Outsourced Medications: How Can You Know They are Safe?

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"Although Eric Kastango is a member of the 2010-2015 USP Compounding Expert Committee, he is speaking today in his own individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely his own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.“
Exserohilum rostratum

Image courtesy www.cdc.gov
In 1937, more than 100 patients died after the S. E. Massengill Company compounded an elixir of sulfanilamide using diethylene glycol (antifreeze), which it did not recognize as poisonous.

At the time, safety testing of new products was not conducted. The tragedy was the driving force behind the 1938 Federal Food, Drug, and Cosmetic (FD&C) Act, which required drug safety testing for the first time.

Exactly 50 years ago this past week (10/10/62), in response to severe birth defects associated with thalidomide, Congress passed the Kefauver-Harris Amendment to the FD&C Act, requiring drug manufacturers to provide proof of safety and effectiveness.
# NECC Meningitis Outbreak

<table>
<thead>
<tr>
<th>New England Compounding Center (NECC) Meningitis Outbreak</th>
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</thead>
<tbody>
<tr>
<td><strong>Date</strong></td>
</tr>
<tr>
<td><strong>Location</strong></td>
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<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td><strong>Injuries</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Death(s)</strong></td>
</tr>
<tr>
<td><strong>Litigation</strong></td>
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</tbody>
</table>

The scale of the meningitis outbreak may make it the worst among a series of fatal or harmful infections and overdoses linked to pharmacy compounding practices in the US rivaling other key drug safety issues in the past that have led to substantial drug safety legislation.
History of Compounding

- Pharmacy compounding is simply the art and science of preparing customized medications that are not otherwise commercially available.
- Compounding is performed by or under the supervision of a pharmacist pursuant to an order from a licensed prescriber for an individual patient.
- Compounding is an essential element of pharmacy.
History of Compounding

- All states license pharmacists to compound
  - States laws vs. Federal laws (Food & Drug Administration)
  - The federal government, through the Food & Drug Administration (FDA) argues that patient safety is in jeopardy
- Each state has varying degrees of regulations and oversight and enforcement of compounding practices
- State Boards of Pharmacy are primarily responsible for enforcing state laws and regulations pertaining to compounding practices
- Until USP <797>, no consistent compounding standard of practice existed
History of Compounding

- Lack of consistent regulations has created abuses by pharmacists who run compounding operations as manufacturers (by preparing non-patient specific formulations) under the guise of pharmacies.
- Outsource vendors or any pharmacy that provides non-patient specific compounded sterile preparations must register with the FDA as a manufacturer.
- TJC (The Joint Commission) has little interest in surveying for compliance with USP <797>.
The intent of the chapter was:

- “to prevent patient harm and fatality from microbial contamination (nonsterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients in CSPs.”

- Became effective January 1, 2004
- Revised December 2007
- Revisions official June 1, 2008
- Currently undergoing another revision (2010-2015)
USP Chapter <797>

- The chapter applies to *all practice settings* where CSPs are prepared and stored
  - health care institutions
  - Pharmacies
  - physician practice
  - other facilities
- Since it is numbered <1000, it is an *enforceable standard*
History of Sterile Compounding

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

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

*Helmus M, Alverson, SP, Monk-Tutor, MR. Instruction on compounded sterile preparations at U.S. schools of pharmacy. AJHP. Volume 64, Nov 1, 2007: 2267-74.
As a result of these pressures, three different decisions are being made by hospital pharmacists:

- **High Risk**: Use non-Sterile components (epidurals, alum). Avoid high risk: requires most extensive facility renovation and controls. Can these be outsourced or eliminated?
- **Low Risk**: Simple, or single, sterile component mixing (1 vial into 1 delivery container). Examine low/medium risk compounding. Can we outsource more?
- **Medium Risk**: Uses multiple sterile components (Batch compounding, TPNs). Examine products being compounded. Can ready to use products be substituted for things we compound?
- **No Risk**: (premixed or RTU single doses). Increased quality control measures from USP 797 may lead to hospitals increasing outsourcing to reduce overall compliance burden.
Pharmacy Compounding or Manufacturing?

- The slides that follow present the traditional differentiators between compounding and manufacturing.
- There are some areas of overlap which will also be discussed.
Pharmacy vs. Manufacturing

The Patient-Prescriber-Pharmacist Triad (IRON TRIAD) is one of the critical elements of pharmacy not present in manufacturing.
## Pharmacy vs. Manufacturing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Compounding</th>
<th>Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity, duration, and distribution of medication</td>
<td>Small, short, and local to individual patients</td>
<td>Large, long, and nationally to wholesalers and pharmacies</td>
</tr>
<tr>
<td>Approximate history</td>
<td>From unrecorded BC era</td>
<td>Since late 1800s</td>
</tr>
<tr>
<td>Main legal regulation</td>
<td>State State Boards of Pharmacy</td>
<td>Federal Food and Drug Administration</td>
</tr>
<tr>
<td>Quality/Performance testing</td>
<td>little or none</td>
<td>pre, in, and post-process</td>
</tr>
<tr>
<td>Therapeutic paradigm</td>
<td>matches drug to patient</td>
<td>matches patient to drug</td>
</tr>
</tbody>
</table>

Adapted from: United States Pharmacopeia (USP) Compounding Pharmacy Stakeholders Forum, August 21, 2001, USP Headquarters, Rockville, MD. David W Newton, PhD, Chair of USP Parenteral Compounding Expert Committee
Pharmacy vs. Manufacturing

- Non patient-specific compounding is permitted by some state boards of pharmacy in certain circumstances:
  - Shared Services
  - Central Fill Operation
  - Outsourcing
Vendor Qualification: Onsite Visit

- Conduct an onsite visit of operation
  - Initially (before contracting)
  - Annually
  - Anytime you want
- Vendor should be comfortable with unannounced visits by customers
Review the following during your evaluation

- Has vendor performed a gap analysis of their operation against USP 797 and if so, what are the results?
- Regulatory inspection reports from State Boards of Pharmacy (SBOP) or FDA
- CAPA (corrective and preventive action) program, employee training records, sterility and stability data
Review the following during your evaluation

- Management controls to ensure operational control and fitness
- Observation of personnel work practices and compare against vendor policy and procedure
- Evaluate procedures for establishing sterility and beyond-use dates (BUDs) of CSPs offered to customers
2012 STATE OF PHARMACY COMPOUNGING

Outsourced Compounding

Onsite Visit Conducted

23% Yes

77% No

Less than one quarter of those using outsourced compounding vendors have conducted an onsite visit.

Return to main menu

Continuum of Aseptic Processing Practices

- Nuclear Aseptic Practices
- Traditional Hospital Aseptic Practices
- USP <797>
- FDA (GMP)

Poor

State Boards of Pharmacy (SBOP)

Excellent
Why register with the FDA?

- Pharmacy does not meet the exemptions in **21 CFR Part 207.10**

- Often pharmacies that voluntarily register with the FDA must do so because there is a need to prepare and dispense *non patient-specific* preparations and have no legitimate access to PHI (protected health information).
Why register with the FDA?

- Non patient-specific CSPs to be provided are obviously in excess of what would normally be considered a reasonable number to prepare in anticipation of prescriptions for resale to other entities.

- These compounding entities are not typical FDA manufacturing enterprises however this type of practice is clearly outside of the scope of pharmacy compounding and must therefore FDA requires registration as a manufacturer.
In lieu of a detailed ANDA or NDA submission to the FDA, outsource vendors are expected to have the ability to link its CSPs to specific patient to whom the CSPs are ultimately dispensed*

Outsource vendor is responsible for

- assuring that the hospital/customer have the necessary controls in place to link vendor prescription products, by lot, control numbers, or otherwise, to specific patients
- ensures that CSPs can be traced to patients in the event of a recall

*http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm075828.htm
Pharmacies registered as manufacturers

- Are not true manufacturers like Merck or Pfizer
- Don’t sell approved drugs
- Are not defined by any bright light standard that defines the practices of these operations
- Are not always regularly inspected by the FDA
  - Many of the bigger operations (market leaders) have been inspected by the FDA
  - Quality standards are typically higher but do not assume!
  - Have had 483s or Warning Letters issued against them (FDA Inspections, Compliance, Enforcement, and Criminal Investigations)
- Are not “approved” by the FDA...the FDA does not give its stamp of approval of these operations
The Drug Listing Act of 1972 requires registered drug establishments to provide the FDA with a current list of all drugs manufactured, prepared, propagated, compounded, or processed by it for commercial distribution. (See Section 510 of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 360)).

Drug products are identified and reported using a unique, three-segment number, called the National Drug Code (NDC), which is a universal product identifier for human drugs.

The FDA inputs the full NDC number and the information submitted as part of the listing process into a database known as the Drug Registration and Listing System (DRLS).

Compounded drugs from outsourcing pharmacies may not be listed in the FDA DRLS.

* [http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm](http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm)
National Drug Code (NDC)

- A registered outsourced compounding vendor will be given a labeler code as a drug establishment that allows it to create National Drug Code (NDC) numbers for its products.

- These NDC numbers do not indicate:
  - FDA approval
  - NDA filing
  - A higher degree of quality (e.g., that terminal sterilization rather than an aseptic fill process has been used in compounding the preparation)

- The NDC listing database contains verbiage indicating that any vendor who promotes the presence of an NDC on a package they prepare as evidence of FDA approval is guilty of misbranding under 21 CFR 207.39.
Any off-site pharmacy vendor must be able to:

- Provide qualifications of staff and reassess staff competence regularly
- Describe methods used to validate sterility, pyrogen testing, documentation, labeling and BUD for CSPs
- Provide a list of valid references available to staff for compounding practices
- Demonstrate that if the pharmacy is performing high risk compounding per USP <797>, it performs required quality assurance activities and provides this evidence through proper documentation
- Demonstrate that USP/NF grade products are used to prepare sterile products
- Deliver all CSPs in tamper-resistant packaging
Characteristics to Consider

- Hours of operation/Availability during non-business hours
- Types of sterile CSPs provided
- Recall or liability claims on any of its CSPs
- Up-to-date on standards & practice aseptic technique
- Provide ongoing QA data to its customers on a regular basis
“Passing” a sterility test does not guarantee that every unit in that batch is sterile.

Sterility testing is required to provide extended BUD.

The use of two types of medias is required.

Membrane filtration is the preferred method of sterility testing.

BUDs are not universal and must be verified by each vendor.

Must be based on sterility testing according to USP 71 or other procedures, methods or processes that have been proven to be equivalent or superior with statistical significance.

Challenge external testing labs and vendors on how they accept samples less than the quantities prescribed in USP 71, Table 3.
• **Review articles** about proper conduct of stability and compatibility studies written by Lawrence Trissel.

• Evaluate the information for the following:
  - Materials, test conditions and methods are completely described
  - A Stability-Indicating Assay is used
  - An Analytical Determination is performed at the outset
    - A time-zero determination of drug concentration is essential
  - Replicate assays at adequate /appropriate intervals since single point assays are not robust and do not control for the effects of assay variability and human error
  - Make sure the conclusions drawn fit the results obtained
Redacted Example of Inadequate Stability Study Data

<table>
<thead>
<tr>
<th>SAMPLE INFORMATION</th>
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<tbody>
<tr>
<td>Customer:</td>
</tr>
<tr>
<td>Received:</td>
</tr>
<tr>
<td>Description: AMIODARONE 900MG IN 500ML D5W</td>
</tr>
<tr>
<td>Lot Number:</td>
</tr>
<tr>
<td>Sample #:</td>
</tr>
<tr>
<td>Cmpd Date:</td>
</tr>
<tr>
<td>Storage *:</td>
</tr>
<tr>
<td>Amount / Device: 900mg amiodarone in D5W 500ml</td>
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<tr>
<td>Room Temperature:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS</th>
</tr>
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<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
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<tr>
<td>Potency/Purity¹</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
</tr>
<tr>
<td>Endotoxin²</td>
</tr>
<tr>
<td>Sterility (Bacteria/Fungi)³</td>
</tr>
<tr>
<td>Sterility (Bacteria/Fungi)³</td>
</tr>
<tr>
<td>Sterility (Bacteria/Fungi)³</td>
</tr>
<tr>
<td>Particulate Matter⁴</td>
</tr>
<tr>
<td>Particulate Matter⁴</td>
</tr>
<tr>
<td>Particulate Matter⁴</td>
</tr>
</tbody>
</table>

¹ Potency/Purity
² Endotoxin
³ Sterility (Bacteria/Fungi)
⁴ Particulate Matter
An off-site sterile compounding pharmacy must comply with the rules, regulations, and standards of the:

- State Board of Pharmacy regulations
- **Code of Federal Regulations**, Title 21, Parts 210 and 211 (if registered with the FDA as a manufacturer)
- The Drug Enforcement Agency (**DEA**)  
- The United States Pharmacopeial Convention (**USP**)  
- American Society of Health-System Pharmacists (**ASHP**)  
- The Centers for Medicare/Medicaid Services (**CMS**)  
- The Joint Commission (**TJC**) and other accreditation organizations  
- Other applicable local, state and federal laws (e.g., OSHA)
Resources

- [Outsourcing Sterile Products Preparation: Contractor Assessment Tool](https://www.ashp.org), an electronic tool titled published by ASHP Foundation which was develop with support by PharMEDium Services, LLC.
- CriticalPoint, LLC USP 797 [Gap Analysis Tool](https://www.criticalpoint.com/)
- [Industry View of Outsourcing](https://www.criticalpoint.com/). A presentation by Dennis A. Tribble, Chief Pharmacy Officer for Baxa Corporation.