Latest Developments in USP Monographs and the Compounding of ~~Sterile~~ Radiopharmaceuticals

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Disclosures

Volunteer member on several USP Expert Committees and Expert Panels associated with radiopharmaceutical General Chapters and drug monographs

This presentation is not endorsed by the USP, nor does it represent the views or opinions of the USP

Topics

- Issues with radiopharmaceutical monographs
- New format for radiopharmaceutical monographs
- Current activities – monographs
- Radiopharmaceutical compounding

Issues with Radiopharmaceutical Monographs

- Nearly all radiopharmaceutical monographs need to be 'modernized' to the new USP format and style
- Some monographs exist for drugs that are no longer marketed (e.g., Rose Bengal Sodium I 131 Injection discontinued *ca*. 1983)
- Some monographs, especially those for older drugs and PET drugs, were developed in the absence of sponsors' supporting data and prior to FDA approval
- USP labs are not licensed to handle radioactive materials, so typical testing cannot be performed to verify methods
- Reference standards do not exist for radioactive active ingredients

Issues with Radiopharmaceutical Monographs

- Nearly all need to be updated, especially analytical test methods (e.g., electrophoresis for Tc 99m pentetate) and eliminate animal biodistribution requirements (e.g., Tc 99m products before *ca*. 1990)
- Many recently marketed radiopharmaceuticals do not yet have a monograph (the innovator is often reluctant to share proprietary information prior to generic competition)
- Monographs don't exist for marketed non-radioactive 'kits'

Radiopharmaceutical Expert Panel

- Established in early 2016 under CHM4 EC
- Members:

Corinne Bensimon
Jonathan Fitzsimmons
Umesh Gangadharmath
Ravi Kasliwal‡
Thijs Kroon
Adrian Nunn
David Pipes
Jim Ponto*
Ravi Ravichandran†
Kara Weatherman
Martin Williamson*
Steve Zigler*

* Member CHM4 EC
† USP staff
‡ FDA representative

Initial Tasks

- Compile list of radiopharmaceutical monographs (N=75 current and pending)
- Prioritize tasks – start with 'low-hanging fruit'
- Review each radiopharmaceutical for marketing status in U.S. and other countries
- Recommend deletion of monographs for radiopharmaceuticals that are no longer relevant
  - Each will be published in *PF* for public comment before removal
- Identify sponsors for monographs to be maintained and revised

Standard Monograph Format and Style: Radiopharmaceuticals Don't Fit Well

- USP guideline for submission of monographs

  www.usp.org/sites/default/files/usp_pdf/EN/USPNF/chemical_medicines_rfr_guideline_-28apr16.pdf
- Some test methods for pharmacologic drug masses may not be appropriate for radiopharmaceuticals
  - e.g., infrared/ultraviolet spectroscopy, liquid chromatography, gas chromatography
- Certain tests for radiopharmaceuticals are not described in this guideline
  - e.g., radioactivity, radionuclidic purity, radiochemical purity

Modified Monograph Format and Style for Radiopharmaceuticals

- TITLE (e.g., Fludeoxyglucose F 18 Injection)
- DEFINITION
  - Chemical information (e.g., chemical name)
  - Other important characteristics (e.g., sterile)
  - Amount (e.g., NLT x % and NMT x % of the labeled amount expressed in MBq (mCi)/mL at the time of calibration)
  - Added substances (e.g., may contain buffering agents, preservatives, stabilizing agents or sodium chloride)
  - Specific activity (e.g., does not contain added carrier)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- IDENTIFICATION
  - Radionuclidic Identity (cite <821>)
    - Analysis (e.g., determine half-life or emission energy spectrum)
    - Acceptance Criteria (e.g., half life is x – y min; major photopeak energy is x KeV)
  - Radiochemical Identity
    - Analysis (e.g., comparison to chemical standard)
    - Acceptance Criteria (e.g., NLT x % and NMT x %)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- ASSAY (cite <821>)
- Radioactivity Concentration (Strength)
  - Analysis (e.g., determine MBq (mCi)/mL)
  - Acceptance Criteria (e.g., x % - y % at the time indicated on the label)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- PURITY
  - Radionuclidic Purity (cite <821>)
    - Analysis (e.g., collect emission energy spectrum and determine amount of each radionuclide, decay-correct to expiration time)
    - Acceptance Criteria (e.g., NLT x % corresponds to the intended radionuclide)
  - Radiochemical Purity
    - Analysis (e.g., radiochromatography method)
    - Acceptance Criteria (e.g., NLT x %)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- IMPURITIES
  - Radionuclidic Impurities (cite <821>)
    - Analysis (e.g., collect emission energy spectrum and determine amount of each radionuclide, decay-correct to expiration time)
    - Acceptance Criteria (e.g., NMT x % of the radioactivity decay-corrected to time of expiration)
  - Radiochemical Impurities
    - Analysis (e.g., radiochromatography method)
    - Acceptance Criteria (e.g., NMT x %)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- IMPURITIES (cont'd)
  - [Specific Identified Chemical Impurities]
    (e.g., related compounds that have a Reference Standard; residual solvents such as acetonitrile and ethanol)
    - Analysis (e.g., chromatography method)
    - Acceptance Criteria (e.g., NMT x microgram/mL; or NMT x %)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- Specific Tests
  - Appearance (e.g., clear, colorless, free from visible particulates)
  - pH (e.g., pH is x - y using short-range pH indicator paper)
  - Bacterial Endotoxins Test (cite <85>) (e.g., NMT 175/V USP endotoxin units/mL where V is the maximum administered total dose in mL at the expiration time)
  - Sterility Test (cite <71>) (state exceptions such as sample size or time delay before starting the test)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- Additional Requirements
  - Packaging and Storage (e.g., single-dose or multiple-dose vial; adequately shielded; store at controlled room temperature)
  - Labeling (e.g., date and time of calibration; radioactivity concentration in MBq (mCi)/mL at calibration; total volume or total radioactivity at calibration; expiration date and time; name and quantity of any added preservative or stabilizer; make dosage calculations with correction for radioactive decay; the radionuclide's half-life; "Caution – Radioactive Material"; do not use if cloudy or if it contains visible particulate matter)

Modified Monograph Format and Style for Radiopharmaceuticals (cont'd)

- USP Reference Standards (cite <11>)
  - List (e.g., drug substance RS; drug-related compound RS)

First Monographs Revised

- Fludeoxyglucose F 18 Injection
- Ammonia N 13 Injection
- Proposed revisions of both monographs recently published in Pharmacopeial Forum *PF* 43(3) May-Jun 2017
- Comment period ends July 31, 2017

Summary - Monographs

- Revising radiopharmaceutical monographs is a slow process, but a foundation has been laid to allow progress
- ***Need:*** sponsors for individual radiopharmaceutical products, especially for supporting documentation of analytical methods and results
- ***Need:*** public comment on proposed new and revised monographs published in *PF*

Radiopharmaceutical Compounding

<795> *Pharmaceutical Compounding – Nonsterile Preparations*

- does not apply to radiopharmaceuticals

<797> *Pharmaceutical Compounding – Sterile Preparations*

- contains a short section on radiopharmaceuticals but lacks sufficient details to fully elucidate important differences for radiopharmaceuticals

Compounding of Radiopharmaceuticals

- Similar to sterile compounding of conventional drugs
  e.g., aseptic practices, environmental facilities
- Also similar to hazardous drug compounding
  e.g., prevention and control of contamination
- Unique aspects
  - Radiation protection practices (time, distance, shielding)
  - Supplies: lead shields, absorbent contamination pads
  - Equipment: radioactivity/radiation instruments/monitors
  - Often involves chemical reactions to create radiolabeled compounds

Manufactured Radiopharmaceuticals

- Some radiopharmaceuticals are manufactured in single- or multiple-dose vials ready for use
- Simply withdraw contents into a syringe for administration = DISPENSING (although falls under 'sterile compounding' in <797>)
- Comply with aseptic handling, "use by" dating, etc.

PREPARATION of Radiopharmaceuticals Using FDA-Approved Kits

- Most commonly-used radiopharmaceuticals

  e.g., Tc 99m medronate, In 111 pentetreotide
- Preparation instructions are described in the package insert
- Most often, lyophilized powder in a vial and may include other components/ingredients

Preparation of Radiopharmaceuticals from FDA-Approved Kits (cont'd)

- Similar to reconstitution of drugs for injection
- However, chemical reactions take place (e.g., reduction, chelation) so quality control testing of the reconstituted product is a standard of practice

$$Tc(VII)O_4^- + Sn^{+2} + \text{gluconate} \longrightarrow Tc(V)\text{-gluconate}$$

$$Tc(V)\text{-gluconate} + \text{tetrofosmin} \longrightarrow Tc(V)O_2(\text{tetrofosmin})_2^+$$

Preparation with Minor Deviations

- Package insert instructions are often deficient*:
  - Ambiguous/vague (e.g., may, should, recommend)
  - Restrictive (e.g., specific gauge needle)
- Package insert instructions are often outdated:
  - New clinical indications which may require somewhat different activity, concentration, etc.
  - Changes in technology (e.g., heat block vs. water bath)
  - Radiation protection practices (e.g., add Tc 99m to vial and then dilute with normal saline vs. dilute Tc 99m in syringe and then add to vial)

*Hung JC, Ponto JA, Gadient KR, et al. Deficiencies of product labeling directions for the preparation of radiopharmaceuticals. J Am Pharm Assoc. 2004; 44:30-35.

Extension of Beyond Use Dates (BUDs)

- Package inserts state or suggest 'use-by' times
  - e.g.: "use within _ hours", "should be discarded after _ hours"
  - Primarily based on sterility and stability; very conservative
- Extension of BUD is necessary for supplying radiopharmaceutical doses to hospitals/clinics at some geographic distance
  - Professional practice guidelines support extension of BUD if analytical studies show continued compliance with USP specifications
- SNMMI Recommendations for Beyond-Use Dates (BUD) for Tc-99m Radiopharmaceuticals [2011]
  - Comply with <797> BUD based on risk level (i.e., sterility)
  - Comply with USP monograph specifications (e.g., purity at time of use)
  - Comply with clinical use requirements (e.g., # particles/dose)

http://snmmi.files.cms-plus.com/docs/BUDs_for_Tc99m_radiopharmaceuticals_1382109507530_1.pdf

COMPOUNDING of Radiopharmaceuticals

- Admixing with other drugs (e.g., lidocaine, ascorbic acid)
- Converting one dosage form into a different dosage form
  - Dissolving capsules to prepare an oral liquid
- Preparation using raw materials or radiochemicals
  - rare, usually done during times of product shortages or for radiopharmaceuticals no longer marketed for economic reasons (e.g., P 32 chromic phosphate)
  - may require extensive sterility testing, stability testing, etc

Problems

- Several different definitions of “compounding”
  - Traditional pharmacy extemporaneous compounding
  - State boards of pharmacy
  - FDA
  - USP
  - Professional organizations, standards of practice
  - Accreditation organizations

Problems (cont'd)

- 503A safe harbors for pharmacy compounding "do not apply to … radiopharmaceuticals." [DQSA 2013]
  - FDA draft guidance document for radiopharmaceutical compounding (12/29/2016) is still undergoing public comment
  - Currently, different interpretations by different inspectors
- Related issues
  - Nearly 90% radiopharmaceutical doses are prepared in commercial nuclear pharmacies and transported to hospitals and clinics
  - Crossing state lines (e.g., New York City, Washington D.C.)
  - Patient name on each dose (e.g., cardiac doses for ER)

Problems (cont'd)

- Immediate Use
  - Prime example: Tc-99m autologous red blood cells for localization of GI bleeds
  - Tc-99m sodium pertechnetate is delivered from a commercial nuclear pharmacy but the RBC labeling is performed in the clinic using an FDA-approved kit; but it requires >2 entries into the vial, so it is non-compliant with <797>
  - SNM submitted a petition to USP in 2008
  - Proposed revision of <797> in *PF* 36-3 to allow this, but was never adopted

Problems (cont'd)

- FDA Draft Guidance for Industry: Insanitary Conditions at Compounding Facilities (Aug 2016)
  - specifically includes "compounded or repackaged radiopharmaceuticals"
  - The descriptive list of *Insanitary Conditions in a Sterile Operation* includes several items that may be problematic for radiopharmaceuticals

Insanitary Conditions

- “Performing aseptic manipulations outside of an International Organization for Standardization Class 5 (ISO 5) area.”
  - Mo-99/Tc-99m generators, with auxiliary lead shielding, may be too large and too heavy to place inside ISO 5 hoods. Hence, <797> allows generator elution in ISO 8 or cleaner areas.

Insanitary Conditions (cont'd)

- "Moving quickly in the vicinity of open containers or instruments (e.g., needles)… Quick movement of personnel disrupts the airflow and increase the risk of bringing lesser quality air into the ISO 5 area
  - Compliance with principles of radiation protection (viz., **time**, distance, and shielding) may require relatively quick movements

Insanitary Conditions (cont'd)

- "Conducting aseptic manipulations or placing equipment/supplies in an area that blocks the movement of first pass air around an open container…"
  - Compliance with radiation protection practice requires use of leaded-glass L blocks, vial shields, etc. which may disrupt first pass air

Insanitary Conditions (cont'd)

- "Touching equipment or other surfaces (e.g., walls, telephone, floors) located outside of the ISO 5 area with gloved hands and then proceeding with aseptic manipulations without changing or sanitizing gloves."
  - Frequent and necessary touching of lead syringe shields/carriers, labels for vials and syringes, etc.

SNMMI White Paper

Fall 2016 – SNMMI COR developed a white paper entitled *USP Public Standards for Compounded Sterile Radiopharmaceuticals: Recommendations from SNMMI*

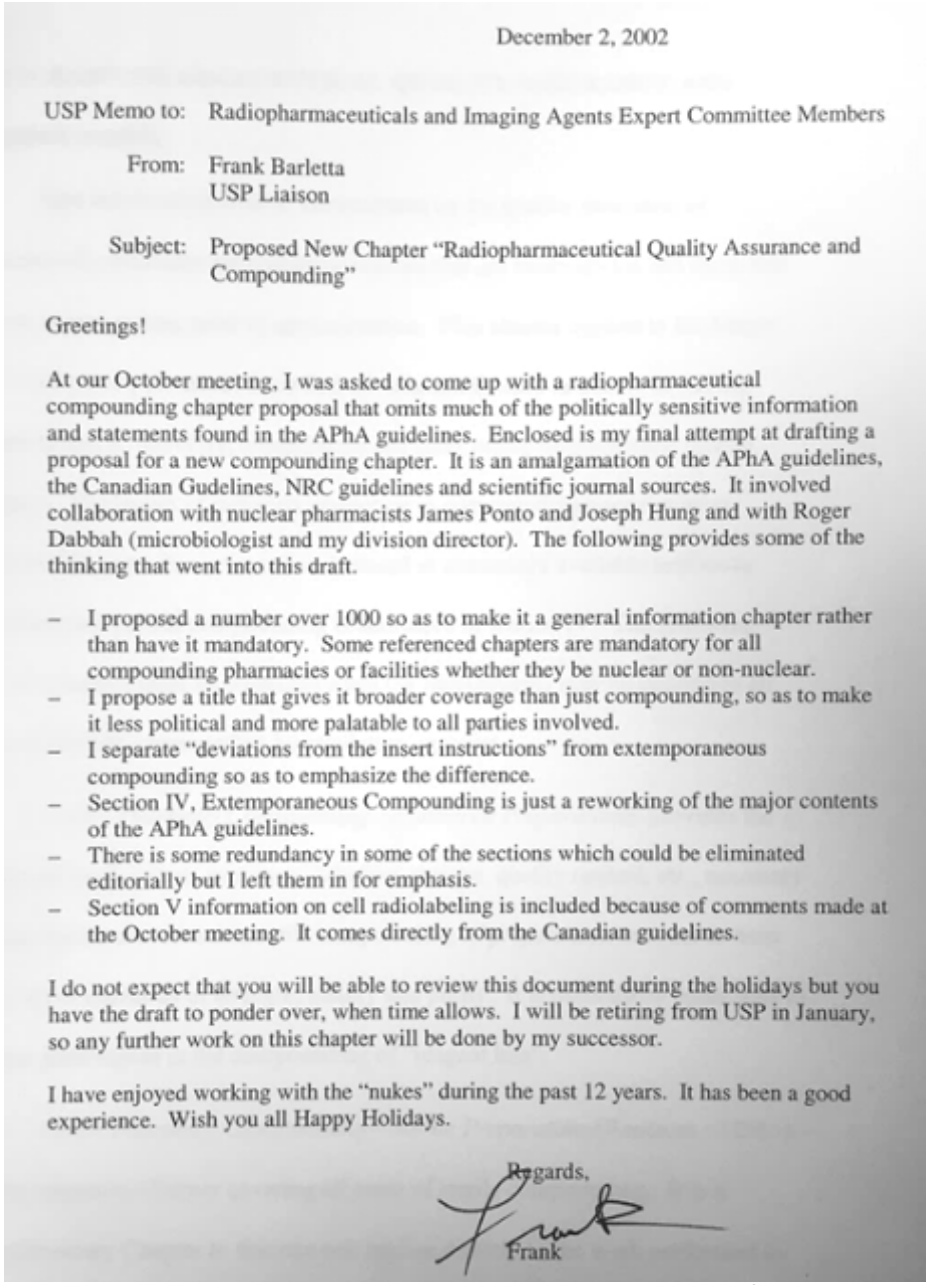
Three recommendations from the white paper:

- Delineate common practices that are defined as sterile compounding within the practice of nuclear pharmacy
- Create a public standard for the preparation, compounding, and dispensing of sterile radiopharmaceuticals with the practice of nuclear pharmacy [i.e., create a new general chapter]
- Reinstate an expert committee dedicated to all standards for radiopharmaceuticals [i.e., chapters and monographs]

http://snmmi.files.cms-plus.com/SNMMI-USP-Recommendations-Final_2016.pdf

Previous Related Work by USP

- 2000-2005 Radiopharmaceuticals and Medical Imaging Drugs (RMI) Expert Committee proposed, and created a draft of, a new general chapter: <1017> *Radiopharmaceutical Quality Assurance and Compounding*.
- But: it was never published in *PF;* Frank Barletta retired in 2003, the committee turned its focus to PET, and chapter <1206> *Sterile Preparations – Pharmacy Practices* was on its way to becoming <797>.



December 2, 2002

USP Memo to: Radiopharmaceuticals and Imaging Agents Expert Committee Members

From: Frank Barletta
USP Liaison

Subject: Proposed New Chapter "Radiopharmaceutical Quality Assurance and Compounding"

Greetings!

At our October meeting, I was asked to come up with a radiopharmaceutical compounding chapter proposal that omits much of the politically sensitive information and statements found in the APhA guidelines. Enclosed is my final attempt at drafting a proposal for a new compounding chapter. It is an amalgamation of the APhA guidelines, the Canadian Gudelines, NRC guidelines and scientific journal sources. It involved collaboration with nuclear pharmacists James Ponto and Joseph Hung and with Roger Dabbah (microbiologist and my division director). The following provides some of the thinking that went into this draft.

- I proposed a number over 1000 so as to make it a general information chapter rather than have it mandatory. Some referenced chapters are mandatory for all compounding pharmacies or facilities whether they be nuclear or non-nuclear.
- I propose a title that gives it broader coverage than just compounding, so as to make it less political and more palatable to all parties involved.
- I separate "deviations from the insert instructions" from extemporaneous compounding so as to emphasize the difference.
- Section IV, Extemporaneous Compounding is just a reworking of the major contents of the APhA guidelines.
- There is some redundancy in some of the sections which could be eliminated editorially but I left them in for emphasis.
- Section V information on cell radiolabeling is included because of comments made at the October meeting. It comes directly from the Canadian guidelines.

I do not expect that you will be able to review this document during the holidays but you have the draft to ponder over, when time allows. I will be retiring from USP in January, so any further work on this chapter will be done by my successor.

I have enjoyed working with the "nukes" during the past 12 years. It has been a good experience. Wish you all Happy Holidays.

Regards,

Frank

Summary

- Preparation, compounding, and dispensing of sterile radiopharmaceuticals involves unique safety considerations (radiation protection practices) and involves special equipment (lead shielding, radiation detectors) that may necessitate some compromises in aseptic handling practices.
- A separate USP chapter on Preparation, Compounding, and Dispensing of Sterile Radiopharmaceuticals would serve the profession well in defining and describing standards for these activities, especially in relationship with the FDA Draft Guidance on Compounding and Repackaging of Radiopharmaceuticals

USP Stakeholders Workshop on Radiopharmaceutical Compounding

- Held at USP HQ on Feb 1, 2017
- Invited participants included representatives from:
  - Chemical Medicines Monographs 4 Expert Committee
  - Compounding Expert Committee
  - nuclear pharmacists in hospital, commercial, and academic settings
  - FDA
  - SNMMI COR (to present the White Paper)
  - USP staff
- Most participants endorsed a separate chapter

Proposed New General Chapter <825> *Compounding - Radiopharmaceuticals*

- The Compounding Expert Committee and USP staff agreed that creation of a new chapter was appropriate
- Scope and Rationale: http://www.usp.org/usp-nf/notices/825-compounding-radiopharmaceuticals
- Call for candidates for an Expert Panel: http://callforcandidates.usp.org/node/4636
- Very aggressive timeline – draft chapter to be published in the Nov-Dec 2018 *PF* for public comment

Key Issues Page: Standards for Radioactive Articles in USP-NF

- http://www.usp.org/usp-nf/key-issues/standards-radioactive-articles-usp-nf

THANK YOU

QUESTIONS?