USP Chapter <797>
Update on Recent Revisions

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NABP Annual Meeting
Tuesday, May 20, 2008
Members of the SCC Committee

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USP Advisory Groups that Assisted the Committee

- Infection Control Advisory Committee
- Radiopharmaceutical Advisory Committee
- Allergen Extract Working Group
- Compounding Isolator Industry Round Table
- Food and Drug Administration
At the end of this presentation, participants will learn the following:

- Meaning of official date
- What and who Chapter 797 applies to
- Sections in Chapter 797 that are revised and new
- The different compounded sterile preparations (CSP) risk categories
- The specialty categories
- Environmental control sections
- Environmental sampling
- Personnel Training and Evaluation
• Updates on Chapter 797
  ➢ Historical overview of events from the proposed revisions to the finalized chapter

• Overview of changes as published on USP Website
  ➢ www.usp.org
Historical Perspective

- Current official chapter (released in 2004) was revised and proposed revisions posted on USP website (May 2006)
- Pre-Commentary Phase: May 1 – May 15, 2006
- Commentary Phase – May 15-August 15, 2006
- Post Commentary Phase: August 16 to date
- More than 500 comments received
- Committee’s first meeting during Post Commentary period November 2006
- Series of bi-weekly conference call meetings set up to address the volume of comments received.
Revisions and New

- Introduction (revised)
- Definitions section (new)
- Immediate-Use category (new)
- Low-Risk Level with 12-hour BUD (new)
- Single & multiple-dose containers (new)
- Proprietary vial/bag systems (new)
Revisions and New since 2004

- Filter integrity testing for High Risk Level compounding (new)
- Microbiological BUD (revised)
- Personnel training and evaluation (revised)
- Personnel cleansing, garbing, gloving (revised)
- Cleaning and Disinfecting the Compounding Area (revised)
- Environmental Quality and Control (revised)
Revisions and New since 2004

- Primary engineering controls (revised)
- Secondary engineering controls (revised)
- Testing and certification of engineering controls (revised)
- Appendices (new)
- Abbreviation and Acronyms (new)
- The Committee clarified language throughout the chapter
Special case or Specialty CSPs and other sections addressed:

- Allergen Extracts
- Hazardous Drugs
- Radiopharmaceuticals
- Multi-Dose and Single-Dose Vials
- Proprietary vial/bag systems
• The official date is June 1, 2008

• The current chapter <797> in USP 31/NF26, released November, 2007 will no longer be the official (current) standard beginning June 1, 2008

• The chapter is on the USP website now and will appear in the second supplement of USP 31/NF26 and in the *Pharmacists’ Pharmacopeia*
• Applies to pre-administration manipulations of compounded sterile preparations including compounding, transportation, and storage.

• Applies to all compounding personnel without distinction as to site or profession – all patients deserve to be protected from errors and contamination
• A Completely revised chapter which is more explicit with major differences between the currently official 2004 chapter

• Notes that **direct contact** is the principal source of contamination in CSPs

• Alternative technologies **are** superior or equivalent

• Chapter <797> applies to CSPs given via application, implantation, inhalation, injection, insertion, instillation, and irrigation
To describe conditions and practices that will help prevent harm, including death, to patients that could result from the following conditions:

- **Microbial contamination (nonsterility)**
- **Excessive bacterial endotoxins**
- **Variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles**
- **Unintended chemical and physical contaminants**
- **Ingredients of inappropriate quality in compounded sterile preparations (CSPs).**
Provides *minimum* practice and quality standards for compounded sterile preparations of drugs and nutrients based on current scientific information and best sterile compounding practices.
• Chapter <797> encourages the use of technology other than those described in the chapter...

“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…”

• Situations where the techniques is advanced and produces best practices is encouraged
There are 29 defined key terms listed in <797> that require consistent usage.

- Some terms are either new or revised.
- Some terms may be new to pharmacists or may not be used consistently.
- Some terms may be for a specific usage within <797>.
Examples of revised or new definitions include:

- Ante area
- Beyond-Use Date
- Buffer Area
- Compounding Aseptic Isolator (CAI)
- Compounding Aseptic Containment Isolator (CACI)
  
  *(This is introduced in the Hazardous drug section – It is a form of isolator that protects personnel from exposure to hazardous drugs while preparing sterile preparations)*

- Critical sites
- Unidirectional flow
- First air
- Direct Compounding Area (DCA)
- Segregated Compounding Area
- Labeling
The DCA is only the portion of the Primary Engineering Control dedicated to the task of Aseptic manipulation.

*Key terms- Primary Engineering Controls  Secondary Engineering Controls
Fourteen areas of responsibility are cited:

- Emphasis on training and education
- Emphasis on compounding accuracy
- Emphasis on avoiding contamination
- Emphasis on patient safety
CSP Risk Categories

- Immediate Use CSPs
- Low-Risk Level
- Low-Risk Level w/12 hour or less Beyond Use Date (BUD)— a subsection of Low Risk Level
- Medium-Risk Level
- High-Risk Level
• Responsibility of the compounding personnel ... think about the risk

• No single rule to determination

• Requires professional judgment

• General descriptive statements to aid compounding personnel

• Study criteria for each risk level... no prescriptive way. For example, Reconstitution of sterile powder before injection versus TPN. Which is the risk level?

• Exception: When non-sterile raw materials are used in compounding this will always create High-Risk Level category
  ➢ Putting sterile products into a non-sterile container also qualifies as high-risk level
Immediate-Use Category

- Exempt from all requirements in <797>
- Only simple aseptic measuring and transfer are needed
- NMT 3 sterile non-hazardous drugs
- NMT 2 entries in one container
- No delays/interruptions
- No contact contamination of ingredients or critical sites
- Important: STUDY THE CRITERIA FOR EACH CATEGORY!!!
Immediate-Use Category

- Dose must be labeled if not administered by the preparer
- Administration must begin within 1 hour after the start of preparation
- Dose must be discarded if administration has not begun within 1 hour after the start of preparation
  (No storing. No recycling.)
Immediate-Use Category

Some Examples:

- At a patient’s bedside
- In an ambulance
- In an ER
- In a war zone
- In a code situation
Intended to accommodate facilities/satellite pharmacies compounding *only* low risk level Compounded Sterile Preparations in environments where the primary engineering controls cannot be located within an ISO Class 7, Clean Room or buffer area. There are specific conditions that have to be met, which include the following:

“The CSPs must be prepared pursuant to a physician’s order for a specific patient, and administration of the CSP must commence within 12 hours of preparation, or as recommended by the manufacturer, whichever is earlier”
Low-Risk Level w/12 hour BUD

- Low-Risk Level remains nearly the same
- New subsection for an ISO 5 device in an uncontrolled air environment
- The primary engineering control must be in a segregated compounding area not in a high traffic area
- All personnel cleansing and garbing requirements apply
- **No Hazardous Drugs**
- Administration must begin within 12 hours or as stated in the package insert, whichever is less
Personnel preparing the CSP must follow the requirements in the

- **Personnel Cleansing and Garbing and Additional Personnel Requirement sections**

....among other sections, listed in the chapter.
<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Room Temp</th>
<th>Refrigerator</th>
<th>Freezer (-25°C and -10°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Use</td>
<td>1 hour</td>
<td>1 hour</td>
<td>N/A</td>
</tr>
<tr>
<td>Low</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Low w/ 12-hr BUD</td>
<td>12 hours or less</td>
<td>12 hours or less</td>
<td>N/A</td>
</tr>
<tr>
<td>Medium</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>
Definitions of Single Dose Vial (SDV) and Multiple Dose Vial (MDV) are in the USP General Notices and Requirements.

**SDVs** – Opened or punctured in ISO 5 environment may be used for up to 6 hours. Opened or punctured in worse than ISO 5 must be used within 1 hour or discarded.

Single dose ampuls MUST be discarded and not stored for any time period.
• **Multiple dose vials** – Contain antimicrobial preservative(s)

• Designed for entry on multiple occasions. BUD – 28 days after initial entry *unless specified otherwise by the manufacturer*

• BUD of 28 days based on USP <51> Antimicrobial Preservative Testing
Proprietary Bag/Vial Systems

- ADD-Vantage; Add-a-Vial, Minibag Plus, etc.
- Follow the manufacturer’s instructions for handling and storing
- These systems and their instructions have been approved by the FDA
Hazardous Drugs

- Hazardous drugs are defined in the definition section
- This hazardous drug section describes the conditions under which Hazardous Drugs can be prepared to concurrently protect compounding personnel from exposure, and patients from microbial and particulate contamination
Hazardous Drugs as CSPs

- Choosing the appropriate Primary Engineering Control

- Class II Type B2
- Class II Type B1
- Class II Type A2
- CACI

NIOSH alert recommends ECs that do not recirculate for use with hazardous drugs that volatilize at room temperature. Consider all repercussions prior to determining best EC for your application

Letter from Ken Mead (NIOSH)
Hazardous Drugs

- Section extensively revised
- Brought into concert with NIOSH Guidelines
- BSC or CACI vented to the outside recommended (optimally should)
- Must be located in separate negative pressure ISO Class 7 with ISO Class 7 ante area
- Low-volume HDs doses exempted (a limit of 5 per week was indicated in the proposed revision)
• Personnel protection specified

• Use of closed-system transfer devices must be within BSC or CACI, only in an ISO class 5 environment

• Disposal according to state and federal regulations

• Consistent with NIOSH guidelines
• PET drugs according to USP <823>

• Any further manipulation of PET drugs is considered compounding and must comply with USP <797>

• Low-Risk Level if 100 mL or less for single dose or 30 mL or less for multiple dose (Technetium-99m/Molybdenum 99 generator eluates)

• Must be prepared in an ISO 5 containment device in an ISO 8 environment or cleaner

• Principals of ALARA followed at all times (As Low As Reasonably Achievable) for personnel exposure minimization
Radiopharmaceuticals

Major addition- allowance for the preparation of radiopharmaceuticals under the Low-Risk Level Compounded Sterile Preparations with 12 hour or less Beyond Use Dates
The chapter now has three sections applicable to radiopharmaceuticals:

- Low-Risk Level Compounded Sterile Preparations with 12 hour or less Beyond Use Dates
- Immediate Use Compounded Sterile preparations
- Radiopharmaceuticals as Compounded Sterile Preparations
• Collaboration with AAOA/JCAAI

• Research and discussions with experts in the field

• Results of a peer-reviewed research study of 26,795 injections (>98/patient) with no infections

• Done in an uncontrolled environment
• Intradermal and subcutaneous MDVs and SDVs (No IV or IM)

• Unpreserved allergen extracts must fully comply with all aspects of chapter <797>

• Allergen extracts are exempt from personnel, environment, and storage requirements only IF all of the following criteria are met:
Allergen Extracts

- Personnel perform hand hygiene with alcohol-based surgical hand scrub
- Hair and beard covers, gown, face mask, and sterile gloves are used
- Compounded by simple aseptic transfer
- Must contain an effective amount of antimicrobial preservative
- For a single patient only
• Gloves are intermittently disinfected with sterile 70% IPA

• Vial stoppers and ampul necks are disinfected with sterile 70% IPA

• Direct contact contamination is avoided

• Allergen extract is labeled with a patient name and BUD
Cleaning and Disinfecting Facilities

- Designed to reduce bioburden in compounding areas
- Use of disinfecting agent such as sterile 70% IPA
- Performed in ISO 5 environment:
  - At the beginning of each work shift
  - At the beginning of each batch
  - At least every 30 minutes
  - Surface contamination is known or suspected
Cleaning and Disinfecting Facilities

- Cleaning should proceed from buffer area (cleanroom) to ante area (cleanest to dirtiest)
- Use suitable dedicated mops and disinfecting cleaners
- Floors, counters, work surfaces – at least daily
- Walls, ceilings, shelving – at least monthly
Personnel Cleansing and Garbing

- Remove outer garments and jewelry (including piercings above the neck)

- Recently, there have been questions about iPod earbuds and Bluetooth headsets. These are not directly mentioned in the chapter, but fall in the same category as earrings etc

- Garb order from dirtiest to cleanest

- Don shoe covers, hair covers, beard covers (any facial hair) and face masks (any order is acceptable)

- Perform hand/arm hygiene

- Don disposable gowns
Dressing Properly

- Shoe covers
- Head and facial hair covers
- Face masks
- Sterile gloves
- Non-shedding gowns
- No makeup
- No externally visible piercings
- No long fingernails or artificial nails
Hair and Jewelry DO Matter!*

* Blood agar cultures courtesy of Francis P. Mitrano, MS, RPh, Director of Pharmacy, Beth Israel Deaconess Medical Center, Boston, MA, November, 2005.
But I was just talking*

* Photo courtesy of Francis P. Mitrano, MS, RPh, Director of Pharmacy, Beth Israel Deaconess Medical Center, Boston, MA, November, 2005.
Personnel Cleansing and Garbing

- Inside the clean area, cleanse hands and arms with alcohol-based surgical hand scrub with persistent activity

- Don sterile powder-free gloves compatible with sterile 70% IPA

- Repeatedly apply sterile 70% IPA to contact areas of gloves whenever nonsterile surfaces are touched (e.g., vials, counter tops, carts)
Hand hygiene\(^1\) is paramount to safety, as this agar imprint of an unwashed hand shows\(^2\)

Personnel Cleansing and Garbing

- All of the cleansing, garbing and gloving requirements also apply to compounding in CAIs and CACIs

- Exception: If the manufacturer of the CAI or CACI provides written documentation of statistically validated testing supporting any garbing component(s) that are not required

- The use of sterile gloves is required when working with an isolator
## Garbing requirements

<table>
<thead>
<tr>
<th>Garb requirement</th>
<th>Immediate -use</th>
<th>Low Risk (12 hr)</th>
<th>Med Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makeup/Jewelry restrictions</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Hand washing</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Hair/facial cover</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Shoe covers</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Low-shed gown</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Sterile Gloves</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Masks</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
• Aimed at creating ISO 5, 7, and 8 environments

• ISO 5 – LAFW, BSC, CAI, CACI are “Primary Engineering Controls”

• Unidirectional airflow for exposure of critical sites is required

• Must maintain ISO 5 during dynamic (in use) working conditions
Environmental Controls

- ISO 7 buffer area and ISO 8 ante area – are “Secondary engineering controls”
- They utilize HEPA filtered air sources
- Must maintain ISO 7 or 8 during dynamic (in use) working conditions
- Minimum 30 air changes per hour of HEPA filtered air (15 ACPH with a recirculating ISO 5 device)
- Airflow and balance testing required at the installation site
Environmental Controls

- ISO 5 Primary engineering control (LAFW, BSC, CAI, CACI) to be in an ISO 7 environment
- Exception: CAI if its design provides ISO 5 and isolation from the room during dynamic operating conditions as placed at your site (including transferring materials in and out) when tested by CETA Guidelines
- Only personnel and materials essential for compounding and cleaning are permitted
While the content of Chapter <797> was expanded in the Environmental Control section, the previous section on *Environmental Monitoring* was deleted.

Two subsections from the Environmental Monitoring section were added to this section. These are:

- Viable and Nonviable Environmental Sampling
- Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices, and Cleaning and Disinfection Procedures
Environmental Sampling

- Designed to demonstrate that the primary and secondary engineering controls, disinfecting procedures, and work practices result in a suitable environment for aseptic compounding

- Utilizes several approaches to assess and evaluate
Environmental Sampling

- Electronic measurement of the total number of airborne particles
- Certification of the ISO 5, 7, and 8 environments every 6 months and when moved
- Count the number of airborne viable microorganisms using volumetric air sampling
- Evaluation semi-annually with certification of the ISO 5, 7, and 8 environments
• Glove fingertip monitoring annually for Low and Medium Risk and semi-annually for High Risk Level

• Surface sampling may be used to evaluate cleaning/disinfecting procedures and work practices

• Surface sampling annually for Low and Medium Risk and semi-annually for High Risk Level
Personnel who prepare CSPs shall be trained conscientiously and skillfully by expert personnel, multi-media instructional sources, and professional publications in:

- Garbing procedures
- Aseptic work practices
- Achieving and maintaining ISO Class 5 environmental conditions
- Cleaning and disinfection procedures
Personnel Training and Evaluation

- Adequate training and evaluation must be completed **BEFORE** preparing CSPs
- Didactic training and pass a written exam
- Observational evaluation of aseptic work practices and associated media fill
- Observational evaluation of proper hand hygiene, garbing, and cleaning and disinfection procedures
Media-fill testing of aseptic work skills:

- All compounding personnel initially

- Personnel who prepare Low- and Medium-Risk Level CSPs – Annually

- Personnel who prepare High-Risk Level CSPs – Semi-annually
If facilities cleaning and disinfection is performed by support personnel:

- They must be initially trained in proper hand hygiene, garbing, and cleaning and disinfection procedures.

- Performance evaluation of support personnel shall be performed regularly by a qualified expert.
Hand hygiene and garbing competency evaluation performed initially and:

- Low- and Medium Risk Level – Annually
- High-Risk Level – Semi-Annually
- Use of Hand Hygiene and Garbing Assessment Form
Personnel Training and Evaluation

• Direct contact contamination is the most likely source of introducing microorganisms

• Aseptic work practices observational evaluation using Aseptic Technique Observational Audit Form

• Glove finger tip sampling after completion of the media-fill preparation
Personnel Training and Evaluation

- Surface cleaning and disinfection sampling and assessment and employee competency evaluation
- Agar contact plates or swab collection
- Incubation to determine the amount of growth
- Low- and Medium Risk Level – Annually
- High-Risk Level – Semi-Annually
<table>
<thead>
<tr>
<th>Classification</th>
<th>Glove Finger Sample</th>
<th>Surface Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt;3 total</td>
<td>&gt;3 per plate</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>N/A</td>
<td>&gt; 5 per plate</td>
</tr>
<tr>
<td>ISO Class 8</td>
<td>N/A</td>
<td>&gt;100 per plate</td>
</tr>
</tbody>
</table>
Verification of Compounding Accuracy and Sterility Section:

- The three different Sterilization methods were slightly revised

- Sterilization by filtration - Filter integrity test for High-Risk Level compounding using filtration is required

- A new subsection on depyrogenation was added to provide a distinction between sterilization by dry heat and depyrogenation
Other Changes in <797>

- “Shall vs. Should” table to help in identifying requirements vs. recommendations shown in Appendix I

- Appendices II-V – information on types of disinfectants, and personnel assessments
• Please visit our website at www.usp.org

• Webinar sessions (90 minutes) is planned:
  ➢ June 5

• Workshops of up to 15 hours ACPE credits are planned:
  ➢ May 22-23 – (Thursday-Friday)

• USP <797> Guidebook 2008 version

• USP Pharmacists’ Pharmacopeia 2008 version
Thank you
Questions?