Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
Report on Licensing for Radium-223 (^{223}Ra) Dichloride
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Subcommittee Members

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Charge

To provide recommendations on licensing of radium-223 (^{223}Ra) dichloride ($^{223}RaCl_2$).

Summary Statement and Recommendations

$^{223}RaCl_2$, currently a non-approved investigational agent undergoing clinical trials in the United States and elsewhere, represents a first-in-class, alpha particle-emitting therapeutic radiopharmaceutical. Based on relevant physical and biological considerations as well as clinical data to date, its intended indication is treatment of skeletal metastases in advanced, castrate-resistant prostate cancer, delivering high biologically effective doses to malignant cells in bone with relative sparing of hematopoietic marrow and other normal tissues. The injection volume for the body weight-adjusted dose of $^{223}RaCl_2$ (50 kBq/kg (1.35 μCi/kg)) is determined based on the vendor-supplied activity concentration in a pre-calibrated solution. Nonetheless, to minimize the probability of a therapeutic misadministration, an appropriate radioassay system (e.g., a dose calibrator) for measurement of the ^{223}Ra activity prior to its administration and the residual activity following its administration is recommended, as with any therapeutic radiopharmaceutical. This would require calibration of the radioassay system using, for example, a National Institute of Standards and Technology (NIST)-traceable ^{223}Ra standard. $^{223}RaCl_2$ does not differ significantly in terms of clinical use and management, radiation safety, and logistics from currently approved radiopharmaceuticals. Therefore, physicians already authorized to use therapeutic radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training, and experience to safely and effectively use $^{223}RaCl_2$. As such, licensing of authorized users of $^{223}RaCl_2$ under § 35.390 (Category (G)(3) or (G)(4)), or § 35.396(d)(2), is therefore recommended.

Clinical Background

Skeletal metastases commonly occur in many different malignancies, particularly advanced castrate-resistant prostate cancer, and are associated with severe morbidity and mortality (1). The resulting bone pain and possible fractures severely compromise the patient's quality of life and thus require effective treatment. Various non-radiotherapeutic modalities are available such as analgesics, hormone therapy, orchiectomy, cytostatic and cytotoxic drugs, bisphosphonates, and surgery, but are not universally effective (2). External-beam radiotherapy is suitable only for well-defined localized bone metastases, and extended-field radiation for more generalized skeletal disease is often accompanied by excessive toxicity (3). In the setting of widely disseminated skeletal metastases, systemic, bone-targeting radionuclide therapies have emerged as a safe, convenient, and reasonably effective palliative and therapeutic modality (4, 5). Current radiopharmaceuticals for palliation of painful skeletal metastases are exclusively beta particle emitters and include phosphorus-32 (^{32}P) sodium phosphate, strontium-89 (^{89}Sr) strontium chloride (Metastron™), yttrium-90 (^{90}Y) yttrium citrate, tin-117m (^{117m}Sn) diethylenetriamine pentaacetic acid (DTPA), samarium-153 (^{153}Sm) lexidronam (Quadramet™), thulium-170 (^{170}Tm) ethylene diamine

tetramethylene phosphonate (EDTMP), lutecium-177 (^{177}Lu) EDTMP, and rhenium-186 (^{186}Re) and rhenium-188 (^{188}Re) hydroxyethylidene diphosphonate (HEDP) (4,5). Currently approved radiopharmaceuticals for bone pain palliation include ^{32}P sodium phosphate, ^{89}Sr strontium chloride, and ^{153}Sm lexidronam, while the others remain investigational.

$^{223}RaCl_2$ (half-life: 11.43 days) is a calcium-mimetic alpha-particle emitter[1] which either avidly localizes in bone (particularly areas of active bone re-modeling typical of skeletal metastases)[2] or is rapidly excreted (6). ^{223}Ra has only short-lived radioactive progeny, radon-219 (^{219}Rn) (physical half-life: 3.96 seconds), polonium-215 (^{215}Po) (0.00178 second), bismuth-211 (^{211}Bi) (2.17 minutes), lead-211 (^{211}Pb) (36.1 minutes) and thallium-207 (^{207}Tl) (4.77 minutes) (6). The alpha emissions of ^{223}Ra and its progeny are short-range, high-linear energy transfer (LET), and high-relative biological effectiveness (RBE) radiations and should deliver highly localized, highly cytocidal radiation to metastatic cells in bone with relative sparing of the near-by bone marrow (6). In addition, ^{223}Ra and its progeny emit a number of externally countable and imageable x- and gamma-rays (81, 84, 154, and 269 keV) usable for pharmacokinetic studies, radiation dosimetry, and activity calibration (7). In principle, therefore, $^{223}RaCl_2$ potentially may provide more effective, less toxic palliation of skeletal metastases than current beta particle-emitting radiopharmaceuticals. Importantly, if approved by the US Food and Drug Administration (FDA), it would represent the very first alpha particle-emitting radiopharmaceutical in routine (i.e., non-investigational) clinical use[3] in the United States.

$^{223}RaCl_2$ has been extensively studied in patients in Europe as well as the United States (6, 8-13). Two open-label Phase-I trials (37 patients) and three double-blind Phase-II trials (255 patients) assessed radiation dosimetry, safety, and efficacy (decline in serum levels of prostate-specific antigen (PSA) and bone alkaline phosphatase (ALP) and prolongation of survival). Injected single doses varied from 5.2-252 kBq/kg (0.14-6.8 μCi/kg) body mass. Repeated treatment regimens varied in number of doses and time-dose schedule. A Phase-II clinical trial in patients with symptomatic, hormone-refractory prostate cancer showed improvement in survival, PSA levels, and ALP levels compared with placebo (i.e., no treatment), with no differences in hematologic toxicity. An international double-blind, placebo-controlled randomized trial (ALpharadin in SYMptomatic Prostate CAncer [ALSYMPCA]) was subsequently undertaken to compare $^{223}RaCl_2$ with placebo in patients with symptomatic, androgen-independent prostate cancer with skeletal metastases. The study was stratified based on ALP levels at registration, bisphosphonate use, and prior treatment with docetaxel. A total of 921 patients from 19 countries were enrolled, with overall survival being the primary endpoint. Importantly, the data demonstrated a statistically significant reduction in the risk of death for patients randomized to the $^{223}RaCl_2$ arm of the study (hazard ratio = 0.695; p = 0.00185), with a median overall survival of 14 months versus 11.2 months in the placebo arm. The overall survival benefit was seen across all sub-groups. The time

[1] Other potential clinical alpha particle-emitting, bone-seeking agents include thorium-227 (^{227}Th) EDTMP, ^{227}Th tetraazacyclododecane tetra(methylene) phosphonic acid (DOTMP), and ^{212}Bi DOTMP (4,5) but these are not as advanced in terms of clinical use as ^{223}Ra chloride.

[2] The propensity for internalized radium to localize in bone has long been recognized. For example, radium watch dial painters in the 1920s and 30s subsequently developed bone cancers and leukemias as a result of ingesting the radium-266 (^{226}Ra)-containing paint when "twirling" their paint brush tips to a fine point in their mouths. Importantly, ^{226}Ra has a much longer half-life, 1,600 years, than ^{223}Ra, a critically important factor related to its carcinogenecity in bone.

[3] The FDA's revised policy on "Expanded Access to Investigational Drugs for Treatment Use" (21 CFR Parts 312 and 316, Federal Register Vol 74, No 155 August 13, 2009) allows the use of agents such as $^{223}RaCl_2$ to be expanded to a larger population beyond compassionate use in individual patients, but such "expanded-access" use would still require compliance with the Investigational New Drug (IND) record-keeping, safety, ethical, and other requirements associated with human-subject experimentation.

to a skeletal-related event was also significantly longer for patients in the $^{223}RaCl_2$ versus placebo arm, 13.6 versus 8.4 months (p = 0.00046). The time to disease progression based on PSA and ALP levels was also significantly longer in the $^{223}RaCl_2$ arm. The patients randomized to $^{223}RaCl_2$ treatment tolerated it well. Both hematologic side-effects (grade-3 or -4 anemia, neutropenia, thrombocytopenia) and gastrointestinal side-effects (nausea, vomiting, diarrhea) did not occur with any greater frequency than with placebo. The former are related to localization of $^{223}RaCl_2$ in bone while the latter are related to its excretion through the intestines. It is noteworthy that the foregoing side-effects associated with therapeutic administration of $^{223}RaCl_2$ are hardly unique. For example, the dose-limiting toxicity associated with iodine-131 (^{131}I) iodide treatment of metastatic thyroid cancer and of radioimmunotherapy of cancer generally is most commonly myelosuppression. Nuclear Medicine physicians, Radiation Oncologists, and other physicians who administer radionuclide therapy are therefore already highly experienced in effectively managing such side-effects.

To summarize the clinical findings to date (6, 8-13), more than 1,000 prostate cancer patients have been treated with $^{223}RaCl_2$ with single and repeated treatments with significant PSA declines and prolonged survival benefit, without therapy-limiting myelotoxicity, gastrointestinal toxicity or other significant normal-tissue toxicity compared to placebo. Although not yet approved by the FDA for routine clinical use, this investigational alpha particle-emitting agent appears to be a promising bone-targeted radionuclide therapy.

Radiation Safety and Logistical Considerations

$^{223}RaCl_2$ and its progeny emit 95%, 4%, and 1% of their total radiation energy in the form of alpha particles, beta particles, and x- and gamma-rays, respectively (6). Alpha particles have very short ranges (of the order of 10 □m in bone and soft tissue) and thus present no external, or direct, radiation hazard. As long as standard universal precautions[4] are observed and internalization is avoided, alpha particles pose no significant radiologic hazard overall - despite their high LET and high RBE. Importantly, this will likewise be the case for alpha particle-emitting radiopharmaceuticals in general. Universal precautions would also safeguard against the internal radiologic hazard of the small beta-particle component among the emissions of ^{223}Ra and its progeny. X- and gamma-rays are, of course, much more penetrating than alpha- and beta-particles but are emitted in very low abundance by ^{223}Ra and its progeny, with energies comparable to those of common diagnostic radionuclides such as a technetium-99m (^{99m}Tc) (gamma-ray energy: 140 keV) and fluorine-18 (^{18}F) (511 keV). At the same time, the single-dose administered activities of $^{223}RaCl_2$, 50 kBq/kg (1.35 μCi/kg) body mass or 3,500 kBq (95 μCi) total for a 70-kg Standard Man, are several orders of magnitude lower than that of routine diagnostic radiopharmaceuticals (for which the administered activities are of the order of 370 MBq = 370,000 kBq (10 mCi = 10,000 μCi)). Thus, for such low-abundance x- and gamma-rays and such low activities, the external, or direct, radiation exposure and shielding requirements for $^{223}RaCl_2$ and its progeny are no greater than those for routinely used diagnostic radiopharmaceuticals - even though $^{223}RaCl_2$ is a therapeutic agent (14). Further, patients do not require medical confinement following $^{223}RaCl_2$ administration and may be treated on an outpatient basis.

As noted, ^{223}Ra has a physical half-life of 11.43 days; its radioactive progeny, ^{219}Rn, ^{215}Po, ^{211}Bi, ^{211}Pb, and ^{207}Tl, have much shorter half-lives, ranging from 0.00178 second to 36.1 minutes. ^{223}Ra and its progeny thus have sufficiently short half-lives for on-site decay-in-storage of radioactively contaminated waste followed by disposal as non-radioactive waste. At the same time, the x- and gamma-rays emitted by ^{223}Ra and its progeny, although low in abundance, are sufficient for assay

[4] Universal precautions (e.g., wearing of disposable gloves) constitute a method of infection control in which all human fluids, tissue etc are handled as if they are know to be infected with transmissible pathogens.

of any such waste. This can be done using conventional survey meters such as Geiger (G-M) counters - in order to verify that the exposure (or count) rates from contaminated or possibly contaminated waste are at or below background levels. Likewise, surveys of ambient exposure rates and of removable radioactive contamination (i.e., "wipes tests") associated with the use of $^{223}RaCl_2$ may be performed with instrumentation (surveys meters and well counters, respectively) already routinely available in Nuclear Medicine facilities.

$^{223}RaCl_2$ is a simple salt of radium, and not a radiolabeled molecule. It therefore requires no synthesis or other preparation by the clinical site and does not undergo any sort of chemical decomposition. Quality control procedures for determination of radiochemical purity and special storage conditions (e.g., refrigeration) are therefore not required for $^{223}RaCl_2$. As distributed by Bayer Healthcare (Pittsburgh, PA), it is provided in a crimped glass vial as an injectable isotonic solution with an activity concentration of 1,000 kBq/ml (27 μCi/ml) at calibration (15). The recommended administered activity is 50 kBq/kg (1.35 μCi/kg) body mass (15). A patient-specific volume of injectate, calculated using the following formula, is drawn directly from the vendor-provided $^{223}RaCl_2$ solution (15):

$$\text{Volume to inject (ml)} = \frac{\text{Body mass (kg) x 50 kBq/kg}}{\text{Decay factor x 1000 kBq/ml}}$$

where the decay factor is the fractional decay factor (as derived from a vendor-provided "decay factor table," for example) for the time interval from the date and time of calibration of the $^{223}RaCl_2$ to the planned date and time of administration.

Implicit in the foregoing dose-prescription algorithm is that the user is *not* required to assay the ^{223}Ra activity prior to its administration or the residual activity following its administration, as is typically done in Nuclear Medicine (especially for therapeutic administrations). Bayer Healthcare has asserted that measurement of the ^{223}Ra activities is *not* necessary, as the patient-specific dose corresponds to a calculated volume of the vendor-supplied solution with the vendor-specified pre-calibrated activity concentration (15). Bayer Healthcare has further asserted that such activity measurements would be potentially unreliable because (a) a setting for ^{223}Ra is not provided on currently available dose calibrators and (b) the pre-administration activity and, in particular, the residual activity would be too low (in the tens of kBq (μCi) range) to measure reliably (15). ^{223}Ra does, however, emit measurable x- and gamma-rays (7), and dose calibrators can thus be calibrated by the end user for ^{223}Ra using a National Institute of Standards and Technology (NIST)-traceable ^{223}Ra standard (16). In addition, assay of the pre-administration and residual ^{223}Ra activities, even if inexact, would help avoid potentially "catastrophic" misadministrations. By verifying that the actual pre-administration activity is consistent with the prescribed activity and that the residual activity is insignificant, clinically important over-dosing and/or under-dosing of the patient (e.g., due to mis-calibration of the vendor-supplied $^{223}RaCl_2$ solution or inaccurate drawing of the patient-specific injectate) as well as administration of an incorrect radionuclide could likely be avoided. Such activity assays would thus provide an additional level of safety at the treatment site independent of the vendor's manufacturing and calibration procedures. In a therapy setting, such redundancy, or cross-checking, is certainly prudent and is standard in Nuclear Medicine, especially in therapeutic applications. An appropriate radioassay system (e.g., a dose calibrator) for measurement of the ^{223}Ra activity prior to its administration or the residual activity following its administration is therefore recommended for the therapeutic use of $^{223}RaCl_2$.

Licensing Considerations

As noted, $^{223}RaCl_2$ represents a first-in-class - that is, an alpha particle-emitting - radiopharmaceutical. As such, it raises the issue of the appropriate NRC licensure for authorized

users of this agent. $^{223}RaCl_2$ should be licensed under § 35.300 of the Code of Federal Regulations (CFR) (Appendix 1). Within the NRC's regulatory framework, there would appear to be several different licensing options for $^{223}RaCl_2$, namely, authorized users who meet training and experience requirements under § 35.390 (Appendix 2), § 35.396 (Appendix 3), or § 35.1000 A (Appendix 4). Despite its alpha-particle emissions, $^{223}RaCl_2$ does not differ fundamentally from current routinely used therapeutic radiopharmaceuticals. Given the similarities in clinical use and radiation safety considerations (as detailed above) between $^{223}RaCl_2$ and current therapeutic radiopharmaceuticals, the use of which is authorized under § 35.390 (Appendix 2), the use of $^{223}RaCl_2$ should likewise be authorized under § 35.390. It would appear that either Category (3) or (4) in § 35.390 would be appropriate for $^{223}RaCl_2$. Category (3) applies to, "Parenteral administration of any beta emitter, or a photon- emitting radionuclide with a photon energy less than 150 keV, for which a written directive is required"; it does not explicitly include or exclude alpha-particle emitters, however. Since ^{223}Ra progeny emit beta particles as well as alpha particles, $^{223}RaCl_2$ technically might be considered a "Category (3)" radiopharmaceutical. However, even if "Category (3)" were interpreted as not applying to $^{223}RaCl_2$, Category (4), which applies to, "Parenteral administration of any other radionuclide, for which a written directive is required," would certainly apply. This same conclusion applies to § 35.396 (Appendix 3). Licensing of $^{223}RaCl_2$ under § 35.1000 (Appendix 4) is not an appropriate option as that would imply it differs significantly in terms of clinical use and management, radiation safety, and logistics from current therapeutic radiopharmaceuticals, and this is not the case. Physicians already authorized to use such radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training, and experience to safely and effectively use $^{223}RaCl_2$, and should not be required to provide additional training-and-experience documentation to be licensed for its use.

References

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 12(Suppl): 6243s-6249s, 2006.

2. Coleman RE. Management of bone metastases. The Oncologist 5: 463-470, 2000.

3. Chow E, Harris K, Fan G, Tsao M, and Sze WM. Palliative radiotherapy trials for bone metastases: A systematic review. J Clin Oncol 25: 1423-1436.

4. Tomblyn M. The role of bone-seeking radionuclides in the palliative treatment of patients with painful osteoblastic skeletal metastases. Cancer Control 19: 137-144, 2012.

5. Ogawa K and Washiyama K. Bone target radiotracers for palliative therapy of bone metastases. Curr Med Chem, 2012 [Epub ahead of print].

6. Bruland OS, Nilsson S, Fisher DR, and Larsen RH. High-linear energy transfer irradiation targeted to skeletal metastases by the □-emitter ^{223}Ra: Adjuvant or alternative to conventional modalities? Clin Cancer Res 12 (Suppl): 6250s-6257s, 2006.

7. Hindorf C, Chittenden S, Aksnes AK, Chris Parker C, and Glenn D. Flux GD. Quantitative imaging of 223Ra-chloride (Alpharadin) for targeted alpha-emitting radionuclide therapy of bone metastases. Nucl Med Commun 33: 726-732, 2012.

8. Nilsson S, Balteskard L, Fossa SD et al. Phase I study of Alpharadin2 (^{223}Ra), and □-emitting bone-seeking agent in cancer patients with skeletal metastases. Eur J Nucl Med Mol Imaging 31: S290 [abstract], 2004.

9. Nilsson S, Balteskard L, Fossa SD, et al. First clinical experiences with emitter radium-223 in the treatment skeletal metastases from breast and prostate cancer. Clin Cancer Res 11:4451-4459, 2005.

10. Nilsson S, Franzen L, Tyrrell C et al. Bone-seeking radium-223 adjuvant to external beam radiotherapy demonstrates significant decline in bone-alkaline phosphatase and PSA in patients with hormone refractory prostate cancer [abstract]. ASCO Prostate Cancer Symposium 2006.

11. Nilsson S, Franzén L, Parker C, Tyrrell C, Blom R, Tennvall J, Lennernäs B, Petersson U, Johannessen DC, Sokal M, Katharine Pigott K, Yachnin JR, Garkavij M, Strang P, Harmenberg J, Bolstad B, and Bruland OS. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: A randomised, multicentre, placebo-controlled phase II study. Lancet Oncol 8: 587-594, 2007.

12. Parker C, Heinrich D, O'Sullivan JM et al. Overall survival benefit of radium-223 chloride (Alpharadin) in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer (CRPC): A phase III randomised trial (ALSYMPCA) [Abstract]. European Multidisciplinary Cancer Congress 2011.

13. Nilsson S, Strang P, Aksnes AK, Franzèn L, Olivier P, Pecking A, Staffurth J, Vasanthan S, Andersson C, and Bruland ØS. A randomized, dose–response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer 48: 678–686, 2012.

14. Cheetham PJ and Petrylak DP. Alpha particles as radiopharmaceuticals in the treatment of bone metastases: mechanism of action of radium-223 chloride (Alpharadin) and radiation protection. Oncology 26: 330-337, 2012.

15. Bayer Healthcare. Medical uses of radium-223 chloride. Presentation to the NRC Advisory Committee on Medical uses of Isotopes (ACMUI), Rockville, MD, April 17th, 2012.

16. Bergeron DE, Zimmerman BE, and Cessna JT. Development of secondary standards for ^{223}Ra. Appl Radiat Isot 68:1367-1370, 2010.

Appendix 1

§ 35.300 Use of unsealed byproduct material for which a written directive is required.

A licensee may use any unsealed byproduct material prepared for medical use and for which a written directive is required that is-

(a) Obtained from:

(1) A manufacturer or preparer licensed under § 32.72 of this chapter or equivalent Agreement State requirements; or

(2) A PET radioactive drug producer licensed under § 30.32(j) of this chapter or equivalent Agreement State requirements; or

(b) Excluding production of PET radionuclides, prepared by:

(1) An authorized nuclear pharmacist;

(2) A physician who is an authorized user and who meets the requirements specified in §§ 35.290, 35.390, or

(3) An individual under the supervision, as specified in § 35.27, of the authorized nuclear pharmacist in paragraph (b)(1) of this section or the physician who is an authorized user in paragraph (b)(2) of this section; or

(c) Obtained from and prepared by an NRC or Agreement State licensee for use in research in accordance with an Investigational New Drug (IND) protocol accepted by FDA; or

(d) Prepared by the licensee for use in research in accordance with an Investigational New Drug (IND) protocol accepted by FDA.

[67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19324, Apr. 21, 2003; 69 FR 55738, Sep. 16, 2004; 71 FR 15009, Mar. 27, 2006; 72 FR 55932 Oct. 1, 2007]

Appendix 2

§ 35.390 Training for use of unsealed byproduct material for which a written directive is required.

Except as provided in § 35.57, the licensee shall require an authorized user of unsealed byproduct material for the uses authorized under § 35.300 to be a physician who-

(a) Is certified by a medical specialty board whose certification process has been recognized by the Commission or an Agreement State and who meets the requirements in paragraphs (b)(1)(ii)(G) and (b)(2) of this section. (Specialty boards whose certification processes have been recognized by the Commission or an Agreement State will be posted on the NRC's Web page.) To be recognized, a specialty board shall require all candidates for certification to:

(1) Successfully complete residency training in a radiation therapy or nuclear medicine training program or a program in a related medical specialty. These residency training programs must include 700 hours of training and experience as described in paragraphs (b)(1)(i) through (b)(1)(ii)(E) of this section. Eligible training programs must be approved by the Residency Review Committee of the Accreditation Council for Graduate Medical Education, the Royal College of Physicians and Surgeons of Canada, or the Committee on Post-Graduate Training of the American Osteopathic Association; and

(2) Pass an examination, administered by diplomates of the specialty board, which tests knowledge and competence in radiation safety, radionuclide handling, quality assurance, and clinical use of unsealed byproduct material for which a written directive is required; or

(b)(1) Has completed 700 hours of training and experience, including a minimum of 200 hours of classroom and laboratory training, in basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material requiring a written directive. The training and experience must include-

(i) Classroom and laboratory training in the following areas-

(A) Radiation physics and instrumentation;

(B) Radiation protection;

(C) Mathematics pertaining to the use and measurement of radioactivity;

(D) Chemistry of byproduct material for medical use; and

(E) Radiation biology; and

(ii) Work experience, under the supervision of an authorized user who meets the requirements in §§ 35.57, 35.390, or equivalent Agreement State requirements. A supervising authorized user, who meets the requirements in § 35.390(b), must also have experience in administering dosages in the same dosage category or categories (*i.e.*, § 35.390(b)(1)(ii)(G)) as the individual requesting authorized user status. The work experience must involve-

(A) Ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys;

(B) Performing quality control procedures on instruments used to determine the activity of dosages, and performing checks for proper operation of survey meters;

(C) Calculating, measuring, and safely preparing patient or human research subject dosages;

(D) Using administrative controls to prevent a medical event involving the use of unsealed byproduct material;

(E) Using procedures to contain spilled byproduct material safely and using proper decontamination procedures;

(F) [Reserved]

(G) Administering dosages of radioactive drugs to patients or human research subjects involving a minimum of three cases in each of the following categories for which the individual is requesting authorized user status-

(*1*) Oral administration of less than or equal to 1.22 gigabecquerels (33 millicuries) of sodium iodide I-131, for which a written directive is required;

(*2*) Oral administration of greater than 1.22 gigabecquerels (33 millicuries) of sodium iodide I-131[2];

(*3*) Parenteral administration of any beta emitter, or a photon- emitting radionuclide with a photon energy less than 150 keV, for which a written directive is required; and/or

(*4*) Parenteral administration of any other radionuclide, for which a written directive is required; and

(2) Has obtained written attestation that the individual has satisfactorily completed the requirements in paragraphs (a)(1) and (b)(1)(ii)(G) or (b)(1) of this section, and has achieved a level of competency sufficient to function independently as an authorized user for the medical uses authorized under § 35.300. The written attestation must be signed by a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, or equivalent Agreement State requirements. The preceptor authorized user, who meets the requirements in § 35.390(b) must have experience in administering dosages in the same dosage category or categories (*i.e.*, § 35.390(b)(1)(ii)(G)) as the individual requesting authorized user status.

[67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19325, Apr. 21, 2003; 68 FR 75389, Dec. 31, 2003; 69 FR 55738, Sep. 16, 2004; 70 FR 16364, Mar. 30, 2005; 71 FR 15009, Mar. 27, 2006; 74 FR 33905, Jul. 14, 2009]

[2] Experience with at least 3 cases in Category (G)(*2*) also satisfies the requirement in Category (G)(*1*)

Appendix 3

§ 35.396 Training for the parenteral administration of unsealed byproduct material requiring a written directive.

Except as provided in § 35.57, the licensee shall require an authorized user for the parenteral administration requiring a written directive, to be a physician who-

(a) Is an authorized user under § 35.390 for uses listed in §§ 35.390(b)(1)(ii)(G)(3) or 35.390(b)(1)(ii)(G)(4), or equivalent Agreement State requirements; or

(b) Is an authorized user under §§ 35.490, 35.690, or equivalent Agreement State requirements and who meets the requirements in paragraph (d) of this section; or

(c) Is certified by a medical specialty board whose certification process has been recognized by the Commission or an Agreement State under §§ 35.490 or 35.690, and who meets the requirements in paragraph (d) of this section.

(d)(1) Has successfully completed 80 hours of classroom and laboratory training, applicable to parenteral administrations, for which a written directive is required, of any beta emitter, or any photon-emitting radionuclide with a photon energy less than 150 keV, and/or parenteral administration of any other radionuclide for which a written directive is required. The training must include—

(i) Radiation physics and instrumentation;

(ii) Radiation protection;

(iii) Mathematics pertaining to the use and measurement of radioactivity;

(iv) Chemistry of byproduct material for medical use; and

(v) Radiation biology; and

(2) Has work experience, under the supervision of an authorized user who meets the requirements in §§ 35.57, 35.390, 35.396, or equivalent Agreement State requirements, in the parenteral administration, for which a written directive is required, of any beta emitter, or any photon-emitting radionuclide with a photon energy less than 150 keV, and/or parenteral administration of any other radionuclide for which a written directive is required. A supervising authorized user who meets the requirements in § 35.390 must have experience in administering dosages as specified in §§ 35.390(b)(1)(ii)(G)(3) and/or 35.390(b)(1)(ii)(G)(4). The work experience must involve—

(i) Ordering, receiving, and unpacking radioactive materials safely, and performing the related radiation surveys;

(ii) Performing quality control procedures on instruments used to determine the activity of dosages, and performing checks for proper operation of survey meters;

(iii) Calculating, measuring, and safely preparing patient or human research subject dosages;

(iv) Using administrative controls to prevent a medical event involving the use of unsealed byproduct material;

(v) Using procedures to contain spilled byproduct material safely, and using proper decontamination procedures; and

(vi) Administering dosages to patients or human research subjects, that include at least 3 cases involving the parenteral administration, for which a written directive is required, of any beta emitter, or any photon-emitting radionuclide with a photon energy less than 150 keV and/or at least 3 cases involving the parenteral administration of any other radionuclide, for which a written directive is required; and

(3) Has obtained written attestation that the individual has satisfactorily completed the requirements in paragraph (b) or (c) of this section, and has achieved a level of competency sufficient to function independently as an authorized user for the parenteral administration of unsealed byproduct material requiring a written directive. The written attestation must be signed by a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, 35.396, or equivalent Agreement State requirements. A preceptor authorized user, who meets the requirements in § 35.390, must have experience in administering dosages as specified in §§ 35.390(b)(1)(ii)(G)(3) and/or 35.390(b)(1)(ii)(G)(*4*).

[70 FR 16365, Mar. 30, 2005; 71 FR 15010. Mar. 27, 2006; 74 FR 33906, Jul. 14, 2009]

Appendix 4

§ 35.1000 Other medical uses of byproduct material or radiation from byproduct material.

A licensee may use byproduct material or a radiation source approved for medical use which is not specifically addressed in subparts D through H of this part if--

(a) The applicant or licensee has submitted the information required by § 35.12(b) through (d); and

(b) The applicant or licensee has received written approval from the Commission in a license or license amendment and uses the material in accordance with the regulations and specific conditions the Commission considers necessary for the medical use of the material.