Important Updates in USP <797> and USP <823>

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Disclosures
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Principal-CriticalPoint, LLC – Healthcare education firm

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

• Target Audience: Pharmacist
• ACPE#: 0202-0000-17-093-L04-P
• Activity Type: Knowledge-based

Learning Objectives
1. Describe U.S. Pharmacopeia (USP) General Chapter <1823> and discuss updates in the draft USP <823>.
2. Discuss proposed USP standards and U.S. Food and Drug Administration draft guidance that affect the dispensing of radiopharmaceuticals.
3. Explain the role that the National Association of Nuclear Pharmacies has taken in nuclear pharmacy topics.

Mission of USP Chapter <797>: 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 34 State Boards of Pharmacy
- Based on current scientific information and best sterile compounding practices
- Recognized as the national standard of practice
- Included in TJC and other accreditation organization requirements if their standards address sterile compounding
- Minimum practice and quality standards for compounding sterile preparations

Do State Boards of Pharmacy recognize the chapter?

Applicable USP Chapters to Nuclear Pharmacies

- USP <797>
  - Pharmaceutical Compounding – Sterile Preparations
  - FAQs
  - PET → USP <823>
  - Radiopharmaceuticals as CSPs
  - Other CSPs
- USP <795>
  - Pharmaceutical Compounding – Nonsterile Preparations

USP Chapter <823>

- Revised in 2010 and chapter became effective May 1, 2012
  - USP 35-NF 30
- FDA has allowed USP Chapter to constitute CGMP standards for investigational and research PET drugs to “allow more flexibility during the development of these drugs”
- Provisions in USP Chapter <823> are generally less specific and explicit than the requirements in Part 212
- Provisions in USP Chapter <823> are “adequate to ensure that investigational and research PET drugs are produced safely under appropriate conditions”

Microbial Risk Levels for CSPs: Representative Radiopharmaceuticals

<table>
<thead>
<tr>
<th>Imaging Agent</th>
<th>Microbial Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m Agents</td>
<td>Low</td>
</tr>
<tr>
<td>Radio-labeled cells</td>
<td>Medium or High</td>
</tr>
<tr>
<td><em>Blood must be handled as a sterile preparation</em></td>
<td></td>
</tr>
<tr>
<td>I-123 MIBG</td>
<td>High</td>
</tr>
<tr>
<td>Rb-82 generator eluate</td>
<td>Immediate</td>
</tr>
<tr>
<td>Interventional drugs</td>
<td>Low</td>
</tr>
<tr>
<td>Persantine, Sincalide, Adenosine</td>
<td></td>
</tr>
</tbody>
</table>
Proposed USP <797>
Summary of Major Changes:

<table>
<thead>
<tr>
<th>Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Risk levels changed to 2 categories distinguished by conditions under which they are made and items within each</td>
</tr>
</tbody>
</table>
| 2 | Proposed Radiopharmaceuticals (RPs) will require segregation if 
 | - unstable or conditions associated with instability change |
| 3 | Proposed Radiopharmaceuticals (RPs) will require segregation if 
 | - instability change is caused by a single variable change |
| 4 | Proposed Radiopharmaceuticals (RPs) will require segregation if 
 | - instability change is not caused by a single variable change |

Definitions and Practice Issues

Current USP 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 (b) and (m)).

- For one patient for immediate administration → a function of medication administration
- This is fundamentally low-risk compounding
- Batching → <797> applies

Proposed SNMII 797 additions

The following language for inclusion in the special practice section of <797>:

- Preparation of sterile radiopharmaceuticals following the aseptic guidelines of this chapter is not considered compounding when:
  1. a radiopharmaceutical product is prepared, diluted, or repackaged in a way that does not conflict with the approved labeling, protocol for the elements describing the stability of radioactive substances, the product as a single dose or 
   single use product, and method of storage by a “Packaging System.”
  2. a radiopharmaceutical product is prepared, diluted, or repackaged with USP approved containers, additional components, and 
   associated materials.
- a radiopharmaceutical product is prepared, diluted, or repackaged with RPh approved containers, additional components, and 
  associated materials.
- a radiopharmaceutical product is prepared, diluted, or repackaged with RPh approved containers, additional components, and 
  associated materials.
- a radiopharmaceutical product is prepared, diluted, or repackaged with RPh approved containers, additional components, and 
  associated materials.

Acceptable Package Insert Deviation?

- The final product should be tested for radiochemical purity. This will ensure the product will localize in the intended area of the body. As long as the final product is greater than the USP purity limit and the appropriate dose (e.g. 1-10 mg of medronate if specified in the PI) there isn’t a problem with adding extra activity. If adding extra activity does not affect sterility or purity, it should be acceptable.
- Guidance should require radiochemical purity testing and stability testing when setting the BUD in the minor deviation section, which is a current practice standard?

Segregated Compounding Area - Proposed

- Requires dedicated space
- Only ISO Class space is the PEC
- Room surfaces must be the same as a cleanroom.
- The air must be located at least 3 meter from the PEC.
- BUDS of CSpC made in RABS (isolators) are limited to 12 hour room temp or 24 hr refrigerated.
- The perimeter of the segregated compounding area must be defined.

Handling of Blood - Proposed

- “When compounding activities require the manipulation of a patient’s blood-derived or other biological material (e.g., radiolabeling of white blood cells), the manipulation must be performed in a separate, dedicated ISO Class 7 area that contains a PEC.”
- “All blood manipulations in the radiolabeling process, except for the centrifuge steps, must be performed inside the dedicated PEC. Dedicated equipment must be used for all blood manipulations. Strict SOPs must be developed and implemented to minimize the risk of patient-to-patient cross-contamination.”
**Secondary Engineering Controls**

- Non-Hazardous Buffer Area
- Ante Area
- ISO Class 7 or 8
- Must be ISO Class 7/8
- HD buffer area
- Positive Pressure
- ISO Class 7
- Negative Pressure
- General Pharmacy and Storage Area

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**The Drug Quality and Security Act (DQSA)**

- Signed into law by President Obama on November 27, 2013
- Divided into 2 major sections called Titles
- **Title I - Compounding Quality Act**
  - Eliminates the unconstitutional provisions of 503A that “…created uncertainty regarding the laws governing compounding.”
  - Requires FDA to engage in two-way communication with state regulators – identified as a major deficiency in FDA’s response to the meningitis outbreak.
  - Preserve and protect the practice of traditional pharmacy compounding

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**DQSA (continued)**

- **Title 1: Compounding Quality Act: 503B - Outsourcing Facilities.**
  - Permit entities engaged in compounding of sterile drugs to register as “outsourcing facilities.”
  - Under Section 503B, pharmacy outsourcers to voluntarily register as “outsourcing facilities,” making them subject to good manufacturing practices, risk-based inspection and other standards
  - As of 12/16/2016, 65 entities have registered with the FDA but not all have been inspected yet

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**2013-2017 FDA Actions**

- FDA cGMP inspections of many pharmacies (including a nuclear pharmacy, 5 contract testing labs and 3 API manufacturers)
- FDA Form 483 is a form issued at the end of an FDA inspection if the FDA has observed any conditions during their visit that may represent violations of the FD&C Act
- Issued documents include:
  - 483s & responses
  - Warning Letters
  - Firm Press Releases
  - Closeout Letters

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**Facility Design Requirements - Proposed**

- Buildings and facilities in which compounding is conducted must be well designed, operated and maintained to prevent CSP microbial contamination.
- Ante-rooms for hand washing, garbing and staging components must meet at least ISO 8 standards and have space pressurization to prevent ingress into compounding areas.
- A buffer area must meet ISO 7 standards and avoid impacting the CSP area.
- Areas for CSP preparation must meet ISO 5 standards achieved through the use of hoods, RABS and/or isolators.
Radiopharmaceutical Conundrum

• Under current law, radiopharmaceuticals that are compounded by entities that are not registered with FDA as outsourcing facilities, and radiopharmaceuticals that are repackaged, are subject to all applicable provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) related to the production of drugs.
• The US Congress explicitly excluded radiopharmaceuticals from section 503A of the FD&C Act
• Compounded radiopharmaceuticals are not eligible for the exemptions under sections 253A from section 505 (concerning new drug approval requirements), section 502(f)(1) (concerning labeling with adequate directions for use), and section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements).
• In addition, Congress did not exempt repackaged radiopharmaceuticals from any provisions of the FD&C Act.

FDA Guidance for Radiopharmaceuticals

• Draft Guidance: “Compounding and Repackaging of Radiopharmaceuticals by State Licensed Nuclear Pharmacies”
  • Published December 2016

FDA Guidance for Radiopharmaceuticals

• This guidance does not address some of the following conditions:
  • Mixing, reconstituting, combining, diluting, or repackaging of a radiopharmaceutical, or other such acts, performed in accordance with directions contained in the FDA-approved labeling.
  • Production of positron emission tomography (PET) drugs.
  • Drug products that are not radiopharmaceuticals.
  • Radioactive biological products that are subject to licensure under section 351 of the Public Health Service (PHS) Act.
  • Radiopharmaceuticals for use in animals.

FDA Guidance for Radiopharmaceuticals

• Enforcement Discretion, continued
  • FDA has developed this guidance to explain the conditions under which it does not intend to take action regarding violations of certain requirements of the FD&C Act when radiopharmaceuticals are compounded or repackaged by State-licensed nuclear pharmacies or Federal facilities that are not outsourcing facilities.

FDA Guidance for Radiopharmaceuticals

Conditions in which the FDA will exercise enforcement discretion

• The radiopharmaceutical is compounded by or under the direct supervision of a licensed, authorized nuclear pharmacist in a State-licensed nuclear pharmacy or a Federal facility that holds a RAM issued by the NRC or by an Agreement State.
• The radiopharmaceutical is compounded in compliance with the following USP Chapters:
  • If it is a non-sterile radiopharmaceutical, it is compounded in accordance with USP Chapter <795> (except for the BUD); or
  • If it is sterile radiopharmaceutical, it is produced in accordance with USP <797> (except for the BUD).
• The compounded radiopharmaceutical is not essentially a copy of a marketed FDA approved radiopharmaceutical.

FDA Guidance for Radiopharmaceuticals

FDA considers a compounded radiopharmaceutical to be essentially a copy of a marketed FDA-approved radiopharmaceutical if:
  • the compounded radiopharmaceutical has the same active ingredient(s) as the approved radiopharmaceutical;
  • the active ingredient(s) in the compounded radiopharmaceutical have the same or similar dosage strength (i.e., radioactive dose(s) the active ingredient(s) in the approved radiopharmaceutical;
  • the approved radiopharmaceutical can be used by the same route of administration as prescribed for the compounded radiopharmaceutical;
FDA Guidance for Radiopharmaceuticals

FDA considers a compounded radiopharmaceutical to be essentially a copy of a marketed FDA-approved radiopharmaceutical if:

- the approved radiopharmaceutical is not on FDA's drug shortage list (see section 506E of the FD&C Act) at the time of compounding and distribution;
- the approved product has not been discontinued and is currently marketed, unless there is a change that produces for an identified individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded radiopharmaceutical and the comparable FDA-approved radiopharmaceutical, and the prescriber's determination is documented in writing on the prescription or order by either (1) the prescribing practitioner, or (2) the compounder, reflecting a conversation with the prescribing practitioner.

Insanitary Conditions at Compounding Facilities

- The policies described in this guidance document specifically address pharmacies, Federal facilities, physicians' offices (including veterinarians' offices), and outsourcing facilities that compound or repackage human or animal drugs (including radiopharmaceuticals), or that mix, dilute, or repackage biological products. For purposes of this guidance, we refer to such entities as "compounding facilities."
- Under sections 503A and 503B of the FD&C Act, compounded human drug products can qualify for exemptions from specified provisions of the FD&C Act if certain conditions are met. However, neither section 503A nor section 503B provides an exemption from section 501(a)(2)(A) of the FD&C Act.

Insanitary Conditions at Compounding Facilities

- Drugs prepared, packed, or held (hereinafter referred to as "produced") under insanitary conditions are deemed to be adulterated, regardless of whether the drugs qualify for exemptions set forth in sections 503A or 503B of the Act.
- Any drug that is produced under insanitary conditions is adulterated under the Act, including compounded human and animal drugs; repackaged drug products; compounded or repackaged radiopharmaceuticals; and mixed, diluted, or repackaged biological products.

Insanitary Conditions at Compounding Facilities

- Although this is a draft for comment, FDA investigators appear to be utilizing this in inspections as the definition of "Insanitary Conditions", which has always been open to a subjective interpretation.
- It applies to both 503A and to 503B with some noted exceptions.
- The FDA points out in bold in lines 87-89, "These are only examples and are not an exhaustive list. Other conditions not described in the guidance may be considered insanitary". This is key and allows the FDA flexibility to make their own interpretations. My take is that FDA investigators will consider this to be the "starting point" and not the end point.
- FDA has made the following statement in regard to both sterile and non-sterile drugs, "Handling beta-lactam, hazardous, or highly potent drugs (e.g., hormones) without providing adequate containment, segregation, and cleaning of work surfaces, utensils, and personnel to prevent cross-contamination".

Insanitary Conditions at Compounding Facilities

- The FDA also considers the following to be "particularly serious" and cleanroom is not defined.
- Cleanroom areas with unsealed, loose ceiling tiles.
- In line 299, the FDA states:

  "If a compounding facility decides to initiate a recall, it should notify its local FDA District recall coordinator as soon as the decision is made."

  This removes all doubt about whether a compounding operation must advise the FDA of recalls.
Summary

- There are specific state and federal rules, regulations and guidance that direct the practice of nuclear pharmacies and handling and dispensing of radiopharmaceuticals.
- PET products are regulated according to USP Chapter <823> or 21 CFR 212.
- The preparation of radiopharmaceuticals are NOT exempt from USP chapter on compounding (<797> and <795>).
- FDA is developing specific guidance for radiopharmaceuticals but the specter of Insanitary Conditions looms large for all pharmacies.

Learning Assessment Questions

1. True or False?
The US Congress explicitly excluded radiopharmaceuticals from section 503A of the FD&C Act
   A. True
   B. False

2. Which of the following activities are considered repackaging?
   A. Mixing, reconstituting, combining, diluting, or repackaging of a radiopharmaceutical, or other such acts, performed in accordance with directions contained in the FDA-approved labeling.
   B. Production of positron emission tomography (PET) drugs.
   C. Removing an FDA-approved radiopharmaceutical from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product.
   D. If a radiopharmaceutical is combined with another ingredient such as blood.

3. Which of the following practice standards are applicable to leukocyte tagging using a technetium-based commercial kit for a patient in the hospital
   A. 21 CFR 211
   B. USP Chapter <797>
   C. USP Chapter <795>
   D. USP Chapter <823>

4. The FDA defines minor deviation as a change in which of following:
   A. The approved labeling in radioactivity
   B. The volume of the dose
   C. The step-by-step procedures made when compounding the radiopharmaceutical from an FDA-approved drug product in a patient-ready dose.
   D. All of the above
   E. None of the above

References
