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3 **Nuclear Regulatory Commission (NRC)**  
4 **Advisory Committee on the Medical Uses of Isotopes (ACMUI)**  
5 **Report on Licensing for Radium-223 (<sup>223</sup>Ra) Dichloride**  
6 **November 20, 2012**  
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10 **Subcommittee Members**

11 Darice Bailey, Susan Langhorst, Steven Mattmuller, Christopher Palestro, Orhan Suleiman, Bruce  
12 Thomadsen, James Welsh, and Pat Zanzonico (Chair)

13  
14 **Charge**

15 To provide recommendations on licensing of radium-223 (<sup>223</sup>Ra) dichloride (<sup>223</sup>RaCl<sub>2</sub>).  
16

17 **Summary Statement and Recommendations**

18 <sup>223</sup>RaCl<sub>2</sub>, currently a non-approved investigational agent undergoing clinical trials in the United  
19 States and elsewhere, represents a first-in-class, alpha particle-emitting therapeutic  
20 radiopharmaceutical. Based on relevant physical and biological considerations as well as clinical  
21 data to date, its intended indication is treatment of skeletal metastases in advanced, castrate-  
22 resistant prostate cancer, delivering high biologically effective doses to malignant cells in bone with  
23 relative sparing of hematopoietic marrow and other normal tissues. The injection volume for the  
24 body weight-adjusted dose of <sup>223</sup>RaCl<sub>2</sub> (50 kBq/kg (1.35 μCi/kg)) is determined based on the  
25 vendor-supplied activity concentration in a pre-calibrated solution. Nonetheless, to minimize the  
26 probability of a therapeutic misadministration, an appropriate radioassay system (e.g., a dose  
27 calibrator) for measurement of the <sup>223</sup>Ra activity prior to its administration and the residual activity  
28 following its administration is recommended, as with any therapeutic radiopharmaceutical. This  
29 would require calibration of the radioassay system using, for example, a National Institute of  
30 Standards and Technology (NIST)-traceable <sup>223</sup>Ra standard. <sup>223</sup>RaCl<sub>2</sub> does not differ significantly  
31 in terms of clinical use and management, radiation safety, and logistics from currently approved  
32 radiopharmaceuticals. Therefore, physicians already authorized to use therapeutic  
33 radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training,  
34 and experience to safely and effectively use <sup>223</sup>RaCl<sub>2</sub>. As such, licensing of authorized users of  
35 <sup>223</sup>RaCl<sub>2</sub> under § 35.390 (Category (G)(3) or (G)(4)), or § 35.396(d)(2), is therefore recommended.  
36

37 **Clinical Background**

38 Skeletal metastases commonly occur in many different malignancies, particularly advanced  
39 castrate-resistant prostate cancer, and are associated with severe morbidity and mortality (1). The  
40 resulting bone pain and possible fractures severely compromise the patient's quality of life and  
41 thus require effective treatment. Various non-radiotherapeutic modalities are available such as  
42 analgesics, hormone therapy, orchiectomy, cytostatic and cytotoxic drugs, bisphosphonates, and  
43 surgery, but are not universally effective (2). External-beam radiotherapy is suitable only for well-  
44 defined localized bone metastases, and extended-field radiation for more generalized skeletal  
45 disease is often accompanied by excessive toxicity (3). In the setting of widely disseminated  
46 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 (<sup>32</sup>P) sodium phosphate, strontium-89 (<sup>89</sup>Sr) strontium chloride  
50 (Metastron™), yttrium-90 (<sup>90</sup>Y) yttrium citrate, tin-117m (<sup>117m</sup>Sn) diethylenetriamine pentaacetic acid  
51 (DTPA), samarium-153 (<sup>153</sup>Sm) lexidronam (Quadramet™), thulium-170 (<sup>170</sup>Tm) ethylene diamine

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

56  
57 <sup>223</sup>RaCl<sub>2</sub> (half-life: 11.43 days) is a calcium-mimetic alpha-particle emitter<sup>1</sup> which either avidly  
58 localizes in bone (particularly areas of active bone re-modeling typical of skeletal metastases)<sup>2</sup> or is  
59 rapidly excreted (6). <sup>223</sup>Ra has only short-lived radioactive progeny, radon-219 (<sup>219</sup>Rn) (physical  
60 half-life: 3.96 seconds), polonium-215 (<sup>215</sup>Po) (0.00178 second), bismuth-211 (<sup>211</sup>Bi) (2.17  
61 minutes), lead-211 (<sup>211</sup>Pb) (36.1 minutes) and thallium-207 (<sup>207</sup>Tl) (4.77 minutes) (6). The alpha  
62 emissions of <sup>223</sup>Ra and its progeny are short-range, high-linear energy transfer (LET), and high-  
63 relative biological effectiveness (RBE) radiations and should deliver highly localized, highly  
64 cytotoxic radiation to metastatic cells in bone with relative sparing of the near-by bone marrow (6).  
65 In addition, <sup>223</sup>Ra and its progeny emit a number of externally countable and imageable x- and  
66 gamma-rays (81, 84, 154, and 269 keV) usable for pharmacokinetic studies, radiation dosimetry,  
67 and activity calibration (7). In principle, therefore, <sup>223</sup>RaCl<sub>2</sub> potentially may provide more effective,  
68 less toxic palliation of skeletal metastases than current beta particle-emitting radiopharmaceuticals.  
69 Importantly, if approved by the US Food and Drug Administration (FDA), it would represent the  
70 very first alpha particle-emitting radiopharmaceutical in routine (i.e., non-investigational) clinical  
71 use<sup>3</sup> in the United States.

72  
73 <sup>223</sup>RaCl<sub>2</sub> has been extensively studied in patients in Europe as well as the United States (6, 8-13).  
74 Two open-label Phase-I trials (37 patients) and three double-blind Phase-II trials (255 patients)  
75 assessed radiation dosimetry, safety, and efficacy (decline in serum levels of prostate-specific  
76 antigen (PSA) and bone alkaline phosphatase (ALP) and prolongation of survival). Injected single  
77 doses varied from 5.2-252 kBq/kg (0.14-6.8 μCi/kg) body mass. Repeated treatment regimens  
78 varied in number of doses and time-dose schedule. A Phase-II clinical trial in patients with  
79 symptomatic, hormone-refractory prostate cancer showed improvement in survival, PSA levels,  
80 and ALP levels compared with placebo (i.e., no treatment), with no differences in hematologic  
81 toxicity. An international double-blind, placebo-controlled randomized trial (ALpharadin in  
82 SYMptomatic Prostate CANcer [ALSYMPCA]) was subsequently undertaken to compare <sup>223</sup>RaCl<sub>2</sub>  
83 with placebo in patients with symptomatic, androgen-independent prostate cancer with skeletal  
84 metastases. The study was stratified based on ALP levels at registration, bisphosphonate use,  
85 and prior treatment with docetaxel. A total of 921 patients from 19 countries were enrolled, with  
86 overall survival being the primary endpoint. Importantly, the data demonstrated a statistically  
87 significant reduction in the risk of death for patients randomized to the <sup>223</sup>RaCl<sub>2</sub> arm of the study  
88 (hazard ratio = 0.695; p = 0.00185), with a median overall survival of 14 months versus 11.2  
89 months in the placebo arm. The overall survival benefit was seen across all sub-groups. The time

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

<sup>2</sup> 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 (<sup>226</sup>Ra)-containing paint when “twirling” their paint brush tips to a fine point in their mouths. Importantly, <sup>226</sup>Ra has a much longer half-life, 1,600 years, than <sup>223</sup>Ra, a critically important factor related to its carcinogenicity in bone.

<sup>3</sup> 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 <sup>223</sup>RaCl<sub>2</sub> 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 to a skeletal-related event was also significantly longer for patients in the  $^{223}\text{RaCl}_2$  versus placebo  
91 arm, 13.6 versus 8.4 months ( $p = 0.00046$ ). The time to disease progression based on PSA and  
92 ALP levels was also significantly longer in the  $^{223}\text{RaCl}_2$  arm. The patients randomized to  $^{223}\text{RaCl}_2$   
93 treatment tolerated it well. Both hematologic side-effects (grade-3 or -4 anemia, neutropenia,  
94 thrombocytopenia) and gastrointestinal side-effects (nausea, vomiting, diarrhea) did not occur with  
95 any greater frequency than with placebo. The former are related to localization of  $^{223}\text{RaCl}_2$  in bone  
96 while the latter are related to its excretion through the intestines. It is noteworthy that the foregoing  
97 side-effects associated with therapeutic administration of  $^{223}\text{RaCl}_2$  are hardly unique. For example,  
98 the dose-limiting toxicity associated with iodine-131 ( $^{131}\text{I}$ ) iodide treatment of metastatic thyroid  
99 cancer and of radioimmunotherapy of cancer generally is most commonly myelosuppression.  
100 Nuclear Medicine physicians, Radiation Oncologists, and other physicians who administer  
101 radionuclide therapy are therefore already highly experienced in effectively managing such side-  
102 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  $^{223}\text{RaCl}_2$  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 for  
108 routine clinical use, this investigational alpha particle-emitting agent appears to be a promising  
109 bone-targeted radionuclide therapy.

### 111 **Radiation Safety and Logistical Considerations**

112  $^{223}\text{RaCl}_2$  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  $\mu\text{m}$  in bone and soft tissue) and thus present no external, or direct,  
115 radiation hazard. As long as standard universal precautions<sup>4</sup> 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  $^{223}\text{Ra}$  and its  
120 progeny. X- and gamma-rays are, of course, much more penetrating than alpha- and beta-  
121 particles but are emitted in very low abundance by  $^{223}\text{Ra}$  and its progeny, with energies  
122 comparable to those of common diagnostic radionuclides such as a technetium-99m ( $^{99\text{m}}\text{Tc}$ )  
123 (gamma-ray energy: 140 keV) and fluorine-18 ( $^{18}\text{F}$ ) (511 keV). At the same time, the single-dose  
124 administered activities of  $^{223}\text{RaCl}_2$ , 50 kBq/kg (1.35  $\mu\text{Ci}/\text{kg}$ ) body mass or 3,500 kBq (95  $\mu\text{Ci}$ ) total  
125 for a 70-kg Standard Man, are several orders of magnitude lower than that of routine diagnostic  
126 radiopharmaceuticals (for which the administered activities are of the order of 370 MBq = 370,000  
127 kBq (10 mCi = 10,000  $\mu\text{Ci}$ )). Thus, for such low-abundance x- and gamma-rays and such low  
128 activities, the external, or direct, radiation exposure and shielding requirements for  $^{223}\text{RaCl}_2$  and its  
129 progeny are no greater than those for routinely used diagnostic radiopharmaceuticals - even  
130 though  $^{223}\text{RaCl}_2$  is a therapeutic agent (14). Further, patients do not require medical confinement  
131 following  $^{223}\text{RaCl}_2$  administration and may be treated on an outpatient basis.

132  
133 As noted,  $^{223}\text{Ra}$  has a physical half-life of 11.43 days; its radioactive progeny,  $^{219}\text{Rn}$ ,  $^{215}\text{Po}$ ,  $^{211}\text{Bi}$ ,  
134  $^{211}\text{Pb}$ , and  $^{207}\text{Tl}$ , have much shorter half-lives, ranging from 0.00178 second to 36.1 minutes.  $^{223}\text{Ra}$   
135 and its progeny thus have sufficiently short half-lives for on-site decay-in-storage of radioactively  
136 contaminated waste followed by disposal as non-radioactive waste. At the same time, the x- and  
137 gamma-rays emitted by  $^{223}\text{Ra}$  and its progeny, although low in abundance, are sufficient for assay

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<sup>4</sup> 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.

138 of any such waste. This can be done using conventional survey meters such as Geiger (G-M)  
139 counters - in order to verify that the exposure (or count) rates from contaminated or possibly  
140 contaminated waste are at or below background levels. Likewise, surveys of ambient exposure  
141 rates and of removable radioactive contamination (i.e., “wipes tests”) associated with the use of  
142 <sup>223</sup>RaCl<sub>2</sub> may be performed with instrumentation (surveys meters and well counters, respectively)  
143 already routinely available in Nuclear Medicine facilities.

144  
145 <sup>223</sup>RaCl<sub>2</sub> is a simple salt of radium, and not a radiolabeled molecule. It therefore requires no  
146 synthesis or other preparation by the clinical site and does not undergo any sort of chemical  
147 decomposition. Quality control procedures for determination of radiochemical purity and special  
148 storage conditions (e.g., refrigeration) are therefore not required for <sup>223</sup>RaCl<sub>2</sub>. As distributed by  
149 Bayer Healthcare (Pittsburgh, PA), it is provided in a crimped glass vial as an injectable isotonic  
150 solution with an activity concentration of 1,000 kBq/ml (27 μCi/ml) at calibration (15). The  
151 recommended administered activity is 50 kBq/kg (1.35 μCi/kg) body mass (15). A patient-specific  
152 volume of injectate, calculated using the following formula, is drawn directly from the vendor-  
153 provided <sup>223</sup>RaCl<sub>2</sub> solution (15):

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

156  
157 where the decay factor is the fractional decay factor (as derived from a vendor-provided “decay  
158 factor table,” for example) for the time interval from the date and time of calibration of the <sup>223</sup>RaCl<sub>2</sub>  
159 to the planned date and time of administration.

160  
161 Implicit in the foregoing dose-prescription algorithm is that the user is *not* required to assay the  
162 <sup>223</sup>Ra activity prior to its administration or the residual activity following its administration, as is  
163 typically done in Nuclear Medicine (especially for therapeutic administrations). Bayer Healthcare  
164 has asserted that measurement of the <sup>223</sup>Ra activities is *not* necessary, as the patient-specific dose  
165 corresponds to a calculated volume of the vendor-supplied solution with the vendor-specified pre-  
166 calibrated activity concentration (15). Bayer Healthcare has further asserted that such activity  
167 measurements would be potentially unreliable because (a) a setting for <sup>223</sup>Ra is not provided on  
168 currently available dose calibrators and (b) the pre-administration activity and, in particular, the  
169 residual activity would be too low (in the tens of kBq (μCi) range) to measure reliably (15). <sup>223</sup>Ra  
170 does, however, emit measurable x- and gamma-rays (7), and dose calibrators can thus be  
171 calibrated by the end user for <sup>223</sup>Ra using a National Institute of Standards and Technology (NIST)-  
172 traceable <sup>223</sup>Ra standard (16). In addition, assay of the pre-administration and residual <sup>223</sup>Ra  
173 activities, even if inexact, would help avoid potentially “catastrophic” misadministrations. By  
174 verifying that the actual pre-administration activity is consistent with the prescribed activity and that  
175 the residual activity is insignificant, clinically important over-dosing and/or under-dosing of the  
176 patient (e.g., due to mis-calibration of the vendor-supplied <sup>223</sup>RaCl<sub>2</sub> solution or inaccurate drawing  
177 of the patient-specific injectate) as well as administration of an incorrect radionuclide could likely be  
178 avoided. Such activity assays would thus provide an additional level of safety at the treatment site  
179 independent of the vendor’s manufacturing and calibration procedures. In a therapy setting, such  
180 redundancy, or cross-checking, is certainly prudent and is standard in Nuclear Medicine, especially  
181 in therapeutic applications. An appropriate radioassay system (e.g., a dose calibrator) for  
182 measurement of the <sup>223</sup>Ra activity prior to its administration or the residual activity following its  
183 administration is therefore recommended for the therapeutic use of <sup>223</sup>RaCl<sub>2</sub>.

#### 185 **Licensing Considerations**

186 As noted, <sup>223</sup>RaCl<sub>2</sub> represents a first-in-class - that is, an alpha particle-emitting -  
187 radiopharmaceutical. As such, it raises the issue of the appropriate NRC licensure for authorized

188 users of this agent.  $^{223}\text{RaCl}_2$  should be licensed under § 35.300 of the Code of Federal  
189 Regulations (CFR) (Appendix 1). Within the NRC's regulatory framework, there would appear to  
190 be several different licensing options for  $^{223}\text{RaCl}_2$ , namely, authorized users who meet training and  
191 experience requirements under § 35.390 (Appendix 2), § 35.396 (Appendix 3), or § 35.1000 A  
192 (Appendix 4). Despite its alpha-particle emissions,  $^{223}\text{RaCl}_2$  does not differ fundamentally from  
193 current routinely used therapeutic radiopharmaceuticals. Given the similarities in clinical use and  
194 radiation safety considerations (as detailed above) between  $^{223}\text{RaCl}_2$  and current therapeutic  
195 radiopharmaceuticals, the use of which is authorized under § 35.390 (Appendix 2), the use of  
196  $^{223}\text{RaCl}_2$  should likewise be authorized under § 35.390. It would appear that either Category (3) or  
197 (4) in § 35.390 would be appropriate for  $^{223}\text{RaCl}_2$ . Category (3) applies to, "Parenteral  
198 administration of any beta emitter, or a photon- emitting radionuclide with a photon energy less  
199 than 150 keV, for which a written directive is required"; it does not explicitly include or exclude  
200 alpha-particle emitters, however. Since  $^{223}\text{Ra}$  progeny emit beta particles as well as alpha  
201 particles,  $^{223}\text{RaCl}_2$  technically might be considered a "Category (3)" radiopharmaceutical. However,  
202 even if "Category (3)" were interpreted as not applying to  $^{223}\text{RaCl}_2$ , Category (4), which applies to,  
203 "Parenteral administration of any other radionuclide, for which a written directive is required,"  
204 certainly apply. This same conclusion applies to § 35.396 (Appendix 3). Licensing of  $^{223}\text{RaCl}_2$   
205 under § 35.1000 (Appendix 4) is not an appropriate option as that would imply it differs significantly  
206 in terms of clinical use and management, radiation safety, and logistics from current therapeutic  
207 radiopharmaceuticals, and this is not the case. Physicians already authorized to use such  
208 radiopharmaceuticals under § 35.390 or § 35.396 already have the requisite education, training,  
209 and experience to safely and effectively use  $^{223}\text{RaCl}_2$ , and should not be required to provide  
210 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)  
290 and (b)(2) of this section. (Specialty boards whose certification processes have been recognized  
291 by the Commission or an Agreement State will be posted on the NRC's Web page.) To be  
292 recognized, a 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  
301 knowledge and competence in radiation safety, radionuclide handling, quality assurance, and  
302 clinical use of 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  
326 decontamination 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-131<sup>2</sup>;
- 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  
338 requirements in paragraphs (a)(1) and (b)(1)(ii)(G) or (b)(1) of this section, and has achieved a  
339 level of 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.  
342 The preceptor authorized user, who meets the requirements in § 35.390(b) must have experience  
343 in administering dosages in the same dosage category or categories (*i.e.*, § 35.390(b)(1)(ii)(G)) as  
344 the 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 <sup>2</sup> Experience with at least 3 cases in Category (G)(2) also satisfies the requirement in Category  
349 (G)(1)
- 350

351

**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  
359 and 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  
362 in 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  
374 in §§ 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  
388 decontamination 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 emitter,  
391 or any photon-emitting radionuclide with a photon energy less than 150 keV and/or at least 3 cases  
392 involving the parenteral administration of any other radionuclide, for which a written directive is  
393 required; and

394 (3) Has obtained written attestation that the individual has satisfactorily completed the  
395 requirements in paragraph (b) or (c) of this section, and has achieved a level of competency  
396 sufficient to function independently as an authorized user for the parenteral administration of  
397 unsealed byproduct material requiring a written directive. The written attestation must be signed by  
398 a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, 35.396, or  
399 equivalent Agreement State requirements. A preceptor authorized user, who meets the  
400 requirements in § 35.390, must have experience in administering dosages as specified in §§  
401 35.390(b)(1)(ii)(G)(3) and/or 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]

403

404

**Appendix 4**

405 **§ 35.1000 Other medical uses of byproduct material or radiation from byproduct material.**

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

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

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