
1
2 **BRIEFING**

3 **(825) Radiopharmaceuticals—Preparation, Compounding, Dispensing,**
4 **and Repackaging.** Radiopharmaceuticals (radioactive drugs) represent a
5 distinct class of drugs where processing activities include the use of
6 radionuclide generators, preparation and dispensing from commercially
7 manufactured radiopharmaceutical kits, the dispensing and repackaging of
8 commercially manufactured radiopharmaceutical finished products into a
9 patient-ready container, compounding sterile and nonsterile
10 radiopharmaceuticals, and the labeling of blood components with
11 radionuclides. These activities occur in an environment where individualized
12 patient needs and the safe handling of radioactive materials demand a high
13 level of professional expertise and clearly defined standards that support
14 these activities. While the original title in the prospectus was restricted to
15 only the compounding of radiopharmaceuticals, the proposed title is the
16 outcome of the consideration of all processing activities.

17 Many aspects of sterile radiopharmaceutical practices are similar to sterile
18 compounding of conventional drugs (e.g., aseptic practices, environmental
19 facilities). However, radiopharmaceutical processing also involves (as
20 applicable) many unique aspects, including worker and public radiation
21 protection measures (e.g., time, distance, shielding, negative pressure
22 gradients), presence and use of special ancillary supplies (e.g., radiation
23 shields, absorbent pads for radioactive contamination control), and special
24 equipment (e.g., radioactivity measuring devices, radiation monitors, remote
25 manipulation systems). Radiation safety considerations often necessitate a
26 deviation from the standard sterile practices described in *Pharmaceutical*
27 *Compounding—Sterile Preparations (797)* and the nonsterile practices
28 detailed in *Pharmaceutical Compounding—Nonsterile Preparations (795)*.

29 The intent of this chapter is to describe practices to provide a reasonable
30 assurance of maintaining patient safety associated with the administration of
31 sterile and nonsterile radiopharmaceuticals, while also ensuring the safety of
32 the individuals performing these radiopharmaceutical processing activities.

33 The current proposed chapter in *PF 44(5)* [Sep.–Oct. 2018] is posted online
34 at <https://www.usp.org/compounding/825-download> with line numbers.
35 Please submit comments using the form available at
36 https://usp.az1.qualtrics.com/jfe/form/SV_2i3rw7KKrcLaZ3D. The Expert
37 Committee seeks stakeholder feedback on the proposed chapter.

38
39
40 (CHM4: R. Ravichandran.)
41 Correspondence Number—C192537

42

43 *Add the following:*

44 **■ (825) RADIOPHARMACEUTICALS—**
45 **PREPARATION, COMPOUNDING,**
46 **DISPENSING, AND REPACKAGING**

47

48 1. INTRODUCTION

49 1.1 Nonsterile Radiopharmaceuticals

50 1.2 Sterile Radiopharmaceuticals

51

52 2. RADIATION SAFETY CONSIDERATIONS

53 2.1 Time

54 2.2 Distance

55 2.3 Shielding

56 2.4 Radiation Contamination Control

57

58 3. PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE

59 3.1 Aseptic Qualifications

60 3.2 Re-evaluation, Retraining, and Requalification

61 3.3 Ancillary Personnel

62 3.4 Hand Hygiene and Garbing for Immediate Use

63 Preparations

64 3.5 Hand Hygiene and Garbing for Buffer Rooms and

65 Segregated Radiopharmaceutical Processing Area

66

67 4. FACILITIES AND ENGINEERING CONTROLS

68 4.1 Facility Design and Environmental Controls

69 4.2 Creating Areas to Achieve Easily Cleanable Conditions

70 4.3 Water Sources

71 4.4 Placement and Movement of Materials

72 4.5 Classified Rooms

73 4.6 Remote Aseptic Processing Involving a Hot-Cell

74 4.7 Environmental Controls

75

76 5. MICROBIOLOGICAL AIR AND SURFACE MONITORING

77 5.1 General Monitoring Requirements

78 5.2 Monitoring Air Quality for Viable Airborne Particles

79 5.3 Monitoring Surfaces for Viable Particles

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6. CLEANING AND DISINFECTING

6.1 Cleaning, Disinfecting, and Sporicidal Agents

6.2 Cleaning Supplies

6.3 Cleaning and Disinfecting the PEC

6.4 Disinfecting Supplies for Classified Rooms and SRPAs

6.5 Disinfecting Critical Sites within the PEC

6.6 Cleaning and Disinfecting Items from Patient Care Areas

7. ASSIGNING BUD

8. DOCUMENTATION

8.1 Master Formulation Record

8.2 Records for Preparation with Minor
Deviation/Compounding

9. PREPARATION

9.1 Preparation Following Manufacturer Instructions

9.2 Preparation with Minor Deviations

9.3 Preparation of Radiolabeled Blood Components

9.4 Immediate Use of Red Blood Cell Labeling

10. COMPOUNDING

10.1 Compounding Nonsterile Radiopharmaceuticals

10.2 Compounding Using Conventionally Marketed Drug
Products

10.3 Sterile Compounding Using a Nonsterile Drug Substance
or Components

11. DISPENSING

11.1 Dispensing and Radioassay

11.2 Labeling

11.3 Direct Infusion Systems

11.4 Transporting Generators Between Facilities

12. REPACKAGING

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Notification About and Recall of Out-of-Specification
Dispensed Radiopharmaceuticals

13.2 Complaint Handling

13.3 Adverse Event Reporting

GLOSSARY

APPENDICES

123
124
125
126

[Appendix 1: Abbreviations](#)
[Appendix 2: Example Designs for Radiopharmaceutical Handling](#)

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1. INTRODUCTION

129 Radiopharmaceuticals, as defined in this chapter (see *Glossary*), are a
130 subset of radioactive materials (RAMs) falling under the control of the US
131 Nuclear Regulatory Commission (NRC) or NRC-contracted agreement state
132 agency. Radiopharmaceuticals are also a subset of prescription drugs falling
133 under the control of the US FDA for manufacturing and marketing. Other
134 federal regulatory authorities (e.g., Department of Transportation) also have
135 control over certain activities related to radiopharmaceuticals. Hence,
136 compliance with these regulations, as applicable, must be ensured in
137 addition to compliance with the standards described in this chapter. [NOTE—
138 Users outside the US must comply with equivalent regulations, as applicable,
139 pertaining to radiopharmaceuticals.]

140 This chapter is intended to provide uniform minimum standards for the
141 preparation, compounding, dispensing, and repackaging of sterile and
142 nonsterile radiopharmaceuticals for humans and animals that occur as part
143 of state-licensed activities (e.g., the practice of pharmacy and the practice of
144 medicine). These standards apply to all radiopharmaceuticals, including
145 those with radionuclides that emit a single photon, a positron, or a
146 therapeutic particle. Furthermore, these standards apply to sterile
147 intravascular radioactive devices (e.g., radioactive microspheres for
148 intravascular brachytherapy).

149 This chapter does not apply to:

- 150 • Radiopharmaceuticals manufactured in FDA-registered manufacturing
151 establishments according to §510 of the Food, Drug, and Cosmetic
152 Act
- 153 • Radiopharmaceuticals compounded in FDA-registered outsourcing
154 establishments according to §503B of the Food, Drug, and Cosmetic
155 Act
- 156 • Aspects of positron emission tomography (PET) drug preparation, as
157 defined in [Positron Emission Tomography Drugs for Compounding,
158 Investigational, and Research Uses \(823\)](#)
- 159 • Administration to patients

160 It is important to note that in each of these scenarios except for patient
161 administration, the further processing and manipulation of the drug product
162 after release falls within the scope of this chapter.

163 This chapter does not apply to the preparation of non-radioactive drugs,
164 including those used as pharmacologic adjuncts for certain nuclear medicine
165 procedures. These drugs must be prepared following standards described in
166 [Pharmaceutical Compounding—Nonsterile Preparations \(795\)](#) and
167 [Pharmaceutical Compounding—Sterile Preparations \(797\)](#).

168 This chapter applies to all practice settings where radiopharmaceuticals are
169 prepared, compounded, dispensed, or repackaged. Practice settings consist
170 of state-licensed nuclear pharmacies, federal nuclear pharmacy facilities,
171 and other healthcare facilities, including, but not limited to: nuclear medicine
172 departments in hospitals and clinics, nuclear cardiology clinics, and other
173 specialty clinics. This chapter applies to all individuals who prepare,
174 compound, dispense, or repackage radiopharmaceuticals. Applicable
175 individuals consist of authorized nuclear pharmacists (ANPs) and authorized
176 user (AU) physicians, as well as individuals working under their supervision.
177 This includes, but is not limited to, student pharmacists, nuclear pharmacy
178 technicians, nuclear medicine technologists and students, and physician
179 residents and trainees.

180 US federal and state radiation regulatory authorities require limiting
181 radiation exposure to personnel who handle radiopharmaceuticals, which
182 necessitates special provisions for radiation protection. The principles of
183 radiation safety involve time, distance, shielding, and radioactive
184 contamination control. Moreover, the use of radiation detection and
185 measuring devices is a necessary component of radiopharmaceutical
186 handling procedures. Hence, strict adherence to all typical aseptic handling
187 practices is not possible in many scenarios where radiopharmaceuticals are
188 handled. Thus, it is necessary to balance aseptic handling practices (patient
189 safety) with radiation protection practices (worker safety). This chapter
190 describes appropriate strategies that provide a reasonable assurance of
191 maintaining, while also ensuring the safety of individuals performing these
192 activities. Because radiopharmaceuticals represent a unique class of
193 prescription drugs, the use of technologies, techniques, materials, and
194 procedures other than those described in this chapter are not prohibited so
195 long as they are documented to be equivalent or superior to those described
196 herein.

197 **1.1 Nonsterile Radiopharmaceuticals**

198 Examples of nonsterile radiopharmaceuticals include oral capsules and oral
199 solutions. For conventionally marketed products, dispensing can proceed as
200 described in *11. Dispensing*. For prepared or compounded preparations, such
201 preparations must comply with applicable identity, quality, and purity
202 standards, as described in manufacturer labeling, *USP* monographs, or other
203 appropriate sources. They can then be dispensed as described in this
204 chapter.

205 **1.2 Sterile Radiopharmaceuticals**

206 Examples of sterile radiopharmaceuticals include injectables (e.g.,
207 intravenous, intrathecal, intraperitoneal, subcutaneous, and intradermal),
208 inhalations, and ophthalmics. For commercially marketed products, see 11.
209 *Dispensing*. For prepared or compounded preparations, such preparations
210 must comply with applicable identity, quality, and purity standards. For
211 compounded preparations involving one or more nonsterile components, a
212 sterilization procedure (e.g., filtration with bubble point testing) must be
213 performed prior to dispensing. For compounded preparations involving one
214 or more components that are not certified to be pyrogen-free, bacterial
215 endotoxin testing, as defined in [Bacterial Endotoxins Test \(85\)](#) must be
216 performed prior to dispensing.

217 It is appropriate to emphasize that the most important factor for
218 maintaining sterility is the avoidance of touch contamination. Disinfection of
219 the vial septum with sterile 70% isopropyl alcohol (IPA) must be performed
220 prior to needle puncture. If the vial shield top is then closed or the vial
221 septum otherwise covered with a piece of radiation shielding, the septum
222 must be re-disinfected with sterile 70% IPA prior to another needle puncture.
223 Some vial shields are constructed such that the vial septum is recessed and
224 difficult to access. One approach for disinfecting the vial septum in this type
225 of vial shield is to use a right-angle forceps to hold a sterile 70% IPA wipe
226 and direct it down onto the vial septum. It is also acknowledged that such
227 vial shields will disrupt first air contacting the vial septum during certain
228 handling conditions. Hence, re-disinfection of the septum with sterile 70%
229 IPA should be performed frequently whenever multiple punctures are
230 occurring (e.g., removing several individual doses from a multiple-dose vial).

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2. RADIATION SAFETY CONSIDERATIONS

233 The handling of radiopharmaceuticals necessitates special radiation
234 regulatory authority required precautions for radiation safety [i.e., as low as
235 (is) reasonably achievable (ALARA) practices]. Principles of radiation safety
236 involve time, distance, shielding, and contamination control. Moreover,
237 radiation detection and measuring devices are necessary. Aseptic handling
238 practices must be balanced with radiation safety considerations, based on
239 the following:

- 240 • Knowledge, experience, and professional judgment related to the type,
241 abundance, and energy of the radioactive emissions
- 242 • The quantity of radioactivity, volume, handling steps, and timing
243 thereof
- 244 • Other factors, which can vary on a case-by-case basis

245

2.1 Time

246 Radiation exposure to personnel is dependent on the amount of radiation
247 handled and the time handling the radiopharmaceuticals; minimizing
248 handling time will minimize radiation exposure. Hence, handlers of
249 radiopharmaceuticals may work quickly in a controlled and safe manner,
250 including multiple hand movements in and out of the ISO Class 5 primary
251 engineering control (PEC) during aseptic processes.

252 **2.2 Distance**

253 Radiation exposure follows the inverse square law; increasing the distance
254 will markedly decrease radiation exposure to personnel. Hence, handlers of
255 radiopharmaceuticals may utilize techniques to increase distance between
256 worker and radiopharmaceutical, such as using remote handling tools to
257 manipulate RAMs.

258 **2.3 Shielding**

259 Radiation exposure to personnel decreases as a function of shielding
260 materials. Therefore, handlers of radiopharmaceuticals may use various
261 shielding materials (e.g., lead, tungsten) in various configurations. The use
262 of shielding, such as L-block, torso, vial, and syringe shields are required
263 throughout the radiopharmaceutical handling process, including within an
264 ISO Class 5 PEC.

265 **2.4 Radiation Contamination Control**

266 RAM contamination (e.g., spills, drips, sprays, volatility) is an important
267 concern for radiation protection. Therefore, various techniques and materials
268 may be used by handlers of radiopharmaceuticals to minimize radioactive
269 contaminations. For example, vial contents are maintained at neutral or
270 negative pressure, because positive pressure in a vial is a common cause of
271 radioactive contamination. Disposable absorbent pads are commonly used to
272 contain such radioactive contamination and, when used in an ISO Class 5
273 PEC, the pads must be clean and low-lint. Vertical air flow in a PEC can be
274 used as a measure for contamination control. When exposure to blood and
275 other potentially infectious material is reasonably anticipated, needleless
276 systems may pose a radiation hazard to employees. Policies must be
277 implemented for handling biohazardous radioactive sharps while minimizing
278 contamination.

279 **RADIATION DETECTORS AND MEASURING DEVICES**

280 Radiopharmaceuticals require measurement with a suitable radiation
281 measuring device (e.g., dose calibrator). These and other necessary
282 equipment, (e.g., monitors, bar code scanner, label printer) may be placed
283 inside an ISO Class 5 PEC.

284 As per license requirements, individuals must wear body and, as required,
285 extremity dosimeters (e.g., a ring worn on a finger) for long-term
286 monitoring of personnel radiation exposure. The body dosimeter should be

287 worn underneath the gown. Any extremity dosimeter must be worn
288 underneath gloves and must not interfere with proper fit of gloves.

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290 **3. PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE**

291 Personnel must be trained to work with radiopharmaceuticals per the
292 policies and procedures authorized by an ANP or AU physician. These
293 employees (e.g., nuclear medicine technologists or nuclear pharmacy
294 technicians) must follow these policies and procedures of the ANP or AU
295 physician and work under their supervision.

296 Individuals that may have a higher risk of contaminating the
297 radiopharmaceutical and the environment with microorganisms (e.g.,
298 personnel with rashes, sunburn, recent tattoos, oozing sores, conjunctivitis,
299 or active respiratory infection) must report these conditions to their
300 supervisor. The designated person is responsible for evaluating whether
301 these individuals should be excluded from working in sterile processing areas
302 before their conditions are resolved because of the risk of microbial
303 contamination to the radiopharmaceutical and the environment.

304

3.1 Aseptic Qualifications

305 Personnel must prove competency, as applicable to their job functions,
306 prior to performing radiopharmaceuticals aseptic tasks that are beyond
307 immediate use. These qualifications must be completed and documented
308 initially, and then successfully repeated every 6 months thereafter under the
309 observation of a trained individual and include the following:

- 310 • Aseptic technique training with a documented assessment (written or
311 electronic)
- 312 • Garbing and hand hygiene competency, as defined by the policies and
313 procedures
- 314 • PEC cleaning
- 315 • Gloved fingertip sampling
- 316 • Media-fill testing

317 For sterile compounding with nonsterile ingredients, these qualifications
318 must be completed successfully and documented every 6 months.

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GLOVED FINGERTIP AND THUMB SAMPLING

320 Appropriate garbing, including sterile gloves, is necessary for personnel
321 who enter and perform tasks in an ISO Class 5 PEC (e.g., aseptic
322 manipulations, cleaning). Personnel that perform such functions must be
323 required to prove their competency in this process, including gloved fingertip
324 sampling.

- 325 • Gloved fingertip sampling must be performed initially with hand-
326 hygiene and garbing three times with zero colony-forming unit (cfu)
- 327 • Gloving fingertip sampling must also be performed post-media fill
328 testing, with NMT 3 cfu total for both hands
- 329 • The gloved fingertip sampling must be performed with touch plates or
330 other devices (e.g., plates, paddles, or slides) that contain a general
331 microbial growth agar [e.g., trypticase soy agar (TSA) soybean-
332 casein digest media] supplemented with neutralizing additives (e.g.,
333 lecithin and polysorbate 80)
- 334 • Do not disinfect gloves immediately before touching the sampling
335 device, as this could cause a false-negative result
- 336 • Using a separate sampling device for each hand, collect a gloved
337 fingertip and thumb sample from both hands by rolling finger pads
338 and thumb pad over the agar surface
- 339 • The plates must be incubated in a temperature-controlled incubator for
340 30°–35° for 48–72 h, and then at 20°–25° for 5–7 additional days

341 MEDIA-FILL TESTING

342 Media-fill challenges are necessary for all personnel who prepare,
343 compound, dispense, and repackage sterile radiopharmaceuticals. This
344 testing must be reflective of the actual manipulations to be carried out by
345 the individual radiopharmaceutical worker and it must simulate the most
346 challenging and stressful conditions to be encountered in the worker's
347 duties.

- 348 • Media-fill tests must be documented as defined by the facility's policies
349 and procedures.
- 350 • Media-fill tests should be performed at the end of a work session in the
351 PEC.
- 352 • Media-fill tests must be performed with a commercial source of
353 soybean-casein digest medium. Those performing sterile-to-sterile
354 processing activities must start with sterile media. Those performing
355 nonsterile-to-sterile compounding must start with nonsterile powder
356 media.
- 357 • The certificate of analysis (CoA) must be filed with documentation of
358 growth promotion testing for each lot of media used.
- 359 • Once the media-fill simulation is completed and the final containers are
360 filled with the test medium, incubate media-filled containers in an
361 incubator for 7 days at 20°–25° followed by 7 days at 30°–35° to
362 detect a broad spectrum of microorganisms. Failure is indicated by
363 visible turbidity or other visual manifestations of growth in the
364 medium in one or more container-closure unit(s) on or before 14
365 days. Investigate media-fill failures to determine possible causes.

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3.2 Re-evaluation, Retraining, and Requalification

REQUALIFICATION AFTER FAILURE

Personnel who fail visual observation of hand hygiene, garbing, and aseptic technique, gloved fingertip and thumb sampling, or media-fill testing must successfully pass re-evaluations in the deficient area(s) before they can resume processing of sterile preparations. The designated person must investigate the cause of failure and determine appropriate retraining requirements. All failures, retraining, and re-evaluations must be documented.

REQUALIFICATION PROGRAM

Personnel must successfully complete requalification every 6 months in the core competencies listed in *3.1 Aseptic Qualifications*. Successful completion must be demonstrated through written testing and hands-on demonstration of skills.

TIMING OF REEVALUATION AND REQUALIFICATION

Visual observation: Personnel must be visually observed while performing hand hygiene and garbing procedures initially, and then at least once every 6 months.

Gloved fingertip and thumb sampling: Personnel must perform fingertip and thumb sampling three times initially, and then every 6 months (in conjunction with media-fill testing).

Media-fill testing: After initial qualification, conduct a media-fill test of all personnel engaged in sterile radiopharmaceutical processing at least every 6 months (in conjunction with gloved fingertip and thumb sampling).

Cleaning and disinfecting: Retrain and requalify personnel in cleaning and sterile processing areas in conjunction with any change(s) in cleaning and disinfecting procedures.

After a pause in sterile radiopharmaceutical processing: Personnel who have not performed radiopharmaceutical processing in more than 6 months must be requalified in all core competencies before resuming duties.

3.3 Ancillary Personnel

Personnel that are authorized to be within the sterile processing area who do not handle sterile preparations are not required to complete training on media-fill testing but are required to complete all other training and testing. Other personnel or visitors (e.g., auditors or regulators) must comply with garbing and gloving standard operating procedures (SOPs) but do not need to prove competency.

3.4 Hand Hygiene and Garbing for Immediate Use Preparations

404 In situations where sterile radiopharmaceuticals cannot be provided to a
405 single patient in a timely manner and the potential benefits to the patient
406 outweigh the potential risks, radiopharmaceuticals may be prepared and
407 dispensed as immediate use. Precautions related to personal hygiene to be
408 followed must include:

- 409 • Hand hygiene: Wash hands and arms up the elbows with soap and
410 water for at least 30 s. If no sink is present, use a suitable alcohol-
411 based hand rub with persistent antimicrobial activity to reduce
412 bioburden on the hands.
- 413 • Garbing: Immediately after hand hygiene, don a clean coat/gown that
414 has not been exposed to a patient or patient care area, and either
415 don sterile gloves or don nonsterile disposable gloves and then
416 disinfect the gloves with sterile 70% IPA. [NOTE—A different lab coat
417 must be worn to care for a patient than the coat/gown used for
418 radiopharmaceutical preparation.]

419 **3.5 Hand Hygiene and Garbing for Buffer Rooms and Segregated** 420 **Radiopharmaceutical Processing Area**

421 In situations involving repackaging, dispensing, preparation or preparation
422 with minor deviations of sterile radiopharmaceuticals in an ISO Class 5 PEC,
423 the following precautions related to personal hygiene are to be followed:

- 424 • Before entering the segregated radiopharmaceutical processing area
425 (SRPA) or buffer room, personnel must remove: outer garments
426 (e.g., bandanas, coats, hats, jackets, scarves, sweaters, vests); all
427 cosmetics; and visible jewelry or piercings that can interfere with the
428 effectiveness of the garb (e.g., rings with protruding elements that
429 may cause tears in gloves). Artificial nails, polish, or extenders are
430 prohibited. Natural nails must be kept neat and trimmed. Remove ear
431 buds and headphones or other similar devices. Radiation dosimetry
432 devices are allowed, as required by the RAM license.
- 433 • Immediately before entering the SRPA or buffer room, personnel must
434 wash hands and arms up the elbows with soap and water for at least
435 30 s and then dry hands using low-lint towels. Alternatively, hand
436 washing may be performed after donning garb, as described below.
- 437 • Personnel must don the following garb (e.g., shoe covers, head/hair
438 covers, face mask) in an order that eliminates the greatest risk of
439 contamination (e.g., dirtiest to cleanest), as defined in facility
440 procedures.
- 441 • If not already performed, personnel must then wash hands and arms
442 up the elbows with soap and water for at least 30 s and then apply a
443 suitable alcohol-based hand rub with persistent antimicrobial activity,

- 444 and then dry hands using low-lint towels. Electronic hand dryers are
445 not permitted.
- 446 • Personnel who performed hand hygiene prior to garbing, as described
447 previously, must perform antiseptic hand cleansing using a suitable
448 alcohol-based hand rub with persistent antimicrobial activity.
 - 449 • Personnel must then don a low-lint gown with sleeves that fit snugly
450 around the wrists and enclosed at the neck (e.g., solid front with
451 back covered and secured, or fastened or zippered up to the neck in
452 front). Disposable gowns are preferred. If reusable gowns are used,
453 they must be laundered daily.
 - 454 • Personnel must then aseptically don sterile, powder-free gloves.
455 Gloves must completely and snugly cover the ends of the gown cuffs
456 so that skin on the wrists and upper hands are completely enveloped.
 - 457 • Because gloves may not remain sterile due to touching or handling
458 potentially nonsterile materials, personnel must perform periodic
459 disinfection of gloves with sterile 70% IPA while balancing the risk of
460 radioactivity contamination.
 - 461 • Personnel must also routinely inspect the gloves that they are wearing
462 for holes, punctures, radioactivity contamination, or tears. If a defect,
463 radioactivity contamination, or malfunction is detected, personnel
464 must immediately remove the gloves, repeat antiseptic hand
465 cleansing using an alcohol-based hand rub with persistent
466 antimicrobial activity, and don new gloves.
 - 467 • Direct personnel touch contamination is the most common source of
468 microorganisms, so personnel must avoid touch contamination of
469 container septa, needle, syringe and needle hubs, and other critical
470 sites.

471 When personnel exit the buffer room or SRPA, the exterior gown, shoe
472 covers, head/hair covers, face masks, and gloves must be properly disposed
473 of and new ones donned for each re-entry into the buffer room or SRPA.

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4. FACILITIES AND ENGINEERING CONTROLS

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4.1 Facility Design and Environmental Controls

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In addition to minimizing airborne contamination, sterile radiopharmaceutical facilities must be designed and controlled to provide a well-lighted and comfortable working environment (see [Physical Environments That Promote Safe Medication Use \(1066\)](#)). The classified rooms must be continuously maintained at a temperature of 25° or cooler and should be continuously maintained at a relative humidity below 60% to minimize the risk for microbial proliferation and provide comfortable conditions for personnel attired in the required garb. The temperature and humidity must be monitored in the classified rooms each day that it is used,

486 either manually or by a continuous recording device, and the results must be
487 readily retrievable, reviewed by the designated person, and documented.
488 Temperature and humidity in the classified rooms must be controlled
489 through an efficient HVAC system. Free-standing humidifiers/dehumidifiers
490 and air conditioners must not be used within the classified room or SRPA.
491 Temperature and humidity monitoring devices must be verified for accuracy
492 at least every 12 months or as required by the manufacturer.

493 The designated person must ensure that each area related to sterile
494 radiopharmaceutical processes meets the classified air quality standard
495 appropriate for the activities to be conducted in that area. They must also
496 ensure that the ISO Class 5 areas are located, operated, maintained,
497 monitored, and certified to have appropriate air quality.

498 TYPES OF SECONDARY ENGINEERING CONTROLS AND DESIGN

499 The PEC must be located in a secondary engineering control (SEC), which
500 may be either a buffer room with ante-room or an SRPA (see *Appendix 2:
501 Example Designs for Radiopharmaceutical Handling* for examples of facility
502 designs).

503 The ISO-classified ante-room must be separated from the surrounding
504 unclassified rooms of the facility with fixed walls and doors, and controls
505 must be in place to minimize the flow of lower-quality air into the more
506 controlled areas. Air supplied to the classified rooms must be introduced
507 through HEPA filters that are located in the ceiling of the buffer and ante-
508 rooms. Returns must be low on the wall or appropriate to remove airborne
509 particles from specific sources, such as refrigerators. Appropriate studies,
510 such as a smoke study of the PEC, must be repeated whenever a change to
511 the placement of the PEC within the room is made. The classified rooms
512 must be equipped with a pressure-differential monitoring system. The ante-
513 room must have a line of demarcation to separate the clean side from the
514 dirty side. The ante-room is entered through the dirty side, and the clean
515 side is the area closest to the buffer room. Required garb must be worn on
516 the clean side of the line of demarcation (see *3. Personnel Qualifications,
517 Training, and Hygiene*).

518 A PEC may be located in an area within an unclassified room, without an
519 ante-room or buffer room. This type of design is called an SRPA. Only sterile
520 radiopharmaceutical preparation, preparation with minor deviations,
521 dispensing, and repackaging may be performed in an SRPA. The SRPA must
522 be located away from unsealed windows, doors that connect to the outdoors,
523 and traffic flow which may adversely affect the air quality in the PEC. An
524 SRPA must not be located adjacent to environmental control challenges
525 (e.g., restrooms, warehouses, or food preparation areas). The impact of
526 activities that will be conducted around or adjacent to the SRPA must be
527 considered carefully when designing such an area. A visible perimeter must

528 establish the boundaries of the SRPA. Access to the SRPA must be restricted
529 to authorized personnel and required materials.

530 The PEC must be located in the buffer room of the classified room or the
531 SRPA in a manner that minimizes conditions that could increase the risk of
532 microbial contamination. For example, strong air currents from opened
533 doors, personnel traffic, or air streams from the HVAC system(s) can disrupt
534 the unidirectional airflow of an open-faced PEC such as a laminar airflow
535 workbench (LAFW) or biological safety cabinet (BSC).

536 It is also critical to control materials (e.g., supplies and equipment) as they
537 move from classified rooms of lower quality to those of higher quality (e.g.,
538 ISO Class 8 ante-room to ISO Class 7 buffer room to ISO Class 5 PEC) to
539 prevent the influx of contaminants. Airlocks and interlocking doors can be
540 used to facilitate better control of air balance between areas of differing ISO
541 classification (e.g., between the buffer room and ante-room), or between a
542 classified room and an unclassified room (e.g., between the ante-room and
543 an unclassified room such as a hallway) See *4.7 Environmental Controls* for
544 a description of air pressure differentials. If a pass-through is used, both
545 doors must never be opened at the same time, and doors must be
546 interlocking.

547 Due to the interdependence of the various rooms or areas that make up a
548 sterile radiopharmaceutical processing facility, it is essential to carefully
549 define and control the dynamic interactions permitted between areas and
550 rooms. When designing doors, consider the placement of door closures, door
551 surfaces, and the movement of the door, all of which can affect airflow.
552 Tacky surfaces must not be used in ISO-classified rooms.

553 THE RADIOPHARMACEUTICAL PROCESSING ENVIRONMENT

554 The PEC must be certified to meet ISO Class 5 or better conditions (see
555 [Table 1](#)) and must be designed to minimize microbial contamination during
556 processing of radiopharmaceuticals during dynamic operating conditions.

557 The airflow in the PEC must be unidirectional (laminar flow), and because
558 of the particle collection efficiency of the filter, the "first air" at the face of
559 the filter is, for the purpose of aseptic processing, free from airborne
560 particulate contamination. HEPA-filtered air must be supplied in critical areas
561 (ISO Class 5; see [Table 1](#)) at a velocity sufficient to sweep particles away
562 from aseptic processing areas and maintain unidirectional airflow during
563 operations. Proper design and control prevents turbulence and stagnant air
564 in the critical area. In situ air pattern analysis via smoke studies must be
565 conducted at the critical area to demonstrate unidirectional airflow and
566 sweeping action over and away from the site under dynamic conditions.

567 TYPES OF PECS AND PLACEMENT

568 Proper placement of the PEC is critical to ensuring an ISO Class 5
569 environment for preparing radiopharmaceuticals. Placement of the PEC must
570 allow for cleaning around the PEC.

571 A PEC provides an ISO Class 5 or better environment for sterile
572 radiopharmaceuticals. The PEC provides unidirectional HEPA-filtered airflow
573 that is designed to minimize microbial contamination of a sterile processing
574 environment. The unidirectional airflow within the PEC helps protect the
575 direct processing area (DPA) from process-generated contamination (e.g.,
576 opening wrappings of sterile containers, worker movement, etc.) as well as
577 from outside sources.

578 **Laminar airflow workbench (LAFW):** An LAFW used for preparing
579 radiopharmaceuticals must provide vertical unidirectional HEPA-filtered
580 airflow. In cases where the LAFW is located within the segregated
581 containment area of a hot-cell, it is acceptable for a horizontal unidirectional
582 HEPA-filtered airflow pattern to be utilized.

583 **Class II biological safety cabinet (BSC):** A Class II BSC is a cabinet
584 with an open front and inward airflow and downward unidirectional HEPA-
585 filtered airflow and HEPA-filtered exhaust. The BSC is designed to provide
586 worker protection from exposure to biohazardous material and to provide an
587 ISO Class 5 or better environment for preparing sterile
588 radiopharmaceuticals.

589 **Placement of PEC:** The PEC must be located out of traffic patterns and
590 away from room air currents that could disrupt the intended airflow patterns
591 inside the PEC. If used only to prepare, prepare with minor deviations,
592 dispense, or repackage sterile radiopharmaceuticals the ISO Class 5 PEC
593 may be placed in an unclassified SRPA. If used to compound sterile
594 radiopharmaceuticals, the PEC must be located within an ISO Class 7 or
595 better buffer room and ISO Class 8 or better ante-room. A dynamic airflow
596 smoke pattern test must be performed initially and at least every 6 months
597 to ensure that the PEC is properly placed into the facility and that workers
598 understand how to utilize the unidirectional airflow to maintain first air as
599 much as possible given the limitations added from the radiation shielding in
600 the DPA.

601 AIR-EXCHANGE REQUIREMENTS

602 For classified rooms, adequate HEPA-filtered airflow to the buffer room(s)
603 and ante-room(s) is required to maintain the appropriate ISO classification
604 during processing activities. Airflow is measured in terms of the number of
605 HEPA-filtered air changes per hour (ACPH). The ACPH may need to be higher
606 to maintain the required ISO classification and microbial state of control
607 depending on these factors: the number of personnel permitted to work in
608 the area, the number of particulates that may be generated from activities
609 and processes in the area, the equipment located in the room, the room
610 pressure, and the effects of temperature. The summary of ACPH
611 requirements is listed in [Table 1](#).

612 A minimum of 30 total HEPA-filtered ACPH must be supplied to ISO Class 7
613 rooms.

- 614 • The total HEPA-filtered air change rate must be adequate to maintain
615 ISO Class 7 under dynamic operating conditions considering factors
616 listed above
- 617 • At least 15 ACPH of the total air change rate in a room must come
618 from the HVAC through HEPA filters located in the ceiling
- 619 • The HEPA-filtered air from the PEC, when added to the HVAC-supplied
620 HEPA-filtered air, increases the total HEPA-filtered ACPH to at least
621 30 ACPH
- 622 • If the PEC is used to meet the minimum total ACPH requirements, the
623 PEC must not be turned off except for maintenance
- 624 • The ACPH from HVAC, ACPH contributed from the PEC, and the total
625 ACPH must be documented on certification reports

626 A minimum of 20 ACPH of HEPA-filtered air must be supplied to ISO Class 8
627 rooms from the HVAC through HEPA filters that are located in the ceiling.

- 628 • The total HEPA-filtered air change rate must be adequate to maintain
629 ISO Class 8 under dynamic operating conditions considering factors
630 listed above
- 631 • Ante-rooms where activity levels are high may require more HEPA-
632 filtered ACPH to maintain ISO Class 8 under dynamic operating
633 conditions
- 634 • The total ACPH must be documented on certification reports

635 **Table 1. Summary of ACPH Requirements for Sterile**
636 **Radiopharmaceutical Processing**

Processing Area	ACPH Requirement
Unclassified SRPA	No requirement
ISO Class 7 area	≥30 ACPH
ISO Class 8 area	≥20 ACPH

637 4.2 Creating Areas to Achieve Easily Cleanable Conditions

638 CLASSIFIED ROOMS

639 The surfaces of ceilings, walls, floors, doors, door frames, fixtures,
640 shelving, work surfaces, counters, and cabinets in the classified room must
641 be smooth, impervious, free from cracks and crevices, and non-shedding, so
642 they can be easily cleaned and disinfected, and to minimize spaces in which
643 microorganisms and other contaminants can accumulate. Surfaces should be
644 resistant to damage by cleaning agents, disinfectants, and tools used to

645 clean. Junctures between the ceiling and the walls and between the wall and
646 the floor must be sealed to eliminate cracks and crevices where dirt can
647 accumulate. If ceilings consist of inlaid panels, the panels must be caulked
648 or otherwise sealed and secured around each panel to seal them to the
649 support frame. Ceiling panels must be washable and soil resistant, designed
650 for use in a clean room environment.

651 Walls must be constructed of, or may be covered with, durable material
652 (e.g., epoxy-painted walls or heavy-gauge polymer) and the integrity of the
653 surface must be maintained. Panels must be joined together and sealed to
654 each other and the support structure. Floors must be smooth, sealed (e.g.,
655 continuous, welded seams), and impervious. Floors must include coving to
656 the sidewall. Classified rooms should minimize dust-collecting overhangs
657 such as utility pipes and ledges such as windowsills. If overhangs or ledges
658 are present, they must be easily cleanable. The exterior lens surface of
659 ceiling light fixtures must be smooth, mounted flush, and sealed. Any other
660 penetrations through the ceiling or walls must be sealed.

661 SRPA

662 The SRPA and all surfaces (e.g., walls, floors, counters, equipment) in the
663 SRPA must be clean, uncluttered, and dedicated to sterile
664 radiopharmaceutical processing activities. Surfaces in the SRPA should be
665 smooth, impervious, free from cracks and crevices, and non-shedding, so
666 they can be easily cleaned and disinfected, and to minimize spaces in which
667 microorganisms and other contaminants can accumulate. Surfaces should be
668 resistant to damage by cleaning agents, disinfectants, and tools used to
669 clean. Dust-collecting overhangs such as utility pipes and ledges such as
670 windowsills should be minimized. If overhangs or ledges are present, they
671 must be easily cleanable.

672 4.3 Water Sources

673 The facility where sterile radiopharmaceuticals are prepared must be
674 designed so that activities such as hand hygiene and garbing should not
675 adversely affect the ability of the PEC to function as designed. Sinks should
676 enable hands-free use with a closed system of soap (i.e., non-refillable) to
677 minimize the risk of extrinsic contamination. In facilities with an ante-room
678 and buffer room, the sink used for hand hygiene may be placed either inside
679 or outside of the ante-room. The buffer room must not contain sink(s),
680 eyewash(es), shower(s), or floor drains. The ante-room must not contain
681 floor drain(s). If installed, sprinkler systems in classified rooms should be
682 recessed and covered, and must be easily cleanable. In a facility with an
683 SRPA design, the sink must be accessible but located at least 1 m from the
684 PEC. The sink must not be located inside the perimeter of the SRPA.

685 4.4 Placement and Movement of Materials

686 Only furniture, equipment, and other materials necessary are permitted in
687 the classified room or SRPA and they should be low-shedding and easily
688 cleaned and disinfected. Their number, design, location, and manner of
689 installation must not adversely impact environmental air quality and must
690 promote effective cleaning and disinfecting. Certain items are not permitted
691 on the clean side of the ante-rooms and in buffer rooms, including, but not
692 limited to, corrugated cardboard, external shipping containers, and
693 nonessential paper (e.g., paper towels and tissues).

694 Carts used to transport components or equipment into classified rooms
695 must be constructed from nonporous materials with cleanable casters and
696 wheels to promote mobility and ensure ease of disinfection. All items must
697 be disinfected by personnel wearing gloves before they are brought into the
698 clean side of ante-room(s), placed into pass-through(s), or brought into an
699 SRPA. In a classified room, carts must not be moved from the dirty side to
700 the clean side of the ante-room unless the entire cart, including casters, is
701 cleaned and disinfected.

702 **4.5 Classified Rooms**

703 Activities and tasks carried out within the buffer room must be limited to
704 only those necessary when working within a controlled environment. Food,
705 drinks, and materials exposed in patient care and treatment areas must not
706 enter ante-rooms or buffer rooms. When processing activities require the
707 manipulation of a patient's blood-derived or other biological material (e.g.,
708 radiolabeling a patient's or donor's blood cells), the manipulations must be
709 clearly separated from routine material-handling procedures and equipment
710 used in radiopharmaceutical preparation activities, and they must be
711 controlled by specific SOPs to avoid any cross-contamination.

712 **4.6 Remote Aseptic Processing Involving a Hot-Cell**

713 A hot-cell device provides an inherent physical segregation for the ISO
714 Class 5 aseptic processing area. If the hot-cell is located in an ISO-classified
715 space, personnel must garb according to requirements listed in *3.5 Hand
716 Hygiene and Garbing for Buffer Rooms and Segregated Radiopharmaceutical
717 Processing Area*. In settings where tasks are carried out within the hot-cell
718 enclosure not within an ISO-classified space by remote means (i.e., no direct
719 intervention by personnel into the ISO Class 5 space), it is not necessary for
720 personnel to don the garbing described in *3.5 Hand Hygiene and Garbing for
721 Buffer Rooms and Segregated Radiopharmaceutical Processing Area* to carry
722 out these aseptic manipulations or to perform other routine tasks in the
723 general area where the hot-cell is located. However, hand and arm
724 incursions into the interior of the hot-cell might be necessary for personnel
725 to stage the materials and supplies necessary for aseptic manipulations. In
726 these instances, personnel must garb in relation to the contamination risk
727 associated with the individual hot-cell/ISO Class 5 relationship.

728 For situations where a PEC device is located within a hot-cell, dynamic
729 airflow smoke pattern tests must show that the staging of supplies and
730 materials does not allow the influx of non-controlled air into the PEC.
731 Personnel can be donned in nonsterile gloves and a low-particulate lab coat
732 for interventions that are outside of the PEC. A failure of the airflow smoke
733 pattern test requires personnel to garb in accordance with *3.5 Hand Hygiene
734 and Garbing for Buffer Rooms and Segregated Radiopharmaceutical
735 Processing Area* for all incursions into the hot-cell.

736 For situations where the hot-cell is an integrated HEPA filtration system
737 with a clear demarcated area that is a PEC, dynamic airflow smoke pattern
738 tests must show that the staging of supplies and materials into the
739 demarcated PEC area does not allow the influx of less than ISO Class 5
740 quality air into the PEC. Personnel can be donned in nonsterile gloves and a
741 low-particulate lab coat for interventions that are outside of the PEC. A
742 failure of the airflow smoke pattern test requires personnel to garb in
743 accordance with *3.5 Hand Hygiene and Garbing for Buffer Rooms and
744 Segregated Radiopharmaceutical Processing Area* for all incursions into the
745 PEC.

746 Since other hot-cell configurations and technologies may exist, verification
747 (either by airflow smoke pattern tests or other manufacturer specified
748 methods) must assure, upon each certification that the staging of materials
749 and supplies does not allow for the intrusion of less than ISO Class 5 air into
750 the designated ISO Class 5 space. A failure of the airflow smoke pattern test
751 requires personnel to garb in accordance with *3.5 Hand Hygiene and Garbing
752 for Buffer Rooms and Segregated Radiopharmaceutical Processing Area* for
753 all incursions into the hot-cell.

754 **4.7 Environmental Controls**

755 All RAM users must comply with the conditions specified in their approved
756 RAM license application and regulations. Pass-through enclosures for
757 transferring radiopharmaceuticals from controlled handling areas (e.g.,
758 buffer room) should be designed to provide reasonable balance between
759 maintenance of air quality and other worker safety concerns (e.g., radiation
760 exposure, physical injury from lifting heavy shielded cases). At a minimum,
761 there must be a system or mechanism in place that assures that both doors
762 cannot be open at the same time. There may be both positive and negative
763 air pressure within the facility; positive air flow to minimize the potential of
764 microbial contamination in sterile drug preparation areas, and negative air
765 flow to minimize potential radioactive contamination from volatile or airborne
766 radiopharmaceuticals. Positive pressure environments must have a minimum
767 differential positive pressure of a 0.02-inch water column between each ISO-
768 classified room (e.g., between the buffer room and ante-room). The
769 pressure differential between the ante-room and the unclassified room must
770 be NLT a positive 0.02-inch water column. Refer to the RAM license for

771 negative pressure obligations. For preparation of sterile
772 radiopharmaceuticals, consideration of both concerns could be addressed as
773 follows:

- 774 1. Buffer room, if present, must be positive pressure compared to the
775 ante-room
- 776 2. Ante-room, if present, must be positive pressure compared to the
777 restricted area
- 778 3. Restricted area must be negative pressure compared to the
779 unrestricted area
- 780 4. SRPA must be negative pressure compared to unrestricted areas in
781 the presence of volatile or airborne radiopharmaceuticals.

782 Various environmental controls for various preparation scenarios [see [Table](#)
783 [5](#) for maximum beyond-use dates (BUDs) for differing environments] are
784 described in the following sections. [Table 2](#) details the limits for particle
785 counts for each specific ISO classification.

786 **Table 2. ISO Classification of Particulate Matter in Room Air^a**

ISO Class	Particle Count ^b /m ³
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

^a Adapted from ISO 14644-1, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.
^b Limits for number of particles $\leq 0.5 \mu\text{m}$ measured under dynamic operating conditions.

787 ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS
788 Any time a pressure differential is required, a pressure monitoring device is
789 required. In a classified room, a pressure differential monitoring system
790 must be used to continuously monitor the pressure differential between the
791 ante-room(s) and buffer room(s) and between the ante-room and the
792 general environment outside the classified room(s) or area(s). The results
793 from the pressure monitoring system must be reviewed and documented at
794 least daily on days the room is used. All pressure monitoring devices must
795 be tested for accuracy and required performance at least every 6 months.

796 AMBIENT ATMOSPHERE FOR IMMEDIATE USE PREPERARATIONS

797 The following requirements should be met in ambient atmosphere
798 environments:

- 799 • Non-patient care space, functionally separate (not another room) from
800 the patient care area, such as a radiopharmaceutical handling space,
801 or hot lab, in a hospital, clinic, or mobile coach
- 802 • A designated space for medication preparation that is clean and free
803 from clutter
- 804 • Low traffic (i.e., few people going in and out or moving around the
805 area)

806 SRPA WITH VERTICAL ISO CLASS 5 PEC(S) FOR RADIOPHARMACEUTICAL 807 PREPARATIONS

808 An SRPA with vertical ISO Class 5 PECs must meet the following
809 requirements:

- 810 1. Area surrounding the PEC may be ambient (non-classified)
811 atmosphere
- 812 2. Area must be clean, uncluttered, and dedicated to the processing of
813 radiopharmaceuticals
- 814 3. Appropriate for preparation, preparation with minor deviations,
815 repackaging, and dispensing of radiopharmaceuticals
- 816 4. A room that meets ISO Class 8 particle-count specifications may be
817 used to store and elute radionuclide generators

818 A BUFFER ROOM WITH AN ISO CLASS 8 ENVIRONMENT WITH VERTICAL ISO 819 CLASS 5 PEC(S) WITH AN ADJACENT ISO CLASS 8 ANTE-ROOM

820 This environment is appropriate for all activities listed in *SRPA with Vertical*
821 *ISO Class 5 PEC(s) for Radiopharmaceutical Preparations*.

822 A BUFFER ROOM WITH AN ISO CLASS 7 ENVIRONMENT WITH VERTICAL ISO 823 CLASS 5 PEC(S) WITH AN ADJACENT ISO CLASS 8 OR BETTER ANTE-ROOM

824 This environment is appropriate for all activities listed in *A Buffer Room*
825 *with an ISO Class 8 Environment with Vertical ISO Class 5 PEC(s) with an*
826 *Adjacent ISO Class 8 Ante-Room* and sterile compounding.

827 HOT-CELL

828 This environment is appropriate for all activities listed in *SRPA with Vertical*
829 *ISO Class 5 PEC(s) for Radiopharmaceutical Preparations*.

830 CERTIFICATION OF PECS AND ENVIRONMENT IN WHICH THE PEC IS 831 LOCATED

832 Certification of the classified areas, including the PEC, must be performed
833 initially and recertification must be performed at least every 6 months using
834 procedures outlined in the current Controlled Environment Testing

835 Association (CETA) certification guide for *Sterile Compounding Facilities*, or
836 an equivalent guideline, and must include:

- 837 • Airflow testing: To determine acceptability of the air velocity, the air
838 exchange rate, and room pressure cascade to ensure that air
839 consistently flows from clean to dirty areas, and that the appropriate
840 quality of air is maintained under dynamic operating conditions.
- 841 • HEPA filter integrity testing: HEPA filters must be leak tested at the
842 factory and then leak tested again after installation and as part of
843 recertification.
- 844 • Total particle counts testing: Conducted under dynamic operating
845 conditions using current, state-of-the-art electronic equipment.
- 846 • Smoke visualization studies: Performed for each PEC under dynamic
847 operating conditions to demonstrate unidirectional airflow and
848 sweeping action over and away from the preparation(s).

849 In cases where technologies exist for hot-cell and PEC configurations that
850 are not consistent for certification by the current CETA standards, other
851 equivalent means for certifying the PEC may be substituted. In this case, the
852 PEC must maintain the environmental equivalent for total particle counts and
853 the protection of the ISO Class 5 area from intrusions of non- or lesser
854 controlled air. Manufacturer verification instructions, along with professional
855 expertise in controlled environment testing, may be used to create a plan for
856 the necessary assurance testing techniques.

857 DAILY MONITORING OF ENVIRONMENT

858 The temperature, humidity, and pressure gradient must be monitored in
859 the classified room each day that preparations are made, either manually or
860 by a continuous recording device. The following guidelines must include:

- 861 • Relative humidity should be kept at 60% or lower
- 862 • Temperature and relative humidity continuous readings must be
863 confirmed daily to have remained within the acceptable range
- 864 • Excursions should be documented and, if applicable, appropriate
865 corrective actions taken
- 866 • Temperature monitoring devices must be verified for accuracy annually
867 or as required by the manufacturer
- 868 • Monitoring of pressure differentials must be performed

869 See [Packaging and Storage Requirements \(659\)](#) for information on
870 controlled room temperature and allowable excursions.

871

872 5. MICROBIOLOGICAL AIR AND SURFACE MONITORING

873 An effective air and surface monitoring program provides information on
874 the environmental quality of the classified rooms where sterile
875 radiopharmaceuticals are processed. In addition, an effective air and surface
876 monitoring program identifies environmental quality trends over time,
877 potential routes of microbiological contamination, and allows for
878 implementation of corrective actions to prevent microbiological
879 contamination of the radiopharmaceuticals. Facilities must develop and
880 implement written air and surface monitoring procedures for all sterile
881 radiopharmaceutical classified rooms. Air and surface monitoring results and
882 the corrective actions must be documented, and records must be readily
883 retrievable as required by jurisdictional laws and regulations, whichever is
884 longer.

885 **5.1 General Monitoring Requirements**

886 The goals of an air and surface monitoring program are to determine
887 whether microbiological contamination is present at unacceptable levels and
888 to assess whether proper personnel practices are being followed, cleaning
889 and disinfecting agents are effective, and environmental quality is
890 maintained.

891 Air and surface monitoring must be performed initially for classified rooms
892 in a facility to establish a baseline level of environmental quality. After initial
893 sampling, the classified rooms must be monitored according to the minimum
894 frequencies described in this section to ensure that the environment remains
895 in a suitable state for aseptic processing tasks.

896 The air and surface monitoring program involves the collection and
897 evaluation of samples from various air and surface locations to detect
898 airborne and surface contaminants. The data from airborne and surface
899 sampling are then used to assess risks for contamination, potential routes of
900 contamination, and the adequacy of cleaning and disinfection agents
901 specified in the facility procedures. Regular review of the sampling data must
902 be performed to detect trends such as elevated levels of microbial
903 bioburden, elevated levels of nonviable particulates, or other adverse
904 changes within the environment.

905 In addition, results from air and surface sampling must be reviewed in
906 conjunction with personnel data (i.e., training records, visual observations,
907 competency assessments) to assess the state of control and to identify
908 potential risks of contamination. Prompt corrective action in response to any
909 adverse findings is essential to maintain the necessary environmental quality
910 for sterile radiopharmaceutical activities. Data must also be reviewed
911 following corrective actions to confirm that the actions taken have been
912 effective in achieving the required air and surface quality levels (see [Table 3](#)
913 and [Table 4](#)).

914 Air and surface monitoring must be conducted during dynamic operating
915 conditions to confirm that the required environmental quality in classified

916 rooms is maintained. Due to radiation exposure concerns for the workers
917 involved, it is permissible for sampling to be carried out at the conclusion of
918 sterile radiopharmaceutical processing. In this case, simulated tasks that are
919 reflective of the routine aseptic activities are permissible. In addition to the
920 specific sampling frequencies described in this section, sampling must be
921 performed in any of the following circumstances:

- 922 • In conjunction with the certification of new facilities and equipment
- 923 • After any modification of facilities or equipment
- 924 • In response to identified problems (e.g., positive growth in sterility
925 tests of compounded radiopharmaceuticals)
- 926 • In response to identified trends (e.g., repeated positive gloved
927 fingertip sampling results or failed media-fill testing involving more
928 than one operator or where a review of the operator technique shows
929 no reasonable flaws in process; repeated observations of air or
930 surface contamination)
- 931 • In response to changes that could impact the controlled area
932 environments (e.g., significant change in cleaning process or the
933 agents involved)

934 The microbiological air and surface monitoring program must include viable
935 impact volumetric airborne particulate sampling and surface sampling.

936 To obtain an air and surface sample that is representative of the typical
937 aseptic operating conditions at the facility, air and surface sampling must be
938 conducted under dynamic or simulated dynamic operating conditions in all
939 PECs and classified rooms. If conducted during actual sterile processing, the
940 monitoring program must be designed and conducted in a manner that
941 minimizes the chance that the sampling itself will contribute to
942 contamination of the sterile radiopharmaceutical or the environment.

943 The air and surface monitoring program must include a diagram of the
944 sampling locations, procedures for collecting samples, frequency of
945 sampling, size of samples (e.g., surface area, volume of air), time of day of
946 sampling in relation to activities in the classified rooms, and action levels
947 that will trigger corrective action. The locations of sampling should be
948 carefully selected based on their relationship to the activities performed in
949 the area. It is important to obtain samples from locations that pose the
950 highest possible contamination risk to the sterile radiopharmaceuticals
951 involved with the operation's processes and that are likely to be
952 representative of the conditions throughout the area. In addition, sampling
953 methods, locations, frequencies, and timing must be clearly described in the
954 established SOPs of the facility.

955 Evaluating results collected over a period of time can be useful in
956 identifying trends or determining that a significant change has occurred,
957 even when the results fall within the specified limits.

958 It is important that personnel be trained in the proper operation of the air
959 and surface sampling equipment to ensure accurate and reproducible
960 sampling. All air sampling devices must be serviced and calibrated as
961 recommended by the manufacturer.

962 **5.2 Monitoring Air Quality for Viable Airborne Particles**

963 A monitoring program for viable airborne particles must be developed and
964 implemented to assess microbiological air quality in all classified rooms.

965 **VIABLE AIR SAMPLING: TIMING AND LOCATIONS**

966 Volumetric active air sampling of all classified spaces using an impaction
967 device must be conducted (e.g., ISO Class 5 PEC and ISO Class 7 and 8
968 areas) during dynamic operating or simulated operating conditions at least
969 every 6 months.

970 Air sampling sites must be selected in all classified spaces. When
971 conducting sampling of the PEC, care should be taken to avoid disturbing
972 unidirectional airflow if taken during actual sterile processing activities.

- 973 1. Follow the manufacturer's instructions for operation of the active air
974 sampling device, including placement of media.
- 975 2. Using the sampling device, test at least 1 m³ or 1000 L of air from
976 each location sampled.
- 977 3. At the end of the sampling, retrieve the media and cover.
- 978 4. Invert the media and incubate at 30°–35° for 48–72 h. Examine for
979 growth. Record the total number of discrete colonies of
980 microorganisms on each plate as cfu/m³ of air on an environmental
981 sampling form based on sample type (i.e., viable air), sample
982 location, and sample date.
- 983 5. Then incubate the inverted media at 20°–25° for 5–7 additional days.
984 Examine the media plates for growth. Record the total number of
985 discrete colonies of microorganisms on each plate as cfu/m³ of air on
986 an environmental sampling form based on sample type (i.e., viable
987 air), sample location, and sample date.

988 Alternatively, two pieces of media may be collected for each sample
989 location and incubated concurrently in separate incubators at 30°–35° for
990 NLT 5 days and at 20°–25° for NLT 5 days. Record the total number of
991 discrete colonies of microorganisms on each plate as cfu/m³ of air on an
992 environmental sampling form based on sample type (i.e., viable air), sample
993 location, and sample date.

994 A general microbiological growth medium that supports the growth of
995 bacteria and fungi must be used [e.g., TSA medium]. Certificates of analysis
996 from the manufacturer must verify that the medium meets the expected
997 growth promotion, pH, and sterilization requirements. Samples must be
998 incubated in a temperature monitored incubator with a calibrated measuring

999 device. The incubator temperature must be monitored during incubation,
1000 either manually or by a continuous recording device, and the results must be
1001 reviewed and documented. The microbiological incubator must be placed in a
1002 location outside of any classified room. All sampling activities must be
1003 performed by trained individuals.

1004 DATA EVALUATION AND ACTION LEVELS

1005 Evaluate cfu counts against the action levels in [Table 3](#), and examine
1006 counts in relation to previous data to identify adverse results or trends. If
1007 two pieces of media were collected at a single location, all recovered growth
1008 on each is documented and action levels are applied individually to each
1009 sampling (i.e., results from each cubic meter of air sampled must be
1010 compared to the action level for that area). If levels measured during the
1011 viable air monitoring program exceed the levels in [Table 3](#) for the ISO
1012 classification levels of the area sampled, the cause must be investigated and
1013 corrective action must be taken. The corrective action plan must be
1014 dependent on the cfu count and the microorganism recovered. Some
1015 examples of corrective action include process or facility improvements,
1016 personnel training, cleaning and disinfecting, or HEPA filter replacement
1017 and/or repair, or reducing the BUD of the radiopharmaceutical during
1018 investigation and while carrying out the corrective action plan. The extent of
1019 the investigation should be consistent with the deviation and should include
1020 an evaluation of trends. The corrective action plan must be documented. If
1021 levels measured during viable air sampling exceed the levels in [Table 3](#), the
1022 genus of any microorganism recovered must be identified (see [Microbial
1023 Characterization, Identification, and Strain Typing \(1113\)](#)) with the
1024 assistance of a microbiologist.

1025 **Table 3. Action Levels for Viable Airborne Particle Air Sampling^a**

ISO Class	Air Sampling Action Levels [cfu/m ³ (1000 L) of air per plate]
5	>1
7	>10
8	>100

^a Adapted from *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. US Department of Health and Human Services, Food and Drug Administration (FDA), September 2004.

1026 5.3 Monitoring Surfaces for Viable Particles

1027 Surface sampling is an important component of the maintenance of a
1028 suitably controlled environment for sterile radiopharmaceutical processing,

1029 especially because transfer of microbial contamination from improperly
1030 disinfected work surfaces via inadvertent touch contact by personnel is a
1031 potential source of contamination of the radiopharmaceutical. Surface
1032 sampling is useful for evaluating facility cleaning and material handling
1033 procedures; work surface cleaning and disinfecting procedures; and
1034 personnel competency in work practices such as proper cleaning and
1035 disinfection. All sampling sites and procedures must be described in the
1036 facility's SOP.

1037 SURFACE SAMPLING: TIMING AND LOCATIONS

1038 Surface sampling of all classified areas and all PECs must be conducted at
1039 least monthly for the detection of microbial contamination. Each classified
1040 area must be sampled (see [Microbiological Control and Monitoring of Aseptic
1041 Processing Environments \(1116\)](#)). The DPA of the PEC and any equipment
1042 permanently contained in it must be sampled. Staging or work surfaces in
1043 classified rooms near the PEC frequently touched surfaces in classified rooms
1044 and pass-through enclosure(s) for all classified rooms are to be evaluated to
1045 determine the locations that pose the greatest risk to the SRPA.

1046 When conducted, surface sampling must be performed at the end of the
1047 radiopharmaceutical aseptic activities or shift, but before the area has been
1048 cleaned and disinfected. However, radiopharmaceutical personnel must also
1049 consider the appropriate exposure and contamination prevention measures
1050 prior to and while collecting samples. If the worker assesses that the risk for
1051 exposure is not in conformance with ALARA safety standards, measures
1052 must be taken to eliminate the risk (e.g., implementation of appropriate
1053 shielding, performing the sampling at a later time or alternate day).

1054 SAMPLING PROCEDURES

1055 Surface sampling devices (e.g., plates, paddles, or slides) containing
1056 microbial growth media must be used for sampling flat surfaces. CoAs from
1057 the manufacturer must verify that the devices meet the expected growth
1058 promotion, pH, and sterilization requirements. Surface sampling devices
1059 must contain general microbial growth media (e.g., TSA) supplemented with
1060 neutralizing additives (e.g., lecithin and polysorbate 80) to neutralize the
1061 effects of any residual disinfecting agents. If used, contact plates must have
1062 a raised convex surface. Sterile swabs wetted with sterile water or a sterile
1063 neutralizing buffer may be used when sampling irregular surfaces and
1064 difficult-to-reach locations, such as crevices, corners, and spaces between
1065 surfaces. After sampling, the sampled area must be thoroughly cleaned and
1066 disinfected.

1067 For the procedures for surface sampling on flat surfaces, use the following:

- 1068 1. Remove the cover from the contact sampling device. Using a rolling
1069 motion, firmly press the media surface onto the surface to be
1070 sampled. The contact sampling device should leave a residue of

- 1071 growth medium on the sample site. After sampling, use a low-lint
1072 sterile wiper to thoroughly clean the sampled area with sterile 70%
1073 IPA.
- 1074 2. Cover each contact sampling device.
 - 1075 3. If using plates, invert the plates and incubate the contact sampling
1076 devices at 30°–35° for 48–72 h. Examine for growth. Record the total
1077 number of discrete colonies of microorganisms on each plate as
1078 cfu/sample on an environmental sampling form based on sample type
1079 (i.e., surface), sample location, and sample date.
 - 1080 4. Incubate the inverted plates at 20°–25° for 5–7 additional days.
1081 Examine the media plates for growth. Record the total number of
1082 discrete colonies of microorganisms (cfu/sample) on the
1083 environmental sampling record based on sample type (i.e., surface),
1084 sample location, and sample date.
 - 1085 5. Alternatively, two devices may be collected for each sample location
1086 and incubated concurrently in separate incubators at 30°–35° for NLT
1087 5 days and at 20°–25° for NLT 5 days.
 - 1088 6. Record the total number of discrete colonies of microorganisms
1089 (cfu/sample) on the environmental sampling record based on sample
1090 type (i.e., surface), location, and date.

1091 For the procedures for surface sampling on irregular surfaces, use the
1092 following:

- 1093 1. Sterile swabs wetted with sterile water or a sterile neutralizing buffer
1094 should be used.
- 1095 2. If using the neutralizing buffer, the residue must be removed from
1096 the surface after sampling using sterile 70% IPA. Swabs sampled
1097 with sterile water must be processed with a neutralizing buffer or
1098 plated in a neutralizing medium.
- 1099 3. After swabbing the area, place the swab in appropriate diluent or
1100 sterile packaging until it can be processed. The swab must be
1101 processed using a diluent and an extraction step to aid in the removal
1102 of any microorganisms from the swab.
- 1103 4. Plate all or a portion of the diluent in TSA (or TSA with neutralizers).
1104 If the diluent is diluted, the dilution factor must be applied to the raw
1105 count to determine the actual total microbial count.
- 1106 5. Incubate the plates at 30°–35° for 48–72 h. Examine for growth.
1107 Record the total number of discrete colonies of microorganisms on
1108 each plate as cfu/sample on an environmental sampling form based
1109 on sample type (i.e., surface), sample location, and sample date.
- 1110 6. Incubate the plates at 20°–25° for 5–7 additional days. Examine for
1111 growth. Record the total number of discrete colonies of
1112 microorganisms on each plate as cfu/sample on the environmental

- 1113 sampling form based on sample type (i.e., surface), sample location,
 1114 and sample date/time.
- 1115 7. Alternatively, two devices may be collected for each area and
 1116 incubated concurrently in separate incubators at 30°–35° for NLT 5
 1117 days and at 20°–25° for NLT 5 days.
- 1118 8. Record the total number of discrete colonies of microorganisms
 1119 (cfu/sample) on the environmental sampling record based on sample
 1120 type (i.e., surface), location, and date.

1121 DATA EVALUATION AND ACTION LEVELS

1122 Evaluate cfu counts against the action levels in [Table 4](#), and examine
 1123 counts in relation to previous data to identify adverse results or trends. If
 1124 two devices were collected at a single location, all recovered growth on each
 1125 is documented and action levels are applied to each device individually (i.e.,
 1126 results from each sampling device must be compared to the action level for
 1127 the area). If levels measured during surface sampling exceed the levels in
 1128 [Table 4](#) for the ISO classification levels of the area sampled, the cause must
 1129 be investigated and corrective action must be taken. The corrective action
 1130 plan must be dependent on the cfu count and the microorganism recovered.
 1131 Some examples of corrective action include process or facility improvements,
 1132 personnel training, cleaning and disinfecting, or HEPA filter replacement
 1133 and/or repair, or reducing the BUD of the radiopharmaceutical during
 1134 investigation and while carrying out the corrective action plan. The extent of
 1135 the investigation should be consistent with the deviation and should include
 1136 an evaluation of trends. The corrective action plan must be documented. If
 1137 levels measured during surface sampling exceed the levels in [Table 4](#), the
 1138 genus of any microorganism recovered must be identified (see [\(1113\)](#)) with
 1139 the assistance of a microbiologist.

1140 **Table 4. Action Levels for Surface Sampling**

ISO Class	Surface Sampling Action Levels (cfu/device or swab)
5	>3
7	>5
8	>50

1141 6. CLEANING AND DISINFECTING

1142 Cleaning and disinfecting are important because surfaces in classified areas
 1143 and SRPAs are a potential source of microbial contamination of sterile
 1144 radiopharmaceuticals. The process of cleaning involves removing organic
 1145 and inorganic materials from surfaces, usually with a manual or mechanical
 1146 process and a cleaning agent. The process of disinfecting involves

1147 destruction of microorganisms, usually with a chemical agent. Surfaces must
 1148 be cleaned prior to being disinfected unless an Environmental Protection
 1149 Agency (EPA)-registered one-step disinfectant cleaner is used to accomplish
 1150 both the cleaning and disinfection in one step. Some EPA-registered one-
 1151 step disinfectant cleaners may have sporicidal properties.

1152 Cleaning and disinfecting surfaces should occur at the minimum
 1153 frequencies specified in [Table 5](#) or if activities are not performed daily,
 1154 cleaning and disinfecting must be completed before initiating activities.

1155 Radioactive decontamination is the act of reducing or removing radioactivity
 1156 from an object or surface and must be balanced with the risk of spreading
 1157 radioactive contamination. At times the best approach may be to shield the
 1158 area until the radiation exposure levels are lower. This balance must be
 1159 specified in SOPs (e.g., trigger levels for safe cleaning). The PEC should be
 1160 checked for radioactive contamination prior to cleaning and disinfecting to
 1161 prevent spreading radioactive contamination in the PEC.

1162 All cleaning and disinfecting activities must be performed by trained and
 1163 appropriately garbed personnel using facility-approved agents and
 1164 procedures that must be described in written SOPs. Cleaning must be
 1165 performed in the direction of clean to dirty areas. The frequency, method(s),
 1166 and location(s) of cleaning and disinfection agent use must be established in
 1167 written SOPs, in accordance with the manufacturer's instructions when
 1168 available, or based on sound microbiological cleaning techniques when
 1169 unavailable, and must be followed by all cleaning personnel. The
 1170 manufacturer's direction or published data for the minimum contact time
 1171 must be followed for the cleaning, disinfecting, and sporicidal agents used.
 1172 All cleaning and disinfecting activities must be documented.

1173 **Table 5. Minimum Frequency for Cleaning and Disinfecting Surfaces**
 1174 **in Classified Rooms and within the Perimeter of the SRPA**

Site	Cleaning	Disinfecting ^a	Applying Sporicidal
PEC(s) and equipment inside the PEC(s)	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield and any exposed surface of equipment inside the PEC to the extent possible as specified by the equipment manufacturer or the assessment of a	Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent possible as specified by the equipment manufacturer or the assessment of a trained microbiologist or	Monthly

Site	Cleaning	Disinfecting ^a	Applying Sporicidal
	<p>trained microbiologist or industrial hygienist. Radioactive contamination may be shielded with appropriate temporary material, providing the material is covered with low-lint absorbent pads or has equivalent low-shedding properties.</p>	<p>industrial hygienist and should be specified by SOPs. When used, remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.</p>	
Surfaces of sink(s)	Daily	Daily	Monthly
Hot-cells (all interior surfaces)	Daily	Daily	Monthly
PEC and the equipment within a PEC located in a hot-cell	<p>Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, the walls, bars, torso shield, and any exposed surface of equipment inside the PEC to the extent possible as specified by the equipment manufacturer or the assessment of a trained microbiologist or industrial hygienist. Radioactive contamination may be shielded with appropriate temporary material providing the material is covered with low-lint absorbent pads or has equivalent low-shedding properties.</p>	<p>Prior to performing sterile processing of radiopharmaceuticals on each day that activities are carried out, exposed surfaces of the equipment should be disinfected to the extent possible as specified by the equipment manufacturer or the assessment of a trained microbiologist or industrial hygienist and should be specified by SOPs. When used, remove low-lint absorbent pads and survey the PEC for radioactive contamination prior to disinfecting. Replace with new pads after disinfecting or as required after spills.</p>	Monthly
Work	Daily	Daily	Monthly

Site	Cleaning	Disinfecting ^a	Applying Sporicidal
surface(s) outside the PEC			
Floor(s)	Daily	Daily	Monthly
Wall(s), door(s), door frame(s), and other fixtures	Monthly	Monthly	Monthly
Ceiling(s)	Monthly	Monthly	Monthly
Storage shelving and storage bins	Monthly	Monthly	Monthly
<p>^a Many disinfectants registered with the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step. Cleaning and disinfecting must be balanced with the risk of spreading radiation contamination. The best approach may be to shield the area until the radiation exposure levels are lower.</p>			

1175 **6.1 Cleaning, Disinfecting, and Sporicidal Agents**

1176 Cleaning and disinfecting agents must be selected and used with careful
1177 consideration of compatibilities, effectiveness, and inappropriate or toxic
1178 residues or fumes. Considerations when selecting and using disinfectants
1179 include their anti-microbial activity, inactivation by organic matter, residue,
1180 shelf life, preparation requirements of the agent, and suitability for surfaces
1181 being disinfected (see [Disinfectants and Antiseptics \(1072\)](#)). After the
1182 disinfectant is applied and wiped on the surface to be disinfected, the
1183 disinfectant must be allowed to dwell for the minimum contact time specified
1184 by the manufacturer, during which time the surface cannot be disturbed.
1185 Sporicidal agents, shown to be effective against *Bacillus* species, must be
1186 used at least monthly to disinfect all surfaces in classified rooms and SRPAs.
1187 The disinfecting agents (e.g., sterile 70% IPA) used in the ISO Class 5 PEC
1188 must be sterile. See [Table 6](#) for a summary of the purpose of the cleaning
1189 disinfectant and sporicidal agents.

1190 **Table 6. Purpose of Cleaning, Disinfecting, and Sporicidal Agents**

Type of Agent	Purpose
Cleaning agent	An agent for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.
Disinfecting agent	A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores.
Sporicidal agent	A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

1191

6.2 Cleaning Supplies

1192 All cleaning supplies (e.g., wipers, sponges, and mop heads) with the
 1193 exception of tool handles and holders must be low-lint. Wipes, sponges, and
 1194 mop heads should be disposable. If disposable cleaning supplies are used,
 1195 they must be discarded after each cleaning activity. Reusable cleaning tools
 1196 must be made of cleanable materials (e.g., no wooden handles) and must be
 1197 cleaned before and after each use. Reusable cleaning tools must be
 1198 dedicated for use in the classified rooms or SRPAs and must not be removed
 1199 from these areas except for disposal. They must be discarded after an
 1200 appropriate amount of time, to be determined based on the condition of the
 1201 tools. Dispose of cleaning supplies used in the classified rooms and SRPAs in
 1202 a manner that minimizes the potential for dispersing particulates into the air
 1203 (e.g., with minimal agitation, away from work surfaces).

1204

6.3 Cleaning and Disinfecting the PEC

1205 Clean and disinfect the PEC at the minimum frequencies specified in [Table](#)
 1206 [5](#). If the PEC contains a removable work tray, all sides of the work tray and
 1207 the area underneath the work tray must be cleaned and disinfected at least
 1208 monthly.

- 1209 1. Remove, if necessary, any particles, debris, or residue with an
 1210 appropriate solution (e.g., [Sterile Water for Injection](#) or [Sterile Water](#)
 1211 [for Irrigation](#)) using sterile, low-lint wipers
- 1212 2. Apply a cleaning agent (e.g., EPA-registered, one-step disinfectant
 1213 cleaner)
- 1214 3. Disinfect with a sterile disinfectant (e.g., sterile 70% IPA)
- 1215 4. Allow the surface to dry completely before beginning activities
- 1216 5. The PEC must be wiped with a sporicidal agent at least monthly

1217

6.4 Disinfecting Supplies for Classified Rooms and SRPAs

1218 No shipping carton(s) or other corrugated or uncoated cardboard are
1219 allowed in the classified room or SRPA. Before items are introduced into a
1220 classified room or SRPA, they must be disinfected with a sporicidal agent or
1221 sterile disinfectant (e.g., sterile 70% IPA). After the sporicidal or sterile
1222 disinfectant is applied, the agent must be allowed to dwell for the minimum
1223 contact time specified by the manufacturer (see *5.1 General Monitoring*
1224 *Requirements*), during which time the item cannot be disturbed. The agent
1225 used for disinfecting the packaging must be compatible with the packaging
1226 and must not alter the product label.

1227 Any item to be transferred into the PEC from the classified room or SRPA
1228 must be disinfected with a sterile disinfectant (e.g., sterile 70% IPA). The
1229 sterile disinfectant must be allowed to dry before using the item.

1230 In the case of PET radiopharmaceuticals being processed by remote means
1231 in a hot-cell, the opening of sterile syringe packages may not be possible by
1232 remote means within the ISO Class 5 area. In this case, the syringes may be
1233 opened and appropriately labeled outside of the ISO Class 5 environment
1234 and placed in disinfected shielding, immediately prior to the forthcoming
1235 dispensing cycle.

1236 **6.5 Disinfecting Critical Sites within the PEC**

1237 Critical sites (e.g., vial stoppers) must be disinfected by wiping them with
1238 sterile 70% IPA in the PEC. The critical site must be wiped ensuring that
1239 both chemical and mechanical actions are used to remove contaminants. The
1240 sterile 70% IPA must be allowed to dry before piercing stoppers.

1241 **6.6 Cleaning and Disinfecting Items from Patient Care Area**

1242 Radiation shielding equipment used in the classified room/SRPA or PEC that
1243 is exposed to patient care areas during the process of administration must
1244 be cleaned and disinfected before returning to any classified room (e.g.,
1245 buffer or ante-room) or SRPA in accordance with the Centers for Disease
1246 Control and Prevention guidelines¹ as noncritical equipment requiring low-
1247 risk disinfection. Syringes that have been used in a patient care area must
1248 not be brought back into the classified room (e.g., buffer or ante-room) or
1249 SRPA for re-assaying or disposal. Equipment that has been exposed to
1250 needles and syringes contaminated with blood-borne pathogens and RAMs
1251 are considered mixed waste (e.g., syringe shields and syringe carrying
1252 containers). This equipment must be cleaned and disinfected in procedures
1253 regulated by the facilities' RAMs license and application. Equipment that
1254 contained mixed waste must be cleaned and disinfected with an appropriate
1255 agent(s) for blood.

1256

1257

7. ASSIGNING BUD

1258 BUDs are based on the risk of microbial contamination with the assumption
 1259 that the radiopharmaceutical should remain chemically and physically stable,
 1260 and its container–closure system should maintain its integrity for the
 1261 duration of the BUD ([Table 7](#)). The time starts at the moment of the first vial
 1262 puncture. The BUDs stated in [Table 7](#) are maximum values in the absence of
 1263 sterility testing, and the assigned BUD may be shorter for a variety of
 1264 reasons discussed below. The individual responsible for the manipulation
 1265 assigns the BUD based on established testing data, either performed in-
 1266 house or obtained from peer-reviewed literature.

1267 **Table 7. Preparation Conditions for Sterile Radiopharmaceuticals**

Preparation Conditions			
Manipulation	PEC	SEC	BUD (h)
Immediate use	—	—	1
Direct infusion system, one needle puncture only (e.g., PET patient infusion system, Rb-82 generator)	—	—	10
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	SRPA	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	SRPA with ISO Class 8 non-viable particle count	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	ISO Class 8 or better buffer room with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	ISO Class 8 or better buffer room ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding	ISO Class 5	ISO Class 7 or better buffer room with ISO Class 8 or better ante-	96

Preparation Conditions			
Manipulation	PEC	SEC	BUD (h)
		room	
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using a nonsterile component and performing sterilization procedure (e.g., filtration with bubble point testing) but without performing Sterility Tests (71) testing	ISO Class 5	ISO 7 or better buffer room with ISO Class 8 or better ante-room	24
Radiolabeled blood components for immediate use [e.g., Tc 99m red blood cells (RBC)]	—	—	1
Radiolabeled blood components (e.g., radiolabeled leukocytes)	ISO Class 5 BSC	ISO 7 or better buffer room with ISO Class 8 or better ante-room	6

1268 For compounded preparations (sterile and nonsterile), the BUD is also
 1269 dependent on maintenance of appropriate quality and purity, including
 1270 radiochemical purity, radionuclidic purity, and other applicable parameters
 1271 as specified in individual monographs or as clinically appropriate.

1272 For preparations with minor deviations involving kits (sterile and
 1273 nonsterile), the kit manufacturer may state or suggest a use-by time in their
 1274 package inserts. For certain radiopharmaceuticals transportation time,
 1275 radionuclide availability, and other factors may necessitate extending
 1276 manufacturer-suggested use-by time to meet patient needs. Assigning a
 1277 BUD longer than the manufacturer-suggested use-by time interval must be
 1278 supported by evidence of the maintenance of appropriate quality and purity,
 1279 including radiochemical purity and radionuclidic purity as specified in
 1280 individual monographs, and other applicable parameters as clinically
 1281 appropriate.

1282 Assignment of a BUD for a radiopharmaceutical must necessarily consider
 1283 several factors, as applicable. Issues of concern include, but are not limited
 1284 to, the following:

- 1285 • Sterility: Maintenance of sterility is a major concern for any sterile
 1286 preparation or product. Good aseptic handling practices in an
 1287 appropriate environmentally-controlled area are the most critical
 1288 factors in ensuring sterility. See [Table 7](#) for maximum BUD. The
 1289 assigned BUD does not exceed the sterility-related times listed in
 1290 [Table 7](#), unless a longer time is justified by [Sterility Tests \(71\)](#).

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- Radiochemical purity: Radiochemical stability is affected by a variety of factors including, but not limited to, storage temperature, amount of radioactivity, radioactivity concentration, presence or absence of antioxidants or other stabilizing agents, and container type (e.g., glass vial vs. plastic syringe). The assigned BUD must be based on stability studies in which these variables are controlled and are representative of the conditions of actual use. For factors that allow a range of values (e.g., storage temperature, amount of radioactivity, radioactivity concentration), studies should be conducted at the extremes of the ranges.
 - Radionuclidic purity: Because radionuclide impurities may decay away more slowly than the primary radionuclide, the radionuclidic purity may decrease over time. For example, the ratio of Mo-99 (half-life of about 66 h) to Tc-99m (half-life of about 6 h) continuously increases over time. *USP* monographs for Tc-99m radiopharmaceuticals require that the radionuclidic impurity Mo-99 not exceed 0.15 mCi Mo-99 per mCi Tc-99m at the time of administration. Hence, calculation of radionuclidic purity at future times is necessary to ensure compliance throughout the assigned BUD.
 - Age of generator: As a generator eluate decays, the desired daughter radionuclide atoms themselves decay to form other nuclides and potential radiolytic products, which may interfere with radiolabeling of kits. For example, as Tc-99m ages, Tc-99m atoms decay to become Tc-99 atoms. More importantly, there should also be increasing amounts of peroxides formed as radiation interacts with water molecules. Increased amounts of Tc-99 and peroxides present in aged Tc 99m can interfere with the radiolabeling of many kits. Hence, extension of the use-by time for Tc-99m pertechnetate intended for radiolabeling of kits must take into account the build-up of Tc-99 and peroxides over time.
 - Number of particles: For radiolabeled particulates, the number of particles per unit radioactivity increases over time as the radionuclide decays. For example, the BUD for Tc-99m albumin aggregated [macroaggregated albumin (MAA)] must take into account the increasing ratio over time of the number of particles per radioactivity patient dose. For example, if an MAA kit is prepared such that the radioactivity patient dose is 200,000 particles at the time of calibration, the same radioactivity patient dose will contain 700,000 particles at 10.85 h after calibration. Hence, calculation of the number of MAA particles in the radioactivity patient dose is necessary to ensure compliance with the prescribed particle range throughout the assigned BUD.
 - Specific activity (molar mass): For some receptor-based radiopharmaceuticals, the mass amount may influence uptake (i.e.,

1335 too much mass may result in saturation of receptor sites with excess
1336 radiopharmaceutical going elsewhere). As radioactivity decays over
1337 time, specific activity decreases resulting in more mass per unit
1338 radioactivity. Hence, in such situations, the assigned BUD must
1339 ensure that the patient dose contains NMT the specified maximum
1340 mass.

- 1341 • Container type: Because radiochemical stability or other quality
1342 attributes of a radiopharmaceutical may be affected by its container
1343 type, the BUD for a radiopharmaceutical dose dispensed in a plastic
1344 syringe may be different than the BUD of that same
1345 radiopharmaceutical maintained in a glass vial.
- 1346 • In the case of manufactured radiopharmaceuticals (both PET and non-
1347 PET) that are distributed to nuclear pharmacies or other healthcare
1348 facilities for terminal distribution/dispensing, the assigned BUD of the
1349 dispensed dose cannot exceed the expiration date/time of the
1350 manufactured radiopharmaceutical.
- 1351 • In the case of radiopharmaceuticals prepared from kits, the BUD of a
1352 dispensed dose cannot exceed the assigned BUD of the finished
1353 preparation.
- 1354 • In the case of compounded radiopharmaceutical, the
1355 radiopharmaceutical may not exceed the shortest BUD of any of its
1356 components.

1357 The facility must have policies and procedures appropriate to the
1358 assignment of BUD and maintain documentation of applicable study results
1359 and calculations. Studies of radiolabeling efficiency and radiochemical
1360 stability should employ quality control testing methods described in the
1361 manufacturer's package insert, *USP* monographs and general chapters, or
1362 other equivalent testing methods and be sufficiently rigorous to allow
1363 statistical confidence in the results.

1364 The facility must have a mechanism to collect and evaluate complaints
1365 associated with the use of radiopharmaceuticals having assigned BUDs.
1366 Policies and procedures should also be in place to re-evaluate the assigned
1367 BUD based on complaints, which may include repeating studies and/or
1368 performing additional studies on radiolabeling efficiency and/or
1369 radiochemical stability.

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1371

8. DOCUMENTATION

1372 Applicable policies and procedures should be established and maintained
1373 for activities involved in preparing, compounding, dispensing, and
1374 repackaging radiopharmaceuticals.

1375 Records (hard-copy or electronic) must be maintained for all activities
1376 involved in repackaging, preparing, preparing with minor deviations,

1377 compounding, and dispensing radiopharmaceuticals. Such records include,
1378 but are not limited to:

- 1379 • Personnel training and testing, including visual assessment of
1380 competency, validation, gloved fingertip testing, and media fill
1381 evaluation initially and follow up testing at specified intervals.
- 1382 • Testing of environmental controls, including ISO classification, ACPH,
1383 pressure differentials, and viable test results
- 1384 • Maintenance and cleaning
- 1385 • End product radiochemical purity and other testing, as applicable,
1386 results of preparations, preparations with minor deviations, and
1387 compounded preparations
- 1388 • Master Formulation Record (MFR) (i.e., preparation with minor
1389 deviation and compounding)
- 1390 • Validation of stability testing to support the assigned BUD from
1391 procedures established by the compounder or derived from accepted
1392 literature
- 1393 • Records of compounded radiopharmaceuticals
- 1394 • Investigations and remedial actions and tracking of events to closure.

1395 **8.1 Master Formulation Record**

1396 MFR are required only for:

- 1397 • Preparation with minor deviations
- 1398 • Compounding as described in *10. Compounding*

1399 MFR are not required for preparation following the manufacturer's
1400 instructions.

1401 Data that must be included in the MFR are as follows:

- 1402 • Name of the radiopharmaceutical
- 1403 • Ingredients and their specifications
- 1404 • Detailed procedure (e.g., heating, components, incubation time)
- 1405 • Range of radioactivity
- 1406 • Range of volume
- 1407 • Equipment to be used
- 1408 • PEC and SEC to be used, if applicable
- 1409 • Quality control tests to be done for final release of the
1410 radiopharmaceutical (e.g., radiochemical purity, pH)
- 1411 • Depyrogenation and sterility procedures and validations, as applicable,
1412 including limits
- 1413 • Personnel
- 1414 • Garbing procedure, if different than standard procedure
- 1415 • Container(s)

- 1416 • BUD assignment and storage conditions

1417 **8.2 Records for Preparation with Minor Deviation/Compounding**

1418 A record for preparation with minor deviation or compounding must include
1419 the following:

- 1420 • Name of radiopharmaceutical
- 1421 • Physical description of the final radiopharmaceutical (e.g., capsule or
1422 solution)
- 1423 • Name and quantity of ingredients including calibration time for
1424 radioactive ingredients (e.g., 100 mCi Tc 99m sodium pertechnetate
1425 @ 13:00)
- 1426 • Total volume
- 1427 • Reference to the MFR
- 1428 • Any deviation from the MFR, if applicable
- 1429 • Name of vendor or manufacturer, lot numbers, and expiration dates of
1430 all ingredients and components
- 1431 • Name of the person who prepared and name of the supervising
1432 personnel (e.g., ANP or AU physician) who verified the final drug
1433 product
- 1434 • Date and time of preparation
- 1435 • Assigned internal identification number (e.g., lot number)
- 1436 • Prescription or order number(s)
- 1437 • Assigned BUD and storage requirements
- 1438 • PEC used
- 1439 • Documentation of quality control results
- 1440 • Reference source of the BUD assignment and storage requirements

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1442 **9. PREPARATION**

1443 The individual responsible for preparing the radiopharmaceutical must
1444 ensure that the final preparation complies with quality and purity
1445 specifications throughout the assigned BUD. This includes, as appropriate for
1446 the preparation, radionuclidic purity, radiochemical purity, chemical purity,
1447 and physical and chemical properties.

1448 **9.1 Preparation Following Manufacturer Instructions**

1449 **NONSTERILE PREPARATIONS**

1450 For nonsterile preparations, follow manufacturer preparation instructions
1451 (e.g., I-131 NaI capsules or solution), taking into account appropriate
1452 radiation safety considerations. Utilize appropriate environmental controls, if
1453 applicable (e.g., chemical fume hood, activated charcoal filters when
1454 handling potentially volatile radionuclides). The area utilized for the

1455 preparation of all nonsterile radiopharmaceuticals should be suitably cleaned
1456 and uncluttered to assure the overall integrity and quality of the prepared
1457 product. There should be a documented process between the preparation
1458 cycles of different nonsterile products, to decrease the likelihood of
1459 contamination from other prepared products.

1460 STERILE PREPARATIONS

1461 For sterile preparations, follow manufacturer preparation instructions,
1462 taking into account appropriate radiation safety considerations. Utilize
1463 appropriate environmental controls and aseptic handling practices to
1464 maintain sterility. The minimum environmental standard for the preparation
1465 of sterile radiopharmaceuticals beyond immediate-use is within an ISO Class
1466 5 PEC. Refer to *4. Facilities and Environmental Controls* and [Table 7](#) on the
1467 location of the PEC and the applicability toward the radiopharmaceutical
1468 BUD.

1469 9.2 Preparation with Minor Deviations

1470 In some cases, radiopharmaceuticals are prepared with minor deviations
1471 that are necessary to accommodate circumstances not contemplated in the
1472 FDA-approved labeling. Note that [General Notices, 5.20.20.1 In](#)
1473 [Compounded Preparations](#) includes the statement: "Deviation from the
1474 specified processes or methods of compounding, although not from the
1475 ingredients or proportions thereof, may occur provided that the finished
1476 preparation conforms to the relevant standards and to preparations
1477 produced by following the specified process." Except for a few receptor-
1478 based radiopharmaceuticals where specific activity is an important
1479 parameter, there is a very broad range of acceptable values for specific
1480 activity and for proportions of ingredients. Hence, deviations from
1481 manufacturer preparation instructions for radiopharmaceuticals must
1482 maintain the same ingredients but may differ in their proportions.

1483 This requires appropriate in-house quality control testing, designed to
1484 validate the quality and purity of the product for the entirety of the BUD or is
1485 supported by appropriate peer-reviewed publications for the minor deviation
1486 utilized.

1487 Examples of minor deviations include, but are not limited to, the following:

- 1488 • Altering the amount of radioactivity or volume added to the vial
- 1489 • Changes in step-by-step operations (e.g., dilute Tc-99m sodium
1490 pertechnetate after rather than before addition to the vial)
- 1491 • Using alternative devices or equipment (e.g., a heating block rather
1492 than a hot water bath, using a different sized needle, different
1493 shielding materials)
- 1494 • Using test methods other than those described in the product labelling
1495 (e.g., radiochemical purity)
- 1496 • Filtering Tc-99m sulfur colloid

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9.3 Preparation of Radiolabeled Blood Components

1498 Handling and radiolabeling of blood components requires special attention
1499 to biological risks and must be handled with universal precautions using
1500 aseptic technique, to avoid introducing new microorganisms into the
1501 preparation that will be administered. Because of microorganisms potentially
1502 present in the original blood sample, the preparation must be administered
1503 as soon as possible but no later than 6 hours after the labeling process is
1504 complete.

1505 The potential presence of microorganisms in a non-immediate use blood
1506 sample may present a risk to the individual performing the preparation as
1507 well as cross-contamination to other blood samples or other non-blood
1508 related radiopharmaceutical products. Hence, equipment and supplies should
1509 never be shared with other activities unless they can first be thoroughly
1510 cleaned and disinfected. Special precautions when labeling of blood
1511 components for non-immediate use include:

- 1512 • Use of an ISO Class 5 BSC located in an ISO Class 7 buffer room
1513 dedicated for blood-labeling processes. There must be complete
1514 physical separation of areas where blood products are being handled
1515 from areas where non-blood products are being handled. If more
1516 than one ISO Class 5 PEC is located within the ISO Class 7 buffer
1517 room, policies and procedures must be in place to include certification
1518 that the SEC meets conditions of air quality at maximum occupancy
1519 under dynamic operating conditions.
- 1520 • Personnel should work in one PEC and with only one labeling
1521 procedure per PEC at a time. Blood products from more than one
1522 patient must never be manipulated at the same workstation at the
1523 same time. Each area should have dedicated supplies, equipment
1524 (including dose calibrator), and waste disposal to eliminate sharing of
1525 these items or overlap in pathways.
- 1526 • Thorough cleaning and disinfection of the ISO Class 5 BSC and all
1527 reusable equipment within prior to starting another blood component
1528 radiolabeling procedure.
- 1529 • If a dedicated dose calibrator is not available, then a means of
1530 preventing the blood container from contaminating the dose
1531 calibrator or a cleaning and disinfection procedure with an
1532 appropriate product must be used to decontaminate the dipper and
1533 liner of the dose calibrator following the radioassay.
- 1534 • Centrifuge should be located within the ISO Class 7 buffer room that is
1535 dedicated for blood labeling processes.
- 1536 • Dedicated (per each labeling process) consumable products (e.g.,
1537 0.9% sodium chloride injection, diluent, tubes, syringes, and other
1538 supplies) necessary to radiolabel each individual patient sample.

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- Blood products must be completely separated from one another to prevent cross-contamination. All tubes and syringes in contact with the patient's blood components must be clearly labeled with the patient's name and at least one additional identifier (e.g., date of birth, medical record number, barcode).
 - Dedicated syringe shields and vial shields.
 - Remove and replace any garb that enters the ISO Class 5 environment before handling anything else not related to performing this procedure.
 - Removal of all disposable items from the ISO Class 5 BSC utilized in each radiolabeling process.
 - Cleaning and disinfection of all reusable equipment and components (e.g., BSC, centrifuge, dose calibrator, syringe shields, vial shields, pigs, ammo cases) after each procedure prior to any further use. Policies and procedures must address cleaning and disinfection processes including the use of an EPA-registered one-step disinfectant with activity against bloodborne pathogens followed by sterile 70% IPA. Sterile 70% IPA alone is not sufficient.
 - After the completion of blood labeling procedures, hand hygiene must be performed.

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9.4 Immediate Use of Red Blood Cell Labeling

1560 In vitro red blood cell labeling must be prepared while following the
1561 conditions below.

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- A dedicated space for blood handling must be designated. This area must be free from clutter and not used for any other radiopharmaceutical preparation or handling
 - Only one labeling procedure at a time or have documented processes that maintain the integrity of samples and environment
 - Dedicated equipment must be used for blood handling (e.g., l-block, syringe shield, vial shield, forceps, needle recapper)
 - If a dedicated dose calibrator is not available, then a means of preventing the blood container from contaminating the dose calibrator or a cleaning and disinfecting procedure with an appropriate product must be used to decontaminate the dipper and liner of the dose calibrator following the radioassay
 - Hand hygiene must be performed (see 4. Facilities and Engineering Controls) before and after procedure
 - The area must be disinfected with sterile 70% IPA prior to beginning the radiolabeling procedure
 - Follow all requirements under 3.4 Hand Hygiene and Garbing for Immediate Use Preparations

- 1580 • A cleaning and disinfecting procedure with an appropriate product
1581 must be used to decontaminate the area and equipment after the
1582 radiolabeling is complete and all disposable components have been
1583 discarded
- 1584 • The start time of the preparation must begin with the initial container
1585 puncture

1586 **10. COMPOUNDING**

1587 Each compounding activity must be based on a pre-established written
1588 procedure and include maintenance of compounding records. The
1589 compounding record must provide traceability (see 8. *Documentation*).

1590 For all sterile compounding processes described in this section, aseptic
1591 handling in an appropriate environment must be performed when
1592 compounding a sterile radiopharmaceutical within an ISO Class 5 PEC. Refer
1593 to 4.7 *Environmental Controls* and [Table 7](#) for further clarification on the
1594 location of the PEC and the applicability of the radiopharmaceutical BUD.

1595 **10.1 Compounding Nonsterile Radiopharmaceuticals**

1596 Compounding nonsterile radiopharmaceuticals is the combining, mixing,
1597 diluting, pooling, reconstituting or otherwise altering a drug or bulk drug
1598 substance other than as provided in the manufacturer's package insert to
1599 create a nonsterile radiopharmaceutical. Examples of compounding
1600 nonsterile radiopharmaceuticals include: changing the dosage form of a
1601 capsule to a solution, changing an intravenous dosage form to an oral
1602 dosage form, and radiolabeling a food for oral administration (e.g., eggs).
1603 Areas intended for nonsterile compounding must be separated from areas
1604 intended for sterile radiopharmaceuticals. Compounding should take into
1605 account RAM licensing requirements for appropriate radiation safety
1606 considerations and utilize appropriate environmental controls, if applicable
1607 (e.g., chemical fume hood, activated charcoal filters when handling
1608 potentially volatile radionuclides). The area utilized for compounding
1609 nonsterile radiopharmaceuticals must be maintained in a clean and
1610 uncluttered condition. The placement of equipment and materials must take
1611 into account a design that prevents cross-contamination from
1612 noncompounding areas.

1613 When feasible, disposable material should be used to reduce the chance of
1614 cross-contamination. Each compound must have a unique MFR (see 8.1
1615 *Master Formulation Record*). The preparation information is documented on
1616 a compounding record. The MFR details the selection of all components. The
1617 ingredients must be obtained from sources in this preferential order: FDA-
1618 approved product; FDA-registered facility; and lastly, if the ingredients for
1619 the compound are not available from either of these two sources, the MFR
1620 must detail the selection of a material that is suitable for the intended use.

1621 The MFR must establish the identity, strength, purity, and quality of the
1622 ingredients by validated means (e.g., CoA).

1623 A BUD for the compound must be validated, taking into account the
1624 stability of the ingredients, any intermediate containers, the final container,
1625 and the storage conditions. A BUD cannot be extended past the labeled
1626 expiration date of any component in the compound. If the compounded
1627 radiopharmaceutical includes components from other preparations or
1628 preparations with minor deviations, the BUD of the final compounded
1629 radiopharmaceutical must not exceed the shortest remaining BUD of any of
1630 those components.

1631 **10.2 Compounding Using Conventionally Marketed Drug Products**

1632 Some compounding activities involve only the addition of a commercially
1633 marketed drug product to a radiopharmaceutical (e.g., [Ascorbic Acid](#)
1634 [Injection](#), [Lidocaine Hydrochloride Injection](#), [Sodium Bicarbonate Injection](#)).

1635 Personnel responsible for compounding must consider all possible
1636 interactions between the components, such as altered chemical stability,
1637 radiochemical stability, solubility, or other parameters (e.g., osmolality)
1638 related to changes in pH, excipients, or other factors, in determining an
1639 appropriate BUD. In some cases, this may require systematic quality control
1640 testing over time to validate the appropriateness of a particular BUD.

1641 Another activity considered a compounding activity is splitting of
1642 commercially marketed kits. Kit-splitting (also referred to as "fractionation")
1643 should be restricted to times of shortage to stretch existing inventory to
1644 meet patient need. For example, the contents of a kit vial can be constituted
1645 with 0.9% sodium chloride injection and aliquoted into other containers for
1646 storage and subsequent radiolabeling. The individual responsible must
1647 consider all possible interactions of kit components with these other
1648 containers (e.g., container walls, closures), as well as possible alterations in
1649 stability (e.g., physical stability, chemical stability) that may affect
1650 radiolabeling yields or performance parameters, when determining an
1651 appropriate BUD. In some cases, systematic quality control testing is
1652 required to validate the appropriateness of a particular BUD.

1653 **10.3 Sterile Compounding Using a Nonsterile Drug Substance or** 1654 **Components**

1655 Some sterile compounding activities involve the use of materials other than
1656 commercially marketed products, such as drug substances and/or
1657 radionuclides. If one or more materials or components are not certified to be
1658 sterile and pyrogen-free, a sterilization procedure (e.g., filtration with bubble
1659 point testing) and testing described in [\(85\)](#) must be performed prior to
1660 dispensing. The individual responsible for compounding is responsible for
1661 ensuring that the final preparation complies with pre-established standards
1662 or acceptability criteria for identity, quality, and purity. The individual

1663 responsible for compounding must consider all possible interactions between
1664 the components, such as altered chemical stability, radiochemical stability,
1665 solubility, or other parameters (e.g., osmolality) related to changes in pH,
1666 excipients, or other factors, in determining an appropriate BUD. In some
1667 cases, this may require systematic quality control testing over time to
1668 validate the appropriateness of a particular BUD.

1669 If compounding involves a bulk drug substance, the radiopharmaceutical
1670 must comply with standards of an applicable *USP* or *NF* monograph, or be a
1671 component of an approved drug product. For this chapter, a bulk drug
1672 substance includes a radioisotope, a ligand, or other substance, such as a
1673 precursor that becomes an active ingredient in the final radiopharmaceutical.
1674 Each bulk drug substance should be manufactured by drug establishments
1675 registered with FDA and be accompanied by a valid CoA or equivalent testing
1676 procedures.

1677 If compounding involves excipients or other inactive ingredients, the
1678 excipients or other inactive ingredients must comply with standards of an
1679 applicable *USP* or *NF* monograph, if one exists. It is also acceptable that any
1680 excipients or other inactive ingredients be approved products, manufactured
1681 by a drug establishment registered with the FDA.

1682 Compounding must not be performed for any radiopharmaceutical that has
1683 been withdrawn from the market because of safety or lack of effectiveness,
1684 unless part of an institutional review board approved investigational study.

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11. DISPENSING

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11.1 Dispensing and Radioassay

1688 Dispensing refers to the manipulations necessary to transfer the prescribed
1689 or ordered amount of radiopharmaceutical into the final container (e.g.,
1690 syringe or vial). Dispensing can take place from single-use or multi-dose
1691 containers of prepared, prepared with minor deviations, compounded, or
1692 manufactured radiopharmaceuticals, and may involve needle changes,
1693 affixing a sterile cap, or dilution (e.g., 0.9% sodium chloride injection) in the
1694 final container. For nonsterile radiopharmaceuticals, an example is obtaining
1695 1 capsule from a container holding 1 or more capsules. For sterile
1696 radiopharmaceuticals, an example is withdrawing a volume of solution from
1697 a single-use or multi-dose vial into a syringe. Labeling of the final patient-
1698 specific dose or ordered amount of a radiopharmaceutical is also a
1699 component of the dispensing process.

1700 Except for an unopened manufacturer container, the final patient dose or
1701 ordered amount must be radioassayed (i.e., in a dose calibrator). The
1702 measured activity should be mathematically corrected for radioactive decay
1703 to the time of scheduled administration (calibration time) (refer to 13.
1704 *Quality Assurance and Quality Control*). However, the activity at calibration
1705 time must always be within federal, state, and local variance limits.

11.2 Labeling

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1707 The labeling of radiopharmaceuticals can fall under the jurisdiction of
1708 numerous regulatory agencies. Individual boards of pharmacy and other
1709 regulatory bodies may have very specific statutes and/or regulations
1710 concerning this process. The requirements specified in this chapter must be
1711 considered the minimum requirements for the labeling of the final inner
1712 container (e.g., syringe, vial) and the outer shielding (e.g., syringe or vial
1713 shielding). Therefore, all personnel distributing and/or dispensing
1714 radiopharmaceuticals should verify that any labeling is in compliance with
1715 the expectations of their respective regulatory oversight agency.

1716 Due to the additional vigilance that should be applied toward therapeutic
1717 and blood-product radiopharmaceuticals, the patient name or, in the case of
1718 a research subject, a unique identifier should be present on all inner
1719 radiopharmaceutical containers and outer shielding.

1720 As part of dispensing, the inner container must be labeled with the
1721 following:

- 1722 • Standard radiation symbol
- 1723 • The words "Caution—Radioactive Material"
- 1724 • For all therapeutic and blood-products, the patient name/identifier
- 1725 • Radionuclide and chemical form (generic name)
- 1726 • Radioactivity with units at time of calibration and the calibration time

1727 As part of dispensing, the outer shielding must be labeled with the
1728 following:

- 1729 • Standard radiation symbol
- 1730 • The words "Caution—Radioactive Material"
- 1731 • For all therapeutic and blood-products, the patient name/identifier
- 1732 • Calibration date and time for the dose
- 1733 • Activity dispensed with units at calibration date and time
- 1734 • Radionuclide and chemical form (generic name)
- 1735 • Volume dispensed (as applicable)
- 1736 • Number of dosage units dispensed (e.g., 2 capsules, as applicable)
- 1737 • BUD (see [Table 7](#)) and special storage and handling instructions for
1738 non-immediate use (e.g., refrigeration, resuspension)

11.3 Direct Infusion Systems

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1740 The information in this chapter is strictly limited to the sterility and aseptic
1741 practices to use for direct infusion systems. The described infusion systems
1742 are approved medical devices by the FDA. The manner in which all necessary
1743 solutions (e.g., radiopharmaceutical and diluent) are used in conjunction
1744 with the system was a consideration in the overall approval process for the

1745 system. Therefore, all operators for the described or future approved direct
1746 infusion systems must follow the "Instructions for Use" in the device
1747 labeling.

- 1748 • Direct infusion generators (e.g., rubidium 82 Cl) may employ a
1749 container of eluant (e.g., bag of 0.9% sodium chloride injection) to
1750 allow administration of the eluate directly to patient(s).
- 1751 • Direct infusion devices (e.g., portable PET patient-infusion system)
1752 provide a method for dispensing and administration from a multi-
1753 dose container of the radiopharmaceutical (e.g., fludeoxyglucose F18
1754 injection) and the diluent (e.g., 0.9% sodium chloride injection)
1755 directly in patients to reduce the radiation exposure to personnel.
- 1756 • In each of these situations, the radiopharmaceutical container must be
1757 attached to or be needle-punctured by the respective direct infusion
1758 system. Given that such direct infusion systems are intended for
1759 multiple patients over the course of several hours, there could be a
1760 sterility concern if not operated properly. Therefore, the following
1761 parameters must be considered by the operator of the system.
 - 1762 • Setup attachment or needle-puncture should be performed in
1763 a defined environment
 - 1764 • Aseptic handling in ambient air with a maximum BUD of 10 h
1765 is allowed for these direct infusion systems (see [Table 7](#))
 - 1766 • The saline bag attached to the device may only be punctured
1767 once and may be used for NMT 10 h. The bag must be labeled
1768 with the date and time of puncture and the BUD
 - 1769 • Any parts of the device that may encounter the septum of the
1770 radiopharmaceutical vial must be disinfected with sterile 70%
1771 IPA prior to puncturing the vial with the needle
 - 1772 • The septum of any vial and the ports of any diluent bag must
1773 be disinfected with a sterile 70% IPA wipe prior to puncturing
 - 1774 • When puncturing the vial in ambient air, it must only be
1775 punctured once
 - 1776 • If there are problems with the infusion device, no sterile
1777 container associated with the system can be repunctured or
1778 transferred to a PEC for further manipulations and the
1779 container, with contents, must be discarded

1780 **11.4 Transporting Generators Between Facilities**

1781 The following guidelines must be followed when transporting generators
1782 between facilities:

- 1783 • The generator needle and/or ports must be capped in ISO Class 8 air
1784 or better with sterile protectors

- 1785 • The generator must be packaged and transported in a manner to
1786 maintain the sterility of the generator system and prevent damage

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12. REPACKAGING

1789 Repackaging refers to the act of removing an FDA-approved
1790 radiopharmaceutical from the container in which it was distributed by the
1791 original manufacturer and placing it into a different container without further
1792 manipulation of the product. Repackaging also includes the act of placing the
1793 contents of multiple containers of the same finished drug product into one
1794 container, as long as the container does not include other ingredients.
1795 Repackaging may be performed for nonsterile radiopharmaceuticals (e.g., I-
1796 131 sodium iodide oral capsules) and for nonsterile radiopharmaceuticals
1797 (e.g., thallous chloride Tl 201 injection).

1798 Except for unopened manufacturer dosage units (e.g., capsules, Xe-133
1799 vials), the repackaged radiopharmaceutical must be radioassayed (i.e., in a
1800 dose calibrator). The inner container should be labeled with the following:

- 1801 • Standard radiation symbol
1802 • The words "Caution—Radioactive Material"
1803 • The radionuclide and chemical form (generic name)
1804 • Radioactivity with units at time of calibration and the calibration time

1805 The outer shielding should be labeled with the following:

- 1806 • Standard radiation symbol
1807 • The words "Caution—Radioactive Material"
1808 • The radionuclide and chemical form (generic name)
1809 • Radioactivity with units at time of calibration and the calibration time
1810 • Volume, or number of units (e.g., capsules), as applicable
1811 • Product expiration or BUD (see [Table 7](#)), as applicable
1812 • Special storage and handling instructions

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13. QUALITY ASSURANCE AND QUALITY CONTROL

1815 Quality assurance (QA) is a system of procedures, activities, and oversight
1816 that ensures that radiopharmaceutical processing consistently meets quality
1817 standards. Quality control (QC) is the sampling, testing, and documentation
1818 of results that, taken together, ensure that specifications have been met
1819 before release of the radiopharmaceutical. See [Quality Assurance in
1820 Pharmaceutical Compounding \(1163\)](#).

1821 A facility's QA and QC programs must be formally established and
1822 documented in SOPs that ensure that all aspects of the preparation of
1823 radiopharmaceuticals are conducted in accordance with this chapter and

1824 applicable federal, state, and local laws and regulations. A designated person
1825 must ensure that the facility has formal, written QA and QC programs that
1826 establish a system of:

- 1827 1. Adherence to procedures,
- 1828 2. Prevention and detection of errors and other quality problems,
- 1829 3. Evaluation of complaints and adverse events, and
- 1830 4. Appropriate investigations and corrective actions.

1831 The SOPs must describe the roles, duties, and training of the personnel
1832 responsible for each aspect of the QA program. The overall QA and QC
1833 program must be reviewed at least once every 12 months by the designated
1834 person. The results of the review must be documented and appropriate
1835 corrective action must be taken, if needed.

1836 **13.1 Notification About and Recall of Out-of-Specification Dispensed** 1837 **Radiopharmaceuticals**

1838 If a radiopharmaceutical is dispensed or administered before the results of
1839 release testing are known, the facility must have procedures in place to:

- 1840 1. Immediately notify the prescriber of a failure of specifications with
1841 the potential to cause patient harm (e.g., sterility, strength, purity,
1842 bacterial endotoxin, or other quality attributes), and
- 1843 2. Determine whether a recall is necessary.

1844 The SOP for recall of out-of-specification dispensed radiopharmaceuticals
1845 must contain procedures to:

- 1846 • Determine the severity of the problem and the urgency for the
1847 implementation and completion of the recall
- 1848 • Determine the distribution of any affected radiopharmaceutical,
1849 including the date and quantity of distribution
- 1850 • Identify patients who have received the radiopharmaceutical
- 1851 • Outline the disposition and reconciliation of the recalled
1852 radiopharmaceutical

1853 The sterile process facility must document the implementation of the recall
1854 procedures. The recall must be reported to appropriate regulatory bodies as
1855 required by applicable jurisdictional laws and regulations (e.g., state board
1856 of pharmacy, state health department).

1857 **13.2 Complaint Handling**

1858 Radiopharmaceutical facilities must develop and implement SOPs for
1859 handling complaints. Complaints may include concerns or reports on the

1860 quality and labeling of, or possible adverse reactions to, a specific
1861 radiopharmaceutical.

1862 A designated person must review all complaints to determine whether the
1863 complaint indicates a potential quality problem with the radiopharmaceutical.
1864 If it does, a thorough investigation into the cause of the problem must be
1865 initiated and completed. The investigation must consider whether the quality
1866 problem extends to other radiopharmaceuticals. Corrective action, if
1867 necessary, must be implemented for all potentially affected
1868 radiopharmaceuticals. Consider whether to initiate a recall of potentially
1869 affected radiopharmaceuticals and whether to cease sterile compounding
1870 until all underlying problems have been identified and corrected.

1871 A readily retrievable written or electronic record of each complaint must be
1872 kept by the facility, regardless of the source of the complaint (e.g., e-mail,
1873 telephone, mail). The record must contain the name of the complainant, the
1874 date the complaint was received, the nature of the complaint, and the
1875 response to the complaint. In addition, to the extent that the information is
1876 known, the following should be recorded: the name and strength of the
1877 radiopharmaceutical and the assigned internal identification number (e.g.,
1878 prescription, order, or lot number).

1879 The record must also include the findings of any investigation and any
1880 follow-up. Records of complaints must be easily retrievable for review and
1881 evaluation for possible trends and must be retained in accordance with the
1882 record keeping requirements in 8. *Documentation*. A radiopharmaceutical
1883 that is returned in connection with a complaint must be quarantined until it
1884 is destroyed after completion of the investigation and in accordance with
1885 applicable jurisdictional laws and regulations.

1886 **13.3 Adverse Event Reporting**

1887 Adverse events potentially associated with the quality of
1888 radiopharmaceuticals must be reported in accordance with the facility's SOPs
1889 and all applicable jurisdictional laws and regulations. In addition, adverse
1890 events potentially associated with the quality of the radiopharmaceutical
1891 preparation should be reported to the applicable jurisdictional regulatory
1892 body (e.g., state boards of pharmacy, state health departments, FDA's
1893 MedWatch program for human drugs, or FDA Form 1932a for animal drugs).

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GLOSSARY

1896 **Administration:** The direct and immediate application of a
1897 radiopharmaceutical to a patient by injecting, infusing, or otherwise
1898 providing a radiopharmaceutical in its final form.

1899 **Airlock:** A space with interlocked doors, constructed to maintain air
1900 pressure control when items move between two adjoining areas (generally
1901 with different air cleanliness standards). The intent of an airlock is to

1902 prevent ingress of particulate matter and microbial contamination from a
1903 lesser-controlled area.

1904 **Ante-room:** An ISO Class 8 or cleaner room with fixed walls and doors
1905 where personnel hand hygiene and garbing procedures and other activities
1906 that generate high particulate levels are performed. The ante-room is the
1907 transition room between the unclassified room of the facility and the buffer
1908 room.

1909 **Aseptic processing or preparation:** A process by which separate, sterile
1910 components (e.g., drugs, containers, or closures) are brought together
1911 under conditions that maintain their sterility. The components can either be
1912 purchased as sterile or, when starting with nonsterile components, can be
1913 separately sterilized prior to combining (e.g., by membrane filtration,
1914 autoclave).

1915 **Aseptic technique:** A type of technique used to keep objects and areas
1916 free of microorganisms and thereby minimize infection risk to the patient. It
1917 is accomplished through practices that maintain the microbe count at an
1918 irreducible minimum.

1919 **As low as (is) reasonably achievable (ALARA):** The effort to maintain
1920 exposures to ionizing radiation as far below the dose limits as practical,
1921 consistent with the purpose for which the licensed activity is undertaken, in
1922 relation to utilization of licensed materials in the public interest. Limiting
1923 exposure time, using adequate shielding, and maintaining the most distance
1924 possible from all radioactive sources (i.e., distance & shielding) are the basic
1925 principles for successfully following ALARA guidelines.

1926 **Beyond-use date (BUD):** For compounded, prepared, repackaged, or
1927 dispensed radiopharmaceuticals, the date and time beyond which it cannot
1928 be administered. Determination of the BUD is based on the stability of
1929 quality attributes, such as sterility, radiochemical purity, radionuclidic purity,
1930 and other applicable parameters.

1931 **Blood components:** Any constituent of blood that is separated by
1932 physical or mechanical means (e.g., white cells, platelets) and used to be
1933 radiolabeled.

1934 **Buffer room:** An ISO Class 8 or cleaner room with fixed walls and doors
1935 where PEC(s) that generate and maintain an ISO Class 5 environment are
1936 physically located. The buffer room may only be accessed through the ante-
1937 room.

1938 **Chemical purity:** The fraction of the total chemical species present in the
1939 radiopharmaceutical as the specified chemical component(s). Hence, a
1940 chemical impurity is the presence of an unwanted nonradioactive chemical.

1941 **Class II biological safety cabinet (BSC):** A cabinet with an open front
1942 and inward and downward unidirectional HEPA-filtered airflow and HEPA-
1943 filtered exhaust. A BSC used to prepare radiopharmaceuticals must be
1944 capable of providing an ISO Class 5 environment.

1945 **Classified room:** An area that maintains an air quality classification based
1946 on the ISO guidelines (i.e., ante-room, buffer room).

1947 **Cleaning agent:** An agent for the removal of residues (e.g., dirt, debris,
1948 microbes, and residual drugs or chemicals) from surfaces.

1949 **Compounding:** The making of an unapproved radiopharmaceutical,
1950 pursuant to a valid prescription, for administration to a patient in situations
1951 where an FDA-approved, commercially manufactured drug product is not
1952 available or appropriate. Examples of compounding include, but are not
1953 limited to, mixing of two or more FDA-approved drug products (except
1954 diluents), not consistent with preparation (see 9. Preparation); alteration of
1955 the FDA-approved dosage form (e.g., making a solution or suspension from
1956 a solid oral dosage form); "extemporaneous" preparation using an FDA-
1957 approved drug substance and/or raw materials.

1958 **Critical site:** A location that includes any component or fluid pathway
1959 surfaces (e.g., vial septa, injection ports) or openings (e.g., needle hubs)
1960 that are exposed and at risk of direct contact with air (e.g., ambient room or
1961 HEPA-filtered), moisture (e.g., oral and mucosal secretions), or touch
1962 contamination.

1963 **Designated person:** One or more individuals assigned to be responsible
1964 and accountable for the performance and operation of the
1965 radiopharmaceutical processing facility and personnel who prepare,
1966 compound, dispense, and repackage radiopharmaceuticals.

1967 **Disinfectant:** A chemical or physical agent used on inanimate surfaces
1968 and objects to destroy fungi, viruses, and bacteria. Sporocidal disinfectant
1969 agents are considered a special class of disinfectants that also are effective
1970 against bacterial endospores.

1971 **Dispensing:** The making and labeling of a patient-specific dose obtained
1972 from a single-use or multi-dose container (e.g., withdrawing a volume of
1973 finished product or preparation from a vial into a syringe). As part of
1974 dispensing, the patient-specific dose may be diluted, as appropriate, to a
1975 larger volume with an appropriate diluent. A sub-set of dispensing is
1976 "repackaging" which is the act of removing an FDA-approved
1977 radiopharmaceutical from the container in which it was distributed by the
1978 manufacturer and placing it into a different container without further
1979 manipulation of the product. It is the responsibility of the individual

1980 responsible for the dispensing to ensure appropriate identity, strength, and
1981 purity throughout the assigned BUD.

1982 **Dynamic operating condition:** Conditions in the SRPA or classified room
1983 in which operating personnel are present and performing actual or simulated
1984 activities. The PEC should contain equipment and materials regularly used
1985 for radiopharmaceutical processing (e.g., low-lint absorbent pads, dose
1986 calibrator, syringe shields).

1987 **Expiration date:** For manufactured drug products (including, but not
1988 limited to, finished radiopharmaceuticals, generators, and kits), the specified
1989 date (and time) beyond which the product cannot be administered. The
1990 expiration date is determined by the manufacturer and cannot be extended
1991 by individual practitioners. A BUD must be assigned to compounded and
1992 prepared radiopharmaceuticals, taking into account conditions outlined in 6.
1993 *Assigning BUD* and [Table 7](#) and established in accordance with a facility's
1994 SOPs.

1995 **First air:** The air exiting the HEPA filter in a unidirectional air stream.

1996 **Garb:** Items such as gloves, gowns, shoe covers, head and facial hair
1997 covers, masks, and other items designed to reduce particle shedding from
1998 personnel and minimize the risk of bacterial contamination to
1999 radiopharmaceuticals.

2000 **High efficiency particulate air (HEPA) filtration:** Being, using, or
2001 containing a filter designed to remove 99.97% of airborne particles
2002 measuring 0.3-micron or greater in diameter passing through it.

2003 **Hot-cell:** A device used for the shielding and the containment of
2004 radioactive materials. The shielding material(s) (e.g., lead) is generally
2005 incorporated into the structure of the unit itself. Radiopharmaceutical
2006 personnel carry out the majority of the tasks within the hot-cell from the
2007 exterior of the unit. This is accomplished by the use of remote manipulation
2008 systems (e.g., manipulator arms) of various designs. Numerous air quality
2009 configurations of the hot-cell may exist, including integrated HEPA filtration
2010 systems to render all or a specified portion (direct compounding area) of the
2011 device capable of certifying to a controlled ISO Class 5 environment. In
2012 other situations, the hot-cell offers only radiation protection and a laminar
2013 flow hood, capable of achieving an ISO Class 5 environment, is placed within
2014 the enclosure to allow for safe aseptic manipulations. A hot-cell may also be
2015 referred to by other designations (e.g., shielded isolator with laminar flow,
2016 PET dispensing station, manipulator hot-cell, shielded isolators for
2017 dispensing, radiopharmaceutical dispensing isolator, etc.). However, the
2018 overall functionality and purpose of these devices remains the same.

2019 **Hot lab:** Nonclassified radiopharmaceutical processing area without a PEC
2020 located within a hospital or clinical site that is only appropriate for immediate
2021 use radiopharmaceuticals.

2022 **Immediate use:** A preparation of a sterile radiopharmaceutical for a
2023 single patient using only sterile FDA-approved starting ingredients when
2024 administration will begin within 1 hour of beginning the preparation (e.g.,
2025 within 1 hour of initial entry or puncture of any container) and is only
2026 required to follow the immediate use standards in this chapter (see 3.4 *Hand*
2027 *Hygiene and Garbing for Immediate Use Preparations* and 9.4 *Immediate*
2028 *Use of Red Blood Cell Labeling*).

2029 **Inverse square law:** The specified physical quantity or intensity of a
2030 radiation emission is inversely proportional to the square of the distance
2031 from the source of the emission.

2032 **ISO class:** An air quality classification from the International Organization
2033 for Standardization.

2034 **Kit:** Commercially manufactured package containing all ingredients
2035 required to prepare a radiopharmaceutical with the exception of the
2036 radionuclide.

2037 **Kit-splitting (fractionation):** The act of dividing the contents of a kit vial
2038 and transferring aliquots into other containers for storage and subsequent
2039 radiolabeling.

2040 **Ligand:** An ion or molecule that binds to a metal atom to form a
2041 coordination complex.

2042 **Line of demarcation:** A visible line on the floor that separates the clean
2043 and dirty sides of the ante-room.

2044 **Low-lint wiper:** A wiper exhibiting few, if any, fibers or other
2045 contamination, visible without magnification, which is separate from, or
2046 easily removed from, the wiper material in a dry condition.

2047 **Media-fill test:** A simulation used to qualify processes and personnel
2048 engaged in sterile radiopharmaceutical processing to ensure that the
2049 processes and personnel are able to prepare radiopharmaceuticals without
2050 bacterial contamination.

2051 **Multiple-dose container:** A container of a sterile radiopharmaceutical for
2052 parenteral administration (e.g., injection or infusion) that is designed to
2053 contain more than one dose of the radiopharmaceutical.

2054 **Negative-pressure room:** A room that is maintained at lower pressure
2055 than the adjacent spaces, and therefore the net airflow is into the room. This
2056 room is appropriate for volatile radiopharmaceuticals (e.g., I-131 NaI).

2057 **One-step disinfectant:** A product with an EPA-registered claim that it
2058 can clean and disinfect a nonporous surface in the presence of light to
2059 moderate organic soiling without a separate cleaning step.

2060 **Pass-through:** An enclosure with sealed doors on both sides that are
2061 interlocked. The pass-through is positioned between two spaces creating an
2062 airlock for the purpose of minimizing particulate transfer while moving
2063 materials from one space to another.

2064 **Patient-specific dose:** A radiopharmaceutical in its final form ready for
2065 administration (e.g., capsule, sterile solution in a syringe) consisting of the
2066 amount (dose) prescribed, ordered, or other intended for a specific patient.

2067 **Perimeter:** A visible line on the floor that defines the boundaries of the
2068 SRPA.

2069 **Positive-pressure room:** A room that is maintained at higher pressure
2070 than the adjacent spaces, and therefore the net airflow is out of the room.

2071 **Preparing:** The act of combining a kit with a radionuclide solution and
2072 other kit components following manufacturer instructions.

2073 **Preparing with minor deviations:** The act of combining a kit with a
2074 radionuclide solution and other kit components generally following
2075 manufacturer instructions but with minor deviations. Examples of minor
2076 deviations include, but are not limited to, altering the amount of activity or
2077 volume added to the vial, changes in step-by-step operations (e.g., dilute Tc
2078 99m solution after, rather than before, addition to the vial), using alternative
2079 devices or equipment (e.g., a heating block rather than a hot water bath),
2080 and using alternative radiochemical purity testing methods. The individual
2081 preparing the radiopharmaceutical must ensure that the final preparation
2082 maintains appropriate quality and purity, including radiochemical purity and
2083 radionuclidic purity, as specified in individual monographs, manufacturer
2084 labeling, or other applicable parameters as clinically appropriate.

2085 **Primary engineering control (PEC):** A device or zone that provides an
2086 ISO Class 5 air quality environment for sterile processing.

2087 **Pyrogen:** A substance that induces a febrile reaction in a patient.

2088 **Radioactive materials (RAM) license:** A document(s) issued by the US
2089 NRC or an Agreement State that authorizes various activities involving the
2090 use of radioactive materials. These uses can include possession, research
2091 and development, distribution, medical use, and other purposes not included
2092 in this list. Only those activities specifically authorized are allowed. The
2093 prospective licensee submits an application stating the type of license(s)
2094 desired, what radionuclides and quantities are requested, the purpose for
2095 requesting a license, training and experience for one or more AUs, for a

2096 radiation safety officer, and for general radiation personnel. The application
2097 also includes a copy of the applicant's Radiation Protection Program detailing
2098 how the applicant will ensure the safety of the employees, the public, and
2099 the environment while engaging in authorized activities. Licensees are
2100 subject to periodic inspection by the licensing agency.

2101 **Radioassay:** Measurement of the amount of radioactivity present in a
2102 container using a suitable instrument, such as a well-type ionization
2103 chamber (dose calibrator).

2104 **Radiochemical purity:** The ratio, expressed as a percentage, of the
2105 radioactivity of the intended active radiopharmaceutical ingredient to the
2106 total radioactivity of all radioactive ingredients and impurities present in the
2107 radiopharmaceutical preparation (see [Radioactivity \(821\)](#)).

2108 **Radionuclidic purity:** The ratio, expressed as a percentage, of the
2109 radioactivity of the intended radionuclide to the total radioactivity of all
2110 radionuclides in the radiopharmaceutical preparation (see [\(821\)](#)).

2111 **Radiopharmaceutical** (radiopharmaceutical preparation/radioactive
2112 drug): (See [\(821\)](#).) A finished dosage form that contains a radioactive
2113 substance in association with one or more other ingredients and that is
2114 intended to diagnose, stage a disease, monitor treatment, or provide
2115 therapy. A radiopharmaceutical includes any nonradioactive reagent kit or
2116 radionuclide generator that is intended to be used in the preparation of any
2117 such substance. The terms "radiopharmaceutical" and "radioactive drug" are
2118 commonly used interchangeably.

2119 **Repackaging:** The act of removing an FDA-approved radiopharmaceutical
2120 from the container in which it was distributed by the original manufacturer
2121 and placing it into a different container without further manipulation of the
2122 product. Repackaging also includes the act of placing the contents of
2123 multiple containers (e.g., vials) of the same finished drug product into one
2124 container, as long as the container does not include other ingredients. If a
2125 radiopharmaceutical is manipulated in any other way, including if it is
2126 reconstituted, diluted, mixed, or combined with another ingredient, that act
2127 is not considered repackaging. It is the responsibility of the individual
2128 responsible for the repackaging to ensure appropriate identity, strength, and
2129 purity throughout the assigned BUD.

2130 **Restricted area:** Any area to which access is controlled for the protection
2131 of individuals from exposures to radiation and radioactive materials.

2132 **Secondary engineering control (SEC):** The area where the PEC is
2133 placed (e.g., a classified room or an SRPA). It incorporates specific design
2134 and operational parameters required to minimize the risk of bacterial or
2135 fungal contamination.

2136 **Segregated radiopharmaceutical processing area (SRPA):** A
2137 designated, unclassified space, area, or room with a defined perimeter that
2138 contains a PEC and is suitable for radiopharmaceutical preparation (with and
2139 without minor deviations), dispensing, and repackaging only. If the SRPA is
2140 used to elute radionuclide generators it must have ISO Class 8 air quality.

2141 **Shielding:** Barriers of appropriate radiation attenuating material, used in
2142 the radiopharmaceutical practice setting, to protect the personnel. These
2143 barriers can be general in nature (e.g., L-block, hot-cell), as to afford
2144 protection from a radiation field, or specific to a container used to hold a
2145 particular radiopharmaceutical (e.g., syringe shield, vial shields, dispensing
2146 "pigs").

2147 **Single-dose containers:** A container of a sterile radiopharmaceutical for
2148 parenteral administration (e.g., injection or infusion) that is designed for use
2149 with a single patient as a single injection/infusion.

2150 **Specific activity:** The radioactivity of a radionuclide per unit mass of the
2151 element or compound (see [Radioactivity—Theory and Practice \(1821\)](#)). The
2152 unit of specific activity is radioactivity per mass expressed on a gram or
2153 mole basis [e.g., mCi/ μ g (MBq/ μ g); Ci/mmol (GBq/mmol)].

2154 **Sporicidal agent:** A chemical or physical agent that destroys bacterial
2155 and fungal spores when used in sufficient concentration for a specified
2156 contact time. It is expected to kill all vegetative microorganisms.

2157 **Start of preparation:** Time at which the needle initially penetrates the
2158 container.

2159 **Sterility:** The absence of viable microorganisms.

2160 **Strength:** The radioactivity concentration of the radiopharmaceutical at
2161 the calibration time (see [\(821\)](#)). The unit of strength is the amount of
2162 radioactivity on a volume basis (e.g., mCi/mL or MBq/mL).

2163 **Unclassified space:** A space not required to meet any air cleanliness
2164 classification based on the ISO.

2165 **Unrestricted use:** An area in which a person could not be exposed to
2166 radiation levels in excess of 2 mrem in any 1 h from external sources.

2167 **Use-by time:** For radiopharmaceuticals prepared from kits, the time
2168 period after preparation during which the radiopharmaceutical should be
2169 used or administered, as suggested or stated by the kit manufacturer.

2170

2171

APPENDICES

2172

Appendix 1: Abbreviations

ACPH	Air changes per hour
ALARA	As low as (is) reasonably achievable
ANP	Authorized nuclear pharmacist
AU	Authorized user
BSC	Biological safety cabinet
BUD	Beyond-use date
CETA	Controlled Environment Testing Association
cfu	Colony-forming unit
CoA	Certificate of analysis
DPA	Direct processing area
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HEPA	High-efficiency particulate air
HVAC	Heating, ventilation, and air conditioning
IPA	Isopropyl alcohol
ISO	International Organization for Standardization
LAFW	Laminar airflow workbench
MFR	Master Formulation Record
MAA	Macroaggregated albumin
NRC	Nuclear Regulatory Commission
PEC	Primary engineering control
PET	Positron emission tomography
RAM	Radioactive material
SEC	Secondary engineering control
SOP	Standard operating procedure
SRPA	Segregated radiopharmaceutical processing area
TSA	Trypticase soy agar

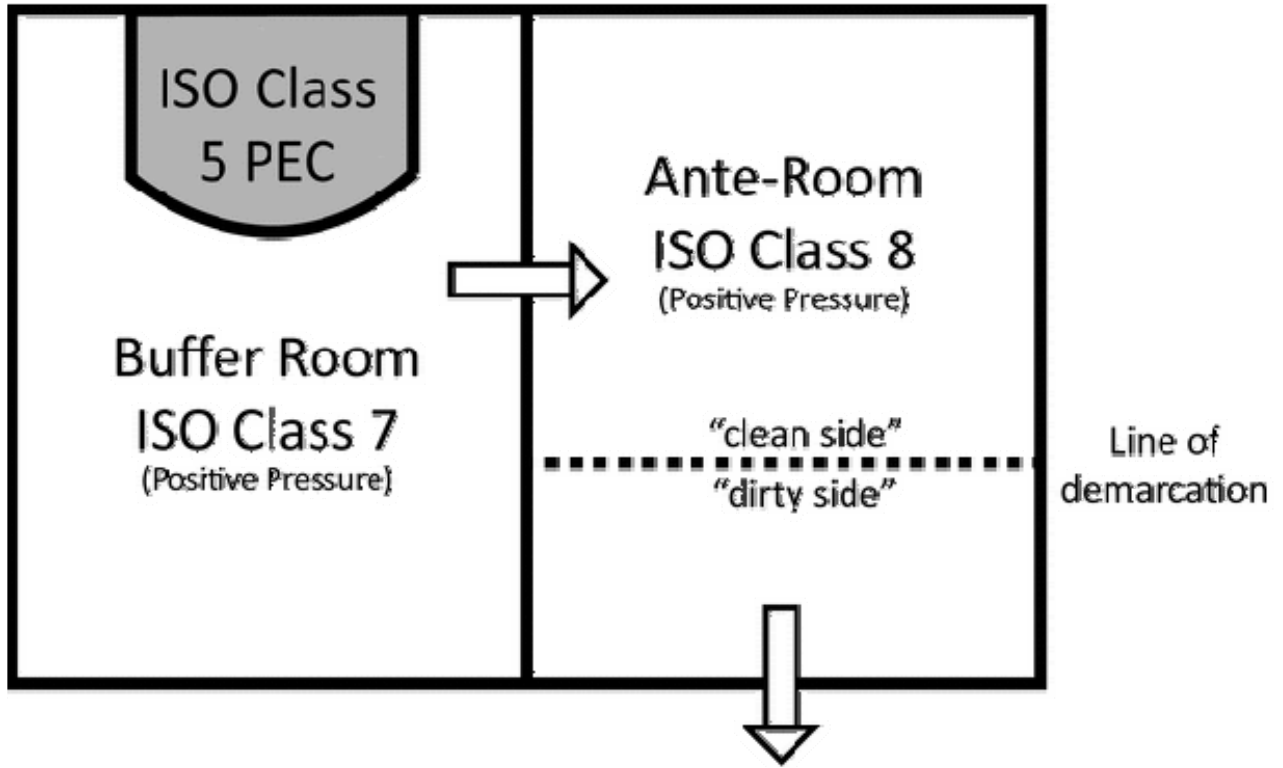
Appendix 2: Example Designs for Radiopharmaceutical Handling

**Type of
Facility Design**

Example Design

Type of Facility Design

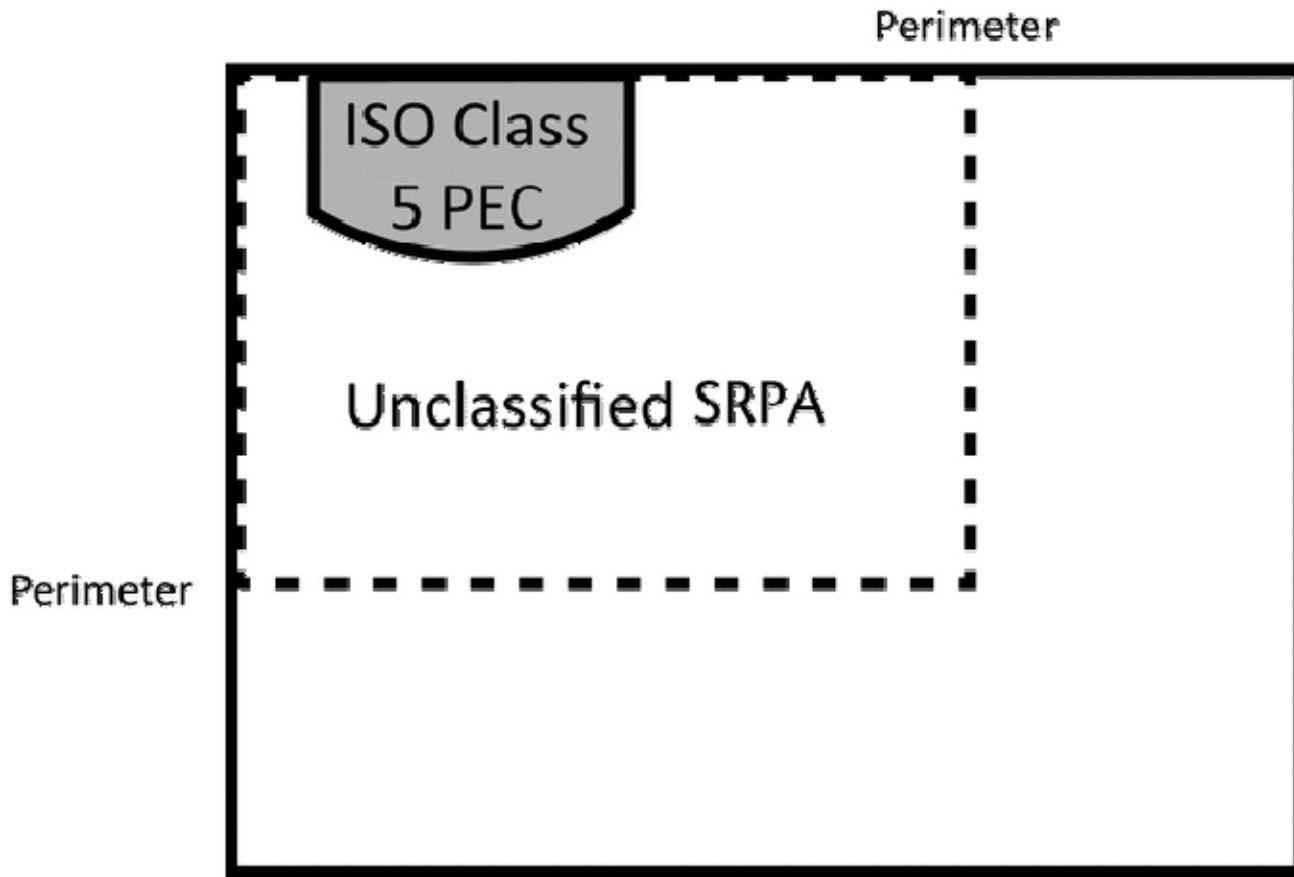
Example Design



Classified room^a

Type of Facility Design

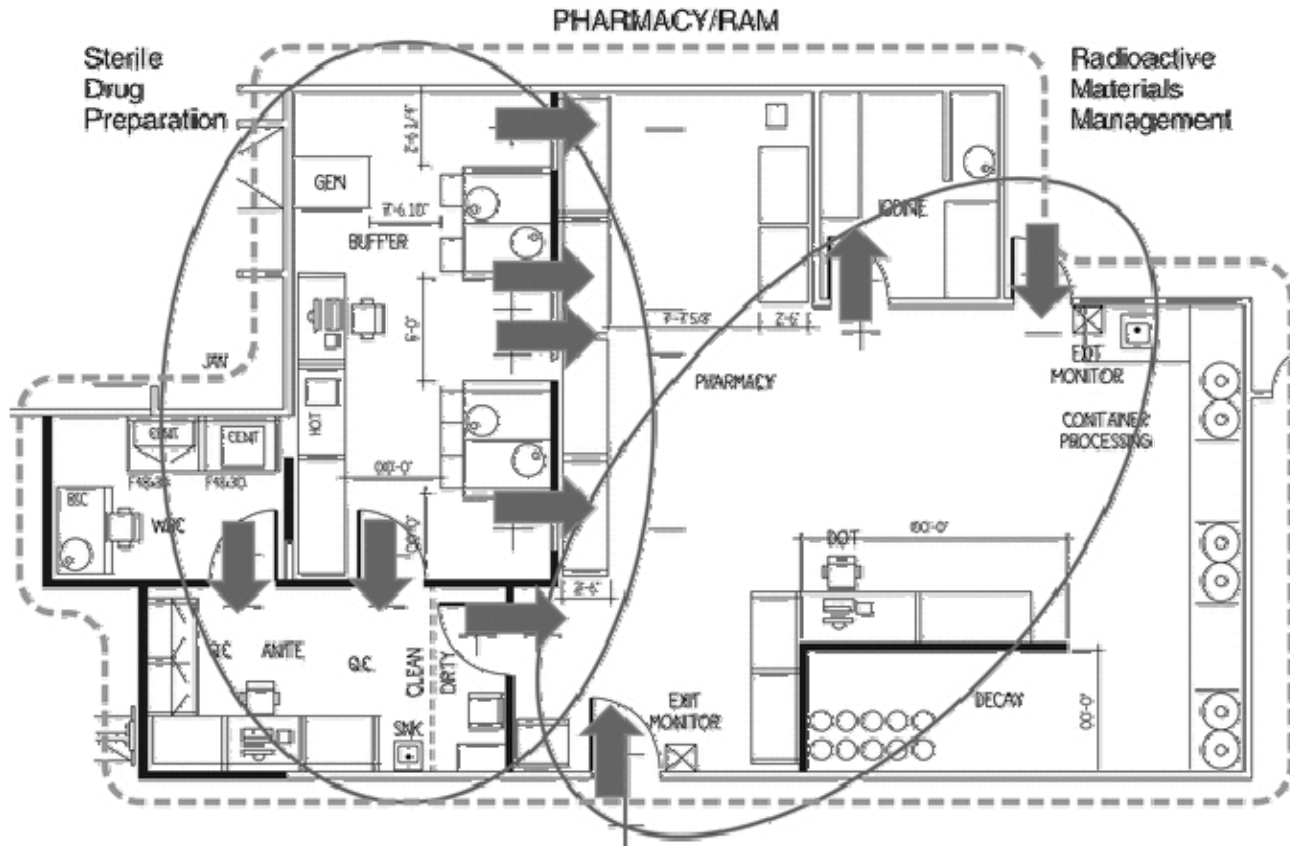
Example Design



SRPA

Type of Facility Design

Example Design



Sterile and nonsterile radiopharmaceutical processing areas^a

^a The arrows indicate the direction of airflow.

2176 ■ 2S(USP42)

2177 ¹ Centers for Disease Control and Prevention. *Guideline for Disinfection and*
2178 *Sterilization in Healthcare Facilities*, 2008.