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Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
Subcommittee Report on Licensing for Radium-223 Chloride

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Subcommittee Members

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Charge

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

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Summary Statement and Recommendations

Ra-223 Cl represents a first-in-class, alpha particle-emitting therapeutic radiopharmaceutical. Based on relevant physical and biological considerations as well as clinic data to date, it appears to be a safe, effective, and convenient treatment for 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 (1.35 $\mu\text{Ci}/\text{kg}$ (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 (eg a dose calibrator) for measurement of the Ra-223 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 standard. Ra-223 Cl 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 \S 35.390 or \S 35.396 already have the requisite education, training, and experience to safely and effectively use Ra-223 Cl. As such licensing of authorized users of Ra-223 Cl under \S 35.390 (Category (G)(3) or (G)(4)), or \S 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.

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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,

47 convenient, and reasonably effective palliative and therapeutic modality (4, 5). Current
48 radiopharmaceuticals for palliation of painful skeletal metastases are exclusively beta particle
49 emitters and include phosphorus-32 (P-32) sodium phosphate, strontium-89 (Sr-89) strontium
50 chloride (Metastron™), yttrium-90 (Y-90) yttrium citrate, tin-117m (Sn-117m) diethylenetriamine
51 pentaacetic acid (DTPA), samarium-153 (Sm-153) lexidronam (Quadramet™), thulium-170 (Tm-
52 170) ethylene diamine tetramethylene phosphonate (EDTMP), lutecium-177 (Lu-177) EDTMP, and
53 rhenium-186 (Re-186) and rhenium-188 (Re-188) hydroxyethylidene diphosphonate (HEDP)
54 (4,5). Currently approved radiopharmaceuticals for bone pain palliation include P-32 sodium
55 phosphate, Sr-89 strontium chloride, and Sm-153 lexidronam, while the others remain
56 investigational.

57
58 Ra-223 Cl (half-life: 11.43 days) is a calcium-mimetic alpha-particle emitter¹ which either avidly
59 localizes in bone (particularly areas of active bone re-modeling typical of skeletal metastases)² or is
60 rapidly excreted (6). Ra-223 has only short-lived radioactive progeny, radon-219 (Rn-219)
61 (physical half-life: 3.96 seconds), polonium-215 (Po-215) (0.00178 second), and bismuth-211 (Bi-
62 211) (2.17 minutes), lead-211 (Pb-211) (36.1 minutes) and thallium-207 (Tl-207) (4.77 minutes)
63 (6). The alpha emissions of Ra-223 and its progeny are short-range, high-linear energy transfer
64 (LET), and high-relative biological effectiveness (RBE) radiations and should deliver highly
65 localized, highly cytotoxic radiation to metastatic cells in bone with relative sparing of the near-by
66 bone marrow (6). In addition, Ra-223 and its progeny emit a number of externally countable and
67 imageable x- and gamma-rays (81, 84, 154, and 269 keV) usable for pharmacokinetic studies,
68 radiation dosimetry, and activity calibration (7). In principle, therefore, Ra-223 Cl potentially may
69 provide more effective, less toxic palliation of skeletal metastases than current beta particle-emitting
70 radiopharmaceuticals. Importantly, if approved by the US Food and Drug Administration (FDA), it
71 would represent the very first alpha particle-emitting radiopharmaceutical in routine (i.e., non-
72 investigational) clinical use.

73
74 Ra-223 Cl has been extensively studied in patients, in Europe in particular as well as the United
75 States (6, 8-13). Two open-label Phase-I trials (37 patients) and three double-blind Phase-II trials
76 (255 patients) assessed radiation dosimetry, safety, and efficacy (decline in serum levels of prostate-
77 specific antigen (PSA) and bone alkaline phosphatase (ALP) and prolongation of survival).
78 Injected single doses varied from 0.14-6.8 μCi/kg body mass. Repeated treatment regimens varied
79 in number of doses and time-dose schedule. A Phase-II clinical trial in patients with symptomatic,
80 hormone-refractory prostate cancer showed improvement in survival, PSA levels, and ALP levels
81 compared with placebo (ie no treatment), with no differences in hematologic toxicity. An
82 international double-blind, placebo-controlled randomized trial (ALpharadin in SYMptomatic
83 Prostate CAncer [ALSYMPCA]) was subsequently undertaken to compare Ra-223 Cl with placebo
84 in patients with symptomatic, androgen-independent prostate cancer with skeletal metastases. The
85 study was stratified based on ALP levels at registration, bisphosphonate use, and prior treatment

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

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)-containing paint when “twirling” their paint brush tips to a fine point in their mouths. Importantly, Ra-226 has a much longer half-life, 1,600 years, than Ra-223, a critically important factor related to its carcinogenicity in bone.

86 with docetaxel. A total of 922 patients from 19 countries were enrolled, with overall survival being
87 the primary endpoint. Importantly, the data demonstrated a statistically significant reduction in the
88 risk of death for patients randomized to the Ra-223 arm of the study (hazard ratio = 0.695; $p =$
89 0.00185), with a median overall survival of 14 months versus 11.2 months in the placebo arm. The
90 overall survival benefit was seen across all sub-groups. The time to a skeletal-related event was also
91 significantly longer for patients in the Ra-223 versus placebo arm, 13.6 versus 8.4 months ($p =$
92 0.00046). The time to disease progression based on PSA and ALP levels was also significantly
93 longer in the Ra-223 arm. The patients randomized to Ra-223 treatment tolerated it well. Both
94 hematologic side-effects (grade-3 or -4 anemia, neutropenia, thrombocytopenia) and gastrointestinal
95 side-effects (nausea, vomiting, diarrhea) did not occur with any greater frequency than with
96 placebo. The former are related to localization of Ra-223 in bone while the latter are related to its
97 excretion through the intestines. It is noteworthy that the foregoing side-effects associated with
98 therapeutic administration of Ra-223 Cl are hardly unique. For example, the dose-limiting toxicity
99 associated with iodine-131 (I-131) iodide treatment of metastatic thyroid cancer and of
100 radioimmunotherapy of cancer generally is most commonly myelosuppression. Nuclear Medicine
101 physicians, Radiation Oncologists, and other physicians who administer radionuclide therapy are
102 therefore already highly experienced in effectively managing such side-effects.

103
104 To summarize the clinical findings to date (6, 8-13), more than 1,000 prostate cancer patients have
105 been treated with Ra-223 Cl with single and repeated treatments with significant PSA declines and
106 prolonged survival benefit, without therapy-limiting myelotoxicity, gastrointestinal toxicity or other
107 significant normal-tissue toxicity compared to placebo. Although not yet approved by the FDA,
108 Ra-223 Cl appears to be the only bone-targeted radionuclide therapy which significantly prolongs
109 survival.

110
111 **Radiation Safety and Logistical Considerations**
112 Ra-223 Cl and its progeny emit 95%, 4%, and 1% of their total radiation energy in the form of alpha
113 particles, beta particles, and x- and gamma-rays, respectively (6). Alpha particles have very short
114 ranges (of the order of 10 μm in bone and soft tissue) and thus present no external, or direct,
115 radiation hazard. As long as standard universal precautions³ are observed and internalization is
116 avoided, alpha particles pose no significant radiologic hazard overall - despite their high LET and
117 high RBE. Importantly, this will likewise be the case for alpha particle-emitting
118 radiopharmaceuticals in general. Universal precautions would also safeguard against the internal
119 radiologic hazard of the small beta-particle component among the emissions of Ra-223 and its
120 progeny. X- and gamma-rays are, of course, much more penetrating than alpha- and beta-particles
121 but are emitted in very low abundance by Ra-223 and its progeny, with energies comparable to
122 those of common diagnostic radionuclides such as a technetium-99m (Tc-99m) (gamma-ray energy:
123 140 keV) and fluorine-18 (F-18) (511 keV). At the same time, the single-dose administered
124 activities of Ra-223 Cl, $\sim 1.5 \mu\text{Ci/kg}$ body mass or $\sim 100 \mu\text{Ci}$ total for a 70-kg Standard Man, are
125 several orders of magnitude lower than that of routine diagnostic radiopharmaceuticals (for which
126 the administered activities are of the order of 10 mCi = 10,000 μCi). Thus, for such low-abundance
127 x- and gamma-rays and such low activities, the external, or direct, radiation exposure and shielding
128 requirements for Ra-223 Cl and its progeny are no greater than those for routinely used diagnostic
129 radiopharmaceuticals - even though Ra-223 Cl is a therapeutic agent (14). Further, patients do not

³ Universal precautions (eg 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.

130 require medical confinement following Ra-223 Cl administration and may be treated on an
 131 outpatient basis. It should be reiterated, however, that Ra-223 Cl is still a non-approved (ie
 132 investigational) radiopharmaceutical.

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

145
 146 Ra-223 Cl is a simple salt of radium, and not a radiolabeled molecule. It therefore requires no
 147 synthesis or other preparation by the clinical site and does not undergo any sort of chemical
 148 decomposition. Quality control procedures for determination of radiochemical purity and special
 149 storage conditions (eg refrigeration) are therefore not required for Ra-223 Cl. As distributed by
 150 Bayer Healthcare (Pittsburgh, PA), it is provided in a crimped glass vial as an injectable isotonic
 151 solution with an activity concentration of 1,000 kBq/ml (27 µCi/ml) at calibration (15). The
 152 recommended administered activity is 50 kBq/kg (1.35 µCi/kg) body mass (15). A patient-specific
 153 volume of injectate, calculated using the following formula, is drawn directly from the vendor-
 154 provided Ra-223 Cl (15):

$$155$$

$$156 \quad \text{Volume to inject (ml)} = \frac{\text{Body mass (kg)} \times 50 \text{ kBq/kg}}{\text{Decay factor} \times 1000 \text{ kBq/ml}}$$

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 158 where the decay factor is the fractional decay factor (as derived from a vendor-provided “decay
 159 factor table,” for example) for the time interval from the date and time of calibration of the Ra-223
 160 Cl to the planned date and time of administration.

161
 162 Implicit in the foregoing dose-prescription algorithm is that the user is *not* required to assay the Ra-
 163 223 activity prior to its administration or the residual activity following its administration, as is
 164 typically done in Nuclear Medicine (especially for therapeutic administrations). Bayer Healthcare
 165 has asserted that measurement of the Ra-223 activities is *not* necessary, as the patient-specific dose
 166 corresponds to a calculated volume of the vendor-supplied solution with the vendor-specified pre-
 167 calibrated activity concentration (15). Bayer Healthcare has further asserted that such activity
 168 measurements would be potentially unreliable because (a) a setting for Ra-223 is not provided on
 169 currently available dose calibrators and (b) the pre-administration activity and, in particular, the
 170 residual activity would be too low (in the µCi range) to measure reliably (15). Ra-223 does,
 171 however, emit measurable x- and gamma-rays (7), and dose calibrators can thus be calibrated by the
 172 end user for Ra-223 using a National Institute of Standards and Technology (NIST)-traceable Ra-
 173 223 standard (16). In addition, assay of the pre-administration and residual Ra-223 activities, even
 174 if inexact, would help avoid potentially “catastrophic” misadministrations. By verifying that the

175 actual pre-administration activity is consistent with the prescribed activity and that the residual
176 activity is insignificant, clinically important over-dosing and/or under-dosing of the patient (eg due
177 to mis-calibration of the vendor-supplied Ra-223 Cl solution or inaccurate drawing of the patient-
178 specific injectate) as well as administration of an incorrect radionuclide could likely be avoided.
179 Such activity assays would thus provide an additional level of safety at the treatment site
180 independent of the vendor's manufacturing and calibration procedures. In a therapy setting, such
181 redundancy, or cross-checking, is certainly prudent and is standard in Nuclear Medicine, especially
182 in therapeutic applications. An appropriate radioassay system (eg a dose calibrator) for
183 measurement of the Ra-223 activity prior to its administration or the residual activity following its
184 administration is therefore recommended for the therapeutic use of Ra-223 Cl.

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

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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]

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Appendix 2

284 **§ 35.390 Training for use of unsealed byproduct material for which a written directive is**
285 **required.**

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

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

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

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

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

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

308 (A) Radiation physics and instrumentation;

309 (B) Radiation protection;

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

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

312 (E) Radiation biology; and

313 (ii) Work experience, under the supervision of an authorized user who meets the requirements in §§
314 35.57, 35.390, or equivalent Agreement State requirements. A supervising authorized user, who
315 meets the requirements in § 35.390(b), must also have experience in administering dosages in the

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

348 ² Experience with at least 3 cases in Category (G)(2) also satisfies the requirement in Category
349 (G)(1)

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Appendix 3

352 **§ 35.396 Training for the parenteral administration of unsealed byproduct material requiring**
353 **a written directive.**

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

356 (a) Is an authorized user under § 35.390 for uses listed in §§ 35.390(b)(1)(ii)(G)(3) or
357 35.390(b)(1)(ii)(G)(4), or equivalent Agreement State requirements; or

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

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

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

368 (i) Radiation physics and instrumentation;

369 (ii) Radiation protection;

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

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

372 (v) Radiation biology; and

373 (2) Has work experience, under the supervision of an authorized user who meets the requirements in
374 §§ 35.57, 35.390, 35.396, or equivalent Agreement State requirements, in the parenteral
375 administration, for which a written directive is required, of any beta emitter, or any photon-emitting
376 radionuclide with a photon energy less than 150 keV, and/or parenteral administration of any other
377 radionuclide for which a written directive is required. A supervising authorized user who meets the
378 requirements in § 35.390 must have experience in administering dosages as specified in §§
379 35.390(b)(1)(ii)(G)(3) and/or 35.390(b)(1)(ii)(G)(4). The work experience must involve—

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

- 382 (ii) Performing quality control procedures on instruments used to determine the activity of dosages,
383 and performing checks for proper operation of survey meters;
- 384 (iii) Calculating, measuring, and safely preparing patient or human research subject dosages;
- 385 (iv) Using administrative controls to prevent a medical event involving the use of unsealed
386 byproduct material;
- 387 (v) Using procedures to contain spilled byproduct material safely, and using proper decontamination
388 procedures; and
- 389 (vi) Administering dosages to patients or human research subjects, that include at least 3 cases
390 involving the parenteral administration, for which a written directive is required, of any beta
391 emitter, or any photon-emitting radionuclide with a photon energy less than 150 keV and/or at least
392 3 cases involving the parenteral administration of any other radionuclide, for which a written
393 directive is required; and
- 394 (3) Has obtained written attestation that the individual has satisfactorily completed the requirements
395 in paragraph (b) or (c) of this section, and has achieved a level of competency sufficient to function
396 independently as an authorized user for the parenteral administration of unsealed byproduct material
397 requiring a written directive. The written attestation must be signed by a preceptor authorized user
398 who meets the requirements in §§ 35.57, 35.390, 35.396, or equivalent Agreement State
399 requirements. A preceptor authorized user, who meets the requirements in § 35.390, must have
400 experience in administering dosages as specified in §§ 35.390(b)(1)(ii)(G)(3) and/or
401 35.390(b)(1)(ii)(G)(4).

402 [70 FR 16365, Mar. 30, 2005; 71 FR 15010. Mar. 27, 2006; 74 FR 33906, Jul. 14, 2009]

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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.

DRAFT