Missouri Board of Pharmacy
Nuclear Pharmacy Working Group

February 28, 2018
9:00 a.m.
Missouri Division of Professional Registration
3605 Missouri Blvd.
Jefferson City, MO 65109

The Missouri Board of Pharmacy has convened a Nuclear Pharmacy Working Group to review Missouri's regulation of nuclear pharmacy. Notice is hereby given that the Nuclear Pharmacy Working Group will be meeting at 9:00 a.m. on February 28, 2018. A tentative agenda is attached. If any member of the public wishes to attend, s/he should be present at the Missouri Division of Professional Registration, 3605 Missouri Blvd., Jefferson City, Missouri at 9:00 a.m. on February 28, 2018.

The Working Group may go into closed session at any time during the meeting pursuant to § 610.021.(1) for purposes of legal advice. If the meeting is closed, the appropriate section will be announced to the public with the motion and vote recorded in open session minutes.

Notification of special needs as addressed by the Americans with Disabilities Act should be forwarded to the Missouri Board of Pharmacy, P O Box 625, 3605 Missouri Blvd., Jefferson City, Missouri 65102, or by calling (573) 751-0091 to ensure available accommodations. The text telephone for the hearing impaired is (800) 735-2966.

A tentative agenda for this meeting is attached.
TENTATIVE AGENDA
Missouri Board of Pharmacy
Nuclear Pharmacy Working Group

February 28, 2018
9:00 a.m.
Missouri Division of Professional Registration
3605 Missouri Blvd.
Jefferson City, MO 65109

1. Welcome & Introductions

2. 20 CSR 2220-2.500 (Nuclear Pharmacy- Minimum Standards for Operation) & Potential Rule Changes
   a. Current Rule
   b. Working Group Proposed Changes (1-9)

3. Beyond-Use Dates/In-Use Times for Nuclear Pharmacy
4. Product Labeling for the Preparation of Radiopharmaceuticals
5. ISO-8 Buffer Areas & Nuclear Pharmacies
6. Future Agenda Topics/Meetings
6. Adjournment
PURPOSE: This rule defines minimum standards for the operation of nuclear pharmacies and the preparation, labeling, dispensing or delivering of compounded radiopharmaceuticals pursuant to a prescription drug or medication order. This regulation is intended to supplement other regulations of the Board of Pharmacy, as well as those of other state and/or federal agencies.

(1) Definitions.

(A) “Address of Use” means the building or buildings that are identified on the license and where byproduct material may be received, prepared, used, or stored as defined by 10 CFR 35.2 or a temporary job site for providing mobile nuclear medicine services in accordance with 10 CFR 35.80.

(B) “Adult” means an individual 18 or more years of age.

(C) “Agreement State” means any state that has entered into an agreement under subsection 274b of the Atomic Energy Act of 1954, as amended, in which the United States Nuclear Regulatory Commission has relinquished to such states the majority of its regulatory authority over source material, by-product, and special nuclear material in quantities not sufficient to form a critical mass.

(D) “Area of use” means a portion of an address of use that has been set aside for the purpose of receiving, preparing, using or storing byproduct material.

(E) “Authentication of product history” means identifying the purchasing source, the ultimate fate, and any intermediate handling of any component of a radiopharmaceutical or other drug.

(F) “Authentication of product history” means identifying the purchasing source, the ultimate fate, and any intermediate handling of any component of a radiopharmaceutical or other drug.

(G) “Authorized nuclear pharmacist” means a pharmacist who holds a current license issued by the board and who is either certified as a nuclear pharmacist by the Board of Pharmaceutical Specialties, has attained status as an authorized nuclear pharmacist or an authorized user of radioactive material, as specified by the Nuclear Regulatory Commission or Agreement State regulations, including, but not limited to, 10 CFR 35.55, 35.57 and 35.59.

(H) “Contingency Prescription Drug Order”- A radioactive prescription drug order issued for contingency material for a diagnostic purpose.

(I) “Controlled Access Area” means an area outside of the restricted area but inside the pharmacy, access to which will be limited to the public.

(J) The “practice of nuclear pharmacy” means a patient-oriented service that embodies the scientific knowledge and professional judgment required to improve and promote health through the assurance of the safe and efficacious use of radiopharmaceuticals and other drugs.

(K) “NRC” means the United States Nuclear Regulatory Commission.
(L) “Nuclear pharmacy” means the location that provides radiopharmaceutical services and where radiopharmaceuticals and chemicals within the classification of legend drugs, are compounded, dispensed, stored, sold or used for nuclear medicine procedures. The term “nuclear pharmacy” does not include the nuclear medicine facilities of hospitals or clinics where radiopharmaceuticals are compounded or dispensed to patients under the supervision of a licensed physician, authorized by the Nuclear Regulatory Commission or Agreement State regulations.

(M) “Nuclear pharmacy technician” means a person who assists a pharmacist in the practice of nuclear pharmacy:

   (1) is currently registered as a pharmacy technician with the Board of Pharmacy;
   (2) works under the direct supervision of a nuclear pharmacist; and
   (3) (i) has successfully completed a nuclear pharmacy technician training program provided by an accredited college program or an equivalent company sponsored program approved by the Board, or
          (ii) is listed as an “Authorized User of Radioactive Materials” on a nuclear pharmacy's United States Nuclear Regulatory Commission or Agreement State license, provided the nuclear pharmacy is licensed by the Board or in another state.

   (iv) A nuclear pharmacy technician does not include individuals engaged in delivering radiopharmaceuticals provided he/she does not otherwise assist a pharmacist in the practice of pharmacy.

(N) “Preparing” of radiopharmaceuticals means the addition of a radioactive substance, or the use of a radioactive substance in preparation of a single-dose or multiple-dose medication, pursuant to the prescription of an authorized practitioner for a patient who is being treated by that practitioner. Such preparing of radiopharmaceuticals includes, but is not limited to, loading and eluting of radionuclide generators, using manufactured reagent kits to prepare radiopharmaceuticals, preparing reagent kits, aliquoting reagents and conducting quality assurance tests of radiochemicals which are to be used as radiopharmaceuticals. Appropriate safety and containment techniques for compounding radiopharmaceuticals shall be used in conjunction with the aseptic techniques required for sterile preparations.

(O) “Prescription Drug Order” means a radioactive prescription drug order issued for a specific patient for a diagnostic or therapeutic purpose.

(P) “Quality control testing” means the performance of appropriate chemical, physical and radionuclidic purity tests on radiopharmaceuticals and the interpretation of the resulting data to determine their suitability for use in humans and animals.

(Q) “Quality assurance procedures” means all activities necessary to assure the quality of the process used to provide radiopharmaceutical services, including authentication of product history and maintenance of all records as required by pertinent regulatory agencies.
(R) “Radiopharmaceutical” means any drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term “radiopharmaceutical” also includes any biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

(S) “Radiopharmaceutical services” means the procurement, storage, handling, compounding, preparation, labeling, quality control testing, dispensing, delivery, transfer, record keeping and disposal of radiochemicals, radiopharmaceuticals and ancillary drugs; the participation in radiopharmaceutical selection and radiopharmaceutical utilization review, and also includes quality assurance procedures, radiological health activities, any consulting activities associated with the use of radiopharmaceuticals, health physics, and any other activities required for provision of pharmaceutical care; the responsibility for advising, where necessary or where regulated, of therapeutic values, hazards and use of radiopharmaceuticals; and the offering or performing of those acts, services, operations, or transactions necessary in the conduct, operation management and control of a nuclear pharmacy.

(T) “Restricted Area” means an area within the pharmacy that is secured from the Controlled Access Area and to which access is limited for the purpose of protecting individuals against exposure to radiation and radioactive materials.

(U) “Temporary job site”- A location where mobile medical services are conducted other than those location(s) of use authorized on the license.

(V) “Therapeutic Prescription Drug Order” means a radioactive prescription drug order issued for a specific patient for blood products or for a therapeutic purpose.

(W) “Transport Container”- A container designed for doses of radiopharmaceutical agents and to prevent or minimize/reduce the emission of radiation or radioactive materials by using appropriate shielding materials. Such container shall include an effective mechanism to prevent contamination of the container with biohazardous materials.

(2) General Requirements for Pharmacists/Pharmacies Providing Radiopharmaceutical Services.

(A) No person may receive, acquire, possess, compound, dispense, transfer, dispose or manufacture for sale or resale any radiopharmaceutical except in accordance with the provisions of this rule and the conditions of rules and regulations promulgated by the Nuclear Regulatory Commission or applicable Agreement State.

(B) For nuclear pharmacies handling radiopharmaceuticals exclusively, the Board of Pharmacy may waive regulations that do not pertain to the practice of nuclear pharmacy.

(C) Nuclear Pharmacies shall post, in a conspicuous area of the pharmacy, a copy of the current registration with the Board of Pharmacy and a copy of the most current U.S. NRC
license which details a listing of its authorized nuclear pharmacists, and/or a copy, of a reference to its specific location within the pharmacy.

(D) A Nuclear Pharmacy must have on file a copy of the current radioactive materials license for the licensed facility requesting any radiopharmaceutical before the radioactive drug is permitted to be dispensed to that facility. The radiopharmaceutical may only be delivered to the authorized addresses or locations listed in, or temporary job sites as authorized by, the NRC/Agreement State license. The authorized physician ordering radiopharmaceuticals is hereby recognized as the patient’s authorized designee for delivery purposes. This regulation is an exemption for Class E permit holders to 20 CSR 2220-2.013 Prescription Requirements, which details authorized delivery sites.

(E) Nuclear pharmacies shall comply with any applicable requirements of other governing agencies regarding its daily operations and the disposal of any biohazardous medical waste.

(F) No pharmacy shall utilize a reusable unit dose container for radioactive doses without either an effective process to decontaminate the container of biohazardous substances or an effective mechanism to avoid contamination of the container. No pharmacy may reuse a unit dose container that remains contaminated with blood or other biohazardous substances. Any container that is returned shall be considered to be contaminated.

(G) Appropriate labeled and shielded disposal containers shall be used for radioactive waste from the preparation of radiopharmaceuticals. Appropriate labeled disposal containers shall be used for biohazardous waste generated from patient cell labeling procedures or returned syringes. Disposal of biohazardous waste shall comply with all applicable local, state and federal requirements.

(H) Nothing in this rule shall be construed as requiring a licensed clinical laboratory, which is also licensed by the Nuclear Regulatory Commission or Agreement State to handle radioactive materials, to obtain the services of a nuclear pharmacist, or to have a pharmacy permit, unless the laboratory is engaged in the commercial sale or resale of radiopharmaceuticals.

(I) Nothing in this rule shall be construed to require a department of nuclear medicine which is located in a hospital, which has a physician board certified in his/her specialty and which is licensed by the Nuclear Regulatory Commission or Agreement State to handle radioactive materials, to obtain the services of a pharmacist or to have a nuclear pharmacy license for radiopharmaceutical preparation, distribution and delivery to patients within that institution. I would suggest striking this entire paragraph because it isn’t needed given the Bd’s limited jurisdiction over hospitals or removing the physician language since we don’t have authority to require bd. certification.

(J) A Class E pharmacy may accept returns as authorized by the NRC/Agreement State regulations.

(3) Permits. Any pharmacy providing radiopharmaceutical services must obtain a Class-E radiopharmaceutical permit from the Board.
(A) A permit to operate a nuclear pharmacy shall only be issued to a person who is, or who employs, an authorized nuclear pharmacist. All personnel performing tasks in the preparation and dispensing of radiopharmaceuticals and ancillary drugs shall be under the direct supervision of an authorized nuclear pharmacist. The pharmacist-in-charge shall be an authorized nuclear pharmacist and be responsible for all operations of the pharmacy.

(B) The permit to operate a nuclear pharmacy is effective so long as the pharmacy also holds a current Nuclear Regulatory Commission and/or Agreement State radioactive materials license. Copies of all regulatory inspection reports shall be made available upon request to the board for inspection.

(C) The nuclear pharmacist-in-charge shall notify the Board of Pharmacy by letter of the outcome of any hearings under state or federal laws or regulations governing radioactive materials involving or against the pharmacy location licensed by the Board. Notification must be within thirty days of the date of the outcome.

(4) Space, Security, Record Keeping and Equipment.

(A) Nuclear pharmacies shall have adequate space and equipment, commensurate with the scope of services provided and as required by the Nuclear Regulatory Commission or Agreement State radioactive materials license or as required by 20 CSR 2220-2.200, 20 CSR 2220-2.400 or other applicable rules of the Board. All pharmacies handling radiopharmaceuticals shall include, but not be limited to, the following areas:

1. Radiopharmaceutical nonsterile and sterile preparation/dispensing area;
2. Radioactive material shipping/receiving area;
3. Radioactive material storage area; and
4. Radioactive waste decay area.

(B) The nuclear pharmacy restricted area shall be secured against unauthorized personnel and must be totally enclosed and lockable.

(C) Nuclear pharmacies shall maintain records of acquisition, inventory and disposition of all radioactive drugs and other radioactive materials in accordance with State Board of Pharmacy, Nuclear Regulatory Commission.

(D) Nuclear pharmacies shall prepare and dispense radiopharmaceuticals in accordance with accepted standards of radiopharmaceutical practice.

(5) Dispensing, Packaging, Labeling.

(A) A radiopharmaceutical shall be dispensed only to a practitioner or facility authorized by the Nuclear Regulatory Commission or an Agreement State to possess, use and administer such drug for patient use, provided that a radiopharmaceutical may be transferred to a person who is authorized to possess and use the drug for nonclinical applications in accordance with the regulations of the NRC/Agreement State and the occasional transfer of bulk quantities of radiopharmaceuticals to other authorized persons to meet shortages. A radiopharmaceutical shall not be dispensed directly to a patient.
The amount of radioactivity shall be determined by dose calibrator, appropriate radiometric methods or decay calculation methods for each individual dose immediately prior to dispensing. Radioactive drugs are to be dispensed only upon a non-refillable prescription order from a practitioner or facility authorized by the Nuclear Regulatory Commission or Agreement State to possess, use and administer radiopharmaceuticals or the practitioner’s/facility’s designated agent. The prescription order/contingency prescription drug order must be taken by an authorized nuclear pharmacist, intern pharmacist, pharmacy technician or designated agents. Only pharmacists may receive prescription orders for therapeutic radiopharmaceuticals and blood products. The prescription record shall contain all information as required in 20 CSR 2220-2.018 Prescription Requirements and shall also include:

1. The date of dispensing and the calibration time of the radiopharmaceutical; and
2. The patient’s name for therapeutic radiopharmaceuticals and blood products.

The labeling requirements in subsection (E) shall not apply to outer United States Department of Transportation Type A transport containers.

The unit dose container of a radiopharmaceutical to be dispensed shall be labeled with—

1. The name and address of the pharmacy;
2. The name and address of the authorized prescriber/facility where the prescription order is to be administered;
3. The date of dispensing and a unique readily retrievable identifier;
5. The standard radiation symbol;
6. The words “Caution Radioactive Material”;
7. The name of the procedure, if known;
8. The name or generally recognized and accepted abbreviation of the radiopharmaceutical radionuclide and chemical form;
9. The requested amount of radioactivity at the calibration date and time;
10. The radiopharmaceutical beyond-use date;
11. The quantity dispensed;
12. If applicable, Molybdenum-99 content to United States Pharmacopoeia (USP) limits of $<0.15 \text{uCi Mo-99 per 1mCi Tc-99m}$ at time of administration or product expiration; and
13. The patient name or the words “Physician’s Use Only” or “Per Physician’s Order” or similar wording in the absence of a patient name. When the prescription is for a therapeutic or blood-product pharmaceutical, the patient name shall appear on the label. The requirements of this paragraph shall be met when the name of the patient is readily retrievable within a reasonable amount of time from the physician upon demand.

The immediate inner container label of a radiopharmaceutical to be dispensed shall be labeled with—

1. The standard radiation symbol;
2. The words “Caution Radioactive Material”;

3. The identity of the radiopharmaceutical;
4. The unique readily retrievable identifier of the radiopharmaceutical; and
5. The patient’s name, if known or the words “Physician’s Use Only” or “Per Physician’s Order” or similar wording in the absence of a patient name..

(G) Radioactive drugs approved by the United States Food and Drug Administration are not subject to the unit dose container labeling requirements in subsection (E) or the radiometric measurement requirements of this rule if the nuclear pharmacy does not process the radioactive drugs in any manner nor violate the original manufacturer product packaging/labeling.

(6) Reference Manuals. Each nuclear pharmacy shall have a current copy of, or electronic access to:
   
   (A) Applicable reference materials required by 20 CSR 2220.2010 and 20 CSR 2220-2.200; and
   
   (B) Agreement State and/or NRC regulations governing the safe storage, handling, use, dispensing, transport and disposal of radioactive material, including but not limited to Title 10 and Title 49 of the United States Code of Federal Regulations.

(7) Special Conditions:

   (A) To comply with NRC exposure guidelines of keeping radiation exposure as low as reasonably achievable (ALARA), an alternate means of pharmacist inspection/verification of the final product/preparation may be used \[if a pharmacist has previously verified the correct ingredients, calculations, prescription drug order information and label have been prepared or selected for use prior to preparation\]. Alternate means may include, but are not limited to, the use of standardized operation protocols, radiation measurement devices, bar-coding technology, or software that requires pharmacist intervention for any action outside of protocols.

OTHER ISSUES TO BE ADDRESSED:

- Required amendments to the sterile compounding rule (need to address things like in-use time vs. beyond-use-date, aseptic technique when moving in and out of the compounding area, staging, hand sanitation)

Kim,  

Thank you for the expedient update.  

I’ve found additional copy/paste regulations for the DOT Type A transport containers. Of note, these regulations are exhaustive and meant to cover all radioactive material (RAM) transport (from our medical use material on the low end to radioactive reactor waste). So Type A is for radiopharmaceutical use whereas the Type B are meant to be the size of 18 wheeler trailer and survive impacts with locomotives.

I also underlined a portion that requires absorbent material in transport containers (the NRC/CFR requires the use absorbent material for all liquid forms of RAM in other regulations – that includes pig containers and kit shields). I point this out because CAH keeps the absorbent material in the cap of the pig out of the buffer area (to minimize particle generation) but the kit shields are required to be used in the PEC and buffer area. As part of dynamic certification testing, the kit shields are used during testing and have yet to cause any issues – mostly because the shields are typically closed when loaded with a kit. As such, the kit effectively blocks the opening for any particles to escape. I can bring examples to our next meeting if you would like (or send pics).

173.412 Additional design requirements for Type A packages.  
In addition to meeting the general design requirements prescribed in §173.410, each Type A packaging must be designed so that—

(a) The outside of the packaging incorporates a feature, such as a seal, that is not readily breakable, and that, while intact, is evidence that the package has not been opened. In the case of packages shipped in closed transport vehicles in exclusive use, the cargo compartment, instead of the individual packages, may be sealed.

(b) The smallest external dimension of the package is not less than 10 cm (4 inches).

(c) Containment and shielding is maintained during transportation and storage in a temperature range of -40 °C (-40 °F) to 70 °C (158 °F). Special attention shall be given to liquid contents and to the potential degradation of the packaging materials within the temperature range.

(d) The packaging must include a containment system securely closed by a positive fastening device that cannot be opened unintentionally or by pressure that may arise within the package during normal transport. Special form Class 7 (radioactive) material, as demonstrated in accordance with §173.469, may be considered as a component of the containment system. If the containment system forms a separate unit of the package, it must be securely closed by a positive fastening device that is independent of any other part of the package.

(e) For each component of the containment system account is taken, where applicable, of radiolytic decomposition of materials and the generation of gas by chemical reaction and radiolysis.

(f) The containment system will retain its radioactive contents under the reduction of ambient pressure to 60 kPa (8.7 psia).

(g) Each valve, other than a pressure relief device, is provided with an enclosure to retain any leakage.
(h) Any radiation shield that encloses a component of the packaging specified as part of the containment system will prevent the unintentional escape of that component from the shield.

(i) Failure of any tie-down attachment that is a structural part of the packaging, under both normal and accident conditions, must not impair the ability of the package to meet other requirements of this subpart.

(j) When evaluated against the performance requirements of this section and the tests specified in §173.465 or using any of the methods authorized by §173.461(a), the packaging will prevent—

1. Loss or dispersal of the radioactive contents; and
2. A significant increase in the radiation levels recorded or calculated at the external surfaces for the condition before the test.

(k) Each packaging designed for liquids will—

1. Be designed to provide for ullage to accommodate variations in temperature of the contents, dynamic effects and filling dynamics;
2. Meet the conditions prescribed in paragraph (j) of this section when subjected to the tests specified in §173.466 or evaluated against these tests by any of the methods authorized by §173.461(a); and
3. Either—
   
   i. Have sufficient suitable absorbent material to absorb twice the volume of the liquid contents. The absorbent material must be compatible with the package contents and suitably positioned to contact the liquid in the event of leakage; or
   
   ii. Have a containment system composed of primary inner and secondary outer containment components designed to enclose the liquid contents completely and ensure retention of the liquid within the secondary outer component in the event that the primary inner component leaks.

(l) Each package designed for gases, other than tritium not exceeding 40 TBq (1080Ci) or noble gases not exceeding the A2 value appropriate for the noble gas, will be able to prevent loss or dispersal of contents when the package is subjected to the tests prescribed in §173.466 or evaluated against these tests by any of the methods authorized by §173.461(a).

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“Fear defeats more people than any other one thing in the world.”
-- Ralph Waldo Emerson, writer
Deficiencies of Product Labeling Directions for the Preparation of Radiopharmaceuticals

Joseph C. Hung, James A. Ponto, Katie R. Gadient, Julia A. Frie, Carolyn M. Aksamit, Cassandra L. Enquist, and Katie E. Carrels

ABSTRACT

Objective: To identify potential deficiencies in product labeling (package insert) instructions for the preparation of radiopharmaceuticals.

Methods: Preparation instructions, which include both reconstitution and quality control (QC) directions, as stated in the package inserts were evaluated for all commercially available reconstituted radiopharmaceuticals. Reviews of the package inserts were initially performed by each author, and then all identified deficiencies were compiled and evaluated by all authors. The preparation scenario for each package insert evaluated was based on a centralized nuclear pharmacy operation assuming typical support personnel, standard operating equipment, and workload.

Main Outcome Measure: The instructions as stated in each package insert for the preparation (including QC) were rated as inadequate if a satisfactory preparation could not be prepared by a nuclear pharmacist or physician when instructions were followed exactly.

Results: Identified deficiencies in package insert instructions for the preparation of radiopharmaceuticals fell into the following five categories: (1) absent or incomplete directions (especially with regard to QC procedures); (2) restrictive directions (e.g., specific requirement to use designated needles, chromatography solvents, counting devices), (3) inconsistent directions (e.g., different reconstituted volumes for the same final drug product, unworkable expiration times); (4) impractical directions (e.g., unrealistically low reconstituted activity limits, dangerously high number of radiolabeled particles); and (5) vague directions (e.g., use of the words “should,” “may,” “recommend”).

Conclusion: Manufacturers’ directions for the preparation of radiopharmaceuticals often contain deficiencies and should be viewed as standard guidance rather than as requirements. Just as physicians are permitted to use U.S. Food and Drug Administration (FDA)-approved drugs for off-label indications, nuclear pharmacists should be allowed to use alternative methods for preparing radiopharmaceuticals, provided those methods have been validated to be as good as the stated directions and that the nuclear pharmacists do not engage in activities that fall outside the normal practice of pharmacy. Manufacturers, FDA, nuclear pharmacists, and nuclear physicians should work together to address identified deficiencies in package insert directions.

Keywords: Product labeling, radiopharmaceutical, preparation, reconstitution, quality control, nuclear pharmacy, Food and Drug Administration.

Many radioactive drugs used in the nuclear medicine field can be extemporaneously prepared with the use of a reagent kit and a radioactive solution containing a radioisotope such as technetium Tc 99m, indium In 111, or yttrium Y 90. A radiopharmaceutical reagent kit is simply a sterile reaction vial containing lyophilized (freeze-dried) nonradioactive chemicals that are required to produce a specific radiopharmaceutical after reaction with a radioactive solution. Following reconstitution, quality control (QC) tests (e.g., physical appearance, radiochemical purity, pH) must be performed on the reconstituted radiopharmaceuticals to ensure their safety and effectiveness.

Product labeling, herein referred to as package inserts, for commercially marketed radiopharmaceuticals include a section listing preparation instructions. This section is intended to provide a nuclear pharmacist with the necessary directions for preparing the radiopharmaceutical product on-site, as well as instructions concerning the procedure for QC testing of the individual drug product. In general, information presented in the package insert is based on the clinical and nonclinical data a drug manufacturer has collected regarding the pharmacology, toxicology, adverse effects, and radiation dosimetry for the finished product as prepared in accordance with the specified directions.

Once a drug product (including a radiopharmaceutical) is approved by the U.S. Food and Drug Administration (FDA), the finished drug product, prepared in accordance with the package insert directions, is considered to be safe and effective for use in its labeled indication. However, various package insert instructions for preparing (including QC testing) radiopharmaceuticals are sometimes suboptimal. If strictly followed as stated in a package insert, some of these instructions may present the nuclear pharmacist (or physician) with various obstacle(s), expose him or her to radiation unnecessarily, or potentially lead to errors. Also, some package inserts may contain inadequate or confusing preparation directions. The poor quality, restrictive nature, and/or impracticality of various package insert instructions for preparing and testing radiopharmaceuticals may inhibit the production of safe and effective final products by the nuclear pharmacist.

**Objectives**

The purpose of our project was to identify potential deficiencies in package insert instructions for the preparation of radiopharmaceuticals.

**Methods**

We evaluated preparation instructions, which include both reconstitution and QC directions, as stated in the package inserts for all reconstituted radiopharmaceuticals that are commercially available in the United States (see Table 1). The preparation scenario for each reconstituted radiopharmaceutical was based on a centralized nuclear pharmacy operation or large institutional nuclear pharmacy with typical support personnel (e.g., nuclear pharmacist, pharmacy technician, or nuclear medicine technologist), standard operating equipment (e.g., dose calibrator, QC reagents and equipment), and routine workload (e.g., in-house clinical/research studies, commercial distribution).

The package inserts we evaluated were obtained from three resources: various reagent kits used in our nuclear pharmacy laboratories, the manufacturers, and the official Web sites for the drug products. Reviews of each package insert were conducted separately by each author, and then the problems identified were evaluated by all authors. Every effort was made (e.g., via telephone or written communications with the manufacturers) to ensure that the labeling for each product was the most current version. A total of 31 package inserts, accounting for 24 reconstituted radiopharmaceuticals (generic reagent kits are usually available from several manufacturers), were studied.

Each reviewer was instructed to review the preparation directions, including QC requirements, presented in each package insert as if he or she was about to reconstitute the associated radiopharmaceutical and to evaluate whether the package insert instructions were adequate to allow him or her to complete the preparation process in a practical and unambiguous manner. All identified deficiencies were confirmed by all authors and then categorized. The numbers of deficiencies in each category were then tabulated accordingly (see Table 2).

**Results**

We identified five categories of deficiencies based on the evaluated package insert instructions for the preparation of various radiopharmaceuticals:

1. Absent or incomplete directions (especially with regard to QC procedures).
2. Restrictive directions (e.g., specific requirements to use designated needles, chromatography solvents, counting devices, reconstitution process).

3. Inconsistent directions (e.g., different reconstituted volumes for the same final drug product, unworkable expiration times).

4. Impractical directions (e.g., unrealistically low reconstituted activity limits, dangerously high number of radiolabeled particulate matter).

5. Vague direction (e.g., use of the words “should,” “may,” “recommend”).

Example(s) of each type of deficiency from the reviewed package inserts appear below. Italics indicate text excerpted from a package insert; certain phrases or words are underlined to emphasize our points. We identified a total of 426 deficiencies in the 31 package inserts evaluated (Table 2).

Absence or Incomplete Directions

- Package insert for TechneScan HDP (kit for the preparation of Tc 99m oxidronate injection), Mallinckrodt Inc., St. Louis, Mo., August 2000.
  
  **Comment:** No QC methods or requirements are described.¹

- “The radiochemical purity of the prepared radiopharmaceutical should be checked prior to patient administration”—Step 12 of the Directions for Use section, package insert for CIS-Sulfur Colloid (kit for the preparation of Tc 99m sulfur colloid injection), CIS-US, Inc., Bedford, Mass., July 2002.²

  **Comment:** No specific description of the testing procedure or acceptance limit is given.

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1. This reference is not provided in the text.
2. This reference is not provided in the text.
Table 2. Types and Numbers of Deficiencies Identified in Radiopharmaceutical Package Inserts

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent or incomplete directions</td>
<td>81</td>
</tr>
<tr>
<td>Restrictive directions</td>
<td>41</td>
</tr>
<tr>
<td>Inconsistent directions</td>
<td>9</td>
</tr>
<tr>
<td>Impractical directions</td>
<td>26</td>
</tr>
<tr>
<td>Vague directions</td>
<td>269</td>
</tr>
<tr>
<td>Total number of identified deficiencies</td>
<td>426</td>
</tr>
</tbody>
</table>

Restrictive Directions

- “Remove and cut … and measure the counts per minute (CPM)” — Step 10B of the Directions for Radiolabeling ProstaScint (Capromab Pendetide) with Indium In 111 Chloride section, package insert for ProstaScint (kit for the preparation of In 111 capromab pendetide injection), Cytogen Corporation, Princeton, N.J., August 7, 1997.3

**Comment:** A radionuclide dose calibrator does not measure radioactivity in CPM; therefore, the above statement would seem to indicate that a dose calibrator could not be used in the QC evaluation of In 111 capromab pendetide.

- “Using aseptic venipuncture … fitted with a 19 or 20 gauge needle, withdraw approximately 40 mL whole blood” — Step 2 of the Procedure for Radiolabeling of Autologous Leukocytes With Technetium Tc99m Exmetazime Injection section, package insert for Ceretec (kit for the preparation of Tc 99m exametazime injection), Medi-Physics, Inc., Arlington Heights, Ill., December 2000.4

**Comment:** Does this mean that one cannot use a needle of a different size (e.g., 18 gauge) or a different device (e.g., intravascular catheter) for blood withdrawal? Does this mean that one cannot use a volume of whole blood less than 40 mL (e.g., for a pediatric patient with a markedly elevated white blood cell count) or a volume of whole blood more than 40 mL (e.g., for a neutropenic adult patient)?

- “If required, use nonbacteriostatic normal saline to dilute the sodium pertechnetate Tc 99m solution to the desired concentration prior to addition to the vial.” — Step 3 of the Procedure for the Preparation of Technetium Tc 99m Mertiatide section, package insert for TechneScan MAG3 (kit for the preparation of Tc 99m mertiatide injection), Mallinckrodt Inc., St. Louis, Mo., August 2000.5

**Comment:** It is standard procedure to use the same syringe to withdraw Tc 99m and to dilute with normal saline in order to achieve the required radioactive concentration before adding it to the vial. However, Mackenzie6 showed that the radiation dose to the hands can be substantially reduced if two syringes are used (one for drawing up Tc 99m and another for drawing up a quantity of normal saline and then adding the contents of each syringe separately to a vial to obtain the desired concen-

tration). Bogsrud et al.7 demonstrated that the two syringe approach has no detrimental effects on the labeling efficiency and/or in vitro stability of the final Tc 99m radiopharmaceuticals that we tested.

Inconsistent Directions

- “Using a 10 mL syringe, inject into the shielded vial 5 mL of sterile eluate from a technetium Tc99m generator (see notes 1–3)” — Step 2 of the Procedure for the Preparation of Tc99m Exametazime Injection Without Methyl Blue Stabilizer section, package insert for Ceretec.4

**Comment:** These directions are ambiguous as to whether 5 mL of pertechnetate saline must be used or whether a different volume may be used.

- “Withdraw material with a sterile lead shielded syringe for use within 18 hours of preparation” — Step 10 of the Preparation section, package insert for Cheletec (kit for the preparation of Tc 99m mebrofenin injection), Bracco Diagnostics Inc., Princeton, N.J., February 2000.8

**Comment:** This stated 18-hour expiration time is inconsistent with the statement, “The expiration time of the Sodium Pertechnetate Tc 99m solution is not later than 12 hours after time of elution,” appearing in the Expiration Date section of the package insert for Ultra-TechneKow DTE (Tc 99m generator), Mallinckrodt Inc., St. Louis, Mo., June 2001.9 Hence, confusion exists as to whether the longer expiration time of the reagent kit supersedes the standard expiration time of the pertechnetate solution.

Impractical Directions

- “Using a shielded syringe, slowly inject 1 to 3 mL [up to 1850 MBq (50 mCi)] of sterile sodium pertechnetate Tc-99m solution” — Step 5 of the Reconstitution section, package insert for Macrotec (kit for the preparation of Tc 99m albinum aggregated injection), Bracco Diagnostics Inc., Princeton, N.J., March 2000.10

**Comment:** A product prepared according to the aforementioned instructions would contain an average of 360,000 macroaggregated albumin (MAA) particles per 148 MBq (4 mCi) dose at the time of preparation and 720,000 MAA particles per 148 MBq (4 mCi) at the time of expiration (6 hours after preparation). These particulate doses clearly exceed the Society of Nuclear Medicine’s Procedure Guidelines Manual 2001–200211 suggested limits for administered MAA particles of between 100,000 and 200,000 for adult patients with pulmonary hypertension or right-to-left shunting.
“With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection [925–5550 MBq, (25–150 mCi)] in approximately 1 to 3 mL.”—Step d of the Instructions for Preparation of Technetium Tc99m Sestamibi for Injection section, package insert for Cardiolite (kit for the preparation of Tc 99m sestamibi injection), Bristol-Myers Squibb Medical Imaging, Inc., North Billerica, Mass., December 2001.12

Comment: If the upper limit of the dosage (i.e., 1,110 MBq, 30 mCi), as specified in the package insert, is used for each patient dose, then the maximum number of patient doses that may be dispensed from a reconstituted Cardiolite kit in accordance with the manufacturer’s direction is 5 [i.e., 5,550 MBq (150 mCi)/vial ÷ 1,110 MBq (30 mCi)/patient dose = 5 doses]. Taking into account radioactive decay during the time between preparation and administration, a more realistic number of doses available from a vial prepared according to the package insert directions is closer to 3. Considering that the manufacturer’s bailment and license agreement allows up to 6 doses from a vial and that the vendor does not offer the nuclear pharmacist any reimbursement for underutilized radiopharmaceutical preparation, such an activity limitation for Cardiolite is impractically low.13 It is possible that reconstitution of a reagent kit with more radioactivity than is recommended by the manufacturer may alter the binding proportion between the radioisotope and the drug carrier. In addition, it is also possible that the patient could receive an inadequate amount of the drug carrier when a reagent kit is reconstituted with excessive radioactivity. Either of these scenarios could compromise the ability of the labeling radiopharmaceutical to provide the high-quality images necessary for accurate diagnostic interpretation. It is interesting to note, however, that the bailment for Cardiolite suggests that “other agreed upon number” unit doses may be arranged if the nuclear pharmacist wishes to withdraw additional doses from the reconstituted Tc 99m sestamibi vial, which implies preparation with more activity than stated in the package insert.12,13

Vague Directions

■ “An assay of the radiochemical purity of the prepared injection can be performed using”—Line 1 of the Quality Control section, package insert for AcuTect (kit for the preparation of Tc 99m aptidine injection), Berlex Laboratories, Wayne, N.J., June 2001.14

Comment: Is this procedure optional?

■ “Adherence to the above product reconstitution instruction is recommended”—Instructions for Preparation of Technetium Tc 99m Sestamibi for Injection section, package insert for Cardiolite.12

Comment: Is adherence to the product reconstitution instructions optional?

Discussion

The preparation instructions (i.e., reconstitution, QC testing, and expiration dating) as stated in the package insert for a radiopharmaceutical are intended to ensure, provided these instructions are followed, that the final radiopharmaceutical preparation will be of sufficient quality and purity to meet the label claims regarding safety and efficacy. However, the poor quality or restrictive nature of some manufacturers’ directions, as evidenced above, often makes adhering to the preparation instructions not in the best interest of the patient or the nuclear pharmacist and may, in some instances, even compromise therapy or patient safety.

Typically, a drug sponsor conducts clinical trials using radiopharmaceuticals prepared in accordance with specific, usually narrow-range, preparation instructions in order to minimize the expense, duration, and complexity of the trials. There is no incentive, economic or otherwise, for the sponsor to conduct trials with radiopharmaceuticals prepared using a broad range of different parameters (e.g., reconstitution activities, volumes, expiration times). The preparation instructions used during clinical trials are incorporated into the package insert, which is submitted to FDA as part of a product’s New Drug Application (NDA). Hence, the preparation instructions, being subject to FDA approval, tend to become quite restrictive.

In real life, however, the restrictive nature of package insert instructions, when coupled with a competitive, yet limited, radiopharmaceutical market and geographic constraints on distribution, may well serve to force nuclear pharmacists to deviate from a manufacturer’s directions (e.g., exceed recommended activity, extend the expiry time). In the event that several patients were to receive doses from a single radiopharmaceutical vial prepared with “excessive” radioactivity and each patient (or his or her insurance provider) were billed using a standard drug fee based on usage from a vial prepared with a “standard” amount of radioactivity, the nuclear pharmacist involved would potentially be liable for fraudulent billing under the Federal False Claims Act,15 as well as for possible violation of other civil and criminal laws. In addition, such a deviation from FDA-approved preparation instructions may be judged to be misbranding or adulteration.

Clearly, it is necessary to pursue a sensible “win–win” solution in order to allow nuclear pharmacists to meet the real-world demands of our practice and prepare safe and effective radiopharmaceuticals for our patients (maintaining a competitive edge not only in the radiopharmaceutical marketplace but with other imaging modalities as well), while also upholding the interests of the drug manufacturers (in recuperating their operational and research and development costs), and the general public (in curtailing ever-increasing drug costs). We believe that it is important for manufacturers, FDA, and nuclear pharmacists and physicians to work together to address and correct identified deficiencies in package insert instructions for currently marketed radiopharmaceuticals. For new drugs, sponsors should be encouraged to determine upper limits for reconstituted radioactivity and expiration times and to include these parameters in the preparation instructions used during clinical trials and, subsequently, in the proposed product label-
ing for their NDA submissions. Manufacturers should also be encouraged to establish reasonable and fair pricing schedules for multidose vials, offering, if appropriate, prorated refunds for vials that yield a submaximal number of doses.

Lastly, we believe that the manufacturers’ directions for the preparation of radiopharmaceuticals should be viewed as guidance rather than as required procedure. The examples we cite above under the category of vague directions support this view. Deviations from package insert instructions, however, should not be made without careful consideration and professional judgment. One statement relevant to this issue appears in the General Notices section of the United States Pharmacopeia (USP): “However, there may be deviation from the specified processes or methods of compounding, though not from the ingredients or proportions thereof, provided the finished preparation conforms to the relevant standards laid down herein and to preparations produced following the specified process.”16 Accordingly, we believe that it may be acceptable to deviate from manufacturer’s instructions (USP’s “specified processes”) if the final drug product is of the same quality and purity (i.e., “conforms to the relevant standards … and to preparations produced by the specified processes”).16 Nonetheless, if a pharmacist deviates from a drug product’s manufacturer’s instructions, the possibility of misbranding or adulterating the drug product must be considered.

Prior to 1990, the Nuclear Regulatory Commission (NRC) required that radiopharmaceuticals be prepared in strict accordance with package insert instructions. Pursuant to a petition for rulemaking filed by the American College of Nuclear Physicians and the Society of Nuclear Medicine, NRC revised its regulations to permit licensees to depart from the manufacturer’s instructions when preparing reagent kits.17,18 FDA, in its Nuclear Pharmacy Guideline—Criteria for Determining When to Register as a Drug Establishment,19 allows the compounding of radiopharmaceuticals by discretionary enforcement. Although deviations from package insert instructions are not substantially addressed in this document, FDA noted in its discussion of comments that deviations from instructions or modifications of reagent kits would not require the pharmacy to register as a drug establishment. However, the possibility of misbranding or adulterating a drug product must be considered. Thus, pharmacists must to a large degree rely on their professional judgment as to when and to what extent deviations from preparation instructions are appropriate.

Limitations

The deficiencies of the package inserts were initially reviewed and identified by each author, and a consensus was reached following several group meetings and e-mail correspondences among the authors. The information presented in this article represents a subjective interpretation by all of the authors. Others may have a different perspective on, for example, the definition of a deficien-

Conclusion

Manufacturers’ directions for preparing radiopharmaceuticals are often imperfect and should be viewed as standard guidance rather than as required procedure. Just as physicians are permitted to use FDA-approved drugs for off-label indications, nuclear pharmacists should be allowed to use alternative methods for preparing radiopharmaceuticals, provided those methods have been validated to be as good as the stated directions and that the nuclear pharmacists do not engage in activities that fall outside the normal practice of pharmacy. Manufacturers, FDA, and nuclear pharmacists and physicians should work together to address identified deficiencies in package insert directions.

References

15. Federal False Claims Act 31 USC §3.37.3.729–33.
17. Authorization to prepare radiopharmaceutical reagent kits and elute radiopharmaceutical generators; use of radiopharmaceuticals for therapy, 55 Federal Register 34513–8.
18. Preparation, transfer for commercial distribution, and use of byproduct material for medical use, 60 Federal Register 322–5.