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

Sunday, December 4, 2016
Las Vegas, Nevada

www.ashpadvantage.com/go/sterileiv

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ashp Advantage

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.

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

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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 of 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.

Mr. Kastango is author of the 2004 ASHP Discussion Guide on Sterile Preparation: Summary and Implementation of USP Chapter 797, the ASHP Sterile Product Preparation CD-ROM: A Multimedia Learning Tool, the ASHP web-based 797 Compliance Advisor Gap Analysis Tool for USP Chapter 797, the CriticalPoint web-based educational series on Sterile Compounding, and the Annual National USP <797> Compliance Survey, now in its fifth year. He served on the Expert Panel for the ASHP Research & Education Foundation's 2015 Outsourcing Sterile Products Preparation Vendor Assessment Tool and ASHP's Insourcing Readiness Assessment Tool.

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.

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.
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Best Practices in Ensuring the Quality of Compounded Sterile IV Preparations

UPDATES ON LEGISLATION, STANDARDS, AND BEYOND

Pharmacy Leadership FORUM

A Review of Medication Safety and Use of Technology in the Clean Room

Jerry Fahrni, 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

Husch M et al. *Qual Saf Health Care*. 2005; 14:80-6.

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

Barker KN et al. *Arch Intern Med*. 2002; 162:1897-1903.

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 relavent[1]
- 25% of CSP errors may have mild to catastrophic impact on patients[2]

[1]Flynn et al. *Am J Health Syst Pharm*. 1997; 54:904-12.
[2]Bateman R, Donyai P. *Qual Saf Health Care*. 2010; 19:e29.

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]

[1]Bates DW et al. JAMA. 1997; 277:307-11.
[2]Lahue BJ et al. Am Health Drug Benefits. 2012; 5:413-22.

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

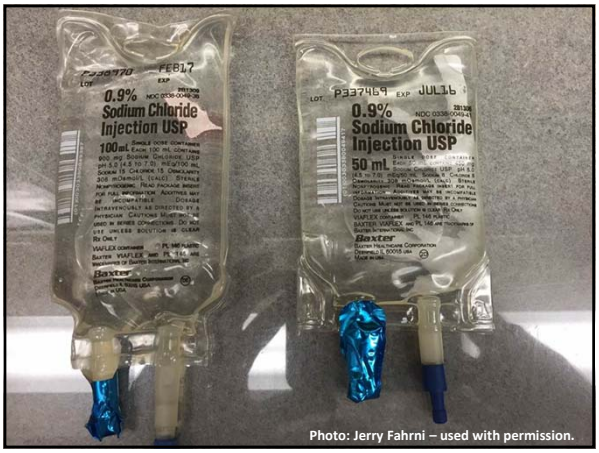


Photo: Jerry Fahrni – used with permission.

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

USP Chapter <797>	ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products	ISMP 2016-2017 Targeted Medication Safety Best Practices for Hospitals
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.	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.	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.

See enlargement, p. 43

NEW BEST PRACTICE

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.

ISMP 2016-2017 Targeted Medication Safety Best Practices for Hospitals.

See enlargement, p. 43

Photo: Jerry Fahrni. Used with permission.

Rationale for Adoption

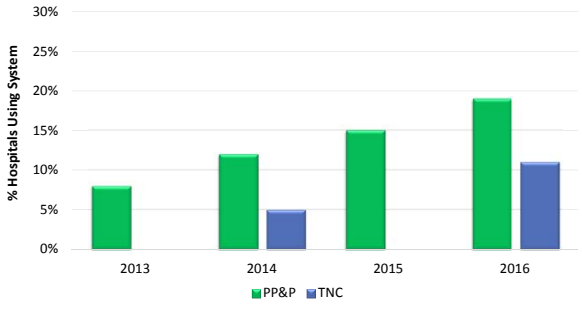
HARD ROI	SOFT ROI
Improved safety through the use of assistive technologies like barcode scanning and gravimetrics	Elimination of bias and reduction of multi-tasking
Cost savings, both direct and indirect	Improved efficiency
Standardized workflow	Improved data collection and availability
Improved documentation	Transforming the role of the pharmacy technician
	Caregiver protection

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



Pharmacy Products & Purchasing *State of Pharmacy Automation*. 2016. The Neuenschwander Company (TNC) – data on file.

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

IVWFMS	Robotic	EHR
9	6	2

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

PhIS = Pharmacy Information System, UX/UI = User experience/User Interface

Forcing Function	Enforcing Function
Will not allow user to proceed if something is not right.	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.	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

ARGUMENTS FOR	ARGUMENTS AGAINST
Gravimetric analysis is utilized in analytical chemistry because it is extremely accurate.	Volumetric analysis is generally considered as accurate as gravimetric analysis when compounding sterile products.
Serves as a forcing function, in that preparers cannot proceed to next steps without scales having confirmed volumes in previous steps	Gravimetrics requires additional time-consuming steps of weighing each item before and after drawing and injecting liquids. Added steps result in added time.
Prevents upstream errors in the preparation process	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.

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**

Meyer GE. *Am J Health Syst Pharm*. 1991; 48:953-66.

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

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

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_ii.html#cgmu2KFSwXfueMlM.99

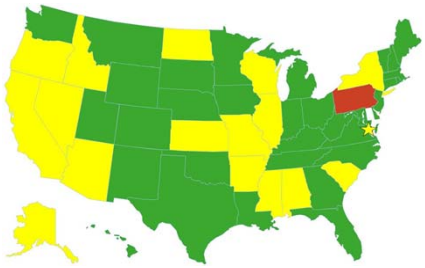
USP Chapter <797>

- 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

July 2016 State Map
SBOP Requiring Compliance with USP <797>

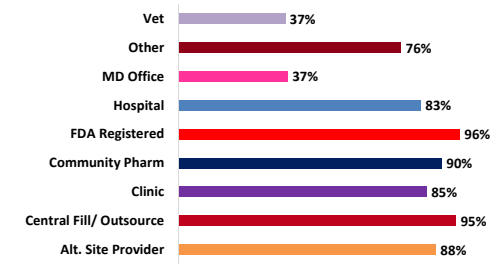


SBOP=state board of pharmacy

Food for Thought

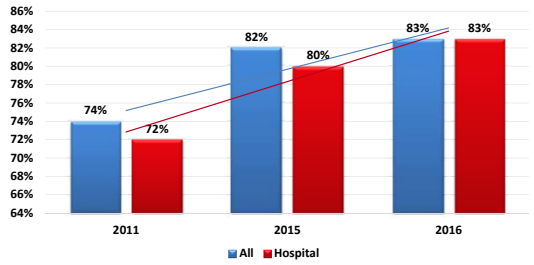
Everything that follows is the result of what you see here

Overall Chapter <797> Compliance by Practice Setting



The USP Chapter <797> Compliance Study: Pharmacy, Purchasing and Products Magazine: October 2016: Cleanrooms & Compounding - Vol. 13 No. 10 - Page 10.

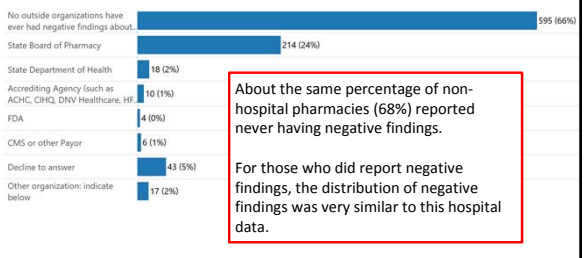
Trend of Overall Compliance with Chapter <797>



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.

The USP Chapter <797> Compliance Study: Pharmacy, Purchasing and Products Magazine: October 2016: Cleanrooms & Compounding - Vol. 13 No. 10 - Page 10.

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



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

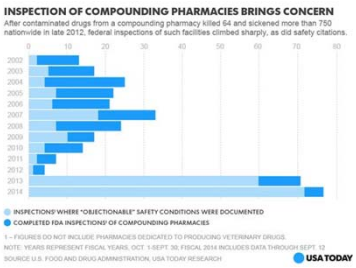
For those who did report negative findings, the distribution of negative findings was very similar to this hospital data.

The USP Chapter <797> Compliance Study: Pharmacy, Purchasing and Products Magazine: October 2016: Cleanrooms & Compounding - Vol. 13 No. 10 - Page 10.

See enlargement, p. 44

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.



Eisler P and Schmaars C. Safety, sanitary problems prompt scores of drug recalls. *USA Today*. October 7, 2014. Available at: www.usatoday.com/story/news/nation/2014/10/07/compounding-pharmacy-recalls-inspections-contamination/16472741/

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

Year	# Unique Documents	# Unique Establishments
2013	88	72
2014	77	61
2015	131	115
2016 (as of 10/11/16)	122	100

www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339771.htm

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/ucm339771.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.

www.fda.gov/ICECI/CriminalInvestigations/ucm484850.htm

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*

www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm498447.htm

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.

www.justice.gov/opa/pr/two-pharmacists-sentenced-prison-adulteration-drugs-connection-alabama-based-compounding

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."

www.justice.gov/opa/pr/two-pharmacists-sentenced-prison-adulteration-drugs-connection-alabama-based-compounding

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

503A	9
Draft Guidance	4
Draft MOU	1
Final Guidance	2
Request for Nominations	2
503B	12
Draft Guidance	3
Final Guidance	5
FR Notice	1
Request for Nominations	2
Revised Draft Guidance	1
Both	6
Draft Guidance	2
Final Rule	1
Proposed Rule	1
Public Docket	1
Request for Nominations	1
Grand Total	27

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

FDA Guidance Documents

- Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act – June 2016, rev 2.

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

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)).

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469119.pdf

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)

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469119.pdf

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)

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469119.pdf

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

FDA Guidance Documents

Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act – April 2016

- 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)

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496287.pdf

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.
- [1]Insanitary 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.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf

FDA – Insanitary 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.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf

FDA – Insanitary Conditions at Compounding Facilities – August 2016

- Drugs prepared, packed, or held (hereinafter referred to as "produced") under insanitary 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 insanitary 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.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf

FDA – Insanitary 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 "Insanitary 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 insanitary".** 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 beta-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".*

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf

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".***

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf

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 Point: 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.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf

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

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

UPDATES ON LEGISLATION, STANDARDS, AND BEYOND

Pharmacy Leadership FORUM

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

Photo courtesy of USP

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

www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/

503A Pharmacies

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

503B Outsourcing Facilities

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

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm

What is an FDA 483?

- Notification of objectionable conditions
- Public information
- Particularly serious conditions

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm

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

www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm514666.pdf

Who inspects compounders?

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

Facility Design Issues

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)

www.usp.org/usp-nf/notices/general-chapter-797-proposed-revision

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

www.cardinalhealth.com/en/thought-leadership/iv-fluid-hang-time.html

What is the BUD for a stock bag?

- Stock bag use
- In-use time

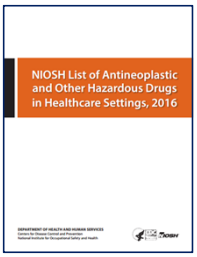
Hazardous Drugs

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

https://www.pppmag.com/digitalmag/Main.php?MagNo=132&PageNo=4#page/4

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 To…

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

USP Chapter <797>	ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products	ISMP 2016-2017 Targeted Medication Safety Best Practices for Hospitals
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.	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.	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.

NEW BEST PRACTICE

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.

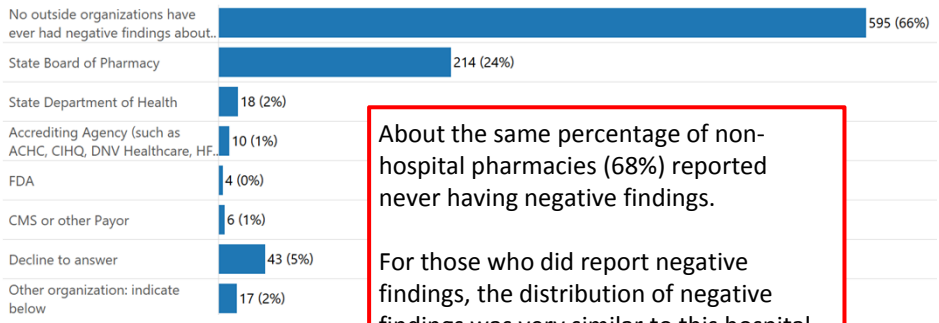
ISMP 2016-2017 Targeted Medication Safety Best Practices for Hospitals.

Gravimetric Analysis

ARGUMENTS FOR	ARGUMENTS AGAINST
Gravimetric analysis is utilized in analytical chemistry because it is extremely accurate.	Volumetric analysis is generally considered as accurate as gravimetric analysis when compounding sterile products.
Serves as a forcing function, in that preparers cannot proceed to next steps without scales having confirmed volumes in previous steps	Gravimetrics requires additional time-consuming steps of weighing each item before and after drawing and injecting liquids. Added steps result in added time.
Prevents upstream errors in the preparation process	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.

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)*



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.

The USP Chapter <797> Compliance Study: Pharmacy, Purchasing and Products Magazine: October 2016: Cleanrooms & Compounding - Vol. 13 No. 10 - Page 10.

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.

For Midyear Attendees in Las Vegas

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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