Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

Presented as a Sunday Symposium at the 50th ASHP Midyear Clinical Meeting and Exhibition

Sunday, December 6, 2015
New Orleans, Louisiana

www.ashpadvantage.com/drugquality

Planned by ASHP Advantage and the Center for Health-System Pharmacy Leadership and supported by an educational grant from Baxter Healthcare Corporation
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

Agenda

2:00 p.m. Welcome & Introductions
Eric S. Kastango, M.B.A., B.S.Pharm., FASHP

2:10 p.m. The Compounding Quality Act: Where Are We Today?
Gabrielle Cosel, M.Sc.

2:40 p.m. Implementing the Drug Supply Chain Security Act’s Track and Trace Requirements: Are We There Yet?
Chris Chandler, Pharm.D.

3:10 p.m. Small Group Discussion

3:20 p.m. Refreshment Break

3:30 p.m. USP Chapter <659>: New Packaging and Storage Definitions
Chris Chandler, Pharm.D.

3:40 p.m. USP Chapter <797>: Changes Are in the Works
Eric S. Kastango, M.B.A., B.S.Pharm., FASHP

4:10 p.m. USP Chapter <800>: Start Preparing Now
Patricia Kienle, B.S.Pharm., M.P.A., FASHP

4:40 p.m. Small Group Discussion

4:50 p.m. Questions and Discussion
All Faculty

Faculty

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

Chris Chandler, Pharm.D.
Vice President, Healthcare Practice
USDM Life Sciences
Chicago, Illinois

Gabrielle Cosel, M.Sc.
Manager, Drug Safety
The Pew Charitable Trusts
Washington, District of Columbia

Patricia C. Kienle, B.S.Pharm., M.P.A., FASHP
Director, Accreditation and Medication Safety
Cardinal Health Innovative Delivery Solutions
Laflin, Pennsylvania

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Activity Overview

A flurry of activity by Congress and the Food and Drug Administration in recent years aimed at improving the quality of the drug supply in the United States, as well as enforceable USP standards for the preparation and safe handling of sterile compounded drugs have had pharmacists scrambling to be in compliance. This activity will explain key provisions in the Drug Quality and Security Act, including new and updated requirements under the Compounding Quality Act. Participants will learn about different conditions for compounding under sections 503A and 503B of the FDCA, evolving FDA oversight and emerging guidance on topics such as repackaging, and tools for hospitals looking to source from FDA-regulated outsourcing facilities. This activity will also examine drug traceability law. Now that the January 1, 2015 requirements for the Drug Supply Chain Security Act are in effect, implementation of the product tracing requirements, lessons learned during the FDA enforcement discretion period, standards for upcoming barcode enhancements, and future electronic deadlines will be reviewed. Finally, the activity will cover critical developments in USP standards, including plans for revision of USP Chapter <797>, strategies to address continued areas of non-compliance, a review of new USP Chapter <659> on Packaging and Storage Requirements, and the pending impact of USP Chapter <800> on pharmacy operations.

Learning Objectives

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

- Review key provisions in the Drug Quality and Security Act (DQSA).
- Describe the current conditions under which facilities that compound sterile products can be exempt from certain requirements under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and understand evolving FDA guidance.
- Based on key track and trace requirements of the Drug Supply Chain Security Act, determine the status of implementation at their own institution.
- Discuss USP Chapter <659> Packaging and Storage Requirements and their impact on operations.
- Prepare a readiness plan for compliance with the proposed revisions to USP Chapter <797>, including possible policies and procedures that may need to be put in place.
- Explain USP Chapter <800> applications for the handling of hazardous drugs during receipt, storage, compounding, dispensing, administration, and disposal.
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.

Live Activity ACPE #: 0204-0000-15-477-L03-P

On-Demand Activity ACPE #: 0204-0000-15-477-H03-P

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

Additional Educational Opportunities Coming in 2016

- **Web-based activity** - Based on today’s live symposium (3.0 hours of CPE, please note that individuals who claim CPE credit for the live symposium or webinar are ineligible to claim credit for the web-based activity)

  For more information and to sign up to receive e-mail updates about this educational series, visit [www.ashpadvantage.com/drugquality](http://www.ashpadvantage.com/drugquality)
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Faculty

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

Eric S. Kastango, M.B.A., B.S.Pharm., 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 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 an active member and Fellow of the American Society of Healthcare Pharmacists and served on the USP Sterile Compounding Committee from 2005-2010 and 2010-2015 USP Council of Experts, Compounding Expert Committee until April 2013. He is currently an Expert Consultant to the USP and is actively working with NABP and state boards of pharmacy to provide training to their sterile compounding inspectors.

Eric 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 and the CriticalPoint web-based educational series on Sterile Compounding and the Annual National USP <797> Compliance Survey now in its fourth year. Eric has over 200 invited national and international professional presentations on various pharmacy practice topics such as pharmacy compounding and quality systems.
Chris Chandler, Pharm.D.
Vice President, Healthcare Practice
USDM Life Sciences
Chicago, Illinois

Chris Chandler, Pharm.D., is Vice President of Healthcare at USDM Life Sciences.

Dr. Chandler graduated from the University of Illinois College of Pharmacy and practiced on a multi-disciplinary healthcare team with the U.S. Department of Veterans Affairs (VA). Within VA, she formed the National Pharmacy Benefits Management Strategic Health Group Clinical Team, Quality Assurance Team for the Consolidated Mail Outpatient Pharmacy Program, and supported GS1 Standards Adoption with the Office of Informatics & Analytics Bar Code Resource Office and at GS1 US.

Dr. Chandler focuses on helping healthcare providers, hospitals, and pharmacies develop supply chain solutions for medical devices and pharmaceuticals that meet regulatory compliance requirements. She and her team specialize in the implementation of the Unique Device Identification (UDI) and the Drug Supply Chain Security Act (DSCSA) regulations.

Dr. Chandler more than 20 years of regulatory standards, informatics, quality assurance, pharmacy benefits management and patient care experience. She supports the Healthcare Provider Community by serving on the Steering Committees of the Parenteral Drug Association Pharmaceutical Cold Chain Interest Group and is a member of the Packaging, Storage, and Distribution Expert Committee to the United States Pharmacopeia.
Gabrielle Cosel, M.Sc.
Manager, Drug Safety
The Pew Charitable Trusts
Washington, District of Columbia


Ms. Cosel holds a Master of Science degree in human rights from the London School of Economics and a Bachelor of Art degree from Yale University.


Ms. Cosel develops numerous research initiatives for Pew, most recently including an upcoming study on state oversight systems for compounding. She was a lead developer of the Pew report, After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs. Prior to joining Pew, Ms. Cosel worked on issues of pharmaceutical safety and appropriate prescribing for the national advocacy organization Community Catalyst.
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Patricia C. Kienle, B.S.Pharm., M.P.A., FASHP  
Director, Accreditation and Medication Safety  
Cardinal Health Innovative Delivery Solutions  
Laflin, Pennsylvania

Patricia Kienle, B.S.Pharm., M.P.A., FASHP, is the 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 Masters 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.

She has served on the Board of Directors of ASHP and as President of the Pennsylvania Society of Hospital Pharmacists. She is a Fellow of ASHP, was named Pharmacist of the Year by the 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, as the pharmacist member of 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 of the USP Expert Committee on Compounding, and Chair of the Subcommittee and Expert Panel on Hazardous Drugs.


She is a frequent presenter to professional groups, with special interests in promoting medication safety, compounding sterile preparations, accreditation and regulatory issues.
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Disclosures

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Learning Objectives

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The 2013 Compounding Quality Act: Where Are We Today?

Gabrielle Cosel, M.Sc.
Manager, Drug Safety
The Pew Charitable Trusts
Washington, DC

The Pew Charitable Trusts

• National nonprofit dedicated to advancing research and policy in the interest of the public
• Work in drug quality, drug supply chain, and U.S. Food and Drug Administration (FDA) regulatory policy
• Engaged in development of 2013 Compounding Quality Act
• Reports, issue briefs, infographics available at: www.pewtrusts.org/drugsafety

Session Orientation

• Drug Quality and Security Act (DQSA 2013) contains two titles:
  – Title I: Compounding Quality Act (CQA)
  – Title II: Drug Supply Chain Security Act (DSCSA)
• This presentation will discuss Title I – the CQA – and its implementation. The next presentation will discuss Title II – the DSCSA.
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Outline
1. Why are we here? What led to the CQA?
2. Overview of the law, differences between section 503A and the new 503B sector
3. FDA implementation to date
4. Understanding FDA oversight of the new 503B sector to inform outsourcing decisions

What led to the Compounding Quality Act?

Multistate outbreak of fungal meningitis and other infections among patients who received contaminated, preservative-free MPA steroid injections from a single compounding pharmacy in MA.
Case Count: 751
Deaths: 64
States affected: 20

U.S. Centers for Disease Control and Prevention, October 23, 2013.
What led to the CQA?

Patient illnesses and deaths associated with contaminated compounded drugs (incomplete list)

<table>
<thead>
<tr>
<th>Date</th>
<th>Cases</th>
<th>Deaths</th>
<th>Adverse Events</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>17</td>
<td>2*</td>
<td>Bacterial bloodstream infections</td>
<td>Calcium Gluconate Infusion</td>
</tr>
<tr>
<td>2013</td>
<td>5</td>
<td></td>
<td>Serious eye infections</td>
<td>Bevacizumab injection</td>
</tr>
<tr>
<td>2013</td>
<td>26</td>
<td></td>
<td>Skin and soft tissue infections</td>
<td>PF methylprednisolone acetate injection</td>
</tr>
<tr>
<td>2012</td>
<td>47</td>
<td></td>
<td>Fungal eye infections, vision loss</td>
<td>Retinal dye and triamcinolone injection</td>
</tr>
<tr>
<td>2012</td>
<td>7</td>
<td></td>
<td>Bacterial bloodstream infections</td>
<td>Fentanyl solution</td>
</tr>
<tr>
<td>2011</td>
<td>19</td>
<td>9</td>
<td>Bacterial bloodstream infections</td>
<td>Parenteral nutrition solution</td>
</tr>
</tbody>
</table>

PF = preservative free
*CDC has not conclusively linked these deaths to the drug in question.

What led to the CQA?

Patient illnesses and deaths associated with contaminated compounded drugs (incomplete list)

Including the 2012-2013 outbreak, Pew’s drug safety project has identified over 25 compounding errors or potential errors (mostly contaminations) associated with 1,074 adverse events, including 90 deaths, since 2001. Because many such events may go unreported this list is likely an underestimation.

Full list and citations:

What led to the CQA?

- Challenges in regulation of compounding
  - Emergence of specialized compounding activity to prepare supplies of drugs for use by providers, rather than patient specific drugs
  - Defining the difference between drug compounding and drug manufacturing
  - Enabling patient access to medically necessary therapies, while ensuring drugs are made to appropriate quality standards

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What led to the CQA?

- 1997: Section 503A of the Food Drug and Cosmetic Act created by FDAMA legislation
  - 503A created exemptions for compounding from FDA drug approvals, good manufacturing practices, and certain labeling requirements
- 2002: Supreme Court held unconstitutional certain advertising restrictions in 503A
  - Severability from rest of 503A unclear, circuit courts rule differently, making national enforcement uncertain

What led to the CQA?

- 2002: FDA Compliance Policy Guide (CPG)
  - FDA guide on enforcing new drug, misbranding, or adulteration provisions of the Food, Drug and Cosmetic Act (FDCA) over compounded drugs, absent clear enforceability of 503A
  - Enforcement when "the scope and nature of a pharmacy’s activities raise the kinds of concerns normally associated with a drug manufacturer"
  - Criteria included: compounding in anticipation of prescriptions outside of limited quantities, presence of commercial-scale equipment, compounding copies of commercially available drugs
- 2004: USP Chapter <797> first published
- 2008: USP Chapter <797> revised
  - Surveys show USP Chapter <797> adoption challenging, providers look increasingly to outsourced compounding

What led to the CQA?

- 2012-13: Multistate meningitis outbreak
  - Congressional working groups quickly formed
  - Determination that certain compounding activities exceeded traditional practice, merited federal oversight
- 2013: CQA passed (Title I of the DQSA)
  - Reinstated 503A by removing unconstitutional advertising provisions
  - Created section 503B: Outsourcing Facilities
Overview of the CQA and Sections 503A/503B

Federal legislators sought to clearly draw the line between pharmacy compounding and manufacturing. But Congress also recognized hospitals and clinics relied on outsourced compounding to have products in stock before they wrote prescriptions. 503B Outsourcing Facility category created to provide an appropriate regulatory home for these suppliers.

Overview of CQA and 503A/503B

- 503A and 503B: two pathways to legally compound drugs and receive certain exemptions from federal law.
- The main difference:
  - 503Bs may compound supplies of drugs without prescriptions, but must meet stricter quality standards: current Good Manufacturing Practices (cGMPs).
  - 503As may compound pursuant to prescriptions (or in limited quantities before receipt) but are exempt from cGMPs. May not compound without prescriptions.
  - Implications for outsourcing sterile compounding by health systems

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Overview of CQA and 503A/503B

- 503B Outsourcing Facility definition:
  - Engaged in the compounding of sterile drugs
  - Registers as an outsourcing facility with FDA (and pays the required annual establishment fee)
  - Complies with the requirements of 503B
- In addition:
  - NOT required to be a licensed pharmacy, but compounding must be under direction of a licensed pharmacist

Overview of CQA and 503A/503B

<table>
<thead>
<tr>
<th>Sterile Drugs</th>
<th>503A Compounding Pharmacies</th>
<th>503B Outsourcing Facilities</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA drug approvals</td>
<td>No, exempt</td>
<td>No, exempt</td>
<td>Yes</td>
</tr>
<tr>
<td>&quot;Adequate directions for use&quot; labeling</td>
<td>No, exempt</td>
<td>No, exempt</td>
<td>Yes</td>
</tr>
<tr>
<td>Good Manufacturing Practice</td>
<td>No, exempt (states set varying quality standards)</td>
<td>Yes (specific standards to be set by FDA)</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary Oversight Body</td>
<td>States*</td>
<td>FDA</td>
<td>FDA</td>
</tr>
<tr>
<td>Prescription Requirements</td>
<td>Pursuant to Rx limited quantities in advance of Rx</td>
<td>Rx not required</td>
<td>Rx not required</td>
</tr>
</tbody>
</table>

* FDA can also enforce applicable federal law, such as on insanitary conditions.

Overview of CQA and 503A/503B

Drugs that 503As and 503Bs can’t make:

<table>
<thead>
<tr>
<th>503A Compounding Pharmacies</th>
<th>503B Outsourcing Facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrably difficult</td>
<td>Cannot compound drugs that are on an FDA list of drugs that present demonstrable difficulties for compounding</td>
</tr>
<tr>
<td>Withdrawn / removed</td>
<td>Cannot compound drugs that are on an FDA list of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective</td>
</tr>
<tr>
<td>Copying an approved drug</td>
<td>Cannot copy a drug that is essentially a copy of an approved product, which includes a drug with the same active pharmaceutical ingredient (API) as an approved drug</td>
</tr>
<tr>
<td>Does not include a drug where there is a change made that produces a clinical difference for an individual patient</td>
<td>Does not include a drug where there is a change made that produces a clinical difference for an individual patient, or a drug in shortage</td>
</tr>
</tbody>
</table>
Overview of CQA and 503A/503B

**Interstate Shipment:**
- 503Bs may ship compounded drugs interstate
- 503As cannot distribute compounded drug interstate representing more than 5% of the total prescription orders dispensed or distributed by that pharmacy unless they are located in a state that has entered into a Memorandum of Understanding that provides for appropriate investigation of complaints related to drugs distributed outside the state and addresses the distribution of inordinate amounts of compounded drug products interstate.

Overview of CQA and 503A/503B

**Use of bulk API by 503As and 503Bs:**

<table>
<thead>
<tr>
<th>503A – Compounding Pharmacies</th>
<th>503B – Outsourcing Facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only use APIs that have United States Pharmacopeial Convention (USP) monographs, or are used in approved drug products, or are on FDA list</td>
<td>Only if drug is on FDA shortage list, or Only if using APIs on a positive list set by the FDA identifying bulk drug substances for which there is a clinical need API must comply with USP monograph if one exists</td>
</tr>
</tbody>
</table>

API must come from facilities registered with the FDA, and be accompanied by a valid certificate of analysis.

Overview of CQA and 503A/503B

**Additional requirements for 503Bs:**
- Report to FDA twice a year information about the products compounded during previous six months
- Report adverse events
- Label compounded drugs with certain information
- Cannot compound a drug that is subject to a REMS with elements to assure safe use or from a bulk drug substance that is a component of such drug unless the outsourcing facility demonstrates it will use controls comparable to the REMS
Overview of CQA and 503A/503B

- A compounding pharmacy that
  - does not register as an outsourcing facility and comply with the conditions under section 503B, and
  - compounds drugs that do not qualify for the exemptions under section 503A is subject to all of the requirements in the FDCA applicable to conventional manufacturers.
- FDA website currently lists over 200 483 forms* issued following inspections of compounding pharmacies.

*483 = a form issued by FDA following an inspection listing observed conditions that may constitute a violation of the FDCA.

Compounding Quality Act Implementation Activity To Date

CQA Implementation

FDA guidance since passage of CQA:

- Nov. 2013: Draft Guidance on 503A and registration and interim product reporting for 503B
- Nov. 2013, reissued Jul. 2014: Request for nominations: Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503B
### CQA Implementation

#### FDA guidance since passage of CQA:
- Jul. 2014: Proposed Rule: Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness
- Jul. 2014: Final Guidance on Section 503A
- Feb. 2015: Draft Guidance on OF adverse event reporting
- Feb. 2015: Draft guidance for entities considering whether to register as OFs

### CQA Implementation

#### FDA guidance since passage of CQA:
- Feb. 2015: Draft Guidance on Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities
- Feb. 2015: Draft Guidance on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application
- Feb. 2015: Draft Memorandum of Understanding Between a State and FDA Addressing Certain Distributions of Compounded Human Drug Products
- Oct. 2015: Final Guidance on Adverse Event Reporting for Outsourcing Facilities; Final Guidance on Compounding under 503A
- Oct. 2015: Interim guidance documents on compounding from bulk substances under 503A and 503B

### CQA Implementation

#### Pharmaceutical Compounding Advisory Committee (PCAC) formed by FDA, beginning to make recommendations regarding lists of drugs 503A and 503B compounders may/may not make. (PCAC vote ≠ FDA final decision)
- Feb 2015: PCAC voted to add 25 drugs to list of drugs withdrawn/removed from market for safety/efficacy reasons
- Feb 2015: PCAC voted to add four bulk drugs to FDA’s positive list for 503Bs: Thymol Iodide, Squaric Acid Dibutyl Ester, Diphenylcyclopropenone, and Cantharidin; voted to NOT add silver protein mild and piracetam
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CQA Implementation
Additional PCAC recommendations:
- June 2015: PCAC voted to add 4 drugs to list of drugs withdrawn/removed from market for safety/efficacy reasons, including acetaminophen drug products greater than 325 mg per dosage unit
- June 2015: PCAC voted to add three bulk drugs to FDA’s positive list for 503As: Brilliant Blue G, tranilast (only topical use), N-acetyl-D-glucosamine; voted to NOT add oxitriptan
- October 2015: PCAC consideration of substances nominated for inclusion on the list of API that may be used by 503A pharmacies to compound drugs

CQA Implementation
Draft guidance on drug repackaging
- Repackaging not part of FDA definition of compounding in 503A or 503B, no statutory exemption from FDCA
- Under guidance, only permitted for FDA-approved drugs (unless an unapproved drug on shortage list); must be done under supervision of pharmacist
- Must be prepared in a way that does not conflict with product label (except for drugs labeled as single-use vials that are repackaged into smaller vials)
- Guidance replaces federal law (FDCA Section 506F) on repackaging by health systems to address shortages
  - FDA maintains enforcement discretion for repackaging a drug that appears on FDA’s drug shortage list, as long as the conditions of the guidance are met

CQA Implementation
Draft guidance on drug repackaging
- Repackaging by state-licensed pharmacies must be
  - pursuant to patient prescription or written order on patient chart, or
  - in advance of receipt of patient prescription, but not to exceed the amount prepared pursuant to a prescription in the previous consecutive 14-day period
    - Could indicate FDA’s thinking on what might constitute permissible amounts of anticipatory compounding
- Repackaging by outsourcing facilities does not require prescription
- Outsourcing facilities must meet GMPs, others must meet USP Chapter <797> standards
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### CQA Implementation

**Draft guidance on drug repacking - BUDs**

<table>
<thead>
<tr>
<th>Sterile drugs</th>
<th>Room Temp</th>
<th>Refrigerated</th>
<th>Frozen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting drug has specific in-use time</td>
<td>Beyond-Use Date (BUD) in accordance with in-use time or expiration date, if shorter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting drug does not have specific in-use time</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>503A (pharmacy)</td>
<td>or expiration date, if shorter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>503B (outsourcing facility)</td>
<td>14 days beyond completion of sterility test, or 28 days from time of repackaging, whichever is shorter</td>
<td>45 days beyond completion of sterility test or 59 days from time of repackaging, whichever is shorter</td>
<td></td>
</tr>
<tr>
<td>Nonsterile drugs</td>
<td>No longer than expiration date</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CQA Implementation

**Draft guidance on mixing, diluting, or repackaging biologics**

- Biologics not covered in Section 503A or 503B, no statutory exemption from FDCA for compounded or repackaged biologics
- Under guidance, only permitted starting with approved biologic, not bulk drug; must be done under supervision of pharmacist
- Must be in prepared in a way that does not conflict with product label (except for drugs labeled as single-use vials that are repackaged into smaller vials)
- Does not apply to blood products, vaccines, or cell or gene therapies

### CQA Implementation

**Draft guidance on mixing, diluting, or repackaging biologics**

- Repackaging by state-licensed pharmacies must be
  - pursuant to patient prescription or written order on patient chart, or
  - in advance of receipt of a prescription, if in a quantity does not exceed the expected demand for the biological product within the BUD, based on a history of receipt of prescriptions for such a biological product for that time period
- Repackaging by outsourcing facilities does not require prescription
- Outsourcing facilities must meet GMPs, others must meet USP Chapter <797> standards
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

CQA Implementation
Draft guidance on mixing, diluting or repackaging biologics - BUDs

<table>
<thead>
<tr>
<th></th>
<th>No testing</th>
<th>Microbial challenge studies demonstrate growth will not progress to unacceptable levels</th>
<th>Container-closure assessment demonstrates compatibility with drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>503A pharmacies</td>
<td>4 hours</td>
<td>24 hours</td>
<td>NA</td>
</tr>
<tr>
<td>503B outsourcing facilities</td>
<td>Mixing or diluting</td>
<td>4 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td></td>
<td>Repackaging</td>
<td>4 hours</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

CQA Implementation
FDA draft Memorandum of Understanding (MOU)

- Establishes responsibilities for states investigating complaints regarding drugs made in their state and shipped to another
- Requires states to monitor for “inordinate” interstate distribution of compounded drugs and notify FDA
- Inordinate distribution: the number of units of compounded human drugs distributed interstate in a month is 30% or greater of all drugs (compounded and non-compounded) distributed or dispensed (interstate and intrastate) in the month
  - Without signed MOU, interstate shipment of compounded drugs limited to 5% of prescription orders – section 503A
- For purposes of MOU, distribution defined as the drug leaves the facility where it was prepared. This includes dispensed drugs sent to patients.

CQA Implementation
Health-system central compounding

- No FDA guidance yet on centralized compounding pharmacies for health-systems
- Anticipatory compounding is allowed, but may be limited in scope. Compounding without prescriptions is not permitted under federal law unless you are a 503B OF
- Restrictions on interstate distribution of compounded drugs, as set by the FDA MOU, would also in theory apply to health-system pharmacies moving compounded drugs across state lines
- Bigger potential implications for central compounding facilities serving a large health-system
- Some health-system pharmacies have registered as 503Bs, including
  - Banner Health, Chandler, AZ
  - SSM St. Clare Health Center, Fenton, MO

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Sourcing from Outsourcing Facilities; Understanding FDA Oversight

Sourcing from OFs

- Currently over 50 outsourcing facilities registered with FDA across 24 states
- FDA January 2014 letter encouraging healthcare organizations to purchase compounded sterile drugs from outsourcing facilities
  - OFs the only sector with clear legal ability to provide non-patient-specific supplies of sterile preparations
- OF compounding under cGMPs is a different paradigm than pharmacy compounding under USP Chapter <797>
  - How to assess OFs?
  - What does FDA oversight mean?

Sourcing from OFs

- Threshold questions:
  - Is the vendor registered with the FDA as a 503B Outsourcing Facility?
    http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm
  - If the vendor compounds supplies of drugs without prescriptions and is not registered with FDA as an OF, they could be in violation of federal law
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Sourcing from OFs

- Threshold questions:
  - Has the OF been inspected by FDA?
  - Has the FDA taken any enforcement actions?
  - 483: A list of possible compliance violations, but does not constitute a final FDA determination. 483s are common right now in OF sector as companies are updating systems to comply with cGMPs
  - Warning Letter: A notification that a company has significantly violated FDA regulations
  - Recall: In a few cases inspections have led to recalls of compounded products due to sterility concerns
  - In all cases, what was the company’s response to these actions?

Sourcing from OFs

- ASHP Guidelines on Outsourcing Sterile Compounding Services
  - http://www.ashp.org/Outsourcing-Compounding-Services
- ASHP Outsourcing Sterile Products Preparation - Vendor Assessment Tool
  - http://outsourcingassessment.org/

THANK YOU

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Implementing the Drug Supply Chain Security Act’s Track and Trace Requirements: Are We There Yet?

FDA Guidance on the Drug Supply Chain Security Act – What You Need to Know for Upcoming Requirements

Chris Chandler, Pharm.D.
Vice President of Healthcare Practice
USDM Life Sciences
Chicago, Illinois

USDM Life Sciences

- USDM Life Sciences has been providing some of the world’s largest medical device and pharmaceutical companies with business process, technology and compliance solutions for more than 14 years. Our Healthcare team spans the entire spectrum to include assisting healthcare providers and distributors with planning and implementing solutions for Medical Device UDI, Pharmaceutical Traceability, GS1 Standards Adoption, and related supply chain challenges.
- Dr. Chandler practiced for over 20 years as a pharmacist at the Department of Veterans Affairs and for GS1 US bringing patient safety, regulatory standards, informatics, quality assurance and pharmacy benefits management experience.

Section Objectives

- Assess your systems and processes for compliance with the DSCSA 2015 authorization and verification requirements.
- Describe your challenges in storing the transaction documentation required for accepting product after July 1, 2015 and the enforcement discretion limitations.
- Understand future implementation requirements for product serialization and traceability in the next decade and the upcoming FDA guidance.
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

The New Healthcare Regulatory Landscape

- With the final FDA Unique Device Identification (UDI) Rule, scanning in U.S. hospitals can now include medical devices marked with standardized unique identifiers allowing automated identification and data capture (AIDC) from procurement through their use in patient procedures to post-market surveillance and adverse event reporting.
- To meet requirements for new DSCSA and FDA Implementation, new technologies will be utilized to scan, transact and store product attributes in the event of suspect or illegitimate product verification and to improve the recall process.
- As Electronic Health Records (EHRs) become the standard to meet requirements for new stages of the Office of the National Coordinator (ONC) and Centers for Medicare & Medicaid Services (CMS) Meaningful Use Rule, the expanded information requires enhanced capabilities for regulated medical product data to flow from supply chain procurement systems to the point of care, enabling traceability to improve patient safety.

The Drug Quality and Security Act

- On November 27, 2013, President Obama signed DQSA into law.
- Title I, the Compounding Quality Act removes certain provisions from the FDCA applicable to US compounders:
  - Compounders can become an “outsourcing facility” able to qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from cGMP requirements or FDA inspection, reporting adverse events or providing FDA with certain information about the products they compound
  - FDA anticipates that state boards of pharmacy will continue their oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding and outsourcing facilities

Title II of the Drug Quality and Security Act

FDA guidance on implementation of the DSCSA covers 5 key areas requiring compliance.
- The first compliance date is January 1, 2015
- The law intends to protect consumers from exposure to counterfeit, stolen, contaminated, or otherwise harmful prescription drug products by building a nationwide electronic, interoperable system to identify and trace distribution
- The law preempts all state and federal drug pedigree laws
All trading partners are required to comply to move products through the supply chain!
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DSCSA Implementation Plan - 2014

- Publish guidance on identification of suspect product and termination of notifications of illegitimate product
- Establish system or database and guidance for Third Party Logistics (3PL) and wholesale distributors reporting to FDA
- Publish draft guidance establishing standards for interoperable exchange of transaction information, history, statement in paper or electronic format

DSCSA Implementation Plan 2015-2023

- Develop regulations on licensing standards for 3PLs and wholesale; stakeholder implementation through 2015-2016
- Publish guidance on grandfathering product and processes for waivers, exceptions, exemptions; Stakeholder implementation through mid-2017
- Establish 15 stakeholder pilots to evaluate methods to enhance the safety and security of supply chain
- Conduct at least five public meetings
- Conduct technology and software assessment for feasibility of small dispenser tracing at package level
- Develop regulations-enhanced drug distribution security system for interoperable electronic tracing at package level; FDA 2017-2021; stakeholders 2021-2023
- Publish final guidance on secure package-level tracing: FDA implementation 2018–2022; stakeholders 2022–2023
- System attributes to enable and standards for interoperable data exchange enhancement

See enlargement, p. 66

DSCSA Implementation Timelines

- Authorized Trading Partners
- Verification at Lot level
- Suspect and Illegitimate Product
- Exchange Transaction Statement, Info, History
- Dispensers by Jul 2015*
- Electronic by 2017
- FDA granted dispensers enforcement allocation until March 5, 2018

- Product Identifier
  - DSCSA = SNI + Lot + Expiry
  - Package marked with Data Matrix Barcode; Linear or Data Matrix on Homogenous Case
- Repackers by Nov 2018
- Wholesalers by Nov 2019
- Dispensers by Nov 2020
- SN = Standardized Numeric Identifier
- NOV 2017
- Exchange Serialized Package Level
- Traceability
- Sunset Lot Level Traceability

See enlargement, p. 66
FDA Enforcement Discretion

- The FDA granted an additional 4 months of enforcement discretion (until Nov 1st and then again until March 1st, 2016) for one of the DSCSA Product Tracing Requirements.
- The extension provides additional time to work with trading partners to ensure the product tracing information is captured and maintained by dispensers when accepting product. Pharmacies are working to implement electronic tracing solutions and are using the extension to onboard suppliers, test the system and train pharmacy staff.
- Ensure your organization and trading partners are compliant with DSCSA SOPs as the enforcement discretion does NOT extend to:
  - Current requirement for dispensers to pass transaction to subsequent owners (“dispenser-to-dispenser sales”)
  - Required verification of transactions to detect suspect and illegitimate product (including quarantine, investigation, notification and recordkeeping)
  - Engaging only with authorized trading partners


Who are DSCSA “Trading Partners?”

- Manufacturer
- Repackager
- Wholesale distributor
- 3PL provider accepting or transferring possession of product
- Dispensers
  - retail or hospital pharmacy
  - chain pharmacies under common control – not in wholesale distribution
  - authorized to dispense/administer prescription drugs and affiliated warehouses or distribution centers under common control – not in wholesale distribution
  - NOT including dispensing for use in animals
  - NOT including practitioners who prescribe/administer in professional practice – see exceptions

Authorized Trading Partners

Effective January 1, 2015, trading partners are required to be licensed:

- by the State from which the drug is distributed; or
  - if the State from which the drug is distributed has not established a licensure requirement, is licensed by the FDA; and
  - if the drug is distributed interstate, is licensed by the State into which the drug is distributed if the State into which the drug is distributed requires licensure
- in the case of a manufacturer or repackager, having a valid FDA registration
- in the case of a dispenser, having a valid license under State law

These requirements must be met to be considered an “authorized trading partner.”
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How to Comply with FDA DSCSA “Authorization” Requirements

Check FDA, state, and local licensing
- Required from and/or into your state? Document FDA or state licensure for all trading partners

Vendor Master Updates and Maintenance
- Complete licensing info – check FDA database and maintain
- Add GS1 Global Location Number (GLN) which also enables the GS1 Global Database Synchronization Network (GDSN)
- Add in primary contact information – will add efficiency for next section on verification, capabilities on Electronic Data Interchange (EDI), Advance Ship Notice (ASN), Electronic Product Code Information Services (EPCIS), GS1 Global Trade Item Number (GTIN) or Health Industry Business Communication Council (HIBCC) Health Industry Number (HIN) whether direct purchase or distributed

Verification of Product

As of January 1, 2015, all trading partners require systems* in place to enable suspect and illegitimate product determination or request for verification from trading partners/FDA:
1. Quarantine the product, including any subsequently received
2. Investigate to determine if illegitimate
   - Validate transaction data in ≤1 business day and ≤48 hours (2 days for dispensers)
   - Verify DSCSA Product Identifier at the serialized package level
  - Enacting in 2017 for manufacturers, 2018 for repackagers, 2019 for wholesalers
  - In 2020 dispensers verify at lot level plus 100% or at least 3 serialized packages
3. Determine if product is illegitimate
  - Assist trading partners with illegitimate product not in possession or control and retain a sample
  - Notify FDA and all immediate trading partners that may have received illegitimate product ≤24 hours after determination (or promptly if not found to be illegitimate)

FDA Suspect Product Scenarios

- New trading partners or sourcing
- Low supply/high demand or high-value product
- Package or container/case/tote is suspicious, damaged, altered, missing information or markings
- Shipping address, postmark, or other information indicating product came from an unexpected foreign entity or source

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**Transaction Information (TI) – Data Required**

- The proprietary or established name or names of the product;
- The strength and dosage form of the product;
- The National Drug Code (NDC) number of the product;
- The container size;
- The lot number of the product;
- The number of containers;
- The date of the transaction;
- The date of the shipment, if more than 24 hours after the date of the transaction;
- The business name and address of the person from whom ownership is being transferred; and
- The business name and address of the person to whom ownership is being transferred.

**Transaction History (TH) – Data Required**

A statement in paper or electronic form that includes the transaction information for each prior transaction going back to the manufacturer of the product.

**Transaction Statement (TS) – Data Required**

Statement in paper or electronic form that the entity transferring ownership in a transaction:

A. is “authorized”;
B. received the product from a person that is “authorized”;
C. received “transaction information” and a “transaction statement” from the prior owner of the product;
D. did not knowingly ship a “suspect product” or “illegitimate product”;
E. had systems and processes in place to comply with DSCSA “verification” requirements;
F. did not knowingly provide false “transaction information”;
G. did not knowingly alter the “transaction history”; and
H. In some cases, an indication that the entity, or an affiliate, purchased the product directly from the manufacturer, exclusive distributor or repackager that purchased the product directly from the manufacturer.
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TI/TH/TS (T3) In A Single Document

See enlargement, p. 66

Sample DSCSA Transaction Documentation

For Drop-Shipment, the wholesaler is exempt from providing the TI, TH, TS to the dispenser if provided by the party conducting the drop-shipment on behalf of wholesaler and TI and TH contain the contact information for the wholesaler

See enlargement, p. 67

Transactions: Returns

Saleable Product
- Manufacturers
  - After Nov. 2017 must verify the SNI on product before redistribution
- Wholesale Distributors
  - Until Nov. 2019 may accept returns from dispensers without receiving TI/TH/TS if written agreement in place
  - After Nov. 2019 must verify SNI on product before redistribution
- Dispensers
  - After Jan. 1, 2015 may return product to original seller without providing TI/TH/TS if written agreement in place
- Repackagers
  - After Jan. 1, 2015 may return product to original seller without providing TI/TH/TS if written agreement
- After Nov. 2018 must verify the DSCSA Product Identifier before redistribution

Non-Saleable Product
- All parties may return product to the manufacturer or repackager (or wholesaler from whom the product was purchased) without providing TI/TH/TS

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General Exemptions to DSCSA T3

- Sales from a dispenser to another dispenser for specific patient need
- Imaging agents, homeopathic or compounded drugs
- Medical devices; combination products consisting of a drug + one or more devices and/or biologics (only under certain circumstances)
- Medical convenience kits containing a drug product (only under certain circumstances)
- Intra-company transfers
- Medical gases
- Blood or blood products intended for transfusion
- IV drugs intended for replenishment of fluids and electrolytes
- Irrigating solutions and sterile waters
- Distribution for public health emergencies
- Product samples
- Charitable organization distribution to a nonprofit affiliate of the organization
- Distribution of minimal quantities of drug by a licensed retail pharmacy to a licensed practitioner for office use
- Dispensing of product pursuant to a prescription to a patient

See enlargement, p. 67

Keep up with Evolving DSCSA Requirements

See enlargement, p. 68

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**EPCIS Example Transaction**

<table>
<thead>
<tr>
<th>Who</th>
<th>What</th>
<th>When</th>
<th>Where</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>3210123456789</td>
<td>sgtin 20887511.007346.123456789</td>
<td>01/01/2015 12:00:01 PM</td>
<td>01234567890123</td>
<td>receiving</td>
</tr>
</tbody>
</table>

**TRANSACTION INFORMATION**
- **Product Brand or Generic Name**: Really Good Drug Product
- **Product strength**: 5%
- **Product dosage form**: Tablet
- **Product National Drug Code (NDC)**: 8751100734
- **Product container size**: 12 Tablets in 1 Blister Package
- **Product lot number**: A1B2C3D4E5
- **Number of containers**: 12
- **Date of the transaction**: 01/01/2015
- **Date of the shipment, if more than 24 hours after the date of the transaction**: 01/03/2015
- **Business name and address of the person from whom ownership is being transferred (or GLN)**: 0039876543212
- **Business name and address of the person to whom ownership is being transferred (or GLN)**: 3210123456789

**GLN= GS1 Global Location Number**

---

**DSCSA Regulatory Implementation Plan**

<table>
<thead>
<tr>
<th>DSCSA Requirement</th>
<th>Activity Description</th>
</tr>
</thead>
</table>
| Authorization- Check supplier license and expiration | • Vendor Letter and Survey  
• Authorized Supplier Listing |
| Verification- Inspection, T3 match and Store T3 | • Good Distribution Practices (GDP) Policy  
• Training, Communication Plan- internal and external  
• Data Retention Plan |
| DSCSA Compliance | • Implementation Plan  
• T3 Compliance Audits  
• Impact- Borrow/ Loan Process, Product Recall Process |
| Improved Process-T3 | • Electronic System- not required until 2017 however paper burden at each pharmacy control point  
• Set Electronic Transaction Vendor Requirements |
| Master Data Management | • Relating T3 Master Data- build a Pharmacy Item Master |

---

**DSCSA Q&A Topic**

<table>
<thead>
<tr>
<th>DSCSA Q&amp;A Topic</th>
<th>USDM White Paper Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the difference between DQSA Title I for Compounding and DQSA Title II or DSCSA?</td>
<td>Page 4</td>
</tr>
<tr>
<td>Are we a trading partner?</td>
<td>Pages 5 and 15</td>
</tr>
<tr>
<td>What is required for Authorization?</td>
<td>Page 6</td>
</tr>
<tr>
<td>What is required for Verification?</td>
<td>Pages 6-8</td>
</tr>
</tbody>
</table>
| What is included in the required Transaction Information? What changes in 2017? | Page 9  
Page 12 |
| What products are exempted? | Page 14 |
| What is required for barcodes in 2017? | Page 15-16 |
| What is required in 2023? | Page 17-18 |
| Where is a summary of all the requirements? | Summary Pages 3 & 21 |

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References


Contact Information

Chris Chandler
VP of Healthcare Practice
cchandler@usdm.com

Knowledge Check - What are DSCSA transactions?

Prior to, or at the time of each transaction in which the dispenser transfers ownership of a product (not including dispensing to a patient), provide the subsequent owner with TH, TI (including lot level information, if provided), and TS, and maintain for not less than 6 years after the transaction:

1. Sales by a dispenser to another dispenser to fulfill a specific patient need is exempt from DSCSA transaction requirements - in other situations such as shortages or restocking a loan- how will you buy/sell products from/to other dispensers?
2. Would restocking medications for your ambulance company constitute a transaction or be exempt as part of your entity or “distribution of minimal quantities of drug by a licensed retail pharmacy to a licensed practitioner for office use”?
3. Organizations are discussing whether 340B medications should be exempt as “charitable distribution”, do you have other charitable distribution to consider?
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Discussion Questions

Compounding Quality Act
- What changes, if any, have you made to your sourcing of sterile preparations following the establishment of the new outsourcing facility sector in 2013?
- Have you worked with an outsourcing facility?
  - If so, have you encountered any challenges in identifying and assessing these suppliers?

What are DSCSA transactions?
- Sales by a dispensing pharmacy to another dispensing pharmacy to fulfill a specific patient need are exempt from DSCSA transaction requirements - in other situations such as shortages or restocking a loan - how will you buy/sell products from/to other dispensers?
- Would restocking medications for your inpatient hospital constitute a transaction or be exempt as part of your entity or “distribution of minimal quantities of drug by a licensed retail pharmacy to a licensed practitioner for office use”?
- Organizations are discussing whether 340B medications should be exempt as “charitable distribution,” do you have other charitable distribution to consider?

Refreshment Break

USP Chapter <659>
Packaging and Storage Requirements

Chris Chandler, Pharm.D.
Vice President of Healthcare Practice
USDM Life Sciences
Chicago, Illinois
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

Purpose

- To provide packaging definitions, auxiliary packaging information, and storage condition definitions relevant to the storage and distribution of active ingredients, excipients, and medical products, such as pharmaceuticals, devices, combination products (e.g., drug-eluting stents, prefilled syringes, delivery devices co-packaged with pharmaceuticals), and dietary supplements

USP Chapter <659>

- Chapter Chair: Chris Chandler
- Chapter Status: New
- Latest PF Publication 2010-2015: PF 41 (3)
- USP Revisions 2010-2015: USP 38

Summary of Work Completed in 2010-2015 Cycle

- Packaging and Storage definitions moved from General Notices into new chapter
- Packaging definitions in other USP chapters moved to <659>
- Current definitions revised to reflect current industry practice and new definitions added
- Chapter reformatted for clarity
- Removed teaspoon definition

Key Issues for the 2015-2020 Cycle

- Expansion of Control Room Temperature Definition
- Storage and Distribution Workshop—May 23-24, 2016
- Monitor industry feedback on the deletion of Teaspoon definition
  - Graduated associated components described in this section are for general use. Graduated markings should be legible, indelible, and on an extraoral surface that does not contact the product. The associated volume markings shall be in metric units and limited to a single measurement scale that corresponds with the dose instructions on the prescription container label (see Prescription Container Labeling 17*).

*http://www.usppf.com/pf/pub/data/v413/CHA_IPR_413_c17.html

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Aligning USP and FDA Definitions
- Our USP Chapter <659> Expert Panel’s FDA Liaison worked closely with USP to revise and align with FDA’s current thinking.
- Refer to Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use open for public comment

Next in 2016 for USP Chapter <659> on Controlled Room Temperature (CRT)
- We published a stimuli article with a brief overview of drug product stability studies and practices, with a focus on temperature control during storage and distribution.
- Recent stability studies support redefining CRT by broadening the permitted range when appropriate for specific products.
- The objectives were to initiate discussion and to solicit public comments regarding a potential revision, as yet unproposed in PF, of USP’s definition for CRT from 20–25°C to 2–30°C. Will post discussions in 2016 in PF and workshop in 2015-16.

Proposal for USP Chapter <1659>
- INTRODUCTION—Background/Scope on Best Practices, Regulations
- TEMPERATURE AND STORAGE
  - Freezer, Refrigerator, Room temperature (also referred to as Ambient temperature)
- LABELING
  - Beyond-use date
  - Black closure system or black bands
  - Cold, Cool, Controlled room temperature; Mean kinetic temperature
  - Excursions
  - Provided the mean kinetic temperature does not exceed 25°C, transient spikes up to 40° are permitted as long as they do not exceed 24 h.
  - Dry place
  - Excessive heat
  - Expiration date
  - Protect from freezing
  - Protect from light
  - Warm
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USP Chapter <659/1659> Packaging

• MATERIALS OF CONSTRUCTION

• PACKAGING COMPONENT
  – Primary packaging component
  – Secondary packaging component
  – Tertiary packaging component
  – Ancillary component
  – Associated component

USP Chapter <659> Packaging System

The sum of packaging components and materials that together contain and protect the article. This includes Primary packaging components as well as Secondary and Tertiary packaging components when such components are required to provide additional protection.

• Child-resistant packaging
• Closure
• Container
• Equivalent container–closure system
• Non-reclosable packaging
• Reclosable packaging
• Restricted delivery system
• Senior-friendly packaging
• Tamper-evident packaging
• Tight container

Non-Injectable Packaging Systems

• Multiple-unit container: A Packaging system that permits withdrawal of successive portions of a non-injection article without changing the safety, strength, quality, or purity of the remaining portion (e.g., bottle of capsules, tablets, and oral or topical liquids).
• Single-unit container: A Packaging system that holds a quantity of a non-injection article intended for administration as a single dose and intended for use promptly after the packaging system is opened.
## Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

### Non-Injectable Packaging Systems

- **Unit-dose container**: A single-unit Packaging system for an article intended for administration by other than the parenteral route as a single dose.
- **Unit-of-use container**: A Packaging system that contains a specific quantity of an article that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. It is not permitted to repackaging Unit-of-Use containers for sale.

### Injection Packaging Systems

- Packaging for sterile products intended for injection must be validated as meeting the containment and protection requirements that are essential for maintaining the article's quality.
  - Refer to Sterile Product Packaging—Integrity Evaluation 1207 for further information regarding sterile product container closure integrity testing and validation.

### Associated Components

- **Dosing cup**: A measuring device consisting of a small cup that may be packaged with oral liquid articles.
- **Dosing spoon**: A measuring device consisting of a bowl and handle that may be packaged with oral liquid articles. The handle may be a graduated tube.
- **Medicine dropper**: A measuring device consisting of a transparent or translucent barrel or tube that is generally fitted with a collapsible bulb. It may be packaged with oral liquid articles.
- **Oral syringe**: A measuring device consisting of a plunger and barrel made of transparent or translucent plastic material and a seal on the end. It may be packaged with oral liquid articles. The syringe should deliver a measured amount of a liquid drug product.
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

Proposed USP Chapter <797>
Changes are coming!
Published Sept 25, 2015
Eric S. Kastango, M.B.A., B.S.Pharm., FASHP, Activity Chair
President and CEO
Clinical IQ, LLC and CriticalPoint, LLC
Madison, New Jersey

I am speaking in my individual capacity and not as a representative of any organization or committee regardless of my status, membership or affiliations with any entity.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of any other organization I may be associated with, nor should they be construed as an “official” explanation or interpretation of any USP chapter or any State Board of Pharmacy rule/law.

Scope of USP Chapter <797>
Compounded sterile preparations affected are:
• Injections
• Aqueous bronchial inhalations
• Baths and soaks for live organs and tissues
• Irrigation solutions for internal body cavities
  – Nasal/Sinus solutions do not have to be sterile, just clean (USP 795)
• Ophthalmics
• Implants
  – Pellets
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

Who does the chapter apply to?
- Applies to all persons who prepare compounded sterile preparation (CSPs)
- all places where CSPs are prepared
- pre-administration manipulations of CSPs including storage, compounding, and transport
- Does not apply to administration!
- Specific chapter language:
  - “shall” is a requirement (must)
  - “should” is a recommendation
- Note: 503b outsourcing sterile compounding facilities will be expected to comply with FDA cGMP regulations.

Mission of Chapter: To Prevent Harm
- Microbial contamination
- Excessive bacterial endotoxins
- Variability in intended strength that exceed monograph limits
- Use of ingredients of inappropriate quality
- Unintended physical and chemical contaminants

USP Chapter <797>
- Enforceable by the FDA and 28 State Boards of Pharmacy (more or less)
- Based on current scientific information and best sterile compounding practices
- Recognized as the national standard of practice
- Included in The Joint Commission (TJC) and other accreditation organization requirements only if their standards address sterile compounding
- Minimum practice and quality standards for compounding sterile preparations
- Published 11/2003
- Official 1/2004
- Revised released 12/2007
- Official 6/2008
- 9/2015
- Out for Public Comment

Photo: CBS News. Used with permission.

This is an image of the fungus growing from a sample taken from a patient’s spinal fluid.

Photo: CBS News. Used with permission.

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Abbreviations

- BUD = beyond-use dating
- CDC = Centers for Disease Control and Prevention
- CACI = containment aseptic compounding isolator
- CAI = compounding aseptic isolator
- CFU = colony-forming unit
- CSP = compounded sterile preparation
- GFS = gloved fingertip sampling
- HD = hazardous drugs
- ISO = International Standards Organization
- MDV = multiple dose vial
- MFT = media fill testing
- PEC = primary engineering control
- RABS = restricted access barrier system
- SDV = single-dose vial
- SOPs = standard operating procedures

Proposed USP Chapter <797>
Summary of Major Changes:

<table>
<thead>
<tr>
<th>Change</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 risk levels changed to 2 categories distinguished by conditions under which they are made and time within which used</td>
<td>Removal of HD handling section and cross-referenced to USP Chapter &lt;800&gt;</td>
</tr>
<tr>
<td>Quarterly requirement for Personnel Monitoring (visual observation of hand hygiene and garbing, MFT and ongoing GFS)</td>
<td>Quarterly requirement for Viable Air sampling and Surface sampling</td>
</tr>
<tr>
<td>BUD and Storage times changed with a maximum BUD of 45 days regardless of sterility testing</td>
<td>Introduction of “In-Use time” (time before which conventionally manufactured product or compounded dilution bag must be used after it is punctured)</td>
</tr>
<tr>
<td>Master formulation and compounding records will be required for all batch and nonsterile compounding</td>
<td>New guidance for sterility testing of CSP prepared in batch sizes of less than 40. (10% rule)</td>
</tr>
<tr>
<td>New placement requirements on use of isolators</td>
<td>Requirement for sterile gloves and sterile sleeves, sterile wipers and cleaning tools that need to be re-sterilized but not sterile disinfectants</td>
</tr>
</tbody>
</table>

Definitions and Practice Issues

- Current Chapter <797> rejects this statement “Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product’s manufacturer and other manufacturer directions consistent with that labeling” [21 USC 321 (k) and (m)].
- For one patient for immediate administration → a function of medication administration
  - This is fundamentally low-risk compounding.
- Batching → USP Chapter <797> applies
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

Briefing of Proposed Changes

• Reorganized, redundancies eliminated, and requirements clarified
• Minor editorial changes have been made to update the chapter to current USP style.
• Organized in a similar manner as 21 CFR Part 211 – US FDA CGMPs
• Key procedures placed in boxes for reference
• All sample documents and media procedures removed
• Hazardous Drug requirements referred to USP Chapter <800>
• Allergen extracts no longer given a carve-out
• Radiopharmaceuticals still need to comply with USP Chapter <797>
• Administration is still out of scope – defer to CDC guidance

Current BUD Paradigm

• Applied only to pre-administration activities (handling, compounding and storage)
  – Once CSP was administered, then USP Chapter <797> was no longer applicable
• Chemical stability must be assured during the use of the CSP
• Not capped: USP Chapter <71> Sterility Test passed has allowed BUD to chemical stability of the drug
  – Not Closure-Container Integrity Test required
• Current USP Chapter <797> is silent on the requirements for compounding multi-dose vials/containers
  – USP Chapter <51> Antimicrobial Effectiveness Test

New Proposed BUD Paradigm

• NEW DEFINITION: The date or time after which a CSP cannot be used and must be discarded
• The BUD is determined from the time the CSP is compounded.
  – One day is equivalent to 24 hours
• BUDs is capped to 42 days refrigerated
• Closure-Container Integrity Test required for frozen CSPs
• CSPs that are made as a MDV must undergo USP Chapter <51> Antimicrobial Effectiveness Testing
Flowchart of BUDs

Changes in BUDs are based on increasing the frequency of monitoring personnel and the environment

1. Aseptically-prepared or terminally-sterilized?
2. Sterility test performed?
3. Preservative added?
4. Only sterile components or any nonsterile component?
5. Storage temperature
   A. Controlled Room Temperature
   B. Refrigerator
   C. Freezer

Proposed USP Chapter <797>: Category 1 CSPs

<table>
<thead>
<tr>
<th>PEC placement</th>
<th>Sterility Testing</th>
<th>Endotoxin Testing</th>
<th>BUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not in ISO classified air</td>
<td>Not required</td>
<td>Not required</td>
<td>≤12 hours room temperature or ≤24 hours refrigerated</td>
</tr>
</tbody>
</table>

Proposed USP Chapter <797>: Storage for Category 2 CSPs

<table>
<thead>
<tr>
<th>BUD Assignment</th>
<th>Sterility Testing</th>
<th>Endotoxin Testing</th>
<th>Sterility Tested, Prepared CSPs</th>
<th>Refrigerated</th>
<th>Frozen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>Made from more than 1 non sterile component</td>
<td>4 days</td>
<td>7 days</td>
<td>46 days</td>
</tr>
<tr>
<td>4 days</td>
<td>9 days</td>
<td>Made with only sterile components</td>
<td>6 days</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Yes (USP &lt;51&gt;)</td>
<td>No</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (USP &lt;51&gt;)</td>
<td>No</td>
<td>42 days</td>
<td>42 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>14 days</td>
<td>28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (USP &lt;51&gt;)</td>
<td>No</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>28 days</td>
<td>42 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes (USP &lt;51&gt;)</td>
<td>42 days</td>
<td>45 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See enlargement, p. 68
In-Use Times

- The time before which a conventionally manufactured product used to make a CSP must be used after it has been opened or punctured, or a CSP must be used after it has been opened or punctured

### In-Use Times for Conventionally Manufactured Products and CSPs Opened, Stored, and Used for Sterile Compounding in ISO Class 5 or Better Air Quality

<table>
<thead>
<tr>
<th>Components</th>
<th>In-Use Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional sterile product</td>
<td></td>
</tr>
<tr>
<td>Ampul</td>
<td>The immediately after opening and passing through a sterile particulate filter</td>
</tr>
<tr>
<td>Pharmacy bulk package</td>
<td>As specified by the manufacturer</td>
</tr>
<tr>
<td>Single-dose container (e.g., bag, bottle, syringe, or vial)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Multiple-dose container</td>
<td>28 days, unless otherwise specified by the manufacturer</td>
</tr>
<tr>
<td>Compound single-dose container</td>
<td>6 hours</td>
</tr>
<tr>
<td>Compound stock solutions</td>
<td>6 hours</td>
</tr>
<tr>
<td>Compound multiple-dose container*</td>
<td>28 days, unless otherwise specified by the original compounding</td>
</tr>
</tbody>
</table>

*The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with USP Chapter <51> at the completion of the sterility test (if conducted) or at the time of preparation (if sterility testing is not performed). The test must be completed and the results obtained on the specific formulation before any of the CSP is released or dispensed. The test needs to be conducted only once on each formulation in the particular container–closure system in which it will be stored or released/dispensed.

See enlargement, p. 69

### In-Use Times for Conventionally Manufactured Products and CSPs Opened, and/or Stored in worse than ISO Class 5 Air

<table>
<thead>
<tr>
<th>Components</th>
<th>In-Use Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional sterile product</td>
<td></td>
</tr>
<tr>
<td>Ampul</td>
<td>Use immediately after opening and passing through a sterile particulate filter</td>
</tr>
<tr>
<td>Pharmacy bulk package</td>
<td>Not applicable. Contents of pharmacy bulk packages must be used only in an ISO Class 5 or better environment.</td>
</tr>
<tr>
<td>Single-dose container (e.g., bag, bottle, syringe, or vial)</td>
<td>Use for a single patient within the time specified by the manufacturer, or by the end of the case or procedure, whichever comes first. Discard remainder.</td>
</tr>
<tr>
<td>Multiple-dose container</td>
<td>28 days, unless otherwise specified by the manufacturer</td>
</tr>
<tr>
<td>Compound single-dose container</td>
<td>Use for a single patient immediately. Discard remainder.</td>
</tr>
<tr>
<td>Compound stock solutions</td>
<td>6 hours</td>
</tr>
<tr>
<td>Compound multiple-dose container*</td>
<td>28 days, unless otherwise specified by the original compounding</td>
</tr>
</tbody>
</table>

*Compounding or repackaging must not occur in worse than ISO Class 5 air.

See enlargement, p. 69
### Preparation of Dilutions: BUD Decision Tree* - General Example

![BUD Decision Tree Diagram]

*This example uses pooling however pooling is not always necessary.

---

### Core Personnel Competencies

- Training to establish the following competencies must be completed before compounding:
  - Hand hygiene and garbing
  - Cleaning and disinfection
  - Measuring and mixing
  - Aseptic manipulation
  - Proper clean room behavior
  - Methods of sterilization and depyrogenation
  - Use of compounding equipment
  - Documentation
  - Understanding air flow patterns
  - Proper use of primary engineering controls

---

### Personnel Garbing for Compounding

<table>
<thead>
<tr>
<th>CSP Category</th>
<th>PEC type</th>
<th>Minimum Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Any</td>
<td>• Non-cotton, low-lint, disposable gown or coveralls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low-lint, disposable covers for shoes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low-lint, disposable covers for head and facial hair that cover the ears and forehead</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sterile gloves and sterile sleeves</td>
</tr>
</tbody>
</table>

| Category 2   | Laminar airflow system (LAPS) and biological safety cabinet (BSC) | Non-cotton, low-lint, disposable gowns or coveralls                                   |
|              |                                                                 | Low-lint, disposable covers for shoes                                                |
|              |                                                                 | Low-lint, disposable covers for head and facial hair that cover the ears and forehead |
|              |                                                                 | Mask                                                                                  |
|              |                                                                 | Sterile gloves and sterile sleeves                                                   |
|              |                                                                 | Eye shield is optional                                                              |

| Category 2   | RABS (CAI or CACI) or isolator | Non-cotton, low-lint, disposable gowns or coveralls                                   |
|              |                                 | Low-lint, disposable covers for shoes                                                |
|              |                                 | Low-lint, disposable covers for head and facial hair that cover the ears and forehead |
|              |                                 | Mask                                                                                  |
|              |                                 | Sterile gloves                                                                        |

---

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Garbing changes/clarifications

- Remove all cosmetics because they shed flakes and particles
- Remove all hand, wrist, and other exposed jewelry or piercings (e.g., rings, watches, bracelets, earrings, and lip or eyebrow rings) that can interfere with the effectiveness of PPE (e.g., fit of gloves, cuffs of sleeves, and eye protection)
- Cover any jewelry that cannot be removed (e.g., surgically implanted jewelry) must be covered
- Ear buds, headphones, and cell phones, or other similar devices are not permitted in the cleanroom
- Dry hands and forearms with either low-lint disposable towels or wipes. No hand dryers mentioned.

Environmental Monitoring – Facility Related Metrics

<table>
<thead>
<tr>
<th>Test</th>
<th>Current</th>
<th>Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-viable air sampling</td>
<td>Every six months</td>
<td>Every six months</td>
</tr>
<tr>
<td>Viable air sampling</td>
<td>Every six months</td>
<td>Quarterly</td>
</tr>
<tr>
<td>Surface sampling</td>
<td>Periodic</td>
<td>Quarterly</td>
</tr>
</tbody>
</table>

Personnel Monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>Current</th>
<th>Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media fill</td>
<td>Annually if only low/medium risk compounded</td>
<td>Quarterly</td>
</tr>
<tr>
<td></td>
<td>Semiannually if high risk compounded</td>
<td></td>
</tr>
<tr>
<td>Failed test</td>
<td>Requalification</td>
<td>Any failed competency must be repeated 3 times prior to restarting</td>
</tr>
<tr>
<td>Gloved fingertip test (following initial test)</td>
<td>Annually if only low/medium risk compounded</td>
<td>Quarterly</td>
</tr>
<tr>
<td></td>
<td>Semiannually if high risk compounded</td>
<td></td>
</tr>
</tbody>
</table>
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### Action Levels for Surface Sampling

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Work Surfaces Sampled Using Contact Plates (CFU/plate)*</th>
<th>Work Surfaces Sampled Using Swabs (CFU/25 cm² or per sample)*</th>
<th>Non-work Surfaces Sampled Using Contact Plates (CFU/plate)*</th>
<th>Non-work Surfaces Sampled Using Swabs (CFU/25 cm² or per sample)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&gt;3</td>
<td>&gt;3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>8</td>
<td>&gt;25</td>
<td>&gt;25</td>
<td>&gt;50</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

*Work surfaces are those surfaces that are in direct contact with materials used in compounding. These action levels are based on the expectation that materials will be disinfected before introduction to an ISO Class 5 area.

*Non-work surfaces are those surfaces that do not come into direct contact with materials used in compounding.

* are considered work surfaces

### Primary Engineering Controls

- Laminar Air Flow Systems (LAFS)
  - Laminar Air Flow Workbenches
  - Laminar Air Flow zones
  - Biological Safety Cabinets (BSC)
- Restricted Access Barrier System (RABS)
  - Compounding aseptic isolator (CAI)
  - Compounding aseptic containment isolator (CACI)
- Isolators
  - Transfer ports
  - Use sporicidal chemical decontamination
  - Constant overpressure requirement

### Secondary Engineering Controls

- Segregated Compounding Area (SCA)
- Positive pressure buffer room with access through a positive pressure anteroom

To meet Category 2, **any** PEC must be located in an ISO Class 7 area

*The use of displacement airflow is NOT permitted*
Facility Design Requirements

- The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in a classified area or in a segregated compounding area must be smooth, impervious, free from cracks and crevices, and non-shedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants can accumulate.
- The buffer area or area inside the perimeter of a segregated compounding area cannot contain water sources (e.g., sinks) or floor drains.

Facility Design Requirements

- The room temperature must be maintained at 20 degrees C or cooler and a humidity below 60% at all times.
  - Temperature and humidity must be controlled through an efficient heating, ventilation, and air conditioning (HVAC) system rather than through use of humidifiers and dehumidifiers, which can contain standing water that can contribute to microbial contamination.

Storage conditions

- Storage under frozen conditions places the container–closure under physical stress, and the degree of stress may depend on the formulation and other factors. Therefore, if a Category 2 CSP is to be stored in a freezer, the integrity of the CSP in the particular container–closure system in which it will be stored must have been demonstrated for 45 days at frozen storage.
- A container–closure integrity test needs to be conducted only once on each formulation and fill volume in the particular container–closure system in which it will be stored or released/dispensed. Once the CSP is thawed, the CSP must not be re-frozen.
SOPs and Master Formulation and Compounding Records

- A Master Formulation Record is required when CSPs are prepared in a batch for multiple patients or when CSPs are prepared from nonsterile ingredients.
- Compounding Record is required for every CSP prepared and requires documentation by all individuals involved in the actual preparation of the CSP.

Urgent-Use CSPs (replaces immediate-use)

- A CSP may be prepared in worse than International Organization for Standardization (ISO) Class 5 air quality (see 4.1 Protection from Airborne Contaminants) in rare circumstances when a CSP is needed urgently (e.g., cardiopulmonary resuscitation) for a single patient, and preparation of the CSP under conditions described for Category 1 or Category 2 would subject the patient to additional risk due to delays in therapy.
- In these circumstances, the compounding procedure must be a continuous process not to exceed 1 hour, and administration of the CSP must begin immediately upon completion of preparation of the CSP.
- Aseptic technique must be followed during preparation, and procedures must be in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other CSPs.

Technology advances

- The statement in the current chapter has been removed:
  - “The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein.”
  - No reference to Rapid Microbiological Methods as an alternative to USP Chapter <71>
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How to Provide Comments to USP

- Go to www.USP.org and search for USP Chapter <797>
- Download the proposed revisions
- Comments must be submitted on Comment Submission Template by email to compoundingsl@usp.org by January 31, 2016
  - Be sure to include line numbers for your comments
- If you have any questions, contact the Healthcare Quality Standards team at Compoundingsl@usp.org

USP Chapter <800>:
Start Preparing Now

Patricia C. Kienle, B.S.Pharm., M.P.A., FASHP
Director, Accreditation and Medication Safety
Cardinal Health Innovative Delivery Solutions
Laflin, Pennsylvania

Patricia Kienle is a member of the USP Compounding Expert Committee, but is not speaking as a representative of USP
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**USP Chapter <800> Hazardous Drugs Handling in Healthcare Setting**
- Status of USP Chapter <800>
  - Federal enforceable standard
- Applicable to all healthcare settings
- All healthcare personnel must comply

**Priority Steps to Prepare**
- Hazardous drug list
- Assessment of risk
- Personnel training
- Personal protective equipment
- Facilities
- Decontaminating and cleaning
- Environmental monitoring

**Hazardous Drug List**
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NIOSH List of Hazardous Drugs

• Sorted into three tables
  – Antineoplastic
  – Non-antineoplastic
  – Reproductive-only hazards
• Identify the drugs and dosage forms you handle

Your List

• Active pharmaceutical ingredient (API) of any hazardous drug (HD) on the list
• Antineoplastics that require manipulation
• Antineoplastics that only require counting or packaging
• Non-antineoplastics and reproductive-only hazards

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**HDs Outside of Pharmacy**
- Look at all areas of your health system
  - Oncology clinics
  - Psychiatry clinics
  - Physician offices
    - OB/GYN
    - Urology
    - Dermatology
    - Podiatry

**Assessment of Risk**

**Handling Hazardous Drugs**

**Default**
- Handle all HD with all the precautions listed in USP Chapter <800>
- Must include all API and all antineoplastics that require any manipulation

**Option**
- May perform an Assessment of Risk for selected dosage forms of HDs that are not antineoplastics and need to be manipulated

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Your Assessment of Risk

- Might include antineoplastics that need no manipulation, such as
  - Methotrexate tablets
  - Conventionally-manufactured HD cream
- Might include dosage forms of drugs on the list of non-antineoplastics
- Might include dosage forms of drugs on the list of reproductive-only hazards

Potential Exposure

- Receipt
- Preparing
- Administration
- Transport
- Spills
- Waste

Facility
Personnel
Environmental Monitoring
PPE
HD List

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Elements of Assessment of Risk

• Drug
• Dosage form
• Risk of exposure
• Packaging
• Manipulation

Your Assessment of Risk

• Identify the potential personnel risk of all dosage forms of all agents on the NIOSH list that you intend to exempt from any portion of USP Chapter <800>

Personnel Training
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Acknowledgement of Risk

- Occupational Safety and Health Administration (OSHA) requires that employees are aware of risks at their worksite
- Employers are responsible for providing appropriate protection for their employees
- “Personnel of reproductive capability shall confirm in writing that they understand the risks of handling hazardous drugs.”
  - Current USP Chapter <797>

Personnel Training

- Compounding standards
  - USP Chapter <795>, USP Chapter <797>, USP Chapter <800>
- Professional guidance documents
  - American Society of Health-System Pharmacists
  - NIOSH
  - Joint Position Statement from Oncology Nursing Society (ONS), American Society of Clinical Oncology (ASCO), and Hematology/Oncology Pharmacy Association (HOPA)
- Competence documentation

Personal Protective Equipment

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**Personal Protective Equipment (PPE)**
- Provided
- Used
- Disposable PPE must not be re-used
- Non-disposable PPE must be properly decontaminated and cleaned
- NIOSH 2014 HD list includes table of PPE based on formulation of the HD and the activity performed

**PPE**
- Gloves must be tested to ASTM D6978
- Gowns must be disposable, resist permeability, close in the back (no open front)
- Two pairs of booties are required in the HD preparation area
  - Outer pair removed when exit the HD area

**Closed System Drug-Transfer Devices**
- CSTDs are supplemental engineering controls
- Recommended for use during compounding
- Required for use during administering

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Facilities

Facilities for Handling HDs

• Receiving
• Storage
• Compounding

Receiving

• Normal/neutral pressure or negative pressure
  – Not positive pressure
• Should be able to identify HD contents from the outside of the container
• Availability of chemo gloves and spill kit
• Document competence
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Storage and Compounding Minimum Requirements

- Separate room
  - Separate from non-hazardous drugs
- Fixed walls
- Negative pressure
- Vented to the outside
- Appropriate number of air changes per hour

Storage

- Negative pressure
  - Unless entity exempt dosage form
- Can store antineoplastics in your negative pressure cleanroom
  - No external shipping containers
  - No corrugated cardboard
  - Requires wiping down items prior to storage

Compounding

- All compounding must be done in negative pressure
  - Unless entity exempt dosage form
- USP Chapter <797> compliant negative pressure cleanroom with positive pressure anteroom = USP Chapter <800> compliance
- USP Chapter <800> removes the “low use” exemption
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Two Options for Sterile Compounding

- BSC/CACI in negative pressure cleanroom served by positive pressure anteroom
- Containment Segregated Compounding Area with a Biological Safety Cabinet (BSC) or Compounding Aseptic Containment Isolator (CACI)
  - Not required to be ISO 7
  - Limited to 12 hour beyond-use date
  - Not currently permitted in USP Chapter <797>

Nonsterile Compounding

- Manipulation of nonsterile HDs requires the same containment practices as with sterile HDs
- Routine nonsterile HD compounding
  - Containment Ventilated Enclosure ("powder hood")
- Occasional nonsterile HD compounding
  - May use existing BSC/CACI with precautions listed in USP Chapter <800>

Decontamination and Cleaning
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

Decontamination and Cleaning

- Surfaces potentially contaminated with HDs must be decontaminated prior to cleaning and disinfecting
- Use a properly-diluted EPA-approved oxidizer designed for use with HDs

Environmental Monitoring

Environmental Monitoring (EM)

- USP Chapter <797> addresses EM for microbial contamination
- USP Chapter <800> recommends wipe samples to detect rogue HD contamination
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

How close to USP Chapter <800> compliance are you?

- Less than 50%
- 50-90%
- Better than 90%

Prepare Now

- HD list
- Assessment of risk
- Personnel training
- PPE
- CSTDs
- Facility issues
- Decontamination and cleaning
- Environmental monitoring

Resources ...

- USP Compounding Compendium, 2015
  - USP Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations
  - USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations
  - Proposed USP Chapter <800> Hazardous Drugs – Handling in Healthcare Settings
- ASHP Guidelines on Handling Hazardous Drugs
Moving Targets: An Update on Legislation and Standards Aimed at Ensuring the Quality of Pharmaceutical and Compounded Drug Products in the U.S.

... Resources

- NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings, 2004
- NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2014
- ONS/ASCO/HOPA Joint Position Statement: Ensuring Healthcare Worker Safety When Handling Hazardous Drugs
  - [www.ons.org/advocacy-policy/positions/practice/hazardous-drugs](www.ons.org/advocacy-policy/positions/practice/hazardous-drugs)

Discussion Questions

USP Chapter <797>
- What are the three major items on your compliance readiness plan for the proposed revisions to USP Chapter <797>?
- How are you going to comply with these changes assuming that they are not changed or removed from the final version of the chapter?

USP Chapter <800>
- How are you planning on handling non-antineoplastic and reproductive-only hazardous drugs?
- What is the best way to evaluate and implement use of closed system drug-transfer devices for administration of hazardous drugs?
## DSCSA Implementation Plan 2015-2023

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Develop regulations on licensing standards for 3PLs and wholesalers; stakeholder implementation through 2017-2018</td>
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</tr>
<tr>
<td>Publish guidance on grandfathering product and processes for waivers, exceptions, exemptions; Stakeholder implementation through mid-2017</td>
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</tr>
<tr>
<td>Establish ≥1 stakeholder pilots to evaluate methods to enhance the safety and security of supply chain</td>
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<tr>
<td>Conduct at least five public meetings</td>
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<tr>
<td>Conduct technology and software assessment for feasibility of small dispenser tracing at package level</td>
<td></td>
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</tr>
<tr>
<td>Develop regulations- enhanced drug distribution security system for interoperable electronic tracing at package level, FDA 2017–2021; stakeholders 2021–2023</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publish final guidance on secure package-level tracing; FDA implementation 2018 – 2022; stakeholders 2022 – 2023</td>
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<td></td>
</tr>
<tr>
<td>▪ System attributes to enable and standards for interoperable data exchange enhancement</td>
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</tr>
</tbody>
</table>

http://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/ucm382022.htm

## TI/TH/TS (T3) In A Single Document

![TI/TH/TS Diagram](image-url)

- **TI** (Transparency of Information)
- **TH** (Transparency of History)
- **TS** (Transparency of Security)

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## Sample DSCSA Transaction Documentation

<table>
<thead>
<tr>
<th>Data Field Name</th>
<th>Sample Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>20140428 Date of Transaction</td>
<td>20140430 Date of Shipment (required if more than 24 hours after the date of the transaction)</td>
</tr>
<tr>
<td>CATLINE PHARMACY 423 OAK STREET CHICAGO IL 60614</td>
<td>Name &amp; Address – Buyer</td>
</tr>
<tr>
<td>BRICK PHARMACEUTICAL 1 BAKER BLVD AURORA IL 60625</td>
<td>Name &amp; Address – Seller</td>
</tr>
<tr>
<td>Seller has complied with each applicable subsection of FDCA Sec. 581(27)(A)–(G)</td>
<td>Transaction Statement (TS); HDMA</td>
</tr>
<tr>
<td>As indicated below, product was purchased directly from the manufacturer, manufacturer’s exclusive distributor or repackager who purchased directly from a manufacturer</td>
<td>Direct Purchase Statement (DPS)</td>
</tr>
<tr>
<td>09999166272 123456 National Drug Code &amp; Lot Number (Lot is only required from manufacturer; when selling product originally bought directly from the manufacturer, the wholesaler may omit lot numbers, initial transaction date, initial shipment date from the manufacturer)</td>
<td></td>
</tr>
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<td></td>
</tr>
</tbody>
</table>

For Drop-Shipments, the wholesaler is exempt from providing the Ti, TH, TS to the dispenser if provided by the party conducting the drop-shipment on behalf of wholesaler, and Ti and TH contain the contact information for the wholesaler.

---

## Keep up with Evolving DSCSA Requirements

[Diagram showing the flow of information and compliance with DSCSA requirements.]

---

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### Sample – ASN Transaction

This is 1 EDI transaction for 72 Each(s). In the serialized future, there will be 72 of these transactions...one for each serial number...

<table>
<thead>
<tr>
<th>Data Field Name</th>
<th>Data Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Transaction</td>
<td>20140430</td>
</tr>
</tbody>
</table>

Example Data from "HDMA Electronic Data Interchange (EDI) Guidelines for the 856 Advance Ship Notice to Support Implementation of DSCSA", Dec 2014

### Proposed USP Chapter <797>: Storage for Category 2 CSPs

<table>
<thead>
<tr>
<th>PEC Placement</th>
<th>Sterility Testing</th>
<th>Endotoxin Testing</th>
<th>Storage</th>
<th>BUD Assignment Method</th>
<th>Preservative Added</th>
<th>Controlled Room</th>
<th>Refrigerated</th>
<th>Frozen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placed in ISO classified air</td>
<td>Based on BUD Assignment below</td>
<td>Required if nonsterile components</td>
<td>&gt;12 hour room temperature or &gt;24 hours refrigerated</td>
<td>Aseptically Prepared CSPs</td>
<td>No</td>
<td>Made from more than 1 non sterile component</td>
<td>4 days</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Terminally Sterilized CSPs</td>
<td>Yes (USP &lt;51&gt;)</td>
<td>28 days</td>
<td>42 days</td>
<td>45 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (USP &lt;51&gt;)</td>
<td>42 days</td>
<td>42 days</td>
<td>45 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>45 days</td>
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</tbody>
</table>

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### In-Use Times For Conventionally Manufactured Products and CSPs Opened, Stored, and Used for Sterile Compounding in ISO Class 5 or Better Air Quality

<table>
<thead>
<tr>
<th>Components</th>
<th>In-Use Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventionally Manufactured Sterile Product</strong></td>
<td></td>
</tr>
<tr>
<td>Ampuls</td>
<td>Use immediately after opening and passing through a sterile particulate filter</td>
</tr>
<tr>
<td>Pharmacy Bulk Package</td>
<td>As specified by the manufacturer</td>
</tr>
<tr>
<td>Single-dose container (e.g., bag, bottle, syringe, or vial)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Multiple-dose container</td>
<td>28 days, unless otherwise specified by the manufacturer</td>
</tr>
<tr>
<td><strong>CSP</strong></td>
<td></td>
</tr>
<tr>
<td>Compounded single-dose container</td>
<td>6 hours</td>
</tr>
<tr>
<td>Compounded stock solutions</td>
<td>6 hours</td>
</tr>
<tr>
<td>Compounded multiple-dose container*</td>
<td>28 days, unless otherwise specified by the manufacturer</td>
</tr>
</tbody>
</table>

*The particular CSP formulation must pass antimicrobial effectiveness testing in accordance with USP Chapter <51> at the completion of the sterility test (if conducted) or at the time of preparation (if sterility testing is not performed). The test must be completed and the results obtained on the specific formulation before any of the CSP is released or dispensed. The test needs to be conducted only once on each formulation in the particular container–closure system in which it will be stored or released/dispensed.

### In-Use Times for Conventionally Manufactured Products and CSPs Opened, and/or Stored in worse than ISO Class 5 Air

<table>
<thead>
<tr>
<th>Components</th>
<th>In-Use Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventionally Manufactured Sterile Product</strong></td>
<td></td>
</tr>
<tr>
<td>Ampuls</td>
<td>Use immediately after opening and passing through a sterile particulate filter</td>
</tr>
<tr>
<td>Pharmacy Bulk Package</td>
<td>Not applicable. Contents of pharmacy bulk packages must be used only in an ISO Class 5 or better environment</td>
</tr>
<tr>
<td>Single-dose container (e.g., bag, bottle, syringe, or vial)</td>
<td>Use for a single patient within the time specified by the manufacturer, or by the end of the case or procedure, whichever comes first. Discard remainder.</td>
</tr>
<tr>
<td>Multiple-dose container</td>
<td>28 days, unless otherwise specified by the manufacturer</td>
</tr>
<tr>
<td><strong>CSP</strong></td>
<td></td>
</tr>
<tr>
<td>Compounded single-dose container</td>
<td>Use for a single patient immediately. Discard remainder.</td>
</tr>
<tr>
<td>Compounded stock solutions</td>
<td>6 hours</td>
</tr>
<tr>
<td>Compounded multiple-dose container*</td>
<td>28 days, unless otherwise specified by the original compounding</td>
</tr>
</tbody>
</table>

*Compounding or repackaging must not occur in worse than ISO Class 5 air.
Self-assessment Questions

1. What does federal law allow outsourcing facilities (OFs) to do under section 503B, that isn’t permitted for compounding pharmacies?
   - OFs may compound copies of commercially available products, but must submit to FDA inspections and oversight.
   - OFs may compound drugs without prescriptions, but must meet good manufacturing practice quality standards.
   - OFs may compound drugs without prescriptions, but must go through FDA drug approvals.
   - OFs may compound drugs using any bulk active ingredient, but must meet good manufacturing practice quality standards.

2. What are the Drug Supply Chain Security Act 2015 requirements for receiving and storing transaction data?
   - Beginning May 1, 2015 a dispenser shall not accept ownership of a product unless provided the TI, TH, and TS.
   - TI include product name, strength, dosage form, NDC, container size, number of containers, and business name/address of the person from and to whom ownership is being transferred; lot and initial transaction date or shipment date are included with exceptions.
   - Utilizing a secure electronic database developed or operated by another entity satisfies the requirement for storing DSCSA transaction data and with a written agreement can relieve all DSCSA trading partner obligations.
   - In all cases, there must be an indication that the entity, or an affiliate, purchased the product directly from the manufacturer, exclusive distributor or repackager that purchased the product directly from the manufacturer.

3. In proposed revisions to USP Chapter <797>, the chapter will require use of which of the following:
   - Sterile gloves and nonsterile wipers.
   - Sterile gloves and sterile wipers.
   - Nonsterile gloves and nonsterile wipers.
   - Nonsterile gloves and sterile wipers.

4. The NIOSH list of Hazardous Drugs is sorted into which three categories?
   - Parenteral, oral, topical hazardous drugs.
   - Antineoplastic, psychiatric, monoclonal antibodies.
   - Trace, hazardous materials, pharmaceutical hazardous drugs.
   - Antineoplastic, non-antineoplastic, reproductive-only hazards.

Answers

1. b  
2. b  
3. b  
4. d

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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 submit.

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 6, 2015 | Code: | CE Hours: | 3.0 |

NEED HELP? Contact eLearning@ashp.org

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