>
<th>Expenses, US$</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient and physician notification</td>
<td>80,038</td>
<td>1286</td>
</tr>
<tr>
<td>Drug costs</td>
<td>386,777</td>
<td></td>
</tr>
<tr>
<td>Patient disease surveillance</td>
<td>26,434</td>
<td>220</td>
</tr>
<tr>
<td>Administrative time (legal, regulatory, finance, and administrative)</td>
<td>204,873</td>
<td>1288</td>
</tr>
<tr>
<td>Pharmacy in-house admixture services</td>
<td>485,845</td>
<td>10,825</td>
</tr>
<tr>
<td>Pharmacy recall (sequester, inventory, and formulary)</td>
<td>59,202</td>
<td>1296</td>
</tr>
<tr>
<td>System hospital B total (drug cost and resources)</td>
<td>109,165</td>
<td></td>
</tr>
<tr>
<td>System hospital C total (drug cost only)</td>
<td>3655</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>1,355,989</td>
<td></td>
</tr>
<tr>
<td>CP-A fee savings (no products purchased × 6 mo)</td>
<td>(481,000)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>874,989</td>
<td>14,915</td>
</tr>
</tbody>
</table>

Abbreviation: CP-A, compounding pharmacy.
Outbreak of *Burkholderia contaminans* linked to Intravenous Fentanyl from an Institutional Compounding Pharmacy

- Occurred at Duke University Hospital from August 31-Sept 6, 2012
- Seven patients affected
- Prepared drug from bulk API: High-risk compounding
- Report published in *JAMA*
Most Recent 2013 events

FDA Actions

- FDA cGMP inspections of >75 pharmacies, contract testing labs (5)
- More than Seventy (70) “483s” (list of inspectional observations) published on FDA website
  [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAFDAElectronicReadingRoom/ucm340853.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAFDAElectronicReadingRoom/ucm340853.htm)
- Closure/remediation against 483s
FDA Observations-Summary

- Lack of procedures to prevent microbial contamination
- Problems with the Environmental Monitoring program
- Problems with batch release
- Lack of validation of the sterilization method
- Inadequate control/cleaning/qualification of critical equipment used in manufacture
- Issues with personnel gowning
- Expiry dating of manufactured medicines not supported by a stability study
- Issues with laboratory procedures or control of contract lab
- Issues with investigations
- Control of incoming raw materials and components
Pharmacy Compounding Minimum Standards (US)

Sterile Compounding
- USP Chapter <797> Pharmaceutical Compounding-Sterile Preparations
  - Minimum standard
  - Last revised June 2008
- USP Compounding Expert Committee working on revision
- USP Chapter <800> Compounding Hazardous Drugs
  - Available online

Non-Sterile Compounding
- USP Chapter <795> Pharmaceutical Compounding-Nonsterile Preparations
  - Minimum standard
  - Last revised June 2011
## State Board of Pharmacy Position on USP Chapter<797>

### Regulatory Status Levels of States/DC as of February 2014

<table>
<thead>
<tr>
<th>No Reference</th>
<th>Indirect</th>
<th>Direct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan</td>
<td>Alaska</td>
<td>Colorado</td>
</tr>
<tr>
<td>Nebraska</td>
<td>Arizona</td>
<td>Florida</td>
</tr>
<tr>
<td>New York</td>
<td>Delaware</td>
<td>Illinois</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>Iowa</td>
<td>Indiana</td>
</tr>
<tr>
<td>Hawaii</td>
<td>Mississippi</td>
<td>Maryland</td>
</tr>
<tr>
<td></td>
<td>New Hampshire</td>
<td>New Mexico</td>
</tr>
<tr>
<td></td>
<td>Ohio</td>
<td>North Carolina</td>
</tr>
<tr>
<td></td>
<td>Oregon</td>
<td>New Jersey</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oklahoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Texas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vermont</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Virginia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W Virginia</td>
</tr>
</tbody>
</table>

### Regulations
- **No sterile compounding regulations whatsoever**
- **Regulations do not cite 797 specifically but do have some mention of sterile compounding**
- **Regulations either codify or are harmonized with 797**

*By emergency rule through July 30, 2014*
State Activity

- In 2013, there have been a total of 27 bills or resolutions filed across 16 states which relate to compounding pharmacies. Of the 25 bills or resolutions posed, 10 have been adopted or enacted into law.

State Activity

New Jersey
- Attestation/Inspection/Cease and Desist

California
- Amending § 1735 in Article 4.5-Compounding
  - Effective date: July 1, 2014
  - All hospitals that perform sterile compounding have to be inspected and licensed
  - Accreditation is no longer acceptable evaluation of compliance with good compounding practices
State Activity

Washington State
- House Bill 1800, passed in 2013, addresses resident and nonresident pharmacy compounding

Louisiana
- Focus on Compounding for Prescriber Use
- Limited to no more than 10% of total dispensing volume

Florida
- Inspecting against USP 797
- Revising state law to harmonize with current version
The Tennessee Board of Pharmacy newly revised rules, issued as emergency rules, primarily focusing on regulation of sterile compounding, became effective on January 31, 2014, and remain in effect until July 30, 2014. These emergency rules also contain other provisions, including increases in licensure and registration fees. The rules are posted on the Tennessee Secretary of State website at http://state.tn.us/sos/rules_filings/01-17-14.pdf.

The rules regarding sterile compounding require preparation in compliance with applicable USP standards for pharmaceutical compounding [1140-07-.02(1)]. The Board of Pharmacy may waive the requirements of any applicable portion of USP standards. All waiver requests must be submitted to the Board of Pharmacy in writing [1140-07-.02(2)].
State Activity-Summarized

- SBOPs are reviewing and revising current regulations/writing new ones
  - Compounding for Office Use
    - Hot topic between FDA and States
- SBOPs are focusing on inspections
  - Resident licenses
  - Non-resident licenses
- SBOPs are getting trained
- Using USP Chapter <797> as standard of practice
The Drug Quality and Security Act (DQSA)

Drug Quality and Security Act (DQSA)

- Current status: signed into law by President Obama on November 27, 2013
- Divided into 2 major sections called Titles
FDA CPG 460.200

- Issued 1992 as a tool to differentiate between pharmacy and manufacturer.
- Obsoleted 12/04/2013
- Compliance Policy Guide 460.200 Pharmacy Compounding is obsolete and was withdrawn.
The Drug Quality and Security Act (DQSA)

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

The Drug Quality and Security Act (DQSA)

Title 1: Compounding Quality Act: 503B - Outsourcing Facilities.

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

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

Source: http://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/default.htm
The Drug Quality and Security Act (DQSA)

- Section 503A (21USC353a) - Traditional compounding
  - State-based regulations – State Boards of Pharmacy
  - Traditional, individualized prescriptions

- Section 503B (21USC353b) - Outsourcing facilities
  - FDA jurisdiction; registration; reporting; cGMPs
  - Manufacture and interstate shipment of larger quantities of compounded drugs without prescriptions
  - Under direct supervision on a pharmacist
What is compounding?

“Compounding” means the preparation of components into a drug product:

1. as the result of a practitioner’s prescription drug order or initiative based on the practitioner/patient/pharmacist relationship in the course of professional practice, or

2. for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing.

Compounding includes the preparation of drugs or devices in anticipation of receiving prescription drug orders based on routine, regularly observed prescribing patterns.

503A – Traditional Compounding

- Now allowed as a matter of federal law
  - Creates a safe harbor for traditional compounding
  - Has been in limbo since 2002 when US Supreme Court ruled 1998 FDAMA unconstitutional
- FDA has stronger authority for dealing with pharmacies who go beyond 503A
- FDA will cooperate/communicate with state Boards
  - Fifty-State BOP Meeting
- Inspections will be based on Risk-based
503A standards

- If not an outsourcing facility, must be:
  - Sterile or non-sterile
  - For a specific patient; based on prescription
  - By licensed pharmacist or physician
  - In anticipation only based on historical patterns or existing relationship with patient or physician
  - Compounding must comply with USP chapters on compounding
    - USP <797>-Sterile
    - USP <795>-Nonsterile
Use bulk from FDA registered facility only
May not compound those on list of drugs removed from the market
No inordinate amounts of what are “essentially copies of commercially available drug products”
Not a product identified as presenting demonstrable compounding difficulties
  - Metered dose inhalers
  - Transdermal systems, others?
Subject to inspection by FDA if not in compliance with USP chapters on compounding
Section 503A

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

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

The Food and Drug Administration is encouraging health care providers to make sure the compounded drugs they buy are mixed in facilities that are registered with the federal agency and are subject to inspections.

As a purchaser of compounded drugs, you play an important role in improving the quality of compounded drugs by requiring compounding pharmacies that supply drugs to your facility to register as outsourcing facilities. Once they register, you and the patients you serve can be assured that FDA will inspect these facilities on a risk-based schedule, hold them to CGMP...
Margaret Hamburg, FDA

“Compounders that don't register with the FDA and also don't meet other criteria for additional regulation will be subject to the same FDA requirements applicable to conventional drug manufacturers, including having to submit New Drug Applications, being required to provide adequate directions for use, and being required to comply with current GMP”
Registered Outsourcing Facilities

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

- “CGMP” is used interchangeably with GMP and stands for “current good manufacturing practices.”
- The CGMPs are not best practice standards.
- CGMPs are minimum guidelines for practice in the manufacture, processing, packing or holding of drug products to be administered to humans or animals.
- CGMPs establish the “what to do” not the “how to do.”
- The CGMPs can be applied to small or large organizations.
- They are not technology-specific.
- The CGMPs are constantly changing, evolving, improving and are the cornerstone of manufacturing practice.
- The CGMPs are contained in the Code of Federal Regulations (CFR).
## CGMP vs. CGCP: Major Differences

<table>
<thead>
<tr>
<th>Requirement</th>
<th>FDA CGMP</th>
<th>SBOP USP 797</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoke Studies</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Stability Testing (SIM)</td>
<td>Y</td>
<td>N-peer literature</td>
</tr>
<tr>
<td>Sterility Testing</td>
<td>Y</td>
<td>Only w/ extended dating</td>
</tr>
<tr>
<td>Cleaning Validation</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Continuous Particle Count</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Sterile Disinfectants</td>
<td>Y</td>
<td>Only IPA</td>
</tr>
<tr>
<td>Sterile Garb</td>
<td>Y</td>
<td>Only gloves</td>
</tr>
<tr>
<td>Reserve Samples</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>
The Drug Quality and Security Act (DQSA)

- Allows 503 B “Outsourcing Facilities”:
  - Elects to register with FDA.
  - Operate under the “…**direct supervision of a licensed pharmacist**…."
  - Registration covers one geographic location or address.
  - Complies with all 503 B regulations.
  - Is NOT required to be a licensed Pharmacy.
  - To fill prescriptions for individual patients...or not?
  - Compounds drugs that are required to be sterile under Federal or State Law.
The Drug Quality and Security Act (DQSA)

- Drugs from 503 B facilities must bear the statements –
  - “This drug is compounded.”
  - NOT for re-sale
  - Office-Use Only

- Have additional labeling requirements-
  - Active & inactive ingredients
  - Storage & handling instructions
Labeling requirements for outsourcing facility compounded products

- “Compounded drug”
- Name, address, phone of outsourcing facility
- Lot and batch numbers
- Established drug name
- Dosage form and strength
- Volume
- Date compounded
- Expiration date
- NDC number
- “Not for Resale”
- List of ingredients; active and inactive
- FDA contact information for adverse events
- Directions for Use
The Drug Quality and Security Act (DQSA) 503B pharmacies

- Under the DQSA a facility is not considered registered until all fees are paid (503B(g)(3)(A) of the FDCA.
- However a facility can register without paying a fee until October 1, 2014.
The Drug Quality and Security Act (DQSA) -

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

Prohibited Acts –

- Wholesaling -
  - There is a carve-out for “drugs used in a healthcare setting.”

- Intentional Falsification of Prescriptions
- Failure to report ADRs
- Misbranding of Drugs
The Drug Quality and Security Act (DQSA)

The “Missing Parts” –

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

- Outsourcing Registration List
  - http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm

- Inspections; Recalls; other Actions
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm

- Regulatory Policy Information
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm

- Compounding FDA Web page
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm
Lists of Products

- Being compiled
- Nominations from industry
  - 503A:
  - 503B:
- ‘Okay to Compound’
- ‘Do Not Compound’
  - Drugs withdrawn for safety or efficacy
  - Demonstrate “demonstrable difficulties to compound”
Pharmacy Compounding Advisory Committee (PCAC)

The Committee provides advice on scientific, technical, and medical issues concerning drug compounding under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and, as required, any other product for which the Food and Drug Administration has regulatory responsibility, and make appropriate recommendations to the Commissioner of Food and Drugs.
Pharmacy Compounding Advisory Committee (PCAC)

The Committee will be composed of a core of 12 voting members including the Chair. Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of:

- pharmaceutical compounding,
- pharmaceutical manufacturing,
- pharmacy,
- medicine,
- and related specialties.
Membership also includes representatives from the National Association of Boards of Pharmacy and the United States Pharmacopoeia, and representatives of patient and public health advocacy organizations. Members will be invited to serve for overlapping terms of up to 4 years.
“FDA’s TEN commandments”

(the compounded drug qualifies for exemptions if...)

1. The drug compounded is for an identified patient based upon the receipt of valid prescription order.
2. The compounding is performed by:
   - A licensed Pharmacist, or
   - licensed Physician authorized by State law to prescribe drugs.
   - Within the Limits on “Anticipatory Compounding”
3. The drug is in compliance with USP guidance on the use of Bulk Drug substances.
4. The drug is manufactured by an FDA registered establishment.
5. The drug product used for compounding is accompanied by a valid Certificate-of-Analysis.
“FDA’s TEN commandments”

(Plane adjusted size: 606x431 to 686x517)

6. The Drug products compounded conforms to applicable USP/NF monographs & the USP chapters on compounding.

7. The Drugs compounded have been NOT withdrawn from the market for safety reasons.

8. The Compounded drugs that are NOT essentially copies of commercially available FDA approved drug products.

9. The Compounding of this drug that has NOT been identified by FDA as presenting any demonstrable difficulties for compounding.

10. You are NOT compounding drugs in a State that has entered into a memo of understanding (MOU) with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate (5% rule).
Summary

- The NECC compounding tragedy has been the catalyst for major changes in how compounding practices in the US will be regulated going forward.
- USP chapters on compounding are federally recognized as the standard of practice in the US.
- If you purchase from an outsourcing facility, ensure that they are a registered establishment.
- There are parallels between USP <797> and CGMPs but 797 and its enforcement lacks the stringency and robustness.
Summary

- There is no substitute for constant vigilance on the part of any compounder, or purchaser of these CSPs.
- Contracting to any Outsourcing provider regardless of licensure does not remove YOUR fiduciary responsibility to the patient!
- *Caveat Emptor!*
Acknowledgements

Thanks to LDT Health Solutions, Inc. for the use of some slides incorporated into this presentation.
Thank you

My contact information:

Eric S. Kastango, MBA, RPh, FASHP

235 Main Street, Suite 292
Madison, NJ 07940
973.765.9393
eric.kastango@clinicaliq.com