

Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical ~~Uses~~ of Isotopes (ACMUI)
Subcommittee Report on Licensing for Radium-223 ~~Chloride~~ (²²³Ra) Dichloride
July 16, 2012

Subcommittee Members

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Charge

To provide recommendations on licensing of radium-223 ~~chloride (Ra-223-Cl~~ (²²³Ra) ~~dichloride~~ (²²³RaCl₂).

Summary Statement and Recommendations

~~Ra-223-Cl~~ ²²³RaCl₂, currently a non-approved investigational agent undergoing clinical trials in the United States, represents a first-in-class, alpha particle-emitting therapeutic radiopharmaceutical. Based on relevant physical and biological considerations as well as ~~clinieclinical~~ data to date, ~~it appears to be a safe, effective, and convenient~~ ~~its intended indication is~~ treatment ~~for~~ 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 ~~Ra-223-Cl~~ (²²³RaCl₂) (50 kBq/kg (1.35 \square Ci/kg (50 kBq/kg)) is determined based on the vendor-supplied activity concentration in a pre-calibrated solution. Nonetheless, to minimize the probability of a therapeutic misadministration, ~~requiring~~ an appropriate radioassay system (e.g., a dose calibrator) for measurement of the ~~Ra-223~~ ²²³Ra 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 ~~Ra-223~~ ²²³Ra standard. ~~Ra-223-Cl~~ ²²³RaCl₂ 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 ~~Ra-223-Cl~~ ²²³RaCl₂. As such, licensing of authorized users of ~~Ra-223-Cl~~ ²²³RaCl₂ under § 35.390 (Category (G)(3) or (G)(4)), or § 35.396(d)(2), is therefore recommended. ~~Importantly, the foregoing considerations, including licensing, are likely to apply to any future alpha-particle-emitting radiopharmaceuticals generally.~~

Comment [a1]: Note removal of word "requiring"

Comment [a2]: Dr. Orhan Suleiman recommended removal of such a general statement, since the route of administration for ²²³RaCl₂ has a large impact on the committee's decision to recommend licensing in 300.

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 ($P-32^{32}P$) sodium phosphate, strontium-89 ($Sr-89^{89}Sr$) strontium chloride (Metastron™), yttrium-90 ($Y-90^{90}Y$) yttrium citrate, tin-117m ($Sn-117m^{117m}Sn$) diethylenetriamine pentaacetic acid (DTPA), samarium-153 ($Sm-153^{153}Sm$) leixidronam (Quadramet™), thulium-170 ($Tm-170^{170}Tm$) ethylene diamine tetramethylene phosphonate (EDTMP), lutecium-177 ($Lu-177^{177}Lu$) EDTMP, and rhenium-186 ($Re-186^{186}Re$) and rhenium-188 ($Re-188^{188}Re$) hydroxyethylidene diphosphonate (HEDP) (4,5). Currently approved radiopharmaceuticals for bone pain palliation include $P-32^{32}P$ sodium phosphate, $Sr-89^{89}Sr$ strontium chloride, and $Sm-153^{153}Sm$ leixidronam, while the others remain investigational.

$Ra-223-Cl^{223}RaCl_2$ (half-life: 11.43 days) is a calcium-mimetic alpha-particle emitter¹ which either avidly localizes in bone (particularly areas of active bone re-modeling typical of skeletal metastases)² or is rapidly excreted (6). $Ra-223^{223}Ra$ has only short-lived radioactive progeny, radon-219 ($Rn-219^{219}Rn$) (physical half-life: 3.96 seconds), polonium-215 ($Po-215^{215}Po$) (0.00178 second), and bismuth-211 ($Bi-211^{211}Bi$) (2.17 minutes), lead-211 ($Pb-211^{211}Pb$) (36.1 minutes) and thallium-207 ($Tl-207^{207}Tl$) (4.77 minutes) (6). The alpha emissions of $Ra-223^{223}Ra$ and its progeny are short-range, high-linear energy transfer (LET), and high-relative biological effectiveness (RBE) radiations and should deliver highly localized, highly cytotoxic radiation to metastatic cells in bone with relative sparing of the near-by bone marrow (6). In addition, $Ra-223^{223}Ra$ 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, $Ra-223-Cl^{223}RaCl_2$ 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.

$Ra-223-Cl^{223}RaCl_2$ has been extensively studied in patients, in Europe in particular 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 \square Ci/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 $Ra-223-Cl^{223}RaCl_2$ with placebo in patients with symptomatic, androgen-independent prostate cancer with skeletal metastases. The study was stratified based on ALP levels at

¹ Other potential clinical alpha particle-emitting, bone-seeking agents include thorium-227 ($Th-227^{227}Th$) EDTMP, $Th-227^{227}Th$ tetraazacyclododecane tetra(methylene) phosphonic acid DOTMP (DOTMP), and $Bi-212^{212}Bi$ DOTMP (4,5) but these are not as advanced in terms of clinical use as Alpharadin™, ^{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-226 ($Ra-226^{226}Ra$)-containing paint when "twirling" their paint brush tips to a fine point in their mouths. Importantly, $Ra-226^{226}Ra$ has a much longer half-life, 1,600 years, than $Ra-223^{223}Ra$, a critically important factor related to its carcinogenicity 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.

90 | registration, bisphosphonate use, and prior treatment with docetaxel. A total of 922921 patients
 91 | from 19 countries were enrolled, with overall survival being the primary endpoint. Importantly, the
 92 | data demonstrated a statistically significant reduction in the risk of death for patients randomized to
 93 | the $\text{Ra-223}^{223}\text{RaCl}_2$ arm of the study (hazard ratio = 0.695; p = 0.00185), with a median overall
 94 | survival of 14 months versus 11.2 months in the placebo arm. The overall survival benefit was
 95 | seen across all sub-groups. The time to a skeletal-related event was also significantly longer for
 96 | patients in the $\text{Ra-223}^{223}\text{RaCl}_2$ versus placebo arm, 13.6 versus 8.4 months (p = 0.00046). The
 97 | time to disease progression based on PSA and ALP levels was also significantly longer in the Ra-
 98 | 223^{223}RaCl_2 arm. The patients randomized to $\text{Ra-223}^{223}\text{RaCl}_2$ treatment tolerated it well. Both
 99 | hematologic side-effects (grade-3 or -4 anemia, neutropenia, thrombocytopenia) and
 100 | gastrointestinal side-effects (nausea, vomiting, diarrhea) did not occur with any greater frequency
 101 | than with placebo. The former are related to localization of $\text{Ra-223}^{223}\text{RaCl}_2$ in bone while the latter
 102 | are related to its excretion through the intestines. It is noteworthy that the foregoing side-effects
 103 | associated with therapeutic administration of $\text{Ra-223-Cl-are}^{223}\text{RaCl}_2$ are hardly unique. For
 104 | example, the dose-limiting toxicity associated with iodine-131 (^{131}I) iodide treatment of
 105 | metastatic thyroid cancer and of radioimmunotherapy of cancer generally is most commonly
 106 | myelosuppression. Nuclear Medicine physicians, Radiation Oncologists, and other physicians who
 107 | administer radionuclide therapy are therefore already highly experienced in effectively managing
 108 | such side-effects.

109 |
 110 | To summarize the clinical findings to date (6, 8-13), more than 1,000 prostate cancer patients have
 111 | been treated with $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ with single and repeated treatments with significant PSA
 112 | declines and prolonged survival benefit, without therapy-limiting myelotoxicity, gastrointestinal
 113 | toxicity or other significant normal-tissue toxicity compared to placebo. Although not yet approved
 114 | by the FDA, Ra-223-Cl for routine clinical use, this investigational alpha particle-emitting agent
 115 | appears to be the only promising bone-targeted radionuclide therapy which significantly prolongs
 116 | survival.

117 | **Radiation Safety and Logistical Considerations**

118 | $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ and its progeny emit 95%, 4%, and 1% of their total radiation energy in the form
 119 | of alpha particles, beta particles, and x- and gamma-rays, respectively (6). Alpha particles have
 120 | very short ranges (of the order of 10 μm in bone and soft tissue) and thus present no external, or
 121 | direct, radiation hazard. As long as standard universal precautions⁴ are observed and
 122 | internalization is avoided, alpha particles pose no significant radiologic hazard overall - despite
 123 | their high LET and high RBE. Importantly, this will likewise be the case for alpha particle-emitting
 124 | radiopharmaceuticals in general. Universal precautions would also safeguard against the internal
 125 | radiologic hazard of the small beta-particle component among the emissions of $\text{Ra-223}^{223}\text{Ra}$ and
 126 | its progeny. X- and gamma-rays are, of course, much more penetrating than alpha- and beta-
 127 | particles but are emitted in very low abundance by $\text{Ra-223}^{223}\text{Ra}$ and its progeny, with energies
 128 | comparable to those of common diagnostic radionuclides such as a technetium-99m ($^{99\text{m}}\text{Tc}$)
 129 | ($^{99\text{m}}\text{Tc}$) (gamma-ray energy: 140 keV) and fluorine-18 (^{18}F) (511 keV). At the same time,
 130 | the single-dose administered activities of Ra-223-Cl , $\text{Ra-223}^{223}\text{RaCl}_2$, 50 kBq/kg (1.535 $\mu\text{Ci/kg}$) body
 131 | mass or $\sim 4903,500$ kBq (95 μCi) total for a 70-kg Standard Man, are several orders of magnitude
 132 | lower than that of routine diagnostic radiopharmaceuticals (for which the administered activities are
 133 | of the order of 370 MBq = 370,000 kBq (10 mCi = 10,000 μCi)). Thus, for such low-abundance x-
 134 | and gamma-rays and such low activities, the external, or direct, radiation exposure and shielding
 135 | requirements for $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ and its progeny are no greater than those for routinely used
 136 |

Comment [a3]: Because this drug is not approved, and this determination is pending with the FDA, Dr. Orhan Suleiman suggested deletion.

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 known to be infected with transmissible pathogens.

137 diagnostic radiopharmaceuticals - even though $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ is a therapeutic agent (14).
 138 Further, patients do not require medical confinement following $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ administration
 139 and may be treated on an outpatient basis. ~~It should be reiterated, however, that Ra-223-Cl is still~~
 140 ~~a non-approved (ie investigational) radiopharmaceutical.~~

141
 142 As noted, $\text{Ra-223}^{223}\text{Ra}$ has a physical half-life of 11.43 days; its radioactive progeny, Rn-219 , Po-
 143 ~~215~~, Bi-214 , Pb-214 , ^{219}Rn , ^{215}Po , ^{211}Bi , ^{211}Pb , and Tl-207 , ^{207}Tl , have much shorter half-lives, ranging
 144 from 0.00178 second to 36.1 minutes. $\text{Ra-223}^{223}\text{Ra}$ and its progeny thus have sufficiently short
 145 half-lives for on-site decay-in-storage of radioactively contaminated waste followed by disposal as
 146 non-radioactive waste. At the same time, the x- and gamma-rays emitted by $\text{Ra-223}^{223}\text{Ra}$ and its
 147 progeny, although low in abundance, are sufficient for assay of any such waste. This can be done
 148 using conventional survey meters such as Geiger (G-M) counters - in order to verify that the
 149 exposure (or count) rates from contaminated or possibly contaminated waste are at or below
 150 background levels. Likewise, surveys of ambient exposure rates and of removable radioactive
 151 contamination (ie.e., "wipes tests") associated with the use of $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ may be
 152 performed with instrumentation (survey meters and well counters, respectively) already routinely
 153 available in Nuclear Medicine facilities.

154
 155 $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ is a simple salt of radium, and not a radiolabeled molecule. It therefore requires
 156 no synthesis or other preparation by the clinical site and does not undergo any sort of chemical
 157 decomposition. Quality control procedures for determination of radiochemical purity and special
 158 storage conditions (e.g., refrigeration) are therefore not required for $\text{Ra-223-Cl}^{223}\text{RaCl}_2$. As
 159 distributed by Bayer Healthcare (Pittsburgh, PA), it is provided in a crimped glass vial as an
 160 injectable isotonic solution with an activity concentration of 1,000 kBq/ml (27 $\mu\text{Ci/ml}$) at calibration
 161 (15). The recommended administered activity is 50 kBq/kg (1.35 $\mu\text{Ci/kg}$) body mass (15). A
 162 patient-specific volume of injectate, calculated using the following formula, is drawn directly from
 163 the vendor-provided $\text{Ra-223-Cl}^{223}\text{RaCl}_2$ solution (15):

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

166
 167 where the decay factor is the fractional decay factor (as derived from a vendor-provided "decay
 168 factor table," for example) for the time interval from the date and time of calibration of the Ra-223
 169 $\text{Cl}^{223}\text{RaCl}_2$ to the planned date and time of administration.

170
 171 Implicit in the foregoing dose-prescription algorithm is that the user is *not* required to assay the Ra-
 172 ^{223}Ra activity prior to its administration or the residual activity following its administration, as is
 173 typically done in Nuclear Medicine (especially for therapeutic administrations). Bayer Healthcare
 174 has asserted that measurement of the $\text{Ra-223}^{223}\text{Ra}$ activities is *not* necessary, as the patient-
 175 specific dose corresponds to a calculated volume of the vendor-supplied solution with the vendor-
 176 specified pre-calibrated activity concentration (15). Bayer Healthcare has further asserted that
 177 such activity measurements would be potentially unreliable because (a) a setting for $\text{Ra-223}^{223}\text{Ra}$
 178 is not provided on currently available dose calibrators and (b) the pre-administration activity and, in
 179 particular, the residual activity would be too low (in the range of kBq (μCi)) to measure
 180 reliably (15). $\text{Ra-223}^{223}\text{Ra}$ does, however, emit measurable x- and gamma-rays (7), and dose
 181 calibrators can thus be calibrated by the end user for $\text{Ra-223}^{223}\text{Ra}$ using a National Institute of
 182 Standards and Technology (NIST)-traceable $\text{Ra-223}^{223}\text{Ra}$ standard (16). In addition, assay of the
 183 pre-administration and residual $\text{Ra-223}^{223}\text{Ra}$ activities, even if inexact, would help avoid potentially
 184 "catastrophic" misadministrations. By verifying that the actual pre-administration activity is
 185 consistent with the prescribed activity and that the residual activity is insignificant, clinically
 186 important over-dosing and/or under-dosing of the patient (e.g., due to mis-calibration of the

187 | vendor-supplied ~~Ra-223-Cl²²³RaCl₂~~ solution or inaccurate drawing of the patient-specific injectate)
 188 | as well as administration of an incorrect radionuclide could likely be avoided. Such activity assays
 189 | would thus provide an additional level of safety at the treatment site independent of the vendor's
 190 | manufacturing and calibration procedures. In a therapy setting, such redundancy, or cross-
 191 | checking, is certainly prudent and is standard in Nuclear Medicine, especially in therapeutic
 192 | applications. An appropriate radioassay system (e.g., a dose calibrator) for measurement of the
 193 | ~~Ra-223-²²³Ra~~ activity prior to its administration or the residual activity following its administration is
 194 | therefore recommended for the therapeutic use of ~~Ra-223-Cl²²³RaCl₂~~.

195

196 | **Licensing Considerations**

197 | As noted, ~~Ra-223-Cl²²³RaCl₂~~ represents a first-in-class - that is, an alpha particle-emitting -
 198 | radiopharmaceutical. As such, it raises the issue of the appropriate NRC licensure for authorized
 199 | users of this agent. ~~Ra-223-Cl²²³RaCl₂~~ should be licensed under § 35.300 of the Code of Federal
 200 | Regulations (CFR) (Appendix 1). Within the NRC's regulatory framework, there would appear to
 201 | be several different licensing options for ~~Ra-223-Cl²²³RaCl₂~~, namely, authorized users who meet
 202 | training and experience requirements under § 35.390 (Appendix 2), § 35.396 (Appendix 3), or §
 203 | 35.1000 A (Appendix 4). Despite its alpha-particle emissions, ~~Ra-223-Cl²²³RaCl₂~~ does not differ
 204 | fundamentally from current routinely used therapeutic radiopharmaceuticals. Given the similarities
 205 | in clinical use and radiation safety considerations (as detailed above) between ~~Ra-223-Cl²²³RaCl₂~~
 206 | and current therapeutic radiopharmaceuticals, the use of which is authorized under § 35.390
 207 | (Appendix 2), the use of ~~Ra-223-Cl²²³RaCl₂~~ should likewise be authorized under § 35.390. It would
 208 | appear that either Category (3) or (4) in § 35.390 would be appropriate for ~~Ra-223-Cl²²³RaCl₂~~.
 209 | Category (3) applies to, "Parenteral administration of any beta emitter, or a photon- emitting
 210 | radionuclide with a photon energy less than 150 keV, for which a written directive is required"; it
 211 | does not explicitly include or exclude alpha-particle emitters, however. Since ~~Ra-223-²²³Ra~~ progeny
 212 | emit beta particles as well as alpha particles, ~~Ra-223-Cl²²³RaCl₂~~ technically might be considered a
 213 | "Category (3)" radiopharmaceutical. However, even if "Category (3)" were interpreted as not
 214 | applying to ~~Ra-223-Cl²²³RaCl₂~~, Category (4), which applies to, "Parenteral administration of any
 215 | other radionuclide, for which a written directive is required," would certainly apply. This same
 216 | conclusion applies to § 35.396 (Appendix 3). Licensing of ~~Ra-223-Cl²²³RaCl₂~~ under § 35.1000
 217 | (Appendix 4) is not an appropriate option as that would imply it differs significantly in terms of
 218 | clinical use and management, radiation safety, and logistics from current therapeutic
 219 | radiopharmaceuticals, and this is not the case. Physicians already authorized to use such
 220 | radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training,
 221 | and experience to safely and effectively use ~~Ra-223-Cl²²³RaCl₂~~, and should not be required to
 222 | provide additional training-and-experience documentation to be licensed for its use.

223

224 | **References**

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271

272

Appendix 1

273 **§ 35.300 Use of unsealed byproduct material for which a written directive is required.**

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

276 (a) Obtained from:

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

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

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

282 (1) An authorized nuclear pharmacist;

283 (2) A physician who is an authorized user and who meets the requirements specified in §§ 35.290,
284 35.390, or

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

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

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

292 [67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19324, Apr. 21, 2003; 69 FR 55738, Sep. 16,
293 2004; 71 FR 15009, Mar. 27, 2006; 72 FR 55932 Oct. 1, 2007]

294

295

Appendix 2

296 **§ 35.390 Training for use of unsealed byproduct material for which a written directive is**
297 **required.**

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

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

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

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

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

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

320 (A) Radiation physics and instrumentation;

321 (B) Radiation protection;

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

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

324 (E) Radiation biology; and

325 (ii) Work experience, under the supervision of an authorized user who meets the requirements in
326 §§ 35.57, 35.390, or equivalent Agreement State requirements. A supervising authorized user, who
327 meets the requirements in § 35.390(b), must also have experience in administering dosages in the
328 same dosage category or categories (*i.e.*, § 35.390(b)(1)(ii)(G)) as the individual requesting
329 authorized user status. The work experience must involve-

- 330 (A) Ordering, receiving, and unpacking radioactive materials safely and performing the related
331 radiation surveys;
- 332 (B) Performing quality control procedures on instruments used to determine the activity of dosages,
333 and performing checks for proper operation of survey meters;
- 334 (C) Calculating, measuring, and safely preparing patient or human research subject dosages;
- 335 (D) Using administrative controls to prevent a medical event involving the use of unsealed
336 byproduct material;
- 337 (E) Using procedures to contain spilled byproduct material safely and using proper
338 decontamination procedures;
- 339 (F) [Reserved]
- 340 (G) Administering dosages of radioactive drugs to patients or human research subjects involving a
341 minimum of three cases in each of the following categories for which the individual is requesting
342 authorized user status-
- 343 (1) Oral administration of less than or equal to 1.22 gigabecquerels (33 millicuries) of sodium
344 iodide I-131, for which a written directive is required;
- 345 (2) Oral administration of greater than 1.22 gigabecquerels (33 millicuries) of sodium iodide I-131²;
- 346 (3) Parenteral administration of any beta emitter, or a photon- emitting radionuclide with a photon
347 energy less than 150 keV, for which a written directive is required; and/or
- 348 (4) Parenteral administration of any other radionuclide, for which a written directive is required; and
- 349 (2) Has obtained written attestation that the individual has satisfactorily completed the
350 requirements in paragraphs (a)(1) and (b)(1)(ii)(G) or (b)(1) of this section, and has achieved a
351 level of competency sufficient to function independently as an authorized user for the medical uses
352 authorized under § 35.300. The written attestation must be signed by a preceptor authorized user
353 who meets the requirements in §§ 35.57, 35.390, or equivalent Agreement State requirements.
354 The preceptor authorized user, who meets the requirements in § 35.390(b) must have experience
355 in administering dosages in the same dosage category or categories (*i.e.*, § 35.390(b)(1)(ii)(G)) as
356 the individual requesting authorized user status.
- 357 [67 FR 20370, Apr. 24, 2002, as amended at 68 FR 19325, Apr. 21, 2003; 68 FR 75389, Dec. 31,
358 2003; 69 FR 55738, Sep. 16, 2004; 70 FR 16364, Mar. 30, 2005; 71 FR 15009, Mar. 27, 2006; 74
359 FR 33905, Jul. 14, 2009]
- 360 ² Experience with at least 3 cases in Category (G)(2) also satisfies the requirement in Category
361 (G)(1)
- 362

363

Appendix 3

364 **§ 35.396 Training for the parenteral administration of unsealed byproduct material requiring**
365 **a written directive.**

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

368 (a) Is an authorized user under § 35.390 for uses listed in §§ 35.390(b)(1)(ii)(G)(3) or
369 35.390(b)(1)(ii)(G)(4), or equivalent Agreement State requirements; or

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

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

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

380 (i) Radiation physics and instrumentation;

381 (ii) Radiation protection;

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

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

384 (v) Radiation biology; and

385 (2) Has work experience, under the supervision of an authorized user who meets the requirements
386 in §§ 35.57, 35.390, 35.396, or equivalent Agreement State requirements, in the parenteral
387 administration, for which a written directive is required, of any beta emitter, or any photon-emitting
388 radionuclide with a photon energy less than 150 keV, and/or parenteral administration of any other
389 radionuclide for which a written directive is required. A supervising authorized user who meets the
390 requirements in § 35.390 must have experience in administering dosages as specified in §§
391 35.390(b)(1)(ii)(G)(3) and/or 35.390(b)(1)(ii)(G)(4). The work experience must involve—

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

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

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

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

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

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

406 (3) Has obtained written attestation that the individual has satisfactorily completed the
407 requirements in paragraph (b) or (c) of this section, and has achieved a level of competency
408 sufficient to function independently as an authorized user for the parenteral administration of
409 unsealed byproduct material requiring a written directive. The written attestation must be signed by
410 a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, 35.396, or
411 equivalent Agreement State requirements. A preceptor authorized user, who meets the
412 requirements in § 35.390, must have experience in administering dosages as specified in §§
413 35.390(b)(1)(ii)(G)(3) and/or 35.390(b)(1)(ii)(G)(4).

414 [70 FR 16365, Mar. 30, 2005; 71 FR 15010. Mar. 27, 2006; 74 FR 33906, Jul. 14, 2009]

415

416

Appendix 4

417 **§ 35.1000 Other medical uses of byproduct material or radiation from byproduct material.**

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

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

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