Radiopharmaceutical Compounding – Past and Present

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• Target Audience: Nuclear Pharmacists
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• Activity Type: Knowledge-based

*This activity is approved for Board Certified Nuclear Pharmacist (BCNP) recertification credit.

Agenda

I. FDA Regulation of Radiopharmaceutical Compounding
   • History of FDA Regulation of Radiopharmaceutical Compounding
   • Thorny Issues in the Regulation of Radiopharmaceutical Compounding

II. Updates on Radiopharmaceutical Compounding
   • APhA-APPM Nuclear Pharmacy Guidelines
   • APhA-APPM Vendor Qualification Check List
   • USP <795> and <797>
   • FDA Listening Session on Radiopharmaceutical Compounding

Learning Objectives

Upon completion of this session, the participant will understand:

1. How FDA’s approach to pharmacy compounding, and radiopharmaceutical compounding in particular, has evolved over time
2. The current legal and regulatory framework applicable to conventional drug compounding, since these will affect FDA’s developing approach to radiopharmaceutical compounding
3. The primary issues of concern to FDA in developing a regulatory approach to nuclear pharmacy compounding
4. APhA’s Compounding Guidelines and APhA’s Vendor Qualification Checklist
5. USP’s radiopharmaceutical standards in <795> and <797> and possible updates to the chapters

Self-Assessment Questions
1. Which of the following are “new drugs” under the Federal Food, Drug, and Cosmetic Act?
   a. Compounded non-radioactive drugs
   b. Compounded radiopharmaceuticals
   c. PET drugs
   d. All of the above

2. Which of the Following Authorities Does/Did Not Apply to Radiopharmaceuticals?
   a. FDA Compliance Policy Guide 7132.16, “Pharmacy Compounding” (1992)
   c. Nuclear Pharmacy Guideline
   d. FDC Act Section 503A, “Pharmacy Compounding”
   e. FDC Act Section 503B, “Outsourcing Facilities”

3. Under former FDA pharmacy compounding CPGs and the current FDC Act, which of the following has never been a permissible reason to compound a copy of, or minor variation from, a commercially available drug?
   a. The commercially available drug is on FDA’s drug shortage list
   b. The pharmacy has determined that a patient is unable to bear the expense of the commercially available product
   c. The prescriber has determined that there is a medical need for a variation for a particular patient

4. In the consensus statement from the organizations representing nuclear pharmacy/nuclear medicine to the FDA in 2014, a minor deviation includes all of the following EXCEPT:
   a. Addition of components not specified in the FDA-approved labeling
   b. Change in quality control instrumentation, such as a NaI(Tl) well chamber instead of a dose calibrator
   c. Change in the quantity of radioactivity added to the kit
   d. Change in the final volume of the kit

5. Under the proposed revision for USP <797>, what is the time limit for the compounding procedure for an Urgent-Use CSP?
   a. 0.25 hour
   b. 0.5 hour
   c. 1 hour
   d. 2 hours

FDA Regulation of Radiopharmaceutical Compounding

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Disclosures

- Hyman, Phelps & McNamara P.C. is outside regulatory counsel to the Council on Radionuclides and Radiopharmaceuticals (CORAR), a trade association of radiopharmaceutical manufacturers and nuclear pharmacy firms
- I am not appearing on behalf of CORAR
- Any views I express are not necessarily those of CORAR.

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I. History of FDA Regulation of Radiopharmaceutical Compounding

Drugs, New Drugs, and Pharmacies under the Federal Food, Drug, and Cosmetic Act

- FDC Act defines “drug” as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or an article intended to affect the structure or function of the body of man or other animals
- A “new drug” is a drug that is not generally recognized by experts as safe and effective
- New drugs are subject to the following requirements (among others):
  - FDA must approve marketing application demonstrating safety and effectiveness
  - Label must bear adequate directions for use
  - Manufacture, processing, packing and holding must comply with cGMPs
  - FDA may inspect any facility in which drugs are manufactured, processed, packed, or held, including inspection of records
  - Establishments must be registered and drugs listed
  - May not be adulterated or misbranded

FDC Act (cont.)

- Pharmacies are exempt from certain of these requirements
  - If a pharmacy (1) complies with local pharmacy law; (2) is regularly engaged in dispensing drugs pursuant to valid prescriptions; and (3) does not prepare or compound drugs other than in the course of business of dispensing drugs at retail, then
  - It is not required to register or list its drugs
  - It may be inspected but is not subject to inspection of “records, files, and papers”

1938 – Late 1970s

- Though compounded drugs fall within the definition of a “new drug”, and FDA now considers them so, FDA took a hands off approach to pharmacy compounding from enactment of the FDC Act in 1938 through the late 1970s
- FDA implicitly acquiesced in a “Practice of Healing Arts” exception under FDC Act
  - Legislative history of 1938 FDC Act explained that Act was not intended as a medical practices act and would not interfere with the practice of the healing arts.
  - 1962 amendments specifically exempted physicians and pharmacists from registration, listing and record inspection requirements (though not premarket approval requirements)
  - FDA recognized that it is impractical to require pharmacies to obtain premarket approval for every compounded drug
  - As a result, FDA did not seek to regulate pharmacy compounding
Late 1970s: FDA Takes Action Against Compounding Outside “Usual Practice”

- Courts upheld enforcement against pharmacies’ compounding of drugs for wholesale distribution, which were promoted for specific indications
- Courts distinguished such activities from the “usual practice of pharmacy,” in which drug is compounded for particular patient based on physician’s prescription

1992: Compliance Policy Guide 7132.16

- By 1992, FDA was concerned that an increasing number of retail pharmacies were “engaged in manufacturing, distributing, and promoting unapproved new drugs … in a manner that is clearly outside the bounds of traditional pharmacy practice …”
- FDA issued Compliance Policy Guide (CPG) 7132.16 in March 1992
- Applied to all human drugs, including radiopharmaceuticals
- Stated FDA’s view that pharmacies are not subject to any general exemption from new drug, adulteration, or misbranding provisions of FDC Act

1997: Enactment of Section 503A, “Pharmacy Compounding”

- Added by FDA Modernization Act of 1997
- Exempts compounded drugs from premarket approval, cGMP, and adequate-directions-for-use-requirements of the FDC Act if they meet specified conditions
- Conditions for exemption:
  - Drug compounded by licensed pharmacist upon receipt of valid prescription for individual identified patient
  - Limited anticipatory compounding
  - Drug compounded in compliance with USP chapters on compounding
  - Bulk drug substances must be manufactured in registered establishment
  - Bulk drug substances must comply with USP or NF monograph if one exists; or if not, must be component of FDA-approved drug, or if not, must be on FDA list of permissible bulk substances (“positive list”)
  - Drug not on FDA’s list of drugs withdrawn or removed from market for safety or effectiveness reasons

Late 1980s: FDA Asserts Jurisdiction to Regulate All Pharmacy Compounding

  - FDA concerned that compounding was becoming a method to avoid new drug approval requirements
  - Sold bulk drug products being supplied to veterinarians for compounding
  - Strategy: limit compounding by cutting off supply of bulk drugs, without directly regulating veterinarians
  - District Courts held FDC Act did not permit FDA to interfere with the practice of medicine
  - Federal Appeals Courts reversed, holding that FDA has comprehensive powers to regulate drugs, and “to regulate drugs is to be involved in the practice of the healing arts.”
- Cases gave FDA legal basis to assert that “practice of healing arts” exception under FDC Act was not absolute, and FDA could set limits
- After veterinary compounding cases, FDA took the position that FDA’s jurisdiction to regulate pharmacy compounding was absolute, and compounding was permitted only in FDA’s enforcement discretion
  - One responsible FDA official acknowledged that this new position might provoke an outcry from physicians and pharmacists, who will object to being in the position of “living in sin”

CPG 7132.16 (cont.)

- Attempted to draw line between compounding on receipt of a valid prescription for an individual patient and manufacturing
- Identified factors FDA would consider in determining whether to take enforcement action
  - Compounding regularly or in inordinate amounts, products that are essentially copies of commercially available approved products
    - Minor deviation from approved product permitted where “documentation substantiates the medical need for the particular variation of the compound”
  - Distributing inordinate amounts of compounds out-of-state
  - Selling compounded wholesale to other entities for resale
  - Using commercial scale manufacturing or testing equipment
  - Using drug substances that were not made in FDA approved facilities

Section 503A (continued)

- Conditions for exemption (cont.)
  - Drug not on list of products presenting demonstrable difficulties for compounding (“negative list”)
  - Pharmacy does not compound regularly or in inordinate amounts drugs that are essentially copies of commercially available approved products
  - May compound a drug in which there is a change that produces for an identified patient a significant difference, as determined by the prescriber, between the compounded drug and the commercially available drug
  - Limits on interstate distribution
    - If state has memorandum of understanding (MOU) with FDA, limits contained in MOU
    - If state does not have MOU, pharmacy may not distribute more than 5% of total orders out-of-state
    - Pharmacy may not advertise or promote compounding of any particular drug or drug type

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Section 503A (cont.)

- Radiopharmaceuticals and PET drugs exempt
- Legislative history: “Nothing in Section 503A is intended to change or otherwise affect current law with respect to radiopharmaceuticals.”

B. FDA Regulation of Radiopharmaceuticals Through FDAMA 1997

1975: FDA Assumes Oversight Over Radioactive Drugs from AEC/NRC

- Prior to 1975, radiopharmaceuticals were regulated by the Atomic Energy Commission (AEC), and FDA did not assert jurisdiction
  - In 1963 FDA had issued an order exempting all radioactive drugs from requirements for new drugs “pending further notice”, to permit gathering of additional facts
- July 1975: FDA issued two notices:
  1. Radiopharmaceuticals: 1963 exemption for radiopharmaceuticals was terminated. Radiopharmaceuticals would thenceforth become subject to FDC Act requirements for premarket approval, registration and listing, cGMPs, labeling and advertising
  2. Nuclear pharmacies: FDA intended in the “near future” to issue nuclear pharmacy regulations distinguishing between manufacturing and “practice of pharmacy”
- Interim enforcement policy: FDA would not take action against a nuclear pharmacy that does not comply with FDC Act, except when necessary to protect the public health, as long as pharmacy complied with state law and was licensed by NRC (successor to AEC) or an Agreement State.

1984 Nuclear Pharmacy Guideline

- FDA did not issue promised regulations but in 1984 issued Nuclear Pharmacy Guideline instead
- 1975 interim enforcement policy revoked: nuclear pharmacies to be regulated like other pharmacies
- Purported to address registration requirement
  - Section 510 of FDC Act requires registration of drug establishments, with exemption for pharmacies
- However, scope was broader than registration. FDA explained that if a pharmacy’s activities are within the practice of pharmacy, it is exempt not only from registration, but also other requirements that flow from it – i.e., cGMPs, inspection, premarket approval
- Described activities that will and will not be considered manufacturing rather than practice of nuclear pharmacy

1984 Nuclear Pharmacy Guideline (cont.)

- Recognized certain nuclear pharmacy activities that “depart from traditional pharmacy practice,” but would not be considered manufacturing
  - Dispensing to physicians and facilities instead of patient
  - Preparing radiopharmaceuticals from reagent kits
  - Dispensing radiopharmaceuticals in multiple dose containers for multiple patients undergoing common procedure
  - Dispensing pursuant to an order without receiving patient name
- However, little useful guidance regarding compounding
  - Compounding of non-commercially available product is permissible as long as it does not fall outside the “normal practice of pharmacy.” Such situations must be decided on case-by-case basis.
  - Pharmacy that routinely prepares a reagent kit from basic ingredients and ships it without a prescription & no longer acting as pharmacy and must register
  - Pharmacist deviating from manufacturer’s instructions must rely on professional judgment about whether modification is appropriate.

1995: FDA Began to Assert Jurisdiction Over PET Drugs

- Preparation of PET drugs, like compounded drugs, was originally considered to be within “practice of pharmacy” exception to FDC Act
- In late 1980’s, at the same time that FDA was asserting its authority to regulate all pharmacy compounding, FDA determined to regulated PET drugs as “new drugs” and PET facilities as manufacturers
- FDA held public hearing in 1993, issued Federal Register notice in 1995
  - New approach vigorously opposed by PET community (and some states)
- PET community got Congress to intervene in FDAMA 1997
  - Moratorium prohibited FDA from regulating PET drugs as new drugs until FDA established appropriate approval procedures and cGMPs for PET drugs
- FDA published Part 212 cGMPs in 2009
- PET drug facilities now required to:
  - Have approved NDA/ANDA for all marketed PET drugs by Dec. 12, 2015
  - Comply with PET cGMPs
  - Register and list
  - Be inspected
  - Pay user fees
C. FDA Approach to Radiopharmaceutical Compounding: FDAMA to Present

1997-2002: Regulatory Vacuum

- CPG 7132.16 revoked in January 1999 because superseded by Section 503A
- Left regulatory vacuum for radiopharmaceutical compounding
  - No CPG or other significant guidance on radiopharmaceutical compounding
  - FDA explained its position on radiopharmaceutical compounding described in July 2000 letter to CORAR:
    - Under “current law” previous to FDAMA, there was no statutory exemption for compounded drugs from new drug, misbranding, and adulteration provisions of FDC Act, so there is no statutory exemption for radiopharmaceuticals now
    - CPG 7132.16 was superseded by Section 503A, but the CPG represented “current law” applicable to radiopharmaceuticals, so CPG still applies to radiopharmaceuticals pending new guidance on compounding of radiopharmaceuticals

2002: Return of CPG

- Advertising prohibition of Section 503A found unconstitutional by Supreme Court in Thompson v. Western States Medical Center (April 2002), and 9th Circuit held that the provision was not severable. Therefore, 503A invalidated in its entirety, at least in the 9th Circuit
- Applied to all drugs, including radiopharmaceuticals
- CPG contained general principles found in CPG 7132.16 and Section 503A
  - No compounding in anticipation of prescription, except in very limited quantities
  - Requirements for bulk and other ingredients
  - Do-not-compound list
  - No-compounding at wholesales
  - No compounds that are essentially copies of commercially available products. Minor variations must be substantiated by “documentation of the medical need … for the particular patient”
  - Interstate shipment restrictions omitted

2013: NECC Disaster and Aftermath

- 2012, New England Compounding Center shipped over 17,000 vials of sterile injectable methylprednisolone from three contaminated lots to health care facilities in 23 states
  - Over 70 died from fungal meningitis, 700 others became sick
- In aftermath of NECC:
  - Congressional hearings critical of lax FDA oversight over compounding pharmacies
  - FDA protested that they were impeded by absence of pharmacy registration, inability to inspect records, and absence of clear statutory authority over pharmacy compounding after Section 503A had been invalidated
  - To provide clearer FDA enforcement authority and oversight over compounding, Congress passed Title I (Compounding Quality Act) of the Drug Quality and Security Act in November 2013

DQSA: Section 503A Reinstated

- 2013 Drug Quality and Security Act (DQSA) repealed advertising restrictions from Section 503A, thereby restoring its validity
  - Radiopharmaceutical and PET exemptions remain
- FDA has been implementing Section 503A by:
  - Requesting nominations for the positive list of bulk drug substances and issuing interim guidance (Oct. 2015)
  - Issuing a draft MOU addressing inadequate interstate shipments of compounded drugs (Feb. 2015)
    - Inordinate if units shipped interstate in a month ≥ 30% of total units of compounded and non-compounded drugs dispensed by pharmacy
  - Issuing a guidance on enforcement under 503A (Oct. 2015)
  - Enforcement action may be taken if any 503A condition is not met
  - Enforcement action may be taken even if 503A conditions are met, if drug is adulterated, non-compliant with compendium standards, or labeling, advertising, or promotion is false or misleading
- FDA enforcement reinvigorated
  - Hundreds of compounding pharmacies inspected since 2013
  - FDA has publicized inspection observations (483s), recalls, Warning Letters and press releases

DQSA: New Section 503B (Outsourcing Facilities)

- Entities may voluntarily register as outsourcing facilities
- Outsourcing facility is a facility at a single location that compounds sterile drugs and complies with 503B conditions
- Radiopharmaceuticals are not excluded
- Benefits
  - Exempt from premarket approval, adequate-directions-for-use requirement, and track & trace requirements
  - May compound and ship without prescriptions for individually identified patients. Therefore, may compound in large quantities for hospitals, clinics, etc.
  - No limits on interstate distribution
  - Need not be a licensed pharmacy (but compounding must be supervised by licensed pharmacist)
Section 503B (cont.)

• Conditions
  – Subject to registration, listing, same adverse event reporting as drug manufacturers, cGMPs, FDA inspections
  – Requirements for bulk drug substances
    • subject to positive and negative list and withdrawn drug list
  – Wholesaling prohibited
  – Special labeling requirements
  – May not compound drug that is essentially a copy of an approved drug unless drug is
    • On FDA's drug shortage list, or
    • Variation produces clinical difference, as determined by prescriber, between compounded drug and approved drug

What About Radiopharmaceutical Compounding?

• Regulatory vacuum again (like 1997-2002)
  – CPG 460.200 revoked in Dec. 2013 because superseded by DQSA
  – Radiopharmaceuticals remain excluded from Section 503A
  • Radiopharmaceutical compounders still “living in sin”
    – Unless nuclear pharmacy registers as an outsourcing facility, radiopharmaceutical compounding is not exempt from premarket approval, cGMPs, labeling, and other statutory requirements for new drugs
    – Like conventional drugs before DQSA, radiopharmaceutical compounding is permitted within enforcement discretion of FDA
  • However, FDA enforcement discretion is not currently limited by any regulation or guidance

FDA Developing Radiopharmaceutical Compounding Guidance

• Feb. 21, 2015: CORAR submitted letter to FDA requesting issuance of guidance on radiopharmaceutical compounding
  – CORAR also included a proposed a draft guidance
• FDA held Listening Sessions on radiopharmaceutical compounding on Sept. 24, 2014 and April 28, 2015
  – Invited attendees were APhA, CORAR, National Association of Nuclear Pharmacies, Society of Nuclear Medicine and Molecular Imaging, and United Pharmacy Partners, Inc.
• FDA is actively working on a guidance

II. Thorny Issues in the Regulation of Radiopharmaceutical Compounding

1. Preparation Versus Compounding

• FDA should regulate compounding but not “preparation”
• Industry understands preparation to include:
  – Preparing a radiopharmaceutical in accordance with instructions in the approved labeling
  – Making minor deviations from the manufacturer’s instructions to take into account geographical distance, improved technology, and other factors not anticipated by manufacturer
• Regulatory issue: How to distinguish between minor deviations and compounding?
  – Opposing considerations:
    • Pharmacies need latitude to deviate from label instructions to take into account patient-specific circumstances
    • But minor deviations should not be a loophole permitting pharmacies to avoid FDA oversight over compounding

Preparation Versus Compounding (cont.)

• Nov. 26, 2014: In response to FDA request for definition of “minor deviations” that should be considered preparation rather than compounding, APhA, CORAR, NANP, SNMMI, and UPPI submitted a joint letter defining terms
  – “Minor deviation” (preparation) is a deviation in
    1) radioactivity,
    2) volume, or
    3) step-by-step procedures for preparing patient-ready dose
  that is necessary to
  a) accommodate improvements in technique or technology,
  b) account for radioactive decay in shipment to patient, or
  c) account for other circumstances not contemplated in manufacturer’s directions
  – Addition of components not specified in labeling is not a minor deviation
  – Quality control testing required
Preparation Versus Compounding (cont.)

- Example of minor deviation in radioactivity: supplemental Tc-99m added for geographically distant patient
- Example of minor deviation in volume: supplemental normal saline added to reduce concentration where supplemental Tc-99m has been added
- Example of minor deviation in step-by-step procedures:
  - Use of smaller sterile evacuated vial than those supplied by manufacturer to reduce radiation exposure to personnel.

2. Identification of Patient on Prescription

- Section 503A and former CPGs require prescription to identify individual patient before dispensing
- Industry practice: for diagnostic radiopharmaceuticals, patient name may be obtained after dispensing, where permitted by state law
- Permits shipping drug to provider to have drug ready in case of emergency, or have drug on hand for evening or weekend hours when nuclear pharmacy is closed
- FDA appears to recognize this difference from conventional pharmacy practice
- Should flexibility on this issue extend to compounding as well as preparation?

3. Compounding Copies of Approved Products

- Notion that routinely compounding copies of approved products constitutes manufacturing is common to former CPGs, Section 503A, and Section 503B
- FDA (and manufacturers) view compounding copies as end-run around premarket approval
- Issue: What exceptions should be permitted?
  - Approved product no longer available
  - Approved product in shortage
  - Slight variation of approved product is medically necessary

Compounding Copies of Drugs in Shortage

- Section 503B precedent: Copy of approved drug may be compounded if it appears on FDA shortage list
- FDC Act Section 506C requires manufacturers of drugs that are intended for use in the prevention or treatment of a debilitating disease or condition to notify FDA of a permanent discontinuance or interruption in manufacturing that is likely to lead to a meaningful disruption in supply
  - Meaningful disruption is a "change in production that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product"
- Radiopharmaceuticals are exempt from requirement to report shortages
  - Radiopharmaceuticals were excluded to avoid possibility of multitude of reports triggered by batch failures
  - Radiopharmaceutical batch sizes are very small in comparison with conventional drugs
  - Failure of single batch may affect ability of manufacturer to fill orders in very short term, but has little ultimate effect on supply
  - Shortfall in one batch can be made up with subsequent batches over the following several days

Compounding Copy Where Medical Necessity

- Precedent
  - Former CPGs: slight variation of approved product may be compounded where substantiated by documentation of the medical need for an individual patient
  - Section 503A and 503B: variation of approved product may be compounded where it produces for an individual patient a significant difference, as determined by prescriber, between the compounded drug and the approved drug
- Issue: Should prescriber’s determination of medical need or "significant difference" be documented?
- Argument in favor: without documentation, requirement for medical need cannot be enforced by FDA and unscrupulous pharmacies will take advantage of the exception to market copies
- Argument against: requirement would burden pharmacies with task of chasing down medical need documentation from prescribers before any compound could be dispensed
  - The prescription itself is adequate evidence that prescriber wants compound to be dispensed

Copies of Drugs in Shortage (cont.)

- Issue: should compounding of copies be permitted where shortage exists that is not on FDA shortage list?
  - Argument in favor
    - Patients should have access to radiopharmaceutical that is in shortage but that may not have been reported to FDA
  - Argument against
    - If shortage is not defined by reference to published FDA list, there is no consistent way to determine whether there is a shortage that permits compounding of copy
    - Though not required to do so, manufacturers routinely report interruptions that threaten shortages, and radiopharmaceutical users also report shortages
4. Interstate Shipment

• Section 503A limits interstate shipment of compounded drugs
  – If pharmacy is in a state with MOU with FDA, limits on interstate shipment determined by MOU
  – If state does not have MOU, out-of-state shipments may not exceed 5% of total prescriptions dispensed or distributed by pharmacy

• Congress believed limit would:
  – Help prevent compounding pharmacies from growing into manufacturers operating interstate to make unapproved drugs
  – Avoid logistical problems states would face inspecting and regulating pharmacies located in other states

• FDA issued draft MOU on Feb. 13, 2015
  – Inordinate interstate distribution if number of units distributed out-of-state in calendar month is greater than 30% of all units dispensed or distributed by pharmacy

Interstate Shipment (cont.)

• Issue 1: Should interstate shipments of compounded radiopharmaceuticals be limited as under Section 503A?
  – Rationale for Section 503A limits applies equally to radiopharmaceuticals

• Issue 2: If so, what limit should apply?
  – Nuclear pharmacies are far fewer than conventional pharmacies and frequently serve two-state or multi-state area, so there is greater need to ship to contiguous states
  – However, need for pharmacy to ship radiopharmaceuticals beyond its own state and contiguous states is relatively rare
  – CORAR proposed interstate shipment limit of 20%, but shipments to contiguous states do not count as interstate

5. cGMPs

• Issue: At radiopharmaceutical compounding Listening Session, FDA asked stakeholders to comment on whether compounded radiopharmaceuticals should comply with cGMPs, similar to those applicable to PET drugs under 21 CFR Part 212

• cGMPs for compounded radiopharmaceuticals would effectively mean cGMPs for entire nuclear pharmacy, even if compounding is small percentage of business

• cGMP requirement for nuclear pharmacies would be inconsistent with FDC Act
  – cGMPs are required by statute for PET drugs and Section 503B pharmacies, but pharmacies compliant with Section 503A (including those that prepare sterile injectables) are exempt from cGMPs
  – No reason to treat nuclear pharmacies differently from Section 503A pharmacies
  – cGMPs inconsistent with retail pharmacy exemption from record inspections

  • Many cGMPs depend on records, which FDA is prohibited from inspecting at pharmacies

cGMPs (cont.)

• cGMPs are unnecessary and unsuited to activities of typical nuclear pharmacy, which does not involve manufacturing but preparation of just-in-time dispensing of unit doses

• Nuclear pharmacies do not have necessary equipment, personnel, floor plan, testing equipment, production and control records necessary for cGMP compliance

Looking Ahead: Key Points

• Nuclear pharmacy compounding (as distinct from preparation) is unlawful under FDC Act. It has historically been permitted in FDA’s discretion, but that discretion is currently not defined in any written document.

• We can expect FDA’s longstanding concerns about compounding to be reflected in the upcoming guidance on nuclear pharmacy compounding
  – Quality of ingredients
  – USP compliance
  – Patient-specific orders
  – Copies of commercially available drugs
  – Large volume of interstate shipment

• FDA’s approach to nuclear pharmacy compounding will have to take into account differences between radiopharmaceuticals and conventional drugs
  – Preparation in accordance with manufacturer instructions is core activity and is not
  – Minor deviations from instructions necessary because of short half life and other factors
  – Dispensing without patient name is accepted practice
  – Different threshold for inordinate interstate shipment because fewer pharmacies
  – Shortages not as easy to identify with certainty because of radiopharmaceutical exemption from reporting

Updates on Radiopharmaceutical Compounding

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Disclosures

• Vivian S. Loveless declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Nuclear Pharmacy Compounding Guidelines

• Prepared by Nuclear Pharmacy Compounding Practice Committee Section on Nuclear Pharmacy Practice (APhA-APPM)
• Approved by the APhA Board of Trustees

Goals of the Guidelines

• Address various issues related to nuclear pharmacy/nuclear medicine compounding practices
• Assist the FDA in the development of new regulatory guidance concerning radiopharmaceutical compounding

Nuclear Pharmacy Compounding Guidelines

• Definition of Compounding
  – “…preparation, mixing, assembling, packaging, or labeling of a drug (including a reagent kit or a radiopharmaceutical)…also includes the preparation of drugs (including radiopharmaceuticals) in anticipation of prescription orders based on routine, regularly observed prescribing patterns.”

Nuclear Pharmacy Compounding Guidelines

• Characteristics differentiating compounding from manufacturing:
  – Existence of specific practitioner-patient-pharmacist relationships
  – Quantity of medication prepared in anticipation of receiving a valid prescription or prescription order
  – Conditions of sale

Nuclear Pharmacy Compounding Guidelines (General Provisions)

• Radiopharmaceutical compounding and dispensing shall be in compliance with requirements of individual state boards of pharmacy and other pertinent regulatory agencies
• “Nuclear pharmacy compounding does not include mixing, reconstituting, or other such acts as performed in accordance or consistent with the directions contained in approved labeling or other manufacturer directions consistent with that labeling.”
Nuclear Pharmacy Compounding Guidelines

• Organization and Personnel
  – Nuclear pharmacists’ responsibilities
  – Nuclear pharmacy technicians’ role
  – Programs designed to enhance and maintain competence in compounding
  – Wear clean clothing appropriate to duties being performed
  – Exclusion of personnel due to illness or open lesion(s)

Nuclear Pharmacy Compounding Guidelines

• Compounding Environment
  – Facilities
  – Equipment

Nuclear Pharmacy Compounding Guidelines

• Sources of Compounding Drug Components
  – Bulk drug substance
  – Excipient

Nuclear Pharmacy Compounding Guidelines - Quality Control

• Quality control of eluate
• Visual inspection
• Assessment of radioactivity
• QC of dose calibrator
• Radionuclidic purity
• Radiochemical purity
• pH
• Verification of macroaggregate particle size and number
• Imprinted labeling
• Microbiological control and BET

Nuclear Pharmacy Compounding Guidelines – Stability

• Extemporaneously compounded parenteral radiopharmaceuticals used ≤ 24 hours unless data support longer storage
• Beyond-use time/date of any radiopharmaceutical or compounded reagent kit may be extended when there is valid supporting scientific stability information
• Compounded drug products should be checked for signs of instability

Nuclear Pharmacy Compounding Guidelines

• Primary packaging of compounded preparations
• Imprinted labeling for compounded preparations
• Compounding records and documents
• Storage requirements

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Radiopharmaceutical Vendor Qualification Checklist

- 2004: Accreditation organizations defined radiopharmaceuticals as medications
- Institutional pharmacy now has responsibility for medication management of radiopharmaceuticals
- 2013: APhA-APPM Nuclear Pharmacy Practice SIG Professional Practices Committee charged with developing evaluation tool for use by hospital pharmacists

Radiopharmaceutical Vendor Qualification Checklist

- Basic screening tool
- Supporting documentation may be needed to substantiate compliance
- Confirmation of appropriate operational procedures via a site visit

Radiopharmaceutical Vendor Qualification Checklist

- Section 1: Regulatory Compliance
- Section 2: Quality and Patient Safety Measures
- Section 3: Medication Administration Safety
- Section 4: Service Excellence – Critical and Essential Business Practices

USP <795> Pharmaceutical Compounding — Nonsterile Preparations

- Referenced in:
  - Nuclear Pharmacy Compounding Guidelines
  - Radiopharmaceutical Vendor Qualification Checklist

USP <795>

- Guidance: Good compounding practices in the preparation of nonsterile compounded formulations
- Good compounding practices
  - “Specialty areas such as radiopharmaceuticals require special training and are beyond the scope of this chapter.”

USP <797> Pharmaceutical Compounding-Sterile Preparations

- January 1, 2004: First became official
- June 1, 2008: 1st revision
- 2nd Revision (End of comment period: January 31, 2016)
USP <797> Pharmaceutical Compounding-Sterile Preparations

- Major proposed revisions include:
  - Reorganization of existing sections
  - Procedural information placed in boxes
  - Collapsing of the 3 CSP microbial risk categories into 2 categories
  - Removed information on handling of hazardous drugs but added cross-references to USP <800>
  - Introduction of the term "in-use time"
  - Definition of CSP

Proposed Revision: Compounded Sterile Preparations

- "A preparation intended to be sterile that is created by combining, diluting, pooling, or otherwise altering a drug product or bulk drug substance. A product produced by reconstituting a conventionally manufactured product for an individual patient strictly in accordance with directions contained in the approved labeling provided by the product manufacturer is not considered a CSP for the purposes of this chapter."

USP <797> Proposed Revisions

- Urgent-Use CSPs
  - CSP prepared in worse than ISO Class 5 air quality in rare circumstances when a CSP is needed urgently
  - Compounding procedure has to be a continuous process completed in ≤ 1 hour
  - Aseptic technique must be used

USP <797> Proposed Revisions

- Radiopharmaceuticals as CSPs
  - Considered compounding if not prepared in strict conformance with manufacturer's package insert
  - ALARA principles apply
  - Radioisotope generator systems eluted in an ISO Class 8 or cleaner air environment
  - Radioisotope system producing a radioisotope with a half-life ≤ 15 minutes can be eluted at the point of care

USP <797> Proposed Revisions

- Visual inspection conducted in accordance with ALARA principles
- Compounding personnel must be gowned and garbed according to Section 3 Personal Hygiene and Personal Protective Equipment
  - Whole body radiation dosimeters worn underneath the gown; ring/wrist badges worn under gloves

USP <797> Proposed Revisions

- Same PPE cannot be worn in cleanroom and patient care area
- Radiolabeling leukocytes: separate, dedicated ISO Class 7 area containing a PEC
- Volatile or gaseous preparations may require pressurization configurations different from what is described in Section 4 Buildings and Facilities
USP <797> Proposed Revisions

- Compounding of nonradioactive compounds may be performed in the same compounding area used for preparing radioactive compounds if:
  - ISO Class 5 area is decontaminated and monitored for radioactivity greater than background levels
  - Dose calibrator remains inside the PEC
  - PEC is operated in accordance with this chapter’s standards when nonradioactive CSPs are being prepared

Points to Consider

- USP monographs
  - Radioactive Drugs Expert Panel
- USP <821>
- USP <800>

Guidance Documents

- Guidance for Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act
- Guidance For Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

9/24/14 FDA Listening Session on Radiopharmaceutical Compounding

- Organizations represented at the meeting:
  - APhA
  - CORAR
  - NANP
  - UPPI
  - SNMMI

Consensus Statement

- Minor deviations from the instructions in the FDA-approved labeling apply:
  - Only to very short-lived radiopharmaceuticals
  - Changes in radioactivity
  - Changes in volume
  - Changes in the step-by-step procedures for preparing the radiopharmaceutical in a patient-ready dose

April 28, 2015: 2nd FDA Listening Session

- FDA raised questions regarding the proposed consensus definitions for “radiopharmaceutical preparation” and “radiopharmaceutical compounding”
- Follow-up on July 15, 2015
Follow-Up Letter

• “Radiopharmaceutical preparation” vs. “radiopharmaceutical compounding”
• Patient-specific prescriptions
• Compounding from Bulk Substances/Shortages
• Interstate distribution

Key Points

• Compounding vs. preparation
• State board of pharmacy regulations
• Unique practice
• Regulatory requirements

Self-Assessment Questions

1. Which of the following are “new drugs” under the Federal Food, Drug, and Cosmetic Act?
   a. Compounded non-radioactive drugs
   b. Compounded radiopharmaceuticals
   c. PET drugs
   d. All of the above

2. Which of the Following Authorities Does/Did Not Apply to Radiopharmaceuticals?
   a. FDA Compliance Policy Guide 7132.16, “Pharmacy Compounding” (1992)
   c. Nuclear Pharmacy Guideline
   d. FDC Act Section 503A, “Pharmacy Compounding”
   e. FDC Act Section 503B, “Outsourcing Facilities”

3. Under former FDA pharmacy compounding CPGs and the current FDC Act, which of the following has never been a permissible reason to compound a copy of, or minor variation from, a commercially available drug?
   a. The commercially available drug is on FDA’s drug shortage list
   b. The pharmacy has determined that a patient is unable to bear the expense of the commercially available product
   c. The prescriber has determined that there is a medical need for a variation for a particular patient
4. In the consensus statement from the organizations representing nuclear pharmacy/nuclear medicine to the FDA in 2014, a minor deviation includes all of the following EXCEPT:
   a. Addition of components not specified in the FDA-approved labeling
   b. Change in quality control instrumentation, such as a NaI(Tl) well chamber instead of a dose calibrator
   c. Change in the quantity of radioactivity added to the kit
   d. Change in the final volume of the kit

5. Under the proposed revision for USP <797>, what is the time limit for the compounding procedure for an Urgent-Use CSP?
   a. 0.25 hour
   b. 0.5 hour
   c. 1 hour
   d. 2 hours