Council on Radionuclides and Radiopharmaceuticals, Inc. (CORAR)
Comments Submitted to NRC on April 27, 2018
All CORAR Comments, Suggestions, and Recommendations in Red Font

Questionnaire on the Evaluation of Tailored Training and Experience Requirements for Different Categories of Radiopharmaceuticals

With regard to Title 10 of the *Code of Federal Regulations* (10 CFR) 35.390, CORAR comments below assume that greater than 90% of all radiopharmaceuticals are prepared by licensed nuclear pharmacists or under the supervision of an Authorized User and delivered in patient-ready doses for administration.]

1. What is the fundamental knowledge that is necessary for a physician to administer <u>any radiopharmaceutical</u> under Title 10 of the *Code of Federal Regulations* (10 CFR) 35.390? Below is a draft list that the U.S. Nuclear Regulatory Commission (NRC) staff has developed. Please add/delete topics from this list.

    a. This section is specific to unsealed byproduct material requiring written directive.

    Radiation physics
        i. Structure and properties of atoms
        ii. Radiation and radioactivity
            - Characteristics of radioactivity
            - Radioactive decay (simple and complex), half-lives, energies, and emissions
            - Calculation of radioactive decay and activity remaining
            - Primary radionuclides and contaminants
        iii. Interaction of radiation with matter (direct and indirect)
            - Radiological properties of low energy photons, beta emissions, alpha emissions, and mixed emissions
        iv. Radionuclide production
        v. Units of radiation and radioactivity

    b. Instrumentation
        i. Operation and use of instrumentation (e.g., gas-filled detectors [ion chambers, survey meters, and dose calibrators], sodium iodide detectors [well counters]) and advantages and disadvantages for measuring and detecting different radionuclides and mixed radionuclides.
        ii. Dosage and dose measurements
        iii. Instrumentation to monitor and measure unit dosage without modification or adjustment, unit dosage with adjustment, unit dosage with modification, multi-dosage, kit preparation, generator elution
        iv. Frequency of calibration
        v. Operation and use of personnel monitoring devices
        vi. Routine quality assurance parameters (including calculations) for detection and measurement of radioactivity

    c. Radiation protection for protection of workers, family members, public, and patient as it relates to the regulations in 10 CFR Parts 19, 20, and 35

i. Radiation protection associated with dose measurements and handling (unit dosage with modification, multi-dosage, kit preparation, generator elution) [CORAR question – Are kit preparation and generator elution applicable to RAM requiring a written directive?]
ii. Performing calculations necessary to comply with regulations (e.g., patient release, medical events)
iii. Maintaining doses as low as reasonably achievable (ALARA), including external and internal exposures
iv. Basic shielding (e.g., syringe shields, aprons) include shielding for specific emissions
v. Protective clothing/devices to include the lens of the eye
vi. Surveys and monitoring
vii. Dosimeters
viii. Minimizing and clean-up of contamination and spills (e.g., when handling unit dosage without modification or adjustment, unit dosage with adjustment, unit dosage with modification, multi-dosage, kit preparation, generator elution)
ix. Ordering, receiving, and unpacking radiopharmaceutical
x. General understanding of radiation safety officer (RSO) responsibilities including their authority to stop work
xi. Understanding public and occupational dose limits
xii. Waste control and radioactive storage
xiii. Radiation protection for patient to prevent unwanted exposure
    - Patient identity verification
    - Appropriate use of a written directive
    - Written directives verification
    - Properly performing radiopharmaceutical therapy delivery equipment
    - Minimizing and clean-up of contamination and spills
xiv. Signage
xv. Appropriate occupational dose guidance for the pregnant worker
xvi. Application of guidance for the nursing mother receiving radiopharmaceuticals

d. Mathematics pertaining to the use and measurement of radioactivity
    i. Decay equations (simple and complex)
    ii. Half value layers
    iii. Exposure calculations (internal and external)
    iv. Calculations associated with instrumentation
    v. Radiation dose (including external and internal dosimetry)
    vi. Converting activity to dose
    vii. Organ/tissue uptake to dose
    viii. Calculations necessary to comply with regulations (e.g., patient release, medical events, etc.)
    ix. Unit dosage with adjustment, unit dosage with modification, multi-dosage, kit preparation, generator elution

e. General patient release determination

i. Transportation and release location
ii. Patient specific parameters, such as living and working conditions
iii. Exposure to sensitive populations – pregnant women and children
iv. Radiation effects due to low energy photons, beta emissions, alpha emissions
v. Combined radiation effects from mixed emissions and mixed half-lives and decay chains
vi. Pharmacological effects of specific drugs and resulting radiation doses, route of administration, and route of elimination [CORAR question - It is not clear what Pharmacological effects are intended here? Perhaps rewording to include specific drug information including pharmacological effects, doses, etc…]
vii. Pharmacological effects on normal adults, pregnant women, fetuses, nursing infants, nursing [lactating] women, and compromised patients and resulting radiation doses, differing routes of administration, and routes of elimination [CORAR question – How does Pharmacological effect differ from vi above? Also, nursing [lactating] women would not be part of the common patient population.]

f. Chemistry of byproduct material for medical use
i. Original and final chemical form
ii. Generators
iii. Kit preparation [CORAR - RAM requiring written directive is not routinely prepared with generator and kits]
iv. Interaction with environment, spills, release to environment

g. Radiation biology
i. Chemical and physical effects of ionizing radiation of alpha emissions, beta emissions, and low energy photos on biological systems (molecular and cellular damage)
ii. Chemical and physical effects of ionizing radiation from mixed emissions and mixed half-lives and decay chains on biological systems
iii. Comparison of relative risks of low level radiation with other health risks
iv. Biological effects of high dose radiation (acute, late, fetal)
v. Biological effects of low dose radiation (acute, late)
vi. Therapeutic use of radionuclides including mechanisms of action of particulate radiation
vii. Pharmacological effects of specific drugs and resulting radiation doses, route of administration and route of elimination [CORAR – Pharmacological effects repeated from “e” above.]
viii. Pharmacological effects on normal adults, pregnant women, fetuses, nursing infants, nursing [lactating] women, and compromised patients and resulting radiation doses, differing routes of administration, and routes of elimination
ix. 4Rs – repair, redistribution, repopulation, and reoxygenation

h. Medical events

i. Definition of a medical event (including patient intervention)
ii. Determination of a medical event occurrence
iii. Evaluation of the medical consequences of a medical event
iv. Root cause analysis and determination of appropriate corrective actions
v. Controls and programs to prevent medical events

i. NRC requirements
   i. General understanding of 10 CFR Parts 19, 20, and 35
   ii. Dose limits in 10 CFR Parts 20 and 35
   iii. Reporting requirements who, when, and where to report – in 10 CFR Parts 20 and 35
   iv. Training requirements
   v. Recordkeeping requirements
   vi. Licensee procedures including (written directive procedures and safety procedures for each use)
   vii. Need for amendments
   viii. Need for notifications
   ix. Need for change or transfer of control
   x. Need for license termination and decommissioning
   xi. Guidance for appropriate 10 CFR 35.1000 uses
   xii. Appropriate waste and transportation requirements
   xiii. Security and control of license material, and access control

2. What additional knowledge is necessary for a physician to administer specific types of radiopharmaceuticals under 10 CFR 35.390? Below is a draft list that NRC staff has developed. Please add/delete topics from this list.

   a. Selection of appropriate radiopharmaceutical indication for use and normal/abnormal response to the treatment

   b. Calculation of clinical dose and risks of prescribing a different dose

   c. Use of dose blockers, if necessary

   d. Route of administration
      i. Ability to determine administration under special patient conditions such as gastrostomy, tracheostomy, renal failure, dialysis, liver failure, incontinence, unable to swallow, ostomies, body tubes/catheters, etc.
      ii. How to perform administration
      iii. Patient risks associated with route of administration
      iv. Radiation protection for workers associated with route of administration

   e. Specific risks associated with toxicity of the radiopharmaceutical (i.e., minor differences between prescribed and administered activity can result in different consequences for patient)

f. Post administration patient monitoring parameters

g. Specific risks associated with the type of radiation emitted (alpha, beta, gamma, low energy photon)

h. Specific risk associated with radiolabeled substrate (chemical component)

i. Specific risks associated with the delivery method of the drug to the target (if the radionuclide needs to be tagged to a chemical component, what happens if it isn't tagged or tagged incorrectly) [CORAR comment – Not sure how the physician would know this if radiopharmaceutical is prepared, QC'd, and dispensed as a patient-ready dose from a licensed radiopharmacy by a licensed nuclear pharmacist.]

j. Medical event specific to a radiopharmaceutical
    i. Prevention (QA/QC on any necessary equipment used to ensure appropriate dose/dosage is delivered)
    ii. Evaluation
    iii. Reporting
    iv. Medical intervention or response if a medical event occurs

k. Post verification (to determine dosage and if medical event occurred)
    i. Appropriate modality (e.g. imaging) [Imaging is not routinely part of written directive radiopharmaceutical]
    ii. Understanding artifacts

l. Patient release instructions specific to a radiopharmaceutical
    i. When to provide discussion and instructions
    ii. Transportation, and release location
    iii. Patient specific parameters, such as living and working conditions
    iv. Exposure to sensitive populations – pregnant women, nursing [lactating] mother and nursing child, and children
    v. Radiation effects due to low energy photons, beta emissions, alpha emissions
    vi. Combined radiation effects from mixed emissions and mixed half-lives and decay chains
    vii. Pharmacological effects of specific drugs and resulting radiation doses, route of administration, and route of elimination
    viii. Pharmacological effects on normal adults, pregnant women, fetuses, nursing infants, nursing [lactating] women, and compromised patients and resulting radiation doses, differing routes of administration, and routes of elimination

m. Radiation Protection specific to radiopharmaceutical
    i. Unique or additional handling concerns
    ii. Unique ordering, receiving, and unpacking concerns
    iii. Calculation, measurement, and preparation of radiopharmaceutical dose
    iv. Disposal of radiopharmaceutical

v. Shielding specific to a radiopharmaceutical
vi. Use of procedures to contain spilled radioactive material and use of proper decontamination procedures
vii. Dosimetry
viii. Volatility
ix. Circumstances which require a call to the RSO and/or the regulator
x. What to do in the event of medical emergency or if the patient dies or cremation is planned
xi. Unique protective clothing or shielding
xii. Remote handling devices, if any

3. CORAR proposes an alternative pathway under 10 CFR 35.390 to administer intravenous therapeutic radiopharmaceuticals containing alpha and beta emitting radioisotopes which have been prepared by a licensed nuclear pharmacist in a state licensed radiopharmacy and dispensed to physicians as patient-ready doses.

   [Please note that under this alternate pathway the Authorized User will not be mixing, radiolabeling, or preparing patient doses. All radiopharmaceuticals will be received in patient-specific, ready-to-inject unit dose form.]

   a. Nuclear Physics & Instrumentation:
      i. Structure and Properties of Atoms
      ii. Radiation and Radioactive Decay
      iii. Production of Radionuclides
      iv. Interaction of Radiation with Matter
      v. Gas-Filled Detectors
      vi. Scintillation Counters
      vii. Personnel Monitoring Devices

   b. Radiation Biology:
      i. Physical Effects of Radiation
      ii. Chemical effects of Radiation
      iii. Cellular Effects of Radiation
      iv. Biological Effects of High Dose Radiation
      v. Biological Effects of Low Dose Radiation
      vi. Therapeutic Application of Particulate Radiation

   c. Regulations and Radiation Protection:
      i. Characteristics of Ionizing Radiation
      ii. Definitions of Radiation Measurement
      iii. Principles of Radiation Protection
      iv. Personnel Monitoring & Safety Precautions
      v. Regulatory Agencies
      vi. Documentation and Regulatory Reporting
      vii. Sealed Reference Sources
      viii. Area Monitoring
      ix. Waste Management & Disposal

x. Packages containing Radioactivity

d. Mathematics Pertaining to Use & Measurement of Radioactivity:
   i. Includes fundamental calculations: decay equation, half-value layers, exposure calculations, instrumentation needs.

e. The goal of the Training and Experience Requirements under the alternate pathway above is to provide licensed medical specialists (such as oncologist, hematology-oncologists, urologists) with competency in cognitive and psychomotor skills necessary to effectively and safely prescribe and administer specific radiopharmaceuticals.

4. How should the physician acquire the knowledge topics listed above? Classroom/laboratory training and supervised work experience (including clinical experience)? Please provide an estimate for the number of hours or clinical experience needed for the knowledge topics listed above.

   a. Training should be contingent upon the radiopharmaceutical, its characteristics and its use – balancing safety and risk to patients, workers and public. Specifically, low risk agents, e.g. patient specific doses of alpha emitters, should have reduced training requirements when compared to higher risk radiopharmaceuticals, e.g. Lu-177;

   b. Consideration should also be given for training in comparable safety hazard experience and training – specifically T&E in chemotherapeutic agents which have similar regulations to protect patients and workers (exposure, volatility, spills, medical event, etc.);

   c. Basic didactic instruction could be covered appropriately in 40 – 80 hours. The majority of T&E should be specific to patient safety – calculating dose, administration, post administration monitoring -- and to general radiation safety for patient, workers and public. Clinical experience should be more than 3 patients if reduces didactic hours – 3 observations and at least 5 patients treated under supervision.

5. How should a physician's knowledge in the topics listed above and ability to function independently be evaluated?

   a. Exam? CORAR recommends that a reasonable demonstration of didactic knowledge be accomplished through exam.
   b. Both a written exam and practical exam? Practical exams require that a student be observed successfully completing a task (e.g. trouble shooting a survey meter malfunction) and would be difficult to standardize on a national basis. Also, attempting to standardize practical exams, through centralized testing sites, would slow down the process of AU certification.
   c. Attestation by a qualified authorized user? Acceptable as per our comments below in "5e."

d. How would you structure a competency model to demonstrate knowledge of the fundamental knowledge areas?

Presentation of basic information as either text or lecture. Illustrative examples and unit self-assessment. Opportunity for Q&A. Unit assessment to demonstrate didactic competency. Should include case studies relevant to content (clinical, regulatory, incident scenarios etc.).

e. Who should administer the written exam and/or practical exam or oversee the competency model – the regulator, medical specialty board, or professional societies?

None of these organizations administer Authorized User written or practical exams today. As mentioned above, CORAR recommends that a reasonable demonstration of didactic knowledge be accomplished through exam. The hands-on laboratory training component of a program can be completed in the nuclear medicine department at the hospital or at a nuclear pharmacy. It must be done under the supervision of a preceptor, who is an authorized user or authorized nuclear pharmacist. Each area of competency should follow the general progression:

i. Explanation and demonstration of a skill to the student
ii. Preceptor assesses the student's level of competency

Also, in past submissions to NRC, CORAR has commented on the shortage of AUs in certain US geographies. Recently, the ACMUI "*Subcommittee on Training and Experience Requirements for All Modalities"* addressed this in their February 19, 2018 report[1] and stated that a potential AU shortage could jeopardize patient access to radiopharmaceutical therapies. Therefore, to ensure patient access to current and future radiopharmaceutical therapies, and in addition to the administration options mentioned above, CORAR encourages the NRC to work with stakeholders to develop manufacturer sponsored programs to provide the attestations necessary, to physicians seeking AU certification, to complete the training and experience requirements.

Finally, oversight from the regulators should ensure that the training and experience programs have enough breadth and depth to protect public/patient health and safety. For example, this can be done by a regulator (or potentially accredited academic institution) reviewing an AU educator's training program syllabus and exam.

[1] Advisory Committee on the Medical Uses of Isotopes (ACMUI) Subcommittee on Training and Experience Requirements for All Modalities; Subcommittee Draft Interim Report February 19, 2018