Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System

Presented as a Sunday Symposium at the 48th ASHP Midyear Clinical Meeting and Exhibition

Sunday, December 8, 2013
Orlando, Florida

Planned and conducted by ASHP Advantage and the Center for Health-System Pharmacy Leadership 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.
Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System

Agenda

2:00 p.m. – 2:15 p.m.  Welcome and Introduction  
Eric S. Kastango, M.B.A., B.S.Pharm., FASHP

2:15 p.m. – 2:50 p.m.  Legislative and Regulatory Actions and Compounding: An Overview and Update  
Kasey Thompson, Pharm.D., M.S.

2:50 p.m. – 3:20 p.m.  Outsourcing and Insourcing at a Large Health System: Assuring Quality and Safety of Sterile Products  
Angela W. Yaniv, Pharm.D.

3:20 p.m. – 3:40 p.m.  Refreshment Break

3:40 p.m. – 4:10 p.m.  Outsourcing and Insourcing at a Small Community Hospital: Practical and Safe Approaches to Overcoming Challenges  
Deborah Barrow, Pharm.D.

4:10 p.m. – 4:40 p.m.  Roundtable Breakouts: Case Studies in Implementation of Safety Strategies  
Eric S. Kastango, M.B.A., B.S.Pharm., FASHP

4:40 p.m. – 5:00 p.m.  Questions & Answers, Panel Discussion

Faculty

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

Deborah Barrow, Pharm.D.  
Director of Pharmacy  
Mariners Hospital  
Tavernier, Florida

Kasey Thompson, Pharm.D., M.S.  
Vice President of the Office of Policy, Planning and Communications  
American Society of Health-System Pharmacists  
Bethesda, Maryland

Angela W. Yaniv, Pharm.D.  
Assistant Director of Pharmacy  
Cleveland Clinic  
Cleveland, Ohio
Disclosure Statement

In accordance with the Accreditation Council for Continuing Medical Education’s Standards for Commercial Support and the Accreditation Council for Pharmacy Education’s Guidelines for Standards for Commercial Support, ASHP Advantage requires that all individuals involved in the development of activity content disclose their relevant financial relationships. A commercial interest is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. A person has a relevant financial relationship if the individual or his or her spouse/partner has a financial relationship (e.g., employee, consultant, research grant recipient, speakers bureau, or stockholder) in any amount occurring in the last 12 months with a commercial interest whose products or services may be discussed in the educational activity content over which the individual has control. The existence of these relationships is provided for the information of participants and should not be assumed to have an adverse impact on presentations.

All faculty and planners for ASHP Advantage education activities are qualified and selected by ASHP Advantage and required to disclose any relevant financial relationships with commercial interests. ASHP Advantage identifies and resolves conflicts of interest prior to an individual’s participation in development of content for an educational activity.

The faculty listed below report relationships pertinent to this activity:

- Eric S. Kastango, M.B.A., B.S.Pharm., FASHP, is Principal of CriticalPoint, LLC.

The following faculty and planners report no relationships pertinent to this activity:

- Deborah Barrow, Pharm.D.
- Kasey Thompson, Pharm.D., M.S.
- Angela W. Yaniv, Pharm.D.
- Erika L. Thomas, M.B.A., B.S.Pharm.
- Susan R. Dombrowski, M.S., B.S.Pharm.

ASHP staff has no relevant financial relationships to disclose.
Activity Overview

In light of unprecedented shortages of medications, pharmacists are outsourcing sterile compounding, which continues to present patient safety challenges. An outbreak of fungal meningitis caused by contaminated preservative-free injectable corticosteroid that had been shipped to 23 states brought national attention to compounding pharmacies. This educational activity will examine the current status of federal oversight of compounding pharmacies and explore strategies that pharmacists can implement to ensure patient safety. Pearls on ensuring the quality of in-house compounded sterile products and assuring facility compliance with USP Chapter <797> will also be presented.

Learning Objectives

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

- Review the current status and role of federal oversight of sterile compounding.
- Discuss factors that health systems should consider when exploring outsourcing of pharmacy sterile compounding.
- Describe a process for assessing facility compliance with USP Chapter <797>.
- Discuss practical strategies for securing i.v. drug products in the event of a shortage.
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 3 hours (0.3 CEUs) of continuing pharmacy education credit (ACPE activity # 0204-0000-13-479-L05-P).

Attendees may print their official statements of continuing pharmacy education credit online after completion of the online evaluation. All statements are available online at the ASHP eLearning portal (http://elearning.ashp.org). For complete activity information, visit www.ashpadvantage.com/safecompound.

Complete instructions for receiving your statement of continuing pharmacy education credit online are available on the next page. Be sure to record the attendance code beginning with “M” announced during the activity.
Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System

CPE Processing Instructions

1. Write down the Attendance Code for each session you attend. These codes are announced during each session. If you miss the code, check with the Room Monitor at the session.


3. Click on My Learning Activities. Then click on 2013 – Midyear Clinical Meeting & Exhibition (Orlando, FL) under Conferences.

4. At the bottom of the page is a field for redeeming Attendance Codes (formerly called CE codes). Enter the Attendance Code(s) from each session, and click Submit.

   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 session.

6. Click on the name of a session and complete the requirements for the session.

7. Click Claim Credit for your profession. It is important that you select the correct profession.
   - Pharmacists and Pharmacy Technicians: Fill in your NABP eProfile ID and birth month and date. Check the box at the bottom and click Claim. You will see a message advising you whether or not your credits were claimed successfully. Your CPE credit will be reported directly to CPE Monitor.
   - Other (International, Students, etc.): Use ASHP Statement of Completion. Check the box at the bottom and click Claim.

You may print your statement of credit by clicking on Print Statement of Credit. If you require a reprint of a statement of credit, you can return here at any time to print a duplicate.

Exhibitors: Additional First Steps

1. Login to www.ashp.org/exhibitorce with your ASHP username and password.

2. Click on the Get Started button.

3. Select the 48th ASHP Midyear Clinical Meeting & Exhibition from the dropdown menu.

4. Select your Exhibiting Company from the list of exhibitors. From here, follow the instructions above.

ASHP is now using the eLearning Portal (http://elearning.ashp.org) for CE Processing, which allows ASHP to report pharmacy credits via CPE Monitor. For more information, visit www.ashp.org/CEtransition

Pharmacists and Pharmacy Technicians: To process your CE on the eLearning Portal, you must enter your NABP e-Profile ID and birth month and date. After you have entered this information once, it is saved for future CE processing. You may obtain your eProfile ID at www.nabp.net.

There may be different directions for workshops and review courses.

| Date of Activity: | Sunday December 8, 2013 | Attendance Code: | M _ _ _ _ _ | CPE Hours: | 3.0 |

NEED HELP? Email educserv@ashp.org
Introduction to Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System

Eric S. Kastango, M.B.A., B.S.Pharm., FASHP
President and CEO, Clinical IQ, LLC
Florham Park, New Jersey
Co-principal, CEO and President of CriticalPoint, LLC
Gaithersburg, Maryland and Florham Park, New Jersey

Disclaimer

• I am an Expert Consultant to USP, but I am not speaking as a member of the Committee, or as a representative of USP or any other organization with which I may be affiliated.
History of Compounding

- Pharmacy compounding is simply the art and science of preparing customized medications for patients
- Compounding is legal under state law
- Non-patient-specific compounding is permitted by state boards of pharmacy
  - Shared services
  - Central fill operation
  - Outsourcing

All states license pharmacists to compound

- State laws vs. federalism
- The federal government through the FDA is arguing that patient safety is in jeopardy
- Schools of pharmacy do not teach sterile compounding skills
  - *American Journal of Health-System Pharmacy (AJHP)* article: 1 in 6 graduates prepared for sterile work
- Compounding is an essential component of pharmacy practice


Pharmacy vs. Manufacturing

The Patient-Prescriber-Pharmacist triad (IRON TRIAD) is one of the critical elements of pharmacy that is not present in manufacturing.
USP Chapter <797> and Compounding Enforcement

- States license pharmacists to compound
- Each state has varying degree of regulations and oversight and enforcement of compounding practices
- In 2012, 8 years after USP Chapter <797> became official, 20 states require direct compliance.
- Until USP Chapter <797>, no consistent and enforceable compounding standard of practice existed.

USP Chapter<797> and Compounding Enforcement (continued)

- National Association of Boards of Pharmacy (NABP)
  - Endorses USP Chapter <797> as the standard for sterile compounding and recommends that states use the USP chapter in gauging compounding practices in their states
  - Chapter <797> is now truly the standard of care in U.S.
  - Several states have directly adopted USP Chapter <797> which will serve as catalyst for others
- The Food and Drug Administration (FDA) is putting pressure on state boards to adopt sterile compounding standards.

State Boards of Pharmacy (BOP) have the sole authority over pharmacy compounding. The FDA does NOT have jurisdiction over traditional compounding.

State Board of Pharmacy Position on USP Chapter<797>

<table>
<thead>
<tr>
<th>No Reference</th>
<th>Indirect</th>
<th>Direct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan</td>
<td>Alaska</td>
<td>Alabama</td>
</tr>
<tr>
<td>New York</td>
<td>Arizona</td>
<td>California</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>Delaware</td>
<td>Idaho</td>
</tr>
<tr>
<td>Hawaii</td>
<td>Iowa</td>
<td>Kansas</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>Maine</td>
<td>Missouri</td>
</tr>
<tr>
<td>Ohio</td>
<td>Montana</td>
<td>North Carolina</td>
</tr>
<tr>
<td>Tennessee</td>
<td>Oregon</td>
<td>Rhode Island</td>
</tr>
<tr>
<td>Vermont</td>
<td>Vermont</td>
<td>Washington</td>
</tr>
<tr>
<td>Washington</td>
<td>Oregon</td>
<td>Utah</td>
</tr>
</tbody>
</table>

Regulations do not cite USP Chapter <797> specifically but do have some mention of sterile compounding.
Regulations either codify or are harmonized with USP Chapter <797>.
What is the best way (and value for the money) to assess USP Chapter <797> compliance?

b. Hire a consultant.
c. Take action when and if a problem is detected in the institution.
d. Take action when and if a problem is reported to the state board of pharmacy or department of public health.

Gap Analysis Resources

- American Society of Health-System Pharmacists (ASHP)
- International Journal of Pharmaceutical Compounding (IJPC)
- International Academy of Compounding Pharmacists (IACP)
- Commercial Tools including
  - CriticalPoint Gap Analysis Tool
  - LDT Health Solutions, Inc. Health Gap Tool
- Something else

State of Compliance

Assessing facility compliance with USP Chapter <797>

- Primary/secondary engineering controls
- General facility design
- Compounding Facility Management
  - Cleaning and disinfecting
  - Equipment calibration
  - Temperature and humidity monitoring
  - Airflows and pressure differential monitoring

Assessing facility compliance with USP Chapter <797>

- Quality management
  - Environmental sampling program
  - General viable air and surface sampling considerations
- Ongoing training and competency
  - Handwashing and garbing
  - Media-fill challenge testing

Sample Study/Gap Analysis Tool

### Questions for Assessing Compliance with USP Chapter <797>

#### Compounding Facility Management: Temperature and Humidity Monitoring

<table>
<thead>
<tr>
<th>Question</th>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled room, walk-in, cold and controlled humidity environment in the pharmacy and other areas (e.g., where solutions and drugs are sterilized) are maintained in USP temperature and humidity ranges for this chapter type.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

#### Compounding Facility Management: Temperature and Humidity Monitoring

<table>
<thead>
<tr>
<th>Question</th>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is ensured that temperature in all controlled storage areas, incubators, and controlled compounding environments are maintained at acceptances and documented manually or electronically.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

#### Compounding Facility Management: Airflow and Pressure Differential Monitoring

<table>
<thead>
<tr>
<th>Question</th>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is evidence that mechanisms exist to report excursions, equip failures, and document actions taken as a result of any out of limit pressure/flow conditions and failures.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Used with permission from CriticalPoint.  
Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System

Kasey K. Thompson, Pharm.D., M.S.
Vice President
Office of Policy, Planning and Communications
American Society of Health-System Pharmacists
Bethesda, Maryland

Kasey K. Thompson, Pharm.D., M.S., is Vice President of the Office of Policy, Planning and Communications at the American Society of Health-System Pharmacists (ASHP) in Bethesda, Maryland. In this role he coordinates strategic planning and policy development for ASHP, and leads the Society’s public relations, government relations, and practices standards development programs. He previously served as the Director of the ASHP Center on Patient Safety and the Director of the ASHP Practice Standards and Quality Division.

Dr. Thompson received his Bachelor of Science degree in cellular biology from Northeastern Oklahoma State University in Tahlequah and a Bachelor of Science degree and a Doctor of Pharmacy degree from the University of Oklahoma, College of Pharmacy in Oklahoma City. He also earned a Master of Science degree in information technology with specialization in informatics from the University of Maryland University College in Adelphi.

Dr. Thompson has published numerous articles, editorials, and book chapters on medication-use safety and quality. He is co-editor of the 2005 book, Medication Safety: A Guide for Health Care Facilities. Dr. Thompson has given presentations nationally and internationally. He has testified before the United States (U.S.) Senate, U.S. House of Representatives, and before a variety of federal agencies. Additionally, he has served on numerous advisory committees and governing boards for various public and private sector organizations.
Legislative and Regulatory Actions and Compounding: An Overview and Update

Compounding Quality Act of 2013 and FD&C Section 503A of 1997

Kasey Thompson, Pharm.D., M.S.
Vice President of the Office of Policy, Planning and Communications
American Society of Health-System Pharmacists
Bethesda, Maryland

Disclaimer

The slides that you have were printed before the legislation was signed into law, therefore, some information may have changed.

Overview

- Section 503A—Pharmacy Compounding—of the federal Food, Drug, and Cosmetic Act (FD&C) of 1997

- Compounding Quality Act of 2013

- Implications for Hospitals and Health-System Pharmacists
**Audience Polling Question**

Do you purchase any compounded sterile preparations from an outsourcer?

- a. Yes
- b. No

---

**Audience Polling Question**

How familiar are you with the details of Section 503A—Pharmacy Compounding—of the Food, Drug, and Cosmetic Act?

- a. Very familiar
- b. Somewhat familiar
- c. Not familiar at all

---

**Audience Polling Question**

How familiar are you with the details of the Compounding Quality Act of 2013?

- a. Very familiar
- b. Somewhat familiar
- c. Not familiar at all
FD&C Section 503A
Pharmacy Compounding


• Severability
  – If any provision is found unconstitutional, the remainder of the Act remains intact
• Removes subsection (c)—Advertising and Promotion—which was previously found unconstitutional
  – Prevented compounding pharmacies from advertising or promoting the compounding of particular drugs

• Became law on November 21, 1997
• Is applicable to hospital and health-system pharmacies
• Definition of Compounding
  – Does NOT include
    • Mixing
    • Reconstituting
    • Other acts performed in accordance with approved labeling/manufacturer directions
FD&C Section 503A

• 503A Does not apply if:
  – Drug product is compounded for an individual patient in response to a valid prescription

• Does not apply if—contd:
  – Compounded by a licensed pharmacist or licensed physician in a state licensed pharmacy or federal facility and based on history of pharmacist or physician receiving valid prescriptions based on established relationship between
    • Pharmacist and physician
    • Patient for whom the prescription order will be provided
    • Physician or licensed practitioner who will write the prescription

• A drug product may be compounded if:
  – Bulk substances
    • Comply with applicable USP standards or National Formulary (NF) monograph (if one exists)
    • Complies with USP chapter on “pharmacy compounding”
      – If no monograph exists, components must be those that are FDA approved
        » If components are unapproved then:
          • Manufacturer must be FDA registered
          • Valid certificate of analysis must be present
FD&C Section 503A

- May not compound if product is on FDA list of drug products that have been removed from the market
- Does not compound “regularly or in inordinate amounts (as defined by FDA) drug products that are “essentially copies” of commercially available drug products.”

FD&C Section 503A

- Essentially a copy of a commercially available drug product does NOT include:
  - Drug product in which a change is made for an individual patient which produces a significant [clinical] difference as determined by the prescriber between the compounded drug and commercially available product

FD&C Section 503A

- Drug product may NOT be compounded if:
  - It is “demonstrably difficult” to compound as determined by FDA
- Memorandum of Understanding (MOUs) between states and FDA can be created to address distribution of “inordinate amounts” of compounded drug products interstate
  - State agency must investigate complaints for products shipped out-of-state
FD&C Section 503A

• MOUs—contd.
  – No MOU is required if licensed pharmacist, pharmacy, or physician distributes out-of-state in quantities that do not exceed 5% of total prescription orders dispensed

• Section 503A does NOT apply to positron emission tomography (PET) drugs or radiopharmaceuticals

Audience Polling Question

Under federal law hospital and health-system pharmacies can distribute compounded products out-of-state as long as quantities do not exceed 5% of total prescription orders dispensed

a. True
b. False

Compounding Quality Act of 2013

Compounding Quality Act

- Creates Section 503B of the FD&C
- Creates Voluntary Outsourcing Facilities

Compounding Quality Act

- Outsourcing Facility—Definition
  - Engaged in compounding of sterile drugs
  - Has elected to register as an outsourcing facility [with the FDA]
  - Complies with all requirements under Compounding Quality Act
  - Is NOT required to be a licensed pharmacy
  - May or may not obtain prescriptions for identified individual patients

Compounding Quality Act

- Definition of Compounding
  - Combining
  - Mixing
  - Diluting
  - Pooling
  - Reconstitution
  - Otherwise altering of a drug or bulk drug substance to create a drug
Compounding Quality Act

Voluntary Outsourcing Facilities
- Requires “direct supervision” by a pharmacist
- Cannot compound from bulk UNLESS
  - Bulk substance appears on list established by Secretary of Health and Human Services (HHS) for which there is a clinical need (Federal Register notice required)
  - Drug compounded from bulk appears on FDA drug shortages list at the time of compounding, distribution, and dispensing

Voluntary Outsourcing Facilities
- Cannot compound from bulk UNLESS—contd.
  - Bulk substance complies with applicable USP monographs
  - Bulk substance is manufactured by an FDA registered (section 510—registration of producers of drugs or devices) establishment
  - Bulk substance has valid certificate of analysis

Non-Bulk Substances
- Must meet applicable USP-NF standards and monographs (if one exists) or pharmacopeia recognized by the Secretary
- Cannot compound drugs that have been removed from the market per list
- Cannot compound copies of FDA-approved drugs
### Compounding Quality Act

- **Voluntary Outsourcing Facilities**
  - Demonstrable difficulties in compounding
    - List created by Secretary
  - Drugs subject to risk evaluation and mitigation strategies (REMS) with elements to assure safe use
    - Outsourcing facility must demonstrate that it utilizes controls comparable to the controls applicable under the REMS
  - No wholesaling

- **Voluntary Outsourcing Facilities**
  - Labeling must include
    - "This is a compounded drug" or comparable as determined by Secretary
    - Name, address, and phone number of outsourcing facility
    - Lot or batch number
    - Established name of the drug
    - Dosage form and strength
    - Quantity or volume

- **Voluntary Outsourcing Facilities**
  - Labeling must include—contd.
    - Date the drug was compounded
    - Expiration date
    - Storage and handling instructions
    - National Drug Code (NDC) (if available)
    - Statement “not for resale”
    - If for office, use the statement “office use only”
    - List of active and inactive ingredients
### Compounding Quality Act

#### Voluntary Outsourcing Facilities
- **Outsourcing facility requirements**
  - **Annual registration**
    - Must note if intends to compound products on FDA drug shortage list.
    - Secretary will list FDA registered outsourcing facilities on FDA website:
      - Name
      - State
      - Bulk compounding (sterile and/or nonsterile)

#### Drug Reporting by Outsourcing Facilities
- Must identify drugs compounded during previous 6-month period upon registration and twice per year thereafter.

#### Risk-Based Inspection Frequency
- Per schedule established by Secretary.
- Risk factors:
  - Compliance history
  - Recalls
  - Inherent risk of drugs compounded
  - Whether facility has been inspected in last 4 years
  - Compounding drug shortages list products
  - Other deemed by Secretary
Compounding Quality Act

• Voluntary Outsourcing Facilities
  – Adverse event reporting required
  – Advisory Committee on Compounding
    • Before issuing regulations the Secretary will convene and consult an advisory committee
      – NABP
      – USP
      – Pharmacists
      – Physicians
      – Patient and public health advocacy organizations

Compounding Quality Act

• Enhanced Communication
  – Submissions from state boards of pharmacy to Secretary
    • Developed in consultation with NABP
    • Describing actions taken against “compounding pharmacies”
    • Expressing concerns that a compounding pharmacy may be acting contrary to Section 503A of the FD&C

• Enhanced Communication
  – Secretary shall notify state boards of pharmacy when
    • Secretary receives registration from outsourcing facility
    • Secretary makes a determination that a pharmacy is acting contrary to section 503A of the FD&C
Compounding Quality Act

- **Severability**
  - Also see Section 503A severability clause

- **U.S. Government Accountability Office (GAO) Study**
  - No later than 36 months after the date of enactment of the law, there must be a report to Congress on pharmacy compounding and the adequacy of State and Federal efforts to assure the safety of compounded drugs

---

Audience Polling Question

An FDA registered outsourcing facility MUST

a. Be a state licensed pharmacy
b. Not receive and dispense individual patient prescriptions
c. Be directly supervised by a pharmacist
d. Distribute compounded product through a wholesaler

---

Conclusions

- The new and clarified laws are not perfect, and there are still significant risks in the system
- Pharmacists need to understand Section 503A of the FD&C
- It is important to understand what it means to be a “voluntary outsourcing facility,” and more importantly what working with a non-registered outsourcer might mean to your patients and practice
- Regulations to implement the Compounding Quality Act still need to be developed
- Many states are and will be developing varied and more restrictive laws and regulations
- Look to ASHP for resources
Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System

Angela W. Yaniv, Pharm.D.
Assistant Director of Pharmacy
Cleveland Clinic
Cleveland, Ohio

Angela Yaniv, Pharm.D., is Assistant Director of Pharmacy at the Cleveland Clinic in Cleveland, Ohio. Her current responsibilities include main campus sterile products management, clean room and sterile products health system consulting, and managing pharmacies serving the Children’s Hospital and the Children’s Hospital for Rehabilitation. Previously, Dr. Yaniv was responsible for oncology pharmacy services at main campus and health system regional oncology practices.

Dr. Yaniv joined the leadership team at Cleveland Clinic in 2007 as the manager for sterile products. In this capacity, she was responsible for the implementation of five clean rooms on the main campus, compliance with USP Chapter <797> requirements, and has tested various technologies for i.v. automation.

Dr. Yaniv received her Bachelor of Science in pharmacy and Doctor of Pharmacy degrees from the University of North Carolina at Chapel Hill. Dr. Yaniv started her career at Duke University Hospital where she worked for fourteen years in various staff roles, including sterile products, operating room pharmacy, and most notably in clinical research. She then moved into operations management where she was responsible for distributive automation including a cart filling robot and automated dispensing cabinets.
Outsourcing and In sourcing at a Large Health System: Assuring Quality and Safety of Sterile Products

Angela W. Yaniv, Pharm.D.
Assistant Director of Pharmacy
Cleveland Clinic
Cleveland, Ohio

Cleveland Clinic Health System

- 81 Locations across Northeast Ohio
- 10 Community Hospitals
- Common Electronic Medical Record
- Health-System Pharmacy and Therapeutics Committee
- Supply Chain Standardization
- Hospital-based Pharmacy Integration Efforts

Cleveland Clinic Main Campus

- 1300 Inpatient Beds
- Outpatient Clinics
- Outpatient Infusion Centers
- Outpatient Surgery and Procedure Areas
- Sterile Products Needs – Wide Variety and High Volume
Scope of Sterile Compounding

• Main Campus
  – Approximately 850,000 compounded doses per year
    • 55% Patient-specific
    • 45% Insourced
  – Wide variety of parenterals
    • IV doses
    • Intrathecal
    • Inhalations
    • Ophthalmic products
    • Irrigations

Scope of Sterile Compounding

• Patient-specific
  – On-demand
  – Products made ahead with USP Chapter <797>
    beyond-use dating (BUD)
  – Low, medium, and high risk
• Insourced
  – Large batches of the same item
  – Extended BUD
    • End-product testing

Scope of Sterile Compounding

• Five Clean Rooms
  – Main Pharmacy
    • Patient-specific
    • Insourcing
  – Heart Center
  – Cancer Center
  – Children’s Hospital
  – Ambulatory Clinics
    • Eye
    • Allergy
    • Rheumatology
Scope of Sterile Compounding

• Cancer Center

USP Chapter <797> Compliance

• Facilities
  – Space
  – Building Materials
  – Air handling/Filtration
  – Maintenance/Testing

• Personnel
  – Training and Competency
    • Knowledge
    • Skills
    • Habits

• Process
  – Materials flow
  – Gowning
  – Hand/glove hygiene
  – Compounding
    • Product segregation
    • Prioritization
  – Cleaning
    • Frequency
    • Methods
  – Documentation

Audience Polling Question

What percentage of your sterile products are outsourced?

a. Less than 1%
b. 1 – 15%
c. 16 – 30%
d. More than 30%
Audience Polling Question
What is the primary reason that you outsource?

a. Inadequate clean room facilities
b. Not enough FTEs to meet demand
c. Inadequate materials storage space
d. Need for products with BUD
e. Need for commercially unavailable products

What We Don’t Make?

• Preparation of some patient-specific products
  – Parenteral nutrition
  – Cardioplegia solutions
  – Pain pump refills (system hospitals)
• Volume less than 1% of compounded doses
• Reasons to outsource
  – Storage space for volume of supplies needed (TPN and cardioplegia)
  – Avoid high risk compounding (pain pump refills for system hospitals)

Outsourcing

• Single Vendor
  – Local
  – Strong working relationship
  – Drop-in visits
  – Compliance with USP Chapter <797> and applicable regulations
  – Quality assurance reporting
Insourcing - Scope

- OR syringes (dilutions)
- Epidurals
- Narcotic infusions/patient controlled analgesia (PCA)
- Pediatric electrolytes
- Pediatric narcotic dilutions
- Repackaging
- Concentrated medications
  - Narcotics/pain management
  - Electrolytes (cardioplegia concentrates)
- Products unavailable due to drug shortages

Insourcing - Scope

- Distribution in automated dispensing cabinets
- Extended dating beyond USP Chapter <797>
- Main campus use only (local)
  - Exception – repackaging due to a drug shortage can be done for other health system locations

Insourcing - Risks

- Assurance of Sterility
  - Sterility testing
    - Internal vs external
    - Interpretation of results
  - Pyrogen testing when required
  - Product quarantine
  - Product recall mechanism
What is the most common source of contamination in compounded sterile products?

a. Airborne particulates
b. Mold spores
c. Touch contamination

Managing the Risks - Sterility

- Personnel
  - Training, training, training
    - Good technique is critical
  - Assessment and feedback
    - Constant improvement of skills
- Environment
  - Particle control
  - Cleaning
  - Monitoring

Managing the Risks - Sterility

- Sterility Testing
  - Sample size according to USP Chapter <71>
  - Commercially available media
  - Inoculated by compounding tech
  - Incubated and read in pharmacy
  - ID of positives by microbiology
Managing the Risks - Sterility

- Validation of sterilizing mechanism
  - Filter testing
  - Biological indicators
- Quarantine
- Product recall mechanism
- Pyrogen testing
  - Nonsterile ingredients

Audience Polling Question

What should be considered to determine a beyond use date for a compounded sterile products?

a. Compounding environment
b. Storage conditions
c. Product stability
d. All of the above

Insourcing - Risks

- Assurance of potency and stability
  - Reference literature
    • Does it match your process?
    • Does it match your materials?
  - Internal testing
    • Not widely available
  - External testing
    • Sourcing
    • Turnaround time for results
    • Every lot or periodic sampling?
Managing the Risks - Stability and BUD

- Primary references
  - Container
  - Concentration
  - Storage
- End-product testing
  - Reference labs
    - Development of in-house testing capability

Insourcing - Risks

- Process – Can you approach good manufacturing practices (GMP) standards?
  - Standard operating procedures
  - Segregation of materials
  - Batch size
  - In-process checks
  - In-process labeling
  - Sterilization methods

Managing the Risks - Process

- Standard Operating Procedures (SOP)
  - Product segregation
    - One product per tech at one time
    - No "like" products in production at the same time
  - In-process check points
  - Batch sizes
- Personnel
  - Training, training, training/Safety, safety, safety
  - Enforcement of SOPs
Managing the Risks - Process

• Define compounding procedures for each product
  – Limit individual variability
  – Repeatable, reliable production
  – Periodic review and updating
  – Document control

Insourcing - Pearl

• Treat insourcing as a business
  – Standardize
  – Determine usage
  – Plan production
    • Allow for quarantine time
    • Avoid just-in-time compounding
  – Dedicate resources
    • Different skill set from one-at-a-time compounding

Managing IV Drug Shortages

• Same thought process as any other drug
  – Evaluate alternative manufacturer(s)
  – Consolidate purchasing and distribution
  – Identify clinical alternatives
  – Repackage to extend supply
  – Consider compounding
    • Recipe availability
    • Methodology
## In Summary

- **Enhance compliance**
  - Facilities
  - Daily practices
  - Create culture of safety

- **Use lowest-risk methods possible**
  - Commercial premixes
  - Sterile-to-sterile compounding

## In Summary

- **Extended BUD**
  - Dot your i’s and cross your T’s
  - Put quality and safety first
  - Meet testing requirements

- **Nonsterile to sterile compounding**
  - Only when there is no other alternative
  - Build in safe processes and quality assurance
Deborah Barrow, Pharm.D.
Director of Pharmacy
Mariners Hospital
Tavernier, Florida

Debbie Barrow, Pharm.D., is Director of Pharmacy at Mariners Hospital in Tavernier, Florida. She brings more than 25 years of expertise in pharmacy practice. She previously served in management roles in radiopharmacy and nuclear pharmacy.

Dr. Barrow earned her Bachelor of Science degree in pharmacy from Mercer School of Pharmacy in Atlanta, Georgia and her Doctor of Pharmacy degree from the University of Florida in Gainesville.

Dr. Barrow was honored with the National Stand Up for Patient Safety Management Award for her multidisciplinary approach in reducing the incidence of Contrast-induced Nephropathy in the Computed Tomography (CT) Suite. Her work on this subject has been published by the National Patient Safety Foundation.
Outsourcing and Insourcing at a Small Community Hospital: Practical and Safe Approaches to Overcoming Challenges

Deborah Barrow, Pharm.D.
Director of Pharmacy
Mariners Hospital
Tavernier, Florida

Mariners Hospital

Mariners Hospital
Baptist Health South Florida

- Florida Keys
- Critical Access Hospital (CAH)
- Chemotherapy outpatient department
- Emergency Department
- Hospital is recognized for excellence
  - 2011 Leapfrog Top Rural Hospital
  - 2009 National Patient Safety Foundation Stand Up for Patient Safety Management Award
Small Hospital Challenges with USP Chapter <797> Compliance

- Expense/space limitations
  - Isolator vs. USP Chapter <797>-compliant location
- Staffing and personnel training
  - Assurance of after-hours nurse competency
- Risk level assessment

Scope of Sterile Compounding

- Minimal in-house compounding
- Purchase whenever possible
  - Premixed solutions
  - Point-of-care activated products
  - Frozen products
  - Purchase commercially-available products whenever possible
- Chemotherapy

What We Don’t Make

- High-risk products
  - Epidural
  - Ophthalmic solutions
- Why products aren’t made?
  - Expensive
    - Need for ongoing staff training and monitoring
  - Lack of staff time
  - Limited space for compounding
### In the Event of a Drug Shortage...

- Therapeutic substitution
- Alternate routes
- Borrow (Florida pedigree laws)
- Restrict use to certain indications
- Investigate using an outsource
- Communicate with medical staff

### Reasons to Outsource

- Ongoing critical drug shortages
- Medications not readily available from commercial sources
- Need to minimize cost
- Reduction or shortages in pharmacy staffing
- Staff available for patient specific drug therapy monitoring

### Assessing the Need to Outsource

- Need for preparations beyond the organization’s pharmacy capabilities
  1. High-risk preparations
  2. Complex preparations
  3. Sterile products rarely prepared
- Cost analysis
Review the Decision to Outsource

- Product is not FDA approved
- Hospital Pharmacist in Charge is ultimately responsible
- Review hospital outsourcing policies and procedure
- Medication management – The Joint Commission ordering
- Pharmacy and Therapeutics Committee approval

When you outsource compounded sterile preparations, the director of pharmacy is released from responsibility for the quality and safety of these products.

a. True
b. False

Managing the Risks: Outsourcing Pharmacy Review and Verification

- Licenses
- Registrations
- Facility
- Staff training and competence
- Quality assurance processes
- Risk management
Managing the Risks: Licenses and Registrations

- Outsourcing pharmacy state license
- Food and Drug (FDA) registration
- Drug Enforcement Administration (DEA) registration
- Pharmacy Compounding Accreditation Board (PCAB) accreditation
- Wholesaler/distributor/state-specific licenses as required
- Licensure of employed pharmacists
- Pharmacy technician certifications
- Personnel background checks

Managing the Risks: Qualifications

- ASHP Foundation Outsourcing Sterile Products Preparation: Contractor Assessment Tool
- Regulatory inspection
- records
  - FDA
  - State Board of Pharmacy
  - Accreditation survey results

Outsourcing Sterile Product Preparation: Contractor Assessment Tool

43
### Managing the Risks: Outsourcing Facility Qualifications

- Certification records for sterile compounding areas
- Documentation of environmental monitoring
- Documentation of calibration and maintenance of equipment
- Appropriate storage and security

### Managing the Risks: Outsourcing Pharmacy Staff Training and Competence

- Pharmacist and technician written training program that meets USP Chapter <797> requirements
- Documentation of ongoing required training and competence, including aseptic technique, garbing, media fill, and glove fingertip testing

### Managing the Risks: Quality Processes

- Written policies and procedures required by USP Chapter <797>
- Written standing operating procedures required by USP Chapter <797>
### Managing the Risks: Quality Monitoring Documents

- Sterility testing for each batch
- Beyond-use dating (BUD) data
- Pyrogen testing
- Stability references and data

### Quality Monitoring Documents: Sources and quality of ingredients

- FDA-approved materials
- USP-NF grade materials
- Other high quality sources
  - Analytical reagent (AR)
  - Certified American Chemical Society (ACS)
  - Food Chemicals Codex (FCC) grade
  - Generally Recognized as Safe (GRAS)
- Verified certificate of analysis (CofA)
- Storage requirements are met
- Adherence to FDA list of compounding drugs withdrawn or removed from market

### Managing the Risks: Quality Process

- Product recall procedures and records
- Labeling and packaging of preparations in compliance with federal and state laws and regulations
### Managing the Risks: Quality Monitoring Documentation

- Upon request
- Online
- Quarterly reports
- Site visit
- Archiving

### Managing the Risks: Outsourcer Safety Measures

- Use of tall man lettering
- Strategies to avoid errors involving look-alike or sound-alike drug names
- Bar coding
- Independent checks

### Risk Management Considerations

- Proof of liability insurance
- Records of any product recalls
- Results of regulatory inspections
- Disciplinary actions from regulatory agencies
- Summary of any product liability lawsuits
- Confidentiality of information (i.e., HIPAA* compliance)

*HIPAA is the Health Insurance Portability and Accountability Act*
Risk Management

• Periodic site visits
• Facility tour
  – Compounding area
  – Warehouse
• Observe processes
• Review quality and compliance documentation

Risk Management Review

• Hospital risk management
• Legal counsel

Summary for Small Rural Hospital

• In-house sterile compounding
  – Low-to-medium risk sterile preparations
  – Isolator
  – Practical preparation
  – Purchase commercially-available products
• Outsourcing
  – Thoroughly investigate company
• In addition to assuring competency of pharmacy staff in sterile product preparation, include other departments such as nursing, radiology
• Isolator selection is important – select an isolator that matches your workflow needs and meets USP Chapter <797> standards
• Subscribe to important electronic updates to stay informed
• Motto – “Small but mighty”
Eric S. Kastango, M.B.A., B.S.Pharm., FASHP
President and CEO
Clinical IQ, LLC
Florham Park, New Jersey

Eric S. Kastango, M.B.A., B.S.Pharm., FASHP, is President and CEO of Clinical IQ, LLC, a health care consulting firm that assists clients who require expertise in the area of USP Chapter <797>, aseptic processing (pharmacy and pharmaceutical based), medical device manufacturing, and the implementation of extemporaneous compounding quality systems.

Mr. Kastango received his Bachelor of Science in pharmacy degree from the Massachusetts College of Pharmacy and Allied Health Sciences and his Master of Business Administration degree from the University of Phoenix. He has training in nuclear pharmacy from Purdue University and didactic training for Six Sigma-Green Belt certification. Since 1980, he has practiced pharmacy in a variety of settings, including hospitals, community, and home care, and 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 Health-System Pharmacists (ASHP) and has served on the ASHP Council on Educational Affairs. He also served on the USP Sterile Compounding Committee from 2005-2010 and was re-elected to the 2010-2015 USP Council of Experts Compounding Expert Committee.

Roundtable Breakouts
Case Studies in Implementation of Safety

Eric S. Kastango, M.B.A., B.S.Pharm., FASHP
President and CEO, Clinical IQ, LLC
Florham Park, New Jersey
Co-principal, CEO and President of CriticalPoint, LLC
Gaithersburg, Maryland and Florham Park, New Jersey

Beyond Use Dating (BUD) and Sterility Testing

• In addition to "relevant" sections of 21 CFR 210 and 211, the FDA has required registered outsourcing pharmacies to comply with USP Chapter <797>.
• Most if not all outsourcing pharmacies claim to meet or exceed USP Chapter <797> requirements
• Areas of interest are sterility testing and beyond-use dating (BUD)

Sterility Testing

• Only required when USP Chapter <797> BUD limits are exceeded or when more than 25 units of high-risk compounded sterile products (CSPs) are prepared
• NO testing is required for any risk-level CSP prepared if handled within the limits, terms and conditions described in USP Chapter <797>
Non-visibility of Microbial Contamination

Numbers of Bacteria per ml in 1L bottle, Millipore Corp. Hospital Pharmacy Filtration Guide (Cat. No. MPR01) Bedford, MA, 1980.3

What is “Sterility”?

• “Free from bacteria or other microorganisms”
  – American Heritage’s definition of sterility
• “Within the strictest definition of sterility, a specimen would be deemed sterile only when there is complete absence of viable microorganisms from it.”
  – USP Chapter <1211> Sterilization and Sterility Assurance of Compendial Articles
• Is it possible to demonstrate complete absence of microorganisms from a CSP?
• Absolute sterility can’t be demonstrated without the complete destruction of every article from the lot of CSPs.

Critical Concepts of Sterilization

• Sterility assurance level (SAL) is the probability of a nonsterile item making it through the validated sterilization process.
• Items terminally sterilized by moist or dry heat, irradiation, or chemical sterilants have an SAL of 10^-6
  – 1 nonsterile item per 1 million items sterilized
• Items prepared aseptically with a 0.22-micron filter have an SAL of 10^-3
  – 1 nonsterile item per 1,000 items sterilized
Standard of Sterility

- USP Chapter <1> Injections
  - Parenteral articles are prepared...to ensure they meet Pharmacopeial requirements for sterility, pyrogens,...
  - Sterility Tests – Preparations for injection meet the requirements under Sterility Tests USP Chapter <71>

Standard of Sterility

- Aseptic processing from USP Chapter <1211>

  "While there is general agreement that sterilization of the final filled container as a dosage form or final packaged device is the preferred process for assuring the minimal risk of microbial contamination in a lot, there is a substantial class of products that are not terminally sterilized but are prepared by a series of aseptic steps."

Probability

- "The sterility of a lot purported to be sterile is therefore defined in probabilistic terms, where the likelihood of a contaminated unit or article is acceptably remote."
Sterility Testing

• USP Chapter <71> Sterility Tests states

“These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by method suitability of the sterilization process or of the aseptic processing procedure.”

Build Quality into the Process

• The quality system used by an outsourcing vendor needs to be more rigorous than currently required by USP Chapter <797>.
• Compliance with Current Good Manufacturing Practices (cGMP) may be required and these regulations stress quality control. More recently developed quality systems stress quality management, quality assurance, and the use of risk management tools, in addition to quality control.

Build Quality into the Process (continued)

• The overarching philosophy articulated in both the cGMP regulations and in robust modern quality systems is that quality should be built into the finished preparation, and testing alone cannot be relied on to ensure preparation quality.
Sterility Testing

• How much do you know about sterility testing according to USP Chapter <71>?
• Using your worksheet, work together as a group to calculate the test sample sizes
• Review findings

Calculating Test Sample Size

<table>
<thead>
<tr>
<th>Products to be tested</th>
<th># Units to be tested</th>
<th>Volume from each tested unit</th>
<th>Total volume to be tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 bags of 2500 ml of parenteral nutrition solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 bags of ceftriaxone 1g in 50 mL D5W</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 fentanyl 200 mcg/ml, 5mL syringe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x 10 ml hydromorphone vial (nonsterile ingredients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Audience Polling Question

Which are the two media used in sterility testing?

a) Fluid thioglycollate medium (FTM) & limulus amebocyte lysate (LAL)
b) LAL & tryptic soy broth (TSB)
c) TSB & FTM
d) Trypticase soy agar (TSA) & TSB
Audience Polling Question

Which of the following is the preferred method of sterility testing?

a) Direct inoculation
b) Filter integrity testing
c) Membrane filtration
d) Something else

End-product Evaluation

Sterility testing required for CSPs that exceed USP Chapter <797> storage periods (all 3 risk levels)

- Comply with USP Chapter <71> standards
  - Two growth media required: tryptic soy broth (TSB) or casein soybean digest media and fluid thioglycollate media (FTM)
  - Membrane Filtration: this is the preferred method if the CSP is filterable
  - Or Direct Inoculation
- Or another method (not in USP Chapter <71>) if verification results demonstrated equivalence to USP Chapter <71> - rapid microbiological methods (RMM)

14 days of incubation is required!

Number of Articles to Be Tested in Relation to the Number of Articles in the Batch
(From USP Chapter <71>)

<table>
<thead>
<tr>
<th>Number Items in Batch</th>
<th>Minimum Number Items to Be Tested for Each Medium if sterility is probative and acceptable?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral/Powdered</td>
<td></td>
</tr>
<tr>
<td>Small sterile products</td>
<td>10% or 4 containers, whichever is the greater 20 containers</td>
</tr>
<tr>
<td>Medium sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Large sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
<tr>
<td>Or other sterile products</td>
<td>2% or 10 containers, whichever is less 10 containers</td>
</tr>
</tbody>
</table>
Minimum Quantity to Be Used for Each Medium
(from USP Chapter 71>)

<table>
<thead>
<tr>
<th>Quantity Per Container</th>
<th>Maximum Quantity to Be Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Microbiological Methods</td>
<td></td>
</tr>
</tbody>
</table>
| • Need to validated to be equivalent to USP Chapter <71>
  – Limit of Detection? 1-10 CFU*/mL
• These methods can be validated as alternative methods to the compendial sterility testing using the validation of alternative microbiological criteria outlined in USP Chapter <1223>

*CFU = colony-forming unit

Rapid Microbiological Methods

• RMM Technologies
  – Adenosine triphosphate (ATP)
  – Solid-phase cytometry (fluorescent cell labeling and laser scanning)
  – CO2 sensing (BacT/ALERT®)
  – Polymerase chain reaction (PCR)
Sterility Testing

- "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 media 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 Chapter <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 Chapter <71>, Table 3

Sterility Testing Quick Reference

<table>
<thead>
<tr>
<th>Key Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct # units</td>
<td>Per USP Chapter &lt;71&gt;, Table 3</td>
</tr>
<tr>
<td>Correct volume/unit</td>
<td>Per USP Chapter &lt;71&gt;, Table 2</td>
</tr>
<tr>
<td>Correct method</td>
<td>Membrane filtration: pool all samples and run through single filter</td>
</tr>
<tr>
<td></td>
<td>Must have justification if using direct inoculation: 1:1 (unit tested and broth used)</td>
</tr>
<tr>
<td></td>
<td>Other methods (not in USP Chapter &lt;71&gt;) if verification demonstrates equivalence to USP Chapter &lt;71&gt;</td>
</tr>
<tr>
<td>Method Suitability</td>
<td>Determines if the sterility testing method is valid for a particular type of CSP and that the drug does not interfere with the sterility test method</td>
</tr>
<tr>
<td>Testing performed</td>
<td></td>
</tr>
<tr>
<td>Correct Media Used</td>
<td>Fluid thioglycollate media (FTM) incubated for 14 days (20-25°C) anaerobic and aerobic bacteria</td>
</tr>
<tr>
<td></td>
<td>Soybean casein-digest media (SCDM) incubated for 14 days (30-35°C) for both aerobic bacteria and fungi</td>
</tr>
</tbody>
</table>

Stability Studies

- 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
Data Analysis

- Sterility test results
  - Every batch or something else?
- Bacterial endotoxins Testing (LAL)
- Particulate Matter Test (per current USP-NF liquid particle count reference standard).
- Chemistry testing chemical identifications

Analysis

<table>
<thead>
<tr>
<th>Sample Information</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Days Specification</td>
<td>Result</td>
</tr>
<tr>
<td>Palmitic Acid</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>Palmitic Acid</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>Palmitic Acid</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Palmitic Acid</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Palmitic Acid</td>
<td>90</td>
<td>60</td>
</tr>
</tbody>
</table>

Analysis

<table>
<thead>
<tr>
<th>Sample Information</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Days Specification</td>
<td>Result</td>
</tr>
<tr>
<td>Eicosanoids</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>Sterility (Racemic)</td>
<td>1</td>
<td>Negative at 14 days</td>
</tr>
<tr>
<td>Sterility (Racemic)</td>
<td>30</td>
<td>Negative at 14 days</td>
</tr>
<tr>
<td>Sterility (Racemic)</td>
<td>90</td>
<td>Negative at 14 days</td>
</tr>
</tbody>
</table>
### Analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Days Specification</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particulate Matter a</td>
<td>1</td>
<td>Below value</td>
<td>Fail</td>
</tr>
<tr>
<td>Particulate Matter b</td>
<td>24</td>
<td>Below value</td>
<td>Fail</td>
</tr>
<tr>
<td>Potency/Purity</td>
<td>How many days?</td>
<td>33 days</td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Below value</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>Sterility*</td>
<td>Pass/Fail</td>
<td>Pass</td>
<td></td>
</tr>
<tr>
<td>Particulate Matter c</td>
<td>How many days?</td>
<td>30 days</td>
<td></td>
</tr>
<tr>
<td>&amp; d</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. USP Chapter <621> HPLC Methodology  
2. USP Chapter <85> turbidimetric or photometric technique.  
3. USP Chapter <71> membrane filtration procedure. Includes tests for aerobic and anaerobic bacteria, and fungi (molds and yeasts)  
4. USP Chapter <788> for LVI*: light obscuration technology

---

*LVI = large volume injections

---

**“Absence of Evidence Does Not Equal Evidence of Absence”**

Dr. David Hussong  
(FDA and the USP Microbiology and Sterility Assurance Expert Committee)
## Analysis

### SAMPLE INFORMATION
- **Customer:**
- **Received:**
- **Description:** AMIODARONE 900MG IN 500ML D5W
- **Lot Number:**
- **Sample #:**
- **Cmpd Date:**

### RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Days Specification</th>
<th>Specification</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency/Purity¹</td>
<td>1</td>
<td>90.0 - 110.0%</td>
<td>99.02% (99.12) mg/container</td>
<td>Amiodarone HCl</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
<td>16</td>
<td>90.0 - 110.0%</td>
<td>95.05% (96.05) mg/container</td>
<td>Amiodarone HCl</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
<td>33</td>
<td>90.0 - 110.0%</td>
<td>94.63% (97.08) mg/container</td>
<td>Amiodarone HCl</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
<td>61</td>
<td>90.0 - 110.0%</td>
<td>88.39% (89.04) mg/container</td>
<td>Amiodarone HCl</td>
</tr>
<tr>
<td>Potency/Purity¹</td>
<td>90</td>
<td>90.0 - 110.0%</td>
<td>91.96% (87.62) mg/container</td>
<td>Amiodarone HCl</td>
</tr>
</tbody>
</table>

---

## Analysis

### SAMPLE INFORMATION
- **Customer:**
- **Received:**
- **Description:** AMIODARONE 900MG IN 500ML D5W
- **Lot Number:**
- **Sample #:**
- **Cmpd Date:**

### RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Days Specification</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin²</td>
<td>1</td>
<td>≤ 10.51 EU/mL</td>
<td>Negative at 14 days</td>
</tr>
<tr>
<td>Sterility (Bacteria/Fungi)³</td>
<td>1</td>
<td>Negative at 14 days</td>
<td></td>
</tr>
<tr>
<td>Sterility (Bacteria/Fungi)³</td>
<td>30</td>
<td>Negative at 14 days</td>
<td></td>
</tr>
<tr>
<td>Sterility (Bacteria/Fungi)³</td>
<td>90</td>
<td>Negative at 14 days</td>
<td></td>
</tr>
</tbody>
</table>
Analysis

SAMPLE INFORMATION
Customer: 
Received: 
Description: AMIODARONE 900MG IN 500ML D5W
Lot Number: 
Sample #: 
Cmpd Date: 

<table>
<thead>
<tr>
<th>Test</th>
<th>Days Specification</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particulate Matter</td>
<td>≥10μm: ≤25mL</td>
<td>Meets</td>
<td>≥10μm: ≤8.3mL</td>
</tr>
<tr>
<td></td>
<td>≥25μm: ≤3μmL</td>
<td>Requirements</td>
<td>≥25μm: ≤0.1μm</td>
</tr>
<tr>
<td></td>
<td>x25μm: ≤3μmL</td>
<td></td>
<td>≥25μm: ≤16.8μm</td>
</tr>
<tr>
<td></td>
<td>≥10μm: ≤25μmL</td>
<td>Fails Requirements</td>
<td>≥10μm: ≤44.1μm</td>
</tr>
<tr>
<td></td>
<td>x25μm: ≤3μmL</td>
<td></td>
<td>≥25μm: ≤1.6μm</td>
</tr>
</tbody>
</table>
Roundtable Discussion 1

Case:

<table>
<thead>
<tr>
<th>Products to be tested</th>
<th># Units to be tested</th>
<th>Volume from each tested unit</th>
<th>Total volume to be tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 bags of 2500 mL of parenteral nutrition solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 bags of ceftriaxone 1 g in 50 ML DSW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 fentanyl 200 mcg/mL, 5 mL syringe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x 10 mL hydromorphone vial (nonsterile ingredients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The following table from USP Chapter <71> specifies the number of items to be tested in each parenteral batch based on the number of units made in each batch.

<table>
<thead>
<tr>
<th>Number of Units Prepared in Batch</th>
<th>Number of Units Tested per Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100</td>
<td>10% or 4 (whichever is greater)</td>
</tr>
<tr>
<td>&gt;100 but ≤500</td>
<td>10 units</td>
</tr>
<tr>
<td>&gt;500</td>
<td>2% or 20 units (which is less)</td>
</tr>
</tbody>
</table>

*The following table from USP Chapter <71> below specifies the minimum quantity of CSPs that may be used if the contents of each unit are of sufficient quantity so that equal appropriate portions may be added to each of the specified sterility test units.

<table>
<thead>
<tr>
<th>Volume Quantity (mL) of CSP</th>
<th>Minimum Quantity to be used per Sterility Test Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mL</td>
<td>Entire contents of CSP</td>
</tr>
<tr>
<td>1 mL to 40 mL</td>
<td>Half the contents of the unit but not &lt; 1 mL</td>
</tr>
<tr>
<td>&gt; 40 mL but ≤ 100 mL</td>
<td>20 mL</td>
</tr>
<tr>
<td>&gt; 100 mL</td>
<td>10% of the contents of the unit but not &lt; 20 mL</td>
</tr>
</tbody>
</table>

Discussion:

What challenges have you faced with sterile compounding in your facility? How were you able to resolve the challenges?

* Used with permission from U.S. Pharmacopeial Convention (USP).
Roundtable Discussion 2

Case:

**Amiodarone Stability Analysis**

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>Acceptance Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency/Purity</td>
<td>How many days?</td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Above/Below acceptable value</td>
<td></td>
</tr>
<tr>
<td>Sterility</td>
<td>Pass/Fail</td>
<td></td>
</tr>
<tr>
<td>Particulate Matter</td>
<td>How many days?</td>
<td></td>
</tr>
</tbody>
</table>

- USP Chapter <621> HPLC methodology
- USP Chapter <85> turbidimetric or photometric technique (need rate of infusion/patient weight/route administration)
- USP Chapter <71> membrane filtration procedure. Includes tests for aerobic and anaerobic bacteria, and fungi (molds and yeasts)
- USP Chapter <788> for light obscuration technology (LVI)

Discussion:

What challenges have you faced with outsourcing sterile compounding at your facility? How were you able to resolve the challenges?
Selected References and Suggested Readings


Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System


Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System


Kienle PC. Cleaning the cleanroom following hazardous drug compounding. Pharm Purch Prod. 2009; 6(9):10-1.


Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System


Creating a Culture of Safety: Practical Approaches to Ensuring the Integrity of I.V. Products in the Health System

Wagner J. CETA’s role relating to the proposed changes in USP 797. *Journal of Controlled Environmental Testing Association.* 2006; 1:12.


Wagner JT. Demystifying biological safety cabinets–getting the most out of the primary engineering controls used in microbiology laboratories. *Clin Microbiol News.* 2007; 29(14):105-11.


**Selected Resources**

ASHP Research and Education Foundation. Outsourcing sterile products preparation: contractor assessment tool (http://www.ashpfoundation.org/sterileproductstool)

ASHP Sterile Compounding Resource Center (http://www.ashp.org/sterilecompounding)

Centers for Disease Control and Prevention web page on multistate fungal meningitis outbreak investigation (http://www.cdc.gov/HAI/outbreaks/meningitis.html)

Food and Drug Administration web page on multistate outbreak of fungal meningitis and other infections (http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/default.htm)
Self-Assessment Questions

1. In approximately how many states do board of pharmacy regulations for sterile product compounding currently require direct compliance with USP chapter <797> requirements?
   a. 10
   b. 20
   c. 30
   d. 45

2. According to state board of pharmacy rules and regulations, who is ultimately held responsible for the integrity of compounded sterile preparations dispensed in health systems?
   a. The state board of pharmacy
   b. The pharmacy technician who compounded it
   c. The supervising pharmacist who checked the pharmacy technician’s compounding work
   d. The pharmacist in charge at the health system

3. Which of the following statements about site visits to prospective vendors of compounded sterile product preparation services is correct when contemplating outsourcing these services?
   a. Site visits are not necessary if comprehensive documentation is provided periodically.
   b. A one-time site visit to tour the facility, observe processes, and review documentation suffices if periodic reports are subsequently provided.
   c. Periodic site visits are needed to tour the facility, observe processes, and review documentation.
   d. An annual site visit to tour the facility, observe processes, and review documentation is required by the state board of pharmacy.

4. Which of the following statements about sterility testing for compounded sterile preparations (CSPs) is correct?
   a. It is required only when USP chapter <797> beyond-use date limits are exceeded or more than 25 units of high-risk CSPs are prepared.
   b. It is required only for high-risk CSPs.
   c. It is required for all CSPs regardless of risk level.
   d. It is not required if the outsourcing pharmacy is registered with the FDA.

5. Which of the following statements about the quality system used by outsourcing vendors for compounded sterile product preparation is correct?
   a. It needs to meet FDA current good manufacturing practices.
   b. It needs to be more rigorous than FDA current good manufacturing practices.
   c. It needs to meet current USP Chapter <797> requirements.
   d. It needs to be more rigorous than current USP Chapter <797> requirements.

Answers: 1) b; 2) d; 3) c; 4) a; 5) d