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Training and Experience Requirements for Different Categories of Radiopharmaceuticals

Comment On: NRC-2018-0230-0001
Training and Experience Requirements for Different Categories of Radiopharmaceuticals

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General Comment

See attached file(s)

Attachments

CORAR Complete Comments to NRC-2018-0230 FINAL (1-24-19)

CORAR

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Michael J. Guastella, MS, MBA
Executive Director

January 24, 2019

May Ma
Office of Administration
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U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

RE: DOCKET ID NRC–2018–0230, TRAINING AND EXPERIENCE REQUIREMENTS FOR DIFFERENT CATEGORIES OF RADIOPHARMACEUTICALS; FEDERAL REGISTER VOL. 83, NO. 209; OCTOBER 29, 2018

Dear Ms. Ma:

The Council on Radionuclides and Radiopharmaceuticals, Inc. (CORAR) appreciates the opportunity to comment on the U.S. Nuclear Regulatory Commission (NRC) request for comment on Training and Experience Requirements for Different Categories of Radiopharmaceuticals; Federal Register Vol. 83, No. 209; October 29, 2018. CORAR is an industry association of firms that manufacture diagnostic and therapeutic radiopharmaceuticals, radionuclides, and other radioactive products primarily used in medicine and research, and also includes firms that operate nuclear pharmacies that prepare and dispense radiopharmaceuticals in patient-ready doses for administration to patients in health care facilities.

On October 29, 2018, the U.S. Nuclear Regulatory Commission (NRC) requested comments on its training and experience (T&E) requirements. The input will be used to determine whether significant regulatory changes to the NRC's T&E requirements for authorized users (AUs) are warranted. CORAR's comments are enclosed for your review and consideration.

CORAR continues to believe that the current 700-hours alternate pathway (under 10 CFR 35.390) of training and experience to become a licensed AU to administer all radiopharmaceutical drugs is excessive with regard to the limited administration of alpha-, beta-, or beta-gamma- emitting radiotherapies (non-imaging radiotherapies). If steps are not taken the modify the training framework in the current rulemaking, we believe that patient access to important radiopharmaceutical drugs, such as Xofigo®, will continue to be limited.

Please do not hesitate to contact me at (202) 547-6582 if you have questions.

Sincerely,

Michael J. Guastella
Executive Director

MG:mdl, gps
Enclosure

Council on Radionuclides and Radiopharmaceuticals, Inc.

COMMENTS ON TRAINING AND EXPERIENCE REQUIREMENTS FOR DIFFERENT CATEGORIES OF RADIOPHARMACEUTICALS; DOCKET ID NRC-2018-0230 PUBLISHED IN FEDERAL REGISTER VOL. 83, NO. 209

Requested Information and Comments

The focus of this request for comments on NRC training and experience (T&E) requirements is to gather information that will permit the NRC staff to determine whether changes to the T&E requirements are warranted for different categories of radiopharmaceuticals for physicians seeking AU status for the medical use of specific categories of radiopharmaceuticals requiring a written directive under 10 CFR 35.300. The specific NRC request for comments includes several areas:

A. Tailored Training & Experience Requirements
B. NRC's Recognition of Medical Specialty Boards
C. Patient Access
D. Other Suggested Changes to the T&E Regulation

The following section provides CORAR comments to selected questions included in Docket ID NRC–2018–0230, Training and Experience Requirements for Different Categories of Radiopharmaceuticals; Federal Register Vol. 83, No. 209; October 29, 2018:

Tailored Training & Experience Requirements

Are the current pathways for obtaining AU status reasonable and accessible?

Before the 2002 Medical Use of Byproduct Material final rule went into effect, hematologists, medical oncologists, and other specialists who sought to administer beta-emitting radiopharmaceuticals such as Zevalin® and Metastron® could become licensed to do so after completing 80 hours of classroom and laboratory training. Under the current framework, the NRC created a licensure pathway under which, with 700 hours of training and experience, physicians would be trained for the full range of activities in handling byproduct material including activities such as eluting molybdenum-99/technetium-99m generators, preparing and dispensing radioactive drugs, as well as administering a wide variety of radionuclides requiring written directives.

In addition, NRC stated in the 2002 final rule that physicians in training would attend to other "clinical matters" including the diagnostic use of the material under the supervision of an AU such as reviewing case histories or interpreting nuclear medicine scans. These diagnostic "clinical matters" also include supervising nuclear medicine technologists, learning about imaging equipment, understanding imaging Quality Assurance standards, and other important clinical skills necessary to ensure comprehensive high quality imaging in the nuclear medicine department. Even though these clinical matters are not specifically required by the NRC, this type of supervised work experience is counted toward the supervised work experience to obtain the required 700 hours. CORAR believes that the T&E requirements necessary to achieve competency in the full range of nuclear medicine clinical activities (e.g. kit preparation, imaging techniques, camera QC, image interpretation, etc.) should not be required for licensed physicians who wish to become limited AUs to safely administer patient-ready doses of non-imaging radiotherapies to their patients. This position also comports with NRC's Medical Use Policy Statements which note that NRC can only intervene into the practice of medicine, if the practice presents a radiation risk to the public.

Another important point from the 2002 final rule is the fact that the NRC retained in its regulations a pathway under which, with 80 hours of training and experience, a "limited authorization" could be achieved for the oral administration of Iodine-131 (67 CFR 20250; 10 CFR 35.392, 10 CFR 35.394). The NRC noted the impeccable safety record of the product, the low risk of therapeutic misadministration, and

the burden placed on patients who might have to travel long distances to unfamiliar settings if their primary treating physician were unable to administer the treatment. In addition, NRC noted that any additional hours would be inconsistent with NRC Medical Policy to minimize intrusion into medical practice since additional hours were not justified by radiation risk.

It is important to note that in previous meetings of the Advisory Committee on the Medical Uses of Isotopes (ACMUI), the *Subcommittee on Training and Experience Requirements for All Modalities* had acknowledged that alpha- and beta- emitters also have an exceptional safety record. CORAR would like to point out that this safety record of handling and administration of alpha- and beta- radiotherapies includes those oncologists who became licensed AUs under the 80 hour alternate pathway. The overall safety record of oral I-131 administration and the non-imaging radiotherapies should support the request for an alternate T&E pathway for non-imaging radiotherapies, delivered to licensed healthcare sites as patient-ready doses prepared at a licensed radiopharmacy, and dispensed by a licensed nuclear pharmacist, or received directly from the manufacturer in a patient-ready dose container, with no additional manipulations needed before patient administration.

With this said, CORAR believes that the current 700 hour training and experience alternate pathway (under 10 CFR 35.390) for physicians who wish to become limited AUs to safely administers patient-ready non-imaging radiotherapy doses is not reasonable and is excessive.

Should the NRC develop a new tailored T&E pathway for these physicians?

CORAR believes that the NRC should develop a new tailored T&E pathway for specialists such as medical oncologist, hematologists, and urologists. The new pathway should provide the training and experience necessary to safely administer non-imaging radiotherapies, with consideration for the following factors:

- The limited role in handling these radiolabeled drugs (which would be dispensed and delivered to them in patient-ready doses from a licensed radiopharmacy, dispensed by a licensed nuclear pharmacist, or received directly from the manufacturer in a patient-ready dose container);
- The radiological safety profiles of radiopharmaceuticals containing alpha-, beta-, and beta-gamma emitting isotopes (non-imaging radiotherapies);
- Physician's experience and training in handling toxic non-radioactive chemical therapies, e.g., cytotoxic chemotherapy agents.

Interested oncologists, hematologists, and urologists who wish to become limited AUs, through a new tailored T&E pathway, will have the opportunity to provide improved continuity of care for their patients. For example, this would be very important for an oncologist who wishes to closely monitor a patient's response to a non-imaging radiotherapy treatment and quickly treat any complications. These clinical efforts would be hampered if the patient was required to travel for treatment due to an AU shortage in the area where the patient lives and is receiving ongoing treatment.

How should the requirements for this fundamental T&E be structured for a specific category of radiopharmaceuticals?

CORAR proposes an alternative pathway under 10 CFR Part 35 Subpart E to administer intravenous therapeutic radiopharmaceuticals containing non-imaging radiotherapies which have been prepared by a licensed nuclear pharmacist in a state licensed radiopharmacy and dispensed to physicians as patient-ready doses or received directly from the manufacturer in a patient-ready dose container. Please note that under this alternate pathway the limited AU will not be mixing, radiolabeling, or preparing patient doses and is not conducting/interpreting imaging studies on the patient. All non-imaging radiotherapies will be received in patient-specific, ready-to-inject unit dose form (patient-ready) or received directly from the manufacturer in a patient-ready dose container. The specific topics of this training were discussed in detail by CORAR in our T&E questionnaire comments to NRC on April 27, 2018 - a copy of the CORAR

T&E questionnaire is attached. It is important to note that CORAR recommendations are consistent with the NRC Consolidated Guidance About Material Licenses[1].

The goal of the T&E Requirements under an alternate pathway 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 non-imaging radiotherapies.

Currently, regulators, medical specialty boards, or professional societies administer Authorized User written or practical exams. In our April 27, 2018 T&E questionnaire comments submitted to NRC, CORAR recommended that a reasonable demonstration of didactic knowledge be accomplished through exam. The hands-on laboratory training component of a program can be completed at a hospital nuclear medicine department, a radiopharmacy, or manufacturer provided location. 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:

- Explanation and demonstration of a skill to the student
- 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[2] and stated that a potential AU shortage could jeopardize patient access to radiopharmaceutical therapies. Therefore, to ensure patient access to current and future non-imaging radiotherapies, and in addition to T&E training options mentioned above, CORAR encourages the NRC to work with stakeholders (including collegiate based AU educator programs or manufacturer sponsored programs) to provide the training/experience/competency requirements necessary, to physicians seeking AU certification, to complete the T&E requirements.

Should AU Competency be periodically assessed? If so, how should it be assessed, how often, and by whom?

The 10 CFR 35.59 requires the recentness of training to be within the 7 years of application. Nonetheless, it is of the opinion of CORAR that AU competency should be assessed if administration of the radiopharmaceutical is not performed in a frequent time frame to remain proficient. This could be assessed by the attending nuclear medicine physician or another AU with current proficiency.

What boards other than those already recognized by the NRC could be considered for recognition for medical uses under 10 CFR 35.300?

At this time, CORAR does not have any recommendations for other boards.

Are the current NRC medical specialty board recognition criteria sufficient? If not, what additional criteria should the NRC use?

The specialty boards requirements for an oncology specialty would be at or above any additional requirements that the NRC could require beyond the radiation training listed previously.

Is there a shortage in the number of AUs for medical uses under 10 CFR 35.300? If so, is the shortage associated with the use of a specific radiopharmaceutical?

[1] https://www.nrc.gov/docs/ML0734/ML073400289.pdf

[2] 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

On March 1, 2018 the ACMUI Subcommittee on Training and Experience Requirements for All Modalities presented their draft interim report on the Training & Experience Requirements for Use of Unsealed Byproduct Material for which a written directive is required under 10 CFR 35.390. In discussing the current status, it was noted that the number of FDA approved radiotherapies were likely to increase in the future. The subcommittee also reported with some concern, the precipitous decrease in the number of first time candidates sitting for the Certification Examination of the American Board of Nuclear Medicine; in 2016 fewer than 50 individuals sat for this examination, in contrast to 80-100 individuals in the past. The subcommittee report went on to state, "…thus the subcommittee views the decrease in the number of nuclear medicine physicians as a potentially serious problem, perhaps not immediately, but certainly in the future."

Declining numbers of AUs in certain parts of the country has been documented and discussed with the NRC in the past. For example, Dr. Joseph Mace, Director of the Radioimmunotherapy Program at Florida Cancer Specialists, in a written statement shared with the NRC on January 26, 2016 described the impact of reduced access to Zevalin (a beta- emitting radiotherapy) in patients for whom it is an especially advantageous treatment option. Dr. Mace's practice includes the St. Petersburg, FL area which has a particularly large population of elderly cancer patients who are less mobile and struggle to travel to appointments. The patient access problem is severe enough for his patients, that Dr. Mace initiated a 'traveling AU" program. In his written statement, he admits that this had modestly increased access to beta emitters, however, he goes on to state that increasing the number of AUs would be more impactful to increasing patient access.

In a letter to the ACMUI on July 11, 2018, Yuan Xue, PhD (Global Regulatory Strategist, Bayer) presented research that demonstrates the impact of limited AU availability on patient access to Xofigo (an alpha- emitting radiotherapy) and the need to improve availability and reduce the need for patients to travel for treatment. For example, the Bayer research demonstrates that for the population of patients in the study who were referred for Xofigo, 37% did not receive the treatment. Among those non-treated patients, approximately 30% did not receive treatment because of limited availability of the product or the need to travel to another facility that offered Xofigo (potentially at great distance).

With more radiotherapies under clinical investigation, we are likely to see more non-imaging radiotherapies approved by the FDA in the future. Without an adequate number of AUs serving patients across the United States we will likely experience greater restrictions on patient access in the future.

Are there certain geographic areas with an inadequate number of AUs? Identify these areas.

The NIH published findings stating that geographic access to general physicians has continued to improve over the past two decades, but most specialties have not diffused to the most rural areas. While substantial variation in the supply of physicians across communities remains, current measures of geographic access to physicians overstate the extent of maldistribution and yield an incorrect ranking of areas according to geographic accessibility of physicians. Rural areas in which there are less than a population of 2500 and not adjacent to a metropolitan area significantly lack access to specialty doctors. For example, this translates to only 1 radiology trained physician per 100,000 population[3].

Also, CORAR would like NRC to consider possible AU shortages in US Territories (e.g. Puerto Rico) and military installations outside the US.

Do current NRC regulations on AU T&E requirements unnecessarily limit patient access to procedures involving radiopharmaceuticals? Explain how.

As discussed earlier, data demonstrates that rural areas are underserved. Therefore, requiring excessive training for patient-ready non-imaging radiotherapy doses (including non-imaging radiotherapies received

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1361233/

directly from the manufacturer in a patient-ready dose container) would be excessive and limit patient care.

Do current NRC regulations on AU T&E requirements unnecessarily limit research and development in nuclear medicine? Explain how.

CORAR believes that the current training and experience requirements discourage certain clinicians from learning about non-imaging radiotherapies. Outside of nuclear medicine, this is particularly acute during hematology, medical oncology, and urology fellowships due to the poor access to non-imaging radiotherapies. This can limit the direct clinical participation in research and development that could accelerate scientific discovery and new innovative treatments.

Should the NRC regulate the T&E of physicians for medical uses?

NRC should regulate T&E from a radiation risk perspective only which justified NRC's decision in 2002 to retain the regulatory pathway under which, only 80 hours of T&E is required to attain limited AU status to administer oral Sodium Iodine-131. This same consideration by the NRC should support the creation of a limited AU pathway under 10 CFR Part 35 Subpart E for tailored T&E for specific non-imaging radiotherapies.

Are there requirements in the NRC's T&E regulatory framework for physicians that are non-safety related?

Safety is a concern whether it be a biohazard, chemical or radioactive hazard. Medical institutions have many guidelines for all types of hazards and training is commensurate to their duties with the material. Additional non-radioactive T&E would be unnecessary and possibly contradictive to OSHA requirements.

How can the NRC transform its regulatory approach for T&E while still ensuring that adequate protection is maintained for workers, the general public, patients, and human research subjects?

CORAR believes that for the category of non-imaging radiotherapies, delivered to licensed healthcare providers as patient-ready doses, with no additional manipulations needed before patient administration, or received directly from the manufacturer in a patient-ready dose container, the current alternate pathway of 200 hours of didactic and 500 hours of experience is not necessary to protect workers, the general public, patients, and human research subjects.

As stated above, CORAR encourages the NRC to develop a new tailored T&E pathway for licensed physician specialists such as medical oncologists, hematologists, and urologists. The new pathway should provide the training and experience necessary to safely administer non-imaging radiotherapies, with consideration for the following factors:

- The limited role in handling these radiolabeled drugs (which would be dispensed and delivered to them in patient-ready doses from a licensed radiopharmacy, dispensed by a licensed nuclear pharmacist, or received directly from the manufacturer in a patient-ready dose container);
- The radiological safety profiles of radiopharmaceuticals containing non-imaging radiotherapies;
- Physician's experience and training in handling toxic non-radioactive chemical therapies, e.g., cytotoxic chemotherapy agents.

Consideration of these factors will allow NRC to improve access to innovative non-imaging radioptherapies while ensuring the safety of the public.

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ATTACHMENT

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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 any radiopharmaceutical 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