Best Practices in Ensuring the Quality of Compounded Sterile IV Preparations: Updates on Legislation, Standards, and Beyond

Presented as a Sunday Symposium at the 51st ASHP Midyear Clinical Meeting and Exhibition

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www.ashpadvantage.com/go/sterileiv

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Best Practices in Ensuring the Quality of Compounded Sterile IV Preparations: Updates on Legislation, Standards, and Beyond

Agenda

1:00 p.m. – 1:10 p.m.
**Introductions and Announcements**
Eric S. Kastango, B.S.Pharm., M.B.A., FASHP

1:10 p.m. – 1:50 p.m.
**A Review of Medication Safety and the Use of Technology in the Clean Room**
Jerry L. Fahrni, Pharm.D.

1:50 p.m. – 2:30 p.m.
**Legislative Update: Overview of Recent FDA Draft Guidances and USP Requirements**
Eric S. Kastango, B.S.Pharm., M.B.A., FASHP

2:30 p.m. – 2:45 p.m.
**Refreshment Break**

2:45 p.m. – 3:25
**Ask-the-Experts: Answers to Common and Recurring Questions on Various Aspects of IV Sterile Compounding**
Patricia C. Kienle, B.S.Pharm., M.P.A., FASHP

3:25 p.m. – 3:40 p.m.
**Roundtable Discussion**

3:40 p.m. – 4:00 p.m.
**Faculty Discussion and Audience Questions**
All Faculty

Faculty

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

**Jerry L. Fahrni, Pharm.D.**
Pharmacist Consultant
Jerry Fahrni Consulting
Fresno, California

**Patricia C. Kienle, B.S.Pharm., M.P.A., FASHP**
Director, Accreditation and Medication Safety
Cardinal Health
Wilkes-Barre, Pennsylvania
Disclosure Statement

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Activity Overview

This activity will begin by examining the use of technology in the clean room to meet new patient safety best practice goals. Following this, faculty will review the current legislative landscape with respect to IV sterile compounding, including highlights and implications of FDA draft guidances on the compounding of human drugs. An update on standards, specifically USP Chapter <797>, will provide pharmacists with information they can use to maintain compliance. Resources and answers for questions that pharmacists continue to pose on various aspects of compounding IV sterile preparations that meet the requirements of the Drug Quality and Security Act (DQSA) will also be addressed.

Learning Objectives

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

- Apply the core elements of technology to best practices in patient safety.
- Review key components of recently released FDA draft guidances related to the compounding of human drugs.
- Develop a readiness plan for compliance with the changes to USP Chapter <797> and FDA guidances on pharmacy operations.
- Explain strategies pharmacy directors can use to obtain sufficient staff and resources to meet the requirements of the Drug Quality and Security Act (DQSA).
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 3.0 hours (0.3 CEUs – no partial credit) of continuing pharmacy education credit.

This activity qualifies for Law CPE

Live Activity ACPE #: 0204-0000-16-473-L03-P

Complete instructions for processing continuing education credit online are listed on the last page.
Faculty Biographies

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

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

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

Since 1980, he has practiced pharmacy in a number of practice settings, including hospitals, community, and home care, in a number of different roles, including the Corporate Vice President of Pharmacy Services for Coram Healthcare Corporation. He has also managed a FDA-registered cGMP manufacturing operation for Baxter Healthcare Corporation. He is actively working with NABP and state boards of pharmacy to provide training to their sterile compounding inspectors.

Mr. Kastango is an active member and Fellow of the American Society of Healthcare Pharmacists (ASHP) and served on the United States Pharmacopeia (USP) Sterile Compounding Committee from 2005-2010 and 2010-2015 USP Council of Experts, Compounding Expert Committee until April 2013. In May 2013, USP recognized Eric and the members of Compounding Expert Committee with an Award for Outstanding Contribution to the USP Standards-Setting Process. He has served on the USP Hazardous Drug Expert Panel since 2010.


He has over 200 invited national and international professional presentations on various pharmacy practice topics such as pharmacy compounding and quality systems.
Jerry L. Fahrni, Pharm.D.
Pharmacist Consultant
Jerry Fahrni Consulting
Fresno, California

Jerry L. Fahrni, Pharm.D., is a pharmacist consultant specializing in implementation and management of healthcare information technologies, pharmacy automation, and operational practices.

Dr. Fahrni earned his Doctor of Pharmacy from the University of California, San Francisco School of Pharmacy in California.

Dr. Fahrni has a diverse background and has served in a variety of pharmacy roles during his career, including more than a decade of experience as a clinical pharmacist in various acute care settings, as well as spending time as a pharmacy technology industry insider. He currently works as an independent pharmacist consultant where he has a passion for helping pharmacies improve operational efficiency, increase patient safety, and drive cost-effective medication use through the use of automation, technology, and informatics.
Best Practices in Ensuring the Quality of Compounded Sterile IV Preparations: Updates on Legislation, Standards, and Beyond

Patricia C. Kienle, B.S.Pharm., M.P.A., FASHP
Director, Accreditation and Medication Safety
Cardinal Health
Wilkes-Barre, Pennsylvania

Patricia Kienle, B.S.Pharm., M.P.A., FASHP, is Director of Accreditation and Medication Safety for Cardinal Health Innovative Delivery Solutions.

Ms. Kienle received her Bachelor of Pharmacy degree from the Philadelphia College of Pharmacy and Science, and her Master of Public Administration from Marywood University in Scranton, Pennsylvania. She completed an Executive Fellowship in Patient Safety from Virginia Commonwealth University and is Adjunct Associate Professor at Wilkes University in Wilkes-Barre, Pennsylvania.

Ms. Kienle has served on the Board of Directors of the American Society of Health-System Pharmacists (ASHP) and as President of the Pennsylvania Society of Hospital Pharmacists (PSHP). She is a Fellow of ASHP, was named Pharmacist of the Year by PSHP, and received the Distinguished Achievement Award in Hospital and Institutional Practice from the American Pharmaceutical Association Academy of Pharmacy Practice and Management and the Distinguished Leadership Award from ASHP. She has served on the Pharmacotherapy Specialty Council of the Board of Pharmaceutical Specialties, the Pennsylvania Patient Safety Authority, the Hospital Professional and Technical Advisory Committee of The Joint Commission, and on the Board of Governors of the National Patient Safety Foundation. She is a current member and vice-chair of the USP Compounding Expert Committee, and chair of the Subcommittee and Expert Panel on Hazardous Drugs.

Ms. Kienle is the author of Compounding Sterile Preparations: ASHP’s Visual Guide to Chapter <797> video and Companion Guide, co-author of Assuring Continuous Compliance with Joint Commission Standards: A Pharmacy Guide, 8th edition, and author of the forthcoming The 800 Answer Book. She also served as editor of Understanding JCAHO Requirements for Hospital Pharmacies. She is a frequent presenter to professional groups, with special interests in promoting medication safety, compounding sterile preparations, accreditation and regulatory issues.
Disclosures

- Faculty and planners report no financial relationships relevant to this activity.

Learning Objectives

- Apply the core elements of technology to best practices in patient safety.
- Review key components of recently released FDA draft guidances related to the compounding of human drugs.
- Develop a readiness plan for compliance with the changes to USP Chapter <797> and FDA guidances on pharmacy operations.
- Explain strategies pharmacy directors can use to obtain sufficient staff and resources to meet the requirements of the Drug Quality and Security Act (DQSA).
A Review of Medication Safety and Use of Technology in the Clean Room

Jerry Fahren, Pharm.D.
Pharmacist Consultant
Fresno, California

Disclaimer

• Although I am a consultant, and have provided services to companies in the pharmacy automation and technology space, I am speaking today in my individual capacity. The views and opinions presented here are entirely my own.

The scope of this problem is daunting since an estimated 90% of hospitalized patients receive medication via the IV route

Safety and Risk Associated with Injectable Medications

Risk associated with Injectable Medications

• Injectable medications have highest risk for error and most severe harm associated with error1
• High degree of complexity – multiple ingredients
• High-risk medications – chemotherapy, opioid analgesics
• High-risk routes of administration – epidural, intrathecal, ophthalmic
• High-risk populations – pediatrics, critical care


Errors Associated with CSPs

• Wrong dose were the most common type of errors found in compounded sterile products (CSPs) 1
• 9% mean compounding error rate for CSPs (roughly 1 of every 11 preparations)1
• 2% of CSP errors were clinically relevant1
• 25% of CSP errors may have mild to catastrophic impact on patients2

Impact of CSP Errors

- **Patients**
  - Emily Jerry: CSP error involving 23.4% sodium chloride instead of 0.9% sodium chloride solution
  - Death of 65-year-old female after being given infusion of rocuronium instead of fosphenytoin
- **Caregivers**
- **Financial**
  - Add more than $5000 to the cost of a hospital stay.¹
  - Injectable medication ADEs estimated to increase the annual US payer costs by $2.7 billion to $5.1 billion.²


The efficacy of IV medication administration hinges on the sterility, accuracy, and labeling of doses prepared in the pharmacy.
Regulatory and Accreditation Issues

Bottom line:
There is nothing in the current USP General Chapters or other regulatory documentation that directly addresses the use of automation and technology during the sterile compounding process or their use inside the hood.

Making the Case for Technology in the Clean Room
### Rationale for Adoption

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<tr>
<td>Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, and mixed; and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispersed, and distributed.</td>
<td>All compounding personnel are responsible for compounding and dispensing sterile products of correct ingredient identity, purity, strength, and sterility and for dispensing them in appropriate containers, labeled accurately and appropriately for the end user.</td>
<td>Use technology to assist in the verification process (e.g., barcode scanning verification of ingredients, gravimetric verification, robotics, IV workflow software) to augment the manual processes.</td>
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See enlargement, p. 43

### BEST PRACTICE 11:

**NEW BEST PRACTICE**

When compounding sterile preparations, perform an independent verification to ensure that the proper ingredients (medications and diluents) are added, including confirmation of the proper amount (volume) of each ingredient prior to its addition to the final container.

- Specifically, eliminate the use of proxy methods of verification for compounded sterile preparations of medications (e.g., the “syringes push-back method” checking a label rather than the actual ingredients).
- Except in an emergency, perform this verification in all locations where compounded sterile preparations are made, including patient care units.
- At a minimum, perform this verification for all high-alert medications (including chemotherapy and parenteral nutrition), pediatric/neonatal preparations, pharmacy-prepared vials/bulk containers, products administered via high-risk routes of administration (e.g., intrathecal, epidural, intracranial), and other compounded sterile preparations that the organization believes are high risk.
- Use technology to assist in the verification process (e.g., barcode scanning verification of ingredients, gravimetric verification, robotics, IV workflow software) to augment the manual processes. It is important that processes are in place to ensure the technology is maintained, the software is updated, and that the technology is always used in a manner that maximizes the medication safety features of these systems.

See enlargement, p. 43

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Rationale for Adoption

<table>
<thead>
<tr>
<th>HARD ROI</th>
<th>SOFT ROI</th>
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<tr>
<td>Improved safety through the use of assistive technologies like barcode scanning and gravimetrics</td>
<td>Elimination of bias and reduction of multi-tasking</td>
</tr>
<tr>
<td>Cost savings, both direct and indirect</td>
<td>Improved efficiency</td>
</tr>
<tr>
<td>Standardized workflow</td>
<td>Improved data collection and availability</td>
</tr>
<tr>
<td>Improved documentation</td>
<td>Transforming the role of the pharmacy technician</td>
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<td></td>
<td>Caregiver protection</td>
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</tbody>
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ROI=return on investment

What technology have you implemented in the clean room other than a TPN (total parenteral nutrition) compounder?

A. IV Workflow Management System
B. Robotics
C. Both ‘B’ and ‘C’
D. None

Semi-Automated IV Workflow Management Systems

**Rationale for Failure to Adopt**

- Fear of and resistance to change
- Limited resources
- Lack of literature
- Lack of best practices
- Poorly defined need and benefit
- Slower than manual process
- Difficulty with previous technology
- Lack of interoperability
- Lack of trained support
- Lack of internal and external support
- Low priority
- High cost and lack of capital

**Currently Available CSP Technology**

**CSP Technology Today**

- IV Workflow Management Systems
- Highly Automated Robotic Systems
- Integrated EHR (Electronic Health Record)
Available CSP Technologies

<table>
<thead>
<tr>
<th>IVWFMS</th>
<th>Robotic</th>
<th>EHR</th>
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<tr>
<td>9</td>
<td>6</td>
<td>2</td>
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</table>

CSP Technology Features

- Bar-code scanning
- Image Capture and Archive
- Gravimetrics
- Recipe Catalogues
- Reference and Compounding Aids
- Interfaced to PhIS
- Remote Access / Telepharmacy
- Workflow / Queue Management
- Web-based UX/UI

Forcing Function

| Process put in place to help prevent user from proceeding if something is not right. |
| Example: An airplane that cannot start both engines if a door is not securely closed. > The plane cannot take off until all doors are secured. |

Enforcing Function

| Process put in place to help prevent user from proceeding if something is not right. |
| Example: Flight attendants walking down the aisle looking for passengers who have not fastened their seatbelts. The plane can take off if a passenger does not comply. |
Gravimetric Analysis

<table>
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<tr>
<th>ARGUMENTS FOR</th>
<th>ARGUMENTS AGAINST</th>
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<tbody>
<tr>
<td>Gravimetric analysis is utilized in analytical chemistry because it is extremely accurate.</td>
<td>Volumetric analysis is generally considered as accurate as gravimetric analysis when compounding sterile products.</td>
</tr>
<tr>
<td>Serves as a forcing function, in that preparers cannot proceed to next steps without scales having confirmed volumes in previous steps</td>
<td>Gravimetrics requires additional time-consuming steps of weighing each item before and after drawing and injecting liquids. Added steps result in added time.</td>
</tr>
<tr>
<td>Prevents upstream errors in the preparation process</td>
<td>H-tech scales utilized are sensitive to air movement under hoods, requiring time to settle and register weights of products placed on them. One hospital using gravimetrics told us that it takes them four or five times longer than when compounding using volumetrics.</td>
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In the Clean Room: A Review of Technology-Assisted Sterile Compounding Systems in the US. 2014.

See enlargement, p. 44

Selecting the Right CSP Technology

If I had an hour to solve a problem I’d spend 55 minutes thinking about the problem and 5 minutes thinking about solutions.

“[Albert Einstein]

Decisions to make and questions to ask

- Define the problem
- Determine whether technology can solve your problem
- Consider a Failure Mode Effects Analysis (FMEA)
- Evaluate your workflow
- Evaluate impact technology have on operations
- Create a list - "would like" vs. "must have"
- Search for a solution to solve your problem and meet your needs
Professionals entrusted with the delivery and administrations of pharmaceuticals have a **fundamental responsibility** to identify and implement interventions that will improve patient quality outcome measures and also reduce overall health-care costs. These interventions include timely and judicious use of therapeutic and technological advances.


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Legislative Update: Overview of Recent FDA Draft Guidance Documents and USP Requirements

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Food for Thought

**Discipline** is something we despise for the moment...We all look for a place to run, an excuse with which to stall. No one enjoys it. Yet those of us who have endured it know that the fruit it produces and the pain from which it ultimately spares us makes it worth the agony.

CHARLES F. STANLEY, How to Handle Adversity

http://notable-quotes.com/d/discipline_quotes_i.i.htmlWgmu2XfSwXuMivM.99

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USP Chapter <797>

- Enforceable by the FDA and 34 State Boards of Pharmacy
- Based on current scientific information and best sterile compounding practices
- Recognized as the national standard of practice
- Included in TJC and other accreditation organization requirements if their standards address sterile compounding
- Minimum practice and quality standards for compounding sterile preparations

Do State Boards of Pharmacy recognize the chapter?

TJC=The Joint Commission
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July 2016 State Map
SBOP Requiring Compliance with USP <797>

SBOP=state board of pharmacy
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Food for Thought

Everything that follows is the result of what you see here
Hospitals have worked hard to catch up to the rest of the provider cohorts in terms of overall compliance with the elements of the chapter however all pharmacies still have significant work to do.

About the same percentage of non-hospital pharmacies (68%) reported never having negative findings. For those who did report negative findings, the distribution of negative findings was very similar to this hospital data.
FDA Inspection of Compounding Pharmacies

Figures do not include pharmacies dedicated to producing veterinary drugs. Note: years represent fiscal years October 1 – September 30. Fiscal year 2014 includes data through 9/12. Source: US Food and Drug Administration, USA Today Research.


2013-2016 FDA Actions

- FDA cGMP inspections of many pharmacies and 5 contract testing labs
- Hospital Pharmacies have not been spared
- FDA Form 483 is a form issued at the end of an FDA inspection if the FDA has observed any conditions during their visit that may represent violations of the FD&C Act
- Closure/remediation against 483s

Notable Hospital Pharmacy 483 Inspections

- National Institutes of Health (NIH) - MD
- Dignity Health- Northridge Hospital Medical Center– CA
- Marlborough Hospital - MA
- Region Care, Inc. (Northwell Health) - NY
- SSM Health Care St. Louis - MO
- University of Washington Medical Center – WA
- University of Michigan – MI
- Nebraska Methodist Medical Center – NE
- Alfred I. duPont Hospital for Children- DE
- *William R. Grace M.D. P. C., New York, NY

www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/us cm339771.htm
FDA Actions

- January 28, 2016: Federal Criminal Charges Filed Against Two Pharmacists for Adulteration of Drugs in Connection with Alabama-Based Compounding Pharmacy
  - Allen and Rogers were charged in connection with the distribution of adulterated drugs, which were compounded at the Meds IV facility and distributed to Birmingham, Alabama-area hospitals in 2011.
  - Allen, 60, of McCalla, Alabama, and Rogers, 48, of Hoover, Alabama, have signed plea agreements, in which both individuals have agreed to plead guilty to two misdemeanor violations of the federal Food, Drug and Cosmetic Act (FDCA) as charged in the Information.

FDA Actions

- April 29, 2016: Federal judge enters order of permanent injunction against Paul W. Franck
  - Florida compounder manufactured and distributed drug products in violation of law

Department of Justice

- June 21, 2016: Two Pharmacists Sentenced to Prison for Adulteration of Drugs in Connection with Alabama-Based Compounding Pharmacy
  - The Department of Justice announced today that two Alabama pharmacists have been sentenced to 12 and 10 months in prison for their roles in the distribution of adulterated drugs, which were compounded at the now-defunct compounding pharmacy Advanced Specialty Pharmacy doing business as Meds IV.
Department of Justice

“Compounding pharmacies are entrusted with protecting the public’s health from any harm their drugs may impose and must comply with the law,” said Principal Deputy Assistant Attorney General Benjamin C. Mizer, head of the Justice Department’s Civil Division. “These cases demonstrate that the Department of Justice will continue to work aggressively with the U.S. Food and Drug Administration (FDA) to protect consumers from drugs compounded under insanitary conditions.”


FDA Guidance Documents

As of October 29, 2016 – The FDA has published twenty-seven (27) draft rules, final rules, draft guidance, final guidance, request for nomination, draft MOU specific to 503A and 503B entities

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/
  ucm166743.htm


www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/
  ucm166743.htm

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FDA Guidance Documents
Pharmacy Compounding of Human Drug Products Under Section 503A

• Section 503A was added to the FD&C Act by the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) (the Modernization Act). Section 503A describes the conditions that must be satisfied for drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following three sections of the FD&C Act:
  - (1) section 501(a)(2)(B) (concerning current good manufacturing practice);
  - (2) section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and
  - (3) section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).


FDA Guidance Documents
Pharmacy Compounding of Human Drug Products Under Section 503A

However, individuals and firms may be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of other requirements of the FD&C Act. Such violations may include, but are not limited to, the following:
1. The drug product must not consist in whole or in part of any filthy, putrid, or decomposed substance, or be prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth or whereby it may have been rendered injurious to health. (Sections 501(a)(1) and (a)(2)(A) of the FD&C Act)
2. If the drug product purports to be a drug that is recognized in an official compendium, its strength must not differ from, and its quality or purity must not fall below, the standards set forth in the compendium, unless the difference is plainly stated on its label. (Section 501(b) of the FD&C Act)


FDA Guidance Documents
Pharmacy Compounding of Human Drug Products Under Section 503A

3. For a drug product not subject to section 501(b) of the FD&C Act, the drug’s strength must not differ from, and its quality or purity must not fall below, that which it purports to have. (Section 501(c) of the FD&C Act)
4. If the drug product purports to be a drug that is recognized in an official compendium, it must be packaged and labeled as prescribed in the compendium. (Section 502(g) of the FD&C Act)
5. The drug product’s labeling, advertising, and promotion must not be false or misleading. (Sections 502(a), 502(bb), 10 and 201(n) of the FD&C Act)

FDA Guidance Documents

Guidance: Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm

This is basically putting an end to Health System 503A operations distributing product to other entities within the healthcare system unless they are close to the pharmacy and both are owned by the same entity.
- Central-Fill Operation/Regionalized Compounding Operations/CIVAS
- The FDA will not take an action "if the drug products are distributed only to healthcare facilities that are owned and controlled by the same entity that owns and controls the hospital pharmacy that are located within a 1 mile radius of the compounding pharmacy." (Line 212)

FDA – Insanitary Conditions at Compounding Facilities – August 2016

Under section 501(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the 16 Act), a drug is deemed to be adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."1 Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death.

1Insanitary conditions are conditions that could cause a drug to become contaminated with filth or rendered injurious to health; the drug need not be actually contaminated. A drug that is actually contaminated with any filthy, putrid, or decomposed substance is deemed to be adulterated under section 501(a)(1) of the FD&C Act.

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FDA – Insanity Conditions at Compounding Facilities – August 2016

• The policies described in this guidance document specifically address pharmacies, Federal facilities, physicians’ offices (including veterinarians’ offices), and outsourcing facilities that compound or repackage human or animal drugs (including radiopharmaceuticals); or that mix, dilute, or repackage biological products. For purposes of this guidance, we refer to such entities as “compounding facilities.”

• Under sections 503A and 503B of the FD&C Act, compounded human drug products can qualify for exemptions from specified provisions of the FD&C Act if certain conditions are met. However, neither section 503A nor section 503B provides an exemption from section 501(a)(2)(A) of the FD&C Act.


FDA – Insanity Conditions at Compounding Facilities – August 2016

• Drugs prepared, packed, or held (hereinafter referred to as “produced”) under insanity conditions are deemed to be adulterated, regardless of whether the drugs qualify for exemptions set forth in sections 503A or 503B of the Act.

• Any drug that is produced under insanity conditions is adulterated under the Act, including compounded human and animal drugs; repackaged drug products; compounded or repackaged radiopharmaceuticals; and mixed, diluted, or repackaged biological products.


FDA – Insanity Conditions at Compounding Facilities – August 2016

• Although this is a draft for comment, FDA investigators appear to be utilizing this in inspections as the definition of “Insanity Conditions”, which has always been open to a subjective interpretation.

• This is an incredibly prescriptive document.

• It applies to both 503A and to 503B with some noted exceptions.

• The FDA points out in bold in lines 87-89, “These are only examples and are not an exhaustive list. Other conditions not described in the guidance may be considered insanity”. This is key and allows the FDA flexibility to make their own interpretations. My take is that FDA investigators will consider this to be the “starting point” and not the end point.

• FDA has made the following statement in regard to both sterile and non-sterile drugs, “Handling beto-lactam, hazardous, or highly potent drugs (e.g., hormones) without providing adequate containment, segregation, and cleaning of work surfaces, utensils, and personnel to prevent cross-contamination”.


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FDA – Insanitary Conditions at Compounding Facilities – August 2016

• FDA has made some definition in regard to the use of sterile instruments for handling sterile components by stating, “Using a non-sterile tool or manually contacting the inner surface of the container or closure. For example, during manual stoppering, (e.g., hand stoppering), personnel touching the top of open containers, or the lower side or bottom of closures. This could contaminate the drug in the vials”.

• The FDA made the following comment, “The ‘sterilizing filter’ is not adequate to accomplish sterilization and is not pharmaceutical grade”. Line 210-211. Note: The FDA repeats this statement again in lines 294-295 and notes that this is “particularly serious”.


FDA – Insanitary Conditions at Compounding Facilities – August 2016

• The FDA also considers the following to be “particularly serious”. “Cleanroom areas with unsealed, loose ceiling tiles”. Cleanroom is not defined.

• Key Points: The FDA states the following in line 299, “If a compounding facility decides to initiate a recall, it should notify its local FDA District recall coordinator as soon as the decision is made”. This now takes away any doubt as to whether a compounding operation has to advise the FDA of recalls.


FDA Guidance Documents

Product Recalls, Including Removals and Corrections – Nov 2003

• See referenced FDA document, “Product Recall, Including Removals and Corrections”. In the Insanitary Guidance Document, FDA says in Line 300, “The compounding facility should also notify the applicable State regulatory body in the State(s) to which the facility ships, drugs, consistent with State laws and guidance”.

• Need to know what this document requires if a drug recall is necessary, in light of the Insanitary Conditions document.

www.fda.gov/Safety/Recalls/IndustryGuidance/ucm129259.htm

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Key Takeaways

• The easy way was using USP chapters on compounding
  – Look at our compliance rates and the # of states that require compliance!
• Pharmacy has chosen the hard way.
• We played “chicken” with the FDA and lost
• The FDA is going to ensure patient safety since we haven’t demonstrated our willingness to self-regulate/comply

Break

Best Practices in Ensuring the Quality of Compounded Sterile IV Preparations

Ask-the-Experts:
Answers to Common and Recurring Questions on Various Aspects of IV Sterile Compounding

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Disclaimer

- Patricia Kienle is a member of the USP Compounding Expert Committee but this talk is not affiliated with or endorsed by USP

FAQs

- Regulatory and Accreditation
- Facility Design
- Beyond-Use Dates
- Hazardous Drugs
- How To...

Regulatory and Accreditation Issues
Are USP Chapters law?

- USP is a standard-setting organization
- Numbering system
- Enforcement

What is the latest version of the USP Chapters?

- USP <795>
- USP <797>
- USP <800>
- Other chapters

How do 503A and B organizations differ?

- The Drug Quality and Security Act (DQSA) included a section that splits section 503 of the Federal Food Drug and Cosmetic Act into two parts:
  - 503A compounding pharmacies
  - 503B outsourcing facilities
503A Pharmacies

- What type of compounding can be done
- Oversight
- Limitations

503B Outsourcing Facilities

- What type of compounding can be done
- Oversight
- Limitations

What is an FDA 483?

- Notification of objectionable conditions
- Public information
- Particularly serious conditions
FDA: Particularly Serious Conditions

- Vermin
- Visible microbial contamination
- Non-microbial contamination in ISO 5 or adjacent areas
- Performing aseptic manipulation outside of ISO 5
- Exposing unprotected sterile product to lower than ISO 5
- Unsealed ceiling tiles
- Production while construction is underway
- Pressure reversals from less clean to cleaner air
- Inadequate “sterilizing filter”
- Inadequate heat sterilization

Who inspects compounders?

- Inspectors
  - FDA
  - State Boards
- Surveyors
  - Accreditation organization

Facility Design Issues


Who inspects compounders?

- Inspectors
  - FDA
  - State Boards
- Surveyors
  - Accreditation organization
What is likely to change in <797>?

• Proposed revised USP <797>
  – Cleanroom must contain separate anteroom and buffer room
  – Compounding isolators must be in cleanroom to use full beyond-use dates (BUDs)

What is a Segregated Compounding Area (SCA)?

• Type of Secondary Engineering Control
• <797> describes an SCA for non-hazardous compounding
• <800> describes a Containment SCA (C-SCA) for hazardous compounding

SCA and C-SCA

• No requirement for ISO classification
• No requirement for HEPA-filtered ceiling air
• Segregated space
  – C-SCA must be a room with fixed walls that is separate from non-hazardous compounding
  – C-SCA must be negative pressure, vented to the outside, and have at least 12 air changes per hour
Are temperature excursions OK?

- Drug storage
  - FDA and USP requirements
- Temperature of the cleanroom
  - Personnel comfort
  - Drug storage

What are the cleanroom humidity requirements?

- Current <797>
- Proposed revised <797>

How do I read my certification report?

- Required components
- Under dynamic/operating conditions
- Controlled Environment Testing Association (CETA) Certification Application Guides (CAGs)
Beyond-Use Dates

Can I extend BUDs?

- You can, but ...
- <797> limits
- Proposed revised <797>
  - Content
  - Aseptic preparation
  - Terminal sterilization

What if the med infuses longer than the BUD?

- BUDs end when administration of the med starts
- Infusion time policies need to be determined by health-system policy
What is the BUD for a stock bag?

- Stock bag use
- In-use time

Hazardous Drugs

What’s the status of <800>?

- Published on February 1, 2016
  - One errata
- Extended official date to July 1, 2018
- FAQs available on the USP web site
Do I use the NIOSH or EPA list of hazardous drugs?

- USP <800> requires use of the NIOSH List of Antineoplastic and Other Hazardous Drugs
- This is different from EPA's list of hazardous materials

NIOSH=National Institute for Occupational Safety and Health, EPA=Environmental Protection Agency

www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf

Do all hazardous drugs need to be handled the same way?

- Active Pharmaceutical Ingredient (API) of any hazardous drug on the list or any antineoplastics that need to be manipulated must be handled with all the containment strategies and work practices listed in <800>
- Allowance for Assessment of Risk
  - Antineoplastics that only need to be packaged or counted
  - Non-antineoplastics
  - Reproductive-only hazards

What requires a negative room?

- Storage
- Compounding
Do hazardous drugs need to be received in a negative room?

- No

What garb is different for hazardous drugs?

- Gloves
- Gowns
- Double shoe covers

Why are CSTDs necessary?

- Closed system drug-transfer devices (CSTD)
- USP <800> requires use for administration of hazardous drugs (when the dosage form allows) and recommends use for compounding
How do I do a media fill test?

- Demonstrates ability to aseptically prepare a compounded sterile preparation (CSP)
- Needs to reflect the most complex CSP mixed

How do I do a gloved fingertip sample?

- Initial test x3 to demonstrate the ability to garb without contaminating yourself
- Recurring test to demonstrate the ability to maintain asepsis during actual compounding
Key Takeaways

- USP <795>, <797>, and <800> are enforceable standards
- Facility design must meet the chapter requirements
- Personnel training and monitoring are key to safe compounding

Which of these changes in your practice are you likely to make after today's presentation?

- Review the 2016-17 Targeted Medication Safety Best Practices for Hospitals from ISMP.
- Read FDA draft guidance on prescription requirements (section 503A).
- Read FDA draft guidance on hospital and health system compounding.
- Read FDA draft guidance on facility definition (section 503B).
- Read FDA draft guidance on insanitary conditions at compounding facilities.
- Discuss with colleagues the impact of changes to USP Chapter <797> and FDA guidances on pharmacy operations.

Roundtable Discussion

What is the biggest challenge for which you don't have an answer yet?
### Rationale for Adoption

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<td>Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, and mixed; and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed.</td>
<td>All compounding personnel...are responsible for compounding and dispensing sterile products of correct ingredient identity, purity, strength, and sterility and for dispensing them in appropriate containers, labeled accurately and appropriately for the end user.</td>
<td>Use technology to assist in the verification process (e.g., barcode scanning verification of ingredients, gravimetric verification, robotics, IV workflow software) to augment the manual processes.</td>
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### BEST PRACTICE 11:
When compounding sterile preparations, perform an independent verification to ensure that the proper ingredients (medications and diluents) are added, including confirmation of the proper amount (volume) of each ingredient prior to its addition to the final container.

- Specifically, eliminate the use of proxy methods of verification for compounded sterile preparations of medications (e.g., the "syringe pull-back method," checking a label rather than the actual ingredients).
- Except in an emergency, perform this verification in all locations where compounded sterile preparations are made, including patient care units.
- At a minimum, perform this verification for all high-alert medications (including chemotherapy and parenteral nutrition), pediatric/neonatal preparations, pharmacy-prepared source/bulk containers, products administered via high-risk routes of administration (e.g., intrathecal, epidural, intraocular), and other compounded sterile preparations that the organization believes are high-risk.
- Use technology to assist in the verification process (e.g., barcode scanning verification of ingredients, gravimetric verification, robotics, IV workflow software) to augment the manual processes. It is important that processes are in place to ensure the technology is maintained, the software is updated, and that the technology is always used in a manner that maximizes the medication safety features of these systems.
Gravimetric Analysis

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<th>ARGUMENTS FOR</th>
<th>ARGUMENTS AGAINST</th>
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<td>Gravimetric analysis is utilized in analytical chemistry because it is extremely accurate.</td>
<td>Volumetric analysis is generally considered as accurate as gravimetric analysis when compounding sterile products.</td>
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<td>Serves as a forcing function, in that preparers cannot proceed to next steps without scales having confirmed volumes in previous steps</td>
<td>Gravimetrics requires additional time-consuming steps of weighing each item before and after drawing and injecting liquids. Added steps result in added time.</td>
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<tr>
<td>Prevents upstream errors in the preparation process</td>
<td>Hi-tech scales utilized are sensitive to air movement under hoods, requiring time to settle and register weights of products placed on them. One hospital using gravimetrics told us that it takes them four or five times longer than when compounding using volumetrics.</td>
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In the Clean Room: A Review of Technology-Assisted Sterile Compounding Systems in the US. 2014.

Hospitals with Negative Findings by Outside Entity (responses = 1148)

- No outside organizations have ever had negative findings about... 595 (66%)
- State Board of Pharmacy 214 (24%)
- State Department of Health 18 (2%)
- Accrediting Agency (such as AC sculptures, CHQ, DDI Healthcare, HF) 10 (1%)
- FDA 4 (0%)
- CMS or other Payor 6 (1%)
- Decline to answer 43 (5%)
- Other organizations indicate below 17 (2%)

About the same percentage of non-hospital pharmacies (68%) reported never having negative findings.

For those who did report negative findings, the distribution of negative findings was very similar to this hospital data.

Roundtable Discussion

What is the biggest challenge for which you don't have an answer yet?
CE Instructions

Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home-study activity. All ACPE-accredited activities processed on the eLearning portal are reported directly to CPE Monitor. To claim credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to www.MyCPEMonitor.net for information and application.

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1. Log in to the ASHP eLearning Portal at elearning.ashp.org with the email address and password used to register for the Midyear. The system validates your meeting registration to grant you access to claim credit.

2. Click on Process CE for the Midyear Clinical Meeting and Exhibition.

3. Enter the attendance code announced during the session and click submits.

4. Click Claim for any session.

5. Complete the evaluation.

6. Once all requirements are complete (indicated with a green check mark), click Claim Credit.

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

| Activity Date: | Sunday, December 4, 2016 | Code: | _ _ _ _ _ _ | CE Hours: | 3.0 |

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