Compounding at a Crossroads: The Federal and State Outlook

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Conflict of Interest Declaration

Christopher J. Topoleski has no actual or potential conflicts of interest in relation to this activity

The Catalyst

New England Compounding Center (NECC) timeline

- September 21, 2012: TN DOH notifies CDC that a patient developed meningitis 19 days after being injected with an epidural steroid at a Tennessee ambulatory surgical center
- September 25, 2012: NECC recalls three lots of preservative-free methylprednisolone acetate
- September 28, 2012: Investigators identify a case of meningitis outside of Tennessee

New England Compounding Center (NECC) timeline (continued)

- October 1, 2012: The FDA began its inspection of NECC's facility.
- October 3, 2012: NECC voluntarily shut down operations and expanded its recall; surrenders MA pharmacy license
- October 4, 2012: The FDA began further testing to identify the fungus causing the contamination; 35 cases, 5 deaths, 23 states receiving product

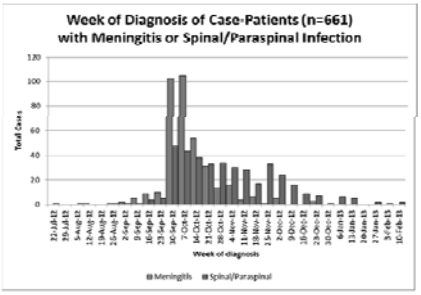
As of March 4, 2013…

720 cases

48 deaths

20 states

Case counts – Infection attributed to NECC products



http://emergency.cdc.gov/HAN/han00342.asp

Sterile Compounding - Post NECC Tragedy

Sterile Production Quality Standards

Compounding: an essential element of pharmacy

- Compounding by licensed pharmacists in all states
- Regulations, oversight, and enforcement varies greatly from state to state
- Until USP <797>, no consistent or enforceable compounding practice standard existed
  - ASHP published technical assistance bulletin and guidelines in 1993 and 2000 which became basis for USP <797>

USP Chapter <797>

- "…to prevent patient harm and fatality from microbal contamination (nonsterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients in CSPs"
- Effective January 1, 2004
- Revised effective June 1, 2008
- Currently undergoing revision (2010-2015)

Where does USP <797> apply?

- All practice settings where CSPs are prepared and stored
  - Hospitals
  - Pharmacies
  - Physician practices
  - Other facilities
- Compounding risk levels assigned from low to high based on variety of factors

However….

- Despite the fact USP Chapter <797> creates uniform standards, only 1 in 6 candidates graduating from pharmacy programs are adequately prepared to produce sterile compounded products
- After 9 years of <797>, less than half the states require direct compliance with the chapter

* Helmus M, Alverson, SP, Monk-Tutor, MR. Instruction on Compounded Sterile Preparations at U.S. Schools of Pharmacy. AJHP, Vol. 64, Nov 1, 2007: 2267-2274

Many factors drive the decision to outsource CSPs

- Need for ready-to-administer form
- Need for specialized products
- Lack of staff expertise
- Workflow management
- Commercial product shortage
- Product is high risk or problem prone to prepare
- Cannot meet quantity needs of facility
- Lack of equipment needed to prepare CSPs in house
- Storage limitations

But…

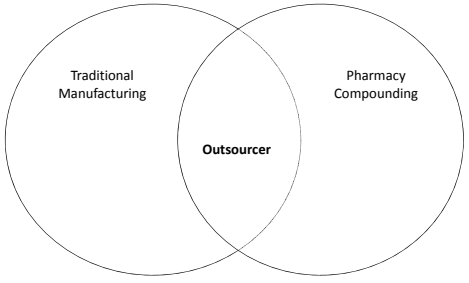
- Lack of uniform regulations and application of quality standards has created ambiguity regarding authority and oversight between State (BoPs) and Federal (FDA) laws
- Further, it may be difficult to differentiate responsible outsourcers from sub-optimal manufacturers operating under the guise of pharmacy compounding

Scope and Risk Factors

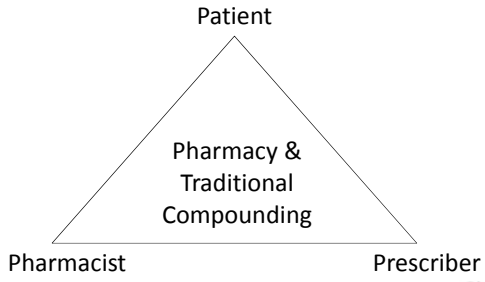
Current challenges

- Defining distinction between traditional compounding, compounding vendors, and manufacturer
- Number of compounding pharmacies unknown
- Number engaged in interstate commerce or distribution

Pharmacy compounding or manufacturing?



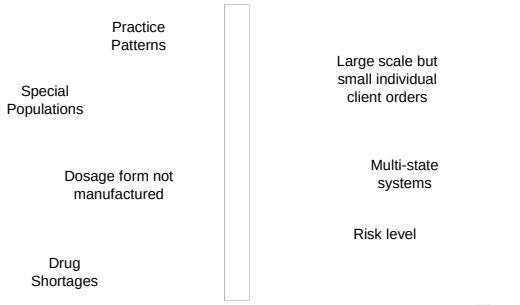
Patient-Prescriber-Pharmacist relationship



Where to draw the line?

- Risk level
- Volume
- Products are sold to a third party for subsequent sale
- Beyond-use dating that exceeds USP <797
- Wide or large networks of distribution to include interstate shipment
- Patient-clinician relationship

Factors graying the line



Health-system considerations

- Anticipatory need in large hospitals
- Limited capabilities or staff at small and rural hospitals and health systems
- Hub and spoke models
  - Increased access and quality
  - Enhanced opportunities for standardization
- Distinction from physician office preparation and utilization

ASHP Engagement

2012

- October
  - Issued alert to membership, highlighted guide to evaluating outsourcers of sterile products
  - Immediately contacted FDA, CDC, and Congress to offer expertise and education
  - Media interviews including CSPAN, NPR, other major media

2012 (Continued)

- November
  - Testified at Senate HELP committee
  - Formal meeting with FDA
  - Relaunched compounding resource center
  - ASHP Webinar
- December
  - Special session at MCM 12
  - Continued follow-up with FDA and Hill staff

2013

- January
  - Continued dialog with FDA and Congress
- February
  - Compounding Summit held in conjunction with AHA and Pew Charitable Trusts
    - Included representatives from health systems, FDA, CDC, NABP, state boards of pharmacy, industry, and professional societies

State versus Federal Oversight

State challenges

- State laws and regulations governing compounding pharmacies extremely variable
- Fewer than half the states require USP Chapter <797>
- Lack of resources mean all pharmacies aren't routinely inspected
- State inspectors may also not be adequately trained or educated in the preparation of CSPs

Impact of state regulations on health systems

- Hospitals rely on state boards of pharmacies to inspect compounding pharmacies to ensure they are following necessary procedures to produce safe medications
- Hospitals often to not have adequate resources or expertise to inspect compounding pharmacies themselves

Compounding: FDA Authority

- March 1992: FDA issued a compliance policy guide to delineate FDA's enforcement policy on pharmacy compounding
- That CPG remained in effect until 1997 when Congress enacted the Food and Drug Administration Modernization Act (FDAMA) of 1997
  - Declared unconstitutional in 2002
- May 2002: FDA issued revised compliance policy guide on pharmacy compounding incorporating elements of FDAMA language

Compounding: FDA Guidance

- Generally, FDA will continue to defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs.
- FDA anticipates that, in such cases, cooperative efforts between the states and the Agency will result in coordinated investigations, referrals, and follow-up actions by the states.

Compounding: FDA Enforcement

- When the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in violations of the law, FDA may consider enforcement action
- While the Agency has identified nine actions that may constitute violations of FD&C law, they have been unsuccessful in exercising enforcement actions

FDA Guidance to Outsource Vendors

- As no NDA/ANDA is on file with the FDA, outsourcers are expected to be able to link each CSP produced to a specific patient
- Outsourcers must assure their customers can trace their CSPs by lot or control number to specific patients in the event of a quality issue or recall

www.fda.gov/ICECI/EnforcementActions/WarninigLetters/2006/ucm07828.htm

What does it mean to be "registered" with the FDA?

- Does not imply a safer product or more stringent processes
- Are not equivalent to a true drug manufacturer
- Are not always regularly inspected by the FDA
- Are not "approved" by the FDA
- FDA approves drugs and biologicals, not manufacturers

FDA proposed framework

- Partnership between state boards of pharmacy and the FDA could eliminate gaps in the enforcement of compounding laws and regulations
- FDA developing proposed federal standards for what it calls "nontraditional compounding"
- Agency says it will need additional legal authority

Who fits in the proposed new category of oversight?

- Products not associated with a patient-specific prescription
- Products shipped across state lines

Additional details of FDA proposal

- Does not take into account quantity of product compounded
- Hospital and health system not target of category
- FDA could develop a list of "do-not-compound" products

Conclusions

Steps to mitigate another NECC-like tragedy

- Clarify the roles of Federal versus state bodies with oversight of sterile compounding
- Better define and standardize licensing and registration of patient care sites, companies, and other entities involved in CSP preparation
- Develop set of standards that combine key elements of USP Chapter <797> and cGMPs for potential third category

Additional areas of study

- Determine the universe of compounding pharmacies
- Education and other resources to increase training of personnel compounding CSPs
- Availability of evidence-based studies to provide extended stability and sterility information
- Increase collaboration among health care organizations

Questions

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Active Learning Questions

Distinguish the difference between traditional pharmacy compounding and "nontraditional" pharmacy compounding and manufacturing

Q) Name 3 ways traditional compounding can differ from this new class of sterile preparation?

Discuss ways ASHP has taken the lead to ensure quality of the sterile compounded products

Discuss the roles of FDA in pharmacy compounding and manufacturing

Q) The FDA is required to inspect and certify all registered entities to ensure they are fully cGMP compliant

Discuss potential legislative action on the Federal and State level

Q) There are two elements to the FDA proposal that puts entities into a “third” tier between manufacturing and compounding. Name both:

Describe the activities that ASHP has initiated in response to the recent compounding tragedy to meet member needs

Q) How many attended the ASHP Webinar?
How many attended the MCM 12 session on compounding?
How many use the ASHP Compounding Resource Page?
What more can ASHP do for its members on this topic?