
Guidance

PET Drug Products – Current Good Manufacturing Practice (CGMP)

02224 02 MAR 11 P3:59

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Brenda Uratani, 301-594-0098.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2002

Compliance

98D-0266

GDL1

Guidance

PET Drug Products – Current Good Manufacturing Practice (CGMP)

Additional copies are available from:

*Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573*

(Internet) <http://www.fda.gov/cder/guidance/index.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

March 2001

Compliance

Draft — Not for Implementation

B.	RECOMMENDATIONS.....	30
XIII.	COMPLAINT HANDLING	30
A.	REGULATORY REQUIREMENTS	30
B.	RECOMMENDATIONS.....	30
XIV.	RECORDS.....	31
A.	REGULATORY REQUIREMENTS	31
B.	RECOMMENDATIONS.....	31
	REFERENCES.....	32

Guidance¹

PET Drug Products – Current Good Manufacturing Practice (CGMP)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This draft guidance is intended to help PET drug producers better understand FDA's thinking concerning compliance with the preliminary draft proposed CGMP regulations if they were to become final after notice and comment rulemaking. The guidance addresses resources, procedures, and documentation for PET drug centers, large and small. In some cases, the guidance provides practical examples of methods or procedures that PET centers could use to comply with possible CGMP requirements. In developing this draft guidance, FDA has taken into consideration relevant issues, concerns, and questions raised at the public meetings held with professional associations, producers of PET drug products, and other interested parties.

Throughout this draft guidance, the term *proposed CGMP regulations (or requirements)* refers to regulations that are still being developed and will be formally proposed under the Agency's notice and comment rulemaking process. If appropriate, this draft guidance will be revised and republished for comment in parallel with the publication of the proposed regulations.

II. BACKGROUND

Section 121(c)(1)(A) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) directs the Food and Drug Administration (FDA) to establish current good manufacturing practice (CGMP) requirements for positron emission

¹ This guidance has been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

Draft — Not for Implementation

42 tomography (PET) drugs. In the future, FDA will be proposing such requirements under
43 21 CFR Part 212. In 1999, FDA published a preliminary draft of the proposed PET
44 CGMP regulations (see FDA's Web site at www.fda.gov/cder/fdama/212draft.htm and
45 notice of availability, 64 FR 51274; September 22, 1999). The FDA received comments
46 on the preliminary draft at a public meeting on the subject (September 28, 1999). The
47 FDA has made changes in the working draft in response to the public comments. A
48 revised preliminary draft of the CGMP regulations is being published in conjunction with
49 this draft guidance. This draft guidance provides more details for discussion purposes
50 on acceptable approaches to complying with the regulations if they were to be published
51 in final form.

52
53 As directed by Congress in the Modernization Act, to aid our development of this
54 proposed regulation, we closely examined the operations of many PET drug producers,
55 including not-for-profit institutions and commercial manufacturers. Since the
56 Modernization Act became law, significant changes have occurred in PET drug
57 production in the United States. The number of PET centers has increased, as has the
58 number of facilities where PET scans are performed. The business of PET drug
59 production has changed as well. Historically, PET drug products were produced by
60 academicians and researchers at PET centers located in universities and similar not-for-
61 profit institutions. An academically oriented PET center is usually characterized by the
62 production of small amounts (a few doses per day) of a few PET drug products for on-
63 site patient use and a larger variety of PET drug products for clinical investigation and
64 academic research.

65
66 An increasing number of PET centers are now operated by large, for-profit corporate
67 entities that contract with academic and medical institutions (many of which have not-
68 for-profit status) to manage the production of PET drugs at those institutions. Most of
69 these PET drug products are administered on site, although often there is some
70 distribution to other local or regional hospitals. In addition, a growing number of
71 independent PET centers are not affiliated with any university or hospital. These for-
72 profit, often contractually managed, and independently operated PET centers distribute
73 PET drug products to significantly greater numbers of patients, sometimes hundreds of
74 miles from the production site.

75
76 Our review of PET drug production leads us to conclude that a PET drug producer's
77 status as either a not-for-profit or for-profit entity does not have a significant bearing on
78 the quality of PET drugs that it produces and distributes for administration to patients, or
79 on the methods, facilities, and controls that a PET center needs to ensure product
80 quality. Instead, production and CGMP differences among PET drug producers are
81 primarily a function of the size, scope, and complexity of their production operations.
82 We also found that certain production standards and controls are necessary to ensure
83 the production of quality PET drugs regardless of differences in the nature and scope of
84 production among PET centers. The Agency believes that the welfare of any particular
85 patient undergoing a PET scan should not depend on where a particular PET drug was
86 manufactured.

87

88 The preliminary draft proposed regulation on CGMP requirements contains the
89 minimum standards that we believe are needed for PET drug production at all types of
90 PET centers. We have designed the CGMP regulations to be sufficiently flexible to
91 accommodate not-for-profit, academically oriented institutions that make PET drug
92 products for their own patients and research use as well as larger commercial
93 producers that serve a greater number of patients in a broader region.

94
95 To assist PET centers in understanding the preliminary draft proposed CGMP
96 regulations, we are developing this guidance. For many aspects of CGMP, including
97 matters such as resources, controls, and documentation, the draft guidance makes
98 different recommendations depending on the size, scope, and complexity of a PET
99 center's operations. The draft guidance provides practical examples of methods and
100 procedures that different types of PET centers could use to comply with the preliminary
101 draft CGMP requirements.

102
103 The preliminary draft proposed regulation also incorporates principles from the United
104 States Pharmacopeia (USP) general chapter on PET drug compounding. The USP
105 contains standards that are of significant regulatory importance for PET drugs.
106 Currently, under section 501(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (the
107 Act), a compounded PET drug is adulterated unless it is produced in compliance with
108 USP compounding standards and official monographs for PET drugs. Section 121(b) of
109 the Modernization Act added this provision as a safety net during the time it takes the
110 Agency to develop the final regulations. Under section 121(b), section 501(a)(2)(C) of
111 the Act will expire 2 years after the date on which we establish approval procedures and
112 CGMP requirements for PET drugs. At that time, compliance with the final version of
113 the regulation will be required. The USP general chapter on PET drug compounding
114 largely reflects the consensus views of the PET community and FDA on how to properly
115 produce PET drug products. Consequently, we believe it is appropriate to incorporate
116 many of the principles and concepts in the USP general chapter into the proposed
117 CGMP requirements.

118 **A. What is a PET Drug?**

119
120
121 PET is a medical imaging modality that requires the use of a unique type of
122 radiopharmaceutical drug. A PET drug exhibits spontaneous disintegration of unstable
123 nuclei by the emission of positrons (β^+) and is used for the purpose of providing dual
124 photon positron emission tomographic images. The radionuclide is generally produced
125 by a particle accelerator (e.g., a cyclotron) and has a short half-life. Currently, a batch,
126 or lot, of a PET drug typically consists of one multiple-dose vial containing the PET drug
127 product in a sterile solution. A sample from the vial, which represents all doses to be
128 administered, is tested to verify that the batch or the lot conforms to all established
129 specifications.

130
131 A finished PET drug product is typically administered to patients within a few minutes to
132 a few hours following preparation. Because of the short half-life of the radionuclide and
133 the mode of production, PET drug products have unique storage, shipping, and

134 handling concerns. Under Section 121 of the Modernization Act, PET producers must
135 use the standards in the USP General Chapter <823> *Radiopharmaceuticals for*
136 *Positron Emission Tomography-Compounding*, until FDA establishes approval
137 procedures and CGMPs for PET drug products.

138
139
140

B. What are CGMPs?

141 Manufacturing practices are the methods, facilities, and controls used in the
142 preparation, processing, packaging, or holding of a drug. A current good manufacturing
143 practice (CGMP) is a minimum standard that ensures the drug meets the requirements
144 of safety and has the identity strength, quality, and purity characteristics it is
145 represented to possess. CGMPs are demonstrated through written documentation of
146 procedures and practices. The documents and practices may be similar or identical to
147 documents and practices requested by other oversight bodies (e.g., NRC and state and
148 local agencies). Documents produced for others, where appropriate, can be used to
149 provide the documentation of compliance with CGMPs. However, because of
150 institutional, local, or state differences, some of these documents may not have
151 sufficient overlap to address the issues in this guidance. Therefore, to ensure uniformity
152 for all patients and human subjects, where overlap does not exist, supplemental
153 documentation should be developed.

154
155
156

C. Distinguishing Between PET Drug Production and the Practice of Pharmacy

157
158

158 FDA regulates the production of PET drug products. Section 121 of the Modernization
159 Act directs FDA to establish appropriate approval procedures for PET drugs pursuant to
160 section 505 of the Act, and appropriate CGMP requirements. In the course of
161 developing these approval procedures and CGMP requirements, a question has been
162 raised concerning how to distinguish PET drug production from the practice of
163 pharmacy (regulation of which FDA has traditionally deferred to State and local
164 authorities).²

165
166

166 FDA has determined that the production of a PET drug product would include all
167 operations to the point of final release of a finished dosage form (includes unit dose
168 containers, multiple dose containers and pharmacy bulk packages), and these activities
169 would be subject to CGMPs. After a distributed PET drug product is received by the
170 receiving facility for administration to patients, FDA generally regards subsequent use of
171 the drug product as part of the practice of medicine and pharmacy. FDA generally will
172 defer to State and local authorities concerning regulation of such activities.

173

² Congress specifically exempted PET drugs from the provisions on pharmacy compounding in section 127 of the Modernization Act (section 503A(e)(1) of the Act)). The U.S. Court of Appeals for the Ninth Circuit declared section 503A to be invalid in its entirety. FDA petitioned the court for a rehearing but this request was denied; the U.S. Supreme Court has granted a petition for certiorari. Pending a decision by the Supreme Court, it is FDA's position that section 503A is invalid only in the Ninth Circuit. Regardless, the approval procedures and CGMP requirements that FDA is developing will be applicable to all PET drugs.

174 Although not part of production, the distribution of PET drug products also would be
175 subject to CGMP requirements. In general, a routine FDA inspection to ensure
176 compliance with CGMP would focus on activities up to the point of final release of a
177 PET drug product.
178

179

180 **In the following sections, the draft guidance introduces each section by**
181 **identifying the relevant draft requirements from the preliminary draft proposed**
182 **regulations. The section then provides more detailed current thinking. Certain**
183 **CGMP requirements in the preliminary draft proposed regulations are self-**
184 **explanatory and have not been further clarified in this guidance.**

185
186

187 **III. PERSONNEL RESOURCES**

188

189 **A. Regulatory Requirements**

190

191 Preliminary draft proposed 21 CFR 212.10 would require a PET center to have a
192 sufficient number of personnel with the necessary education, background, training, and
193 experience to enable them to perform their assigned functions correctly. Each center
194 also would have to provide adequate resources, including equipment and facilities.
195

196

197 The following section of the guidance addresses personnel. Guidance on resources
(equipment and facilities) is provided in Section V.

198

199 **B. Organization and Staffing**

200

201 Staffing levels should correspond to the size and complexity of the operation of the PET
202 center. Staffing levels should enable a PET center to satisfactorily complete all
203 intended tasks in a timely manner. Regardless of the size, scope, or complexity of the
204 operation, there should be clearly written policies describing how the production and
205 quality control units (those persons with authority and responsibility to oversee the
206 process; see Section IV) are staffed and managed. The organizational structure of the
207 PET center and the responsibilities and assigned duties of all staff should be identified.
208

209

210 For a PET center that typically produces a few doses daily of a PET drug for its own
211 patients, it may be adequate to employ one or two persons to accomplish all production
212 and quality control functions. The PET center should demonstrate that the production
213 and quality control functions can be consistently accomplished in a timely and
214 acceptable manner. One individual can be designated to perform the production as well
215 as quality control functions, provided he or she is highly qualified in the performance of
216 all such functions (i.e., has a degree, documented training, and significant experience in
the technical area).
217

218

219 Under current CGMP regulations in 21 CFR Part 211, FDA normally requires second-
person checks at various stages of production as well as test verification. In a PET

220 center with only one person assigned to perform production and quality control tasks,
221 that person should check and recheck his or her own work. Self-checks involve the
222 repetitive confirmation of the operator's own action and should be documented.
223 Examples of self-check activities include reviewing batch records before release of the
224 drug product for distribution and verifying calculations in analytical tests.

225
226 At a PET center that produces larger quantities and/or multiple PET drugs, the staffing
227 level should be adequate to manage production and quality control functions. As
228 production operations become larger and more complex, the potential for error, mix-ups,
229 and/or contamination increases. Personnel should, therefore, be assigned to conduct
230 second-person checks to verify each critical step in production and quality control.

231
232 **C. Personnel Qualifications**

233
234 Each person performing an activity or a function in the production and quality control of
235 a PET drug product should have the appropriate education, training, and experience
236 related to that function and be trained in CGMPs relevant to their assigned tasks. PET
237 centers should have adequate ongoing programs or plans in place for training
238 employees in new procedures and operations and in the areas where deficiencies have
239 occurred.

240
241 PET centers should maintain an updated file (e.g., curriculum vitae, copies of degree
242 certificates, certificate of training) for each employee.

243
244
245 **IV. QUALITY CONTROL**

246
247 **A. Regulatory Requirements**

248
249 Preliminary draft proposed 21 CFR 212.20 would require PET centers to have a quality
250 control unit. Under the proposed regulations, the quality control unit would have the
251 authority and responsibility to perform the following tasks.

- 252
- 253 • Oversee production operations to ensure that PET drug products have
254 adequately defined identity, strength, quality, and purity
 - 255
 - 256 • Examine and approve or reject components, containers, closures, in-process
257 materials, packaging materials, and labeling used in the production of PET
258 drug products to ensure that all these meet their current specifications
 - 259
 - 260 • Examine and approve or reject PET drug products
 - 261
 - 262 • Examine any procedure affecting production, testing, and specifications
 - 263
 - 264 • Review production records for accuracy and completeness
 - 265

- Ensure that all errors are investigated and corrective action is taken

B. The Quality Control Unit

The quality control unit should be the final decision making body on matters within its area of responsibility. The quality control unit should examine each lot of incoming material to ensure that the correct material is received in good condition and is properly identified and stored. Before any material is released for production, the quality control unit should ensure that the material meets its established specifications. Such evaluation can include testing of the material (see Section VI, Control of Components, Containers, and Closures).

The quality control unit should ensure that procedures and specifications affecting production and testing of a PET drug product are adequate for their intended purposes. Procedures and specifications should be reviewed and approved by the quality control unit prior to their implementation.

The quality control unit also should approve proposed changes to procedures or specifications before they are implemented. The quality control unit should investigate errors and ensure that appropriate corrective action is taken to prevent their recurrence.

The quality control unit should review the production batch records and laboratory control records for conformance to established specifications before authorizing the final release or rejection of a batch or lot of PET drug product

The staffing and responsibility of the quality control unit should be consistent with the recommendations provided in Section III of this guidance. Small PET centers are encouraged to use an outside consultant or an independent expert to periodically audit performance of quality control functions. In large PET centers, the quality control unit should be independent from the production unit. Decisions made by the quality control unit to reject batches should not be subject to further review or revocation by another organizational unit or person.

V. FACILITIES AND EQUIPMENT

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.30(a) would require that a PET center have adequate facilities to ensure the orderly handling of materials and equipment, the prevention of mix-ups, and the prevention of contamination of equipment or product by substances, personnel, or environmental conditions.

Proposed 21 CFR 212.30(b) and (c) would require that all equipment that would reasonably be expected to adversely affect the strength, quality, or purity of a PET drug, or give erroneous or invalid test results when improperly used or maintained, is clean,

312 suitable for its intended purposes, properly installed, maintained, and capable of
313 repeatedly producing valid results. Equipment would have to be constructed so that
314 surfaces that contact components, in-process materials, or drug products are not
315 reactive, additive, or absorptive so as to alter the quality of the PET drug product.

316
317 **B. Facilities**

318
319 *1. General*

320
321 The design of the PET drug production facility should promote an orderly
322 operation during the production process. It should also effectively protect
323 the product from contamination originating from personnel and
324 surrounding areas. The facility should contain adequate work areas
325 suitable for the intended tasks (e.g., area for analytical testing, aseptic
326 manipulation, chemical production, radiochemical production, and
327 component storage) and to allow completion of all production-related tasks
328 in an orderly manner. Potential sources of contamination that should be
329 considered include particulate matter and chemical and microbiological
330 materials. The lead-based radiation shielding should be properly covered to
331 prevent lead contamination of the product.

332
333 Phases of production with the potential for microbiological contamination
334 should be performed under appropriate environmental conditions that
335 prevent the possibility of such contamination (e.g., in a laminar airflow
336 workbench (LAFW), or barrier isolator system).

337
338 The placement of equipment and materials should be carefully evaluated
339 to promote efficient operation and eliminate errors, mix-ups, and cross-
340 contamination. All equipment used in production (e.g., particle
341 accelerator, synthesis units, or other specialized equipment) should be
342 appropriately located and housed (e.g., with shielding) so that all the work
343 areas during the normal course of production are easily accessible.

344
345 Related work areas should also be organized and proximally located so as
346 to promote efficient operation and eliminate the potential for errors in the
347 production and control operations. Access to work areas, production and
348 testing equipment, components, containers and closures, and the PET
349 drug products, should be restricted to authorized personnel.

350
351 In small PET centers, the same area or room can be used for multiple
352 purposes. For example, the production (e.g., radiochemical synthesis),
353 laboratory operation (e.g., release testing), and storage of approved
354 components, including containers and closures, can be located in the
355 same room. Components that are approved for use as well as those that
356 are under quarantine can be stored in the same area or on a different
357 shelf in a cabinet, provided each lot is properly labeled as to its status and

358 contents and organized in a manner that avoids mix-up or unintended use.
359 Rejected components, containers and closures, and other materials
360 should be kept separately from quarantined or approved materials.
361

362 In large PET centers having relatively complex operations, separate and
363 well-defined areas or rooms may be warranted for each independent
364 function of the operation, such as production, testing, and storage of
365 components. Large PET centers that handle large numbers of
366 components and PET drug products should organize their production
367 facilities in such a way as to prevent mix-ups and contamination. It is also
368 important to consider what impact a greater number of personnel and
369 activities could have on the aseptic processing portion of the process.
370

371 2. *Aseptic Processing Facility*

372
373 The aseptic work area should be suitable for the preparation of a sterile
374 PET drug product. Air quality in the aseptic processing area should be
375 adequately controlled to limit the presence of microorganisms and
376 particulate matter. Critical activities in the production and testing of a PET
377 drug product that expose the PET drug product or the sterile surface of the
378 container/closure system to the environment should be conducted within
379 an aseptic workstation with a rating of Class 100 (e.g., a LAFW or barrier
380 isolator). Examples of such activities include (1) the aseptic assembly of
381 sterile components (syringe, needle, filter and vial) for sterile filtration of
382 the PET drug product, (2) storage of the sterility samples, and (3) sterility
383 testing of the finished PET drug product. The following precautions should
384 be taken to maintain the appropriate air quality of the aseptic workstation:
385

- 386 • The aseptic workstation should be sanitized before each operation.
387
- 388 • Container assemblies should be prepared at the beginning of the day
389 before other daily activities begin and before additional personnel have
390 entered the room.
391
- 392 • Items within a laminar airflow aseptic workstation should be kept to a
393 minimum and should not interrupt the airflow.
394
- 395 • Operators should wear appropriate lab coats and sanitized gloves
396 when conducting an aseptic manipulation within the aseptic
397 workstation.
398
- 399 • Gloved hands should be frequently sanitized when working in the
400 aseptic workstation. Gloves should be examined for damage (tears or
401 holes) and replaced if they are compromised.
402

403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448

- The surface of nonsterile items (e.g., test tube rack, and the overwrap for sterile syringes, and filters) should be sanitized and wiped with an appropriate disinfectant (e.g., 70 percent isopropyl alcohol) before being placed in the aseptic workstation.

Conditions in the room where aseptic manipulations are conducted should not present a challenge to the operating capability of the aseptic workstation. For example, the room should not be carpeted and should have no overhanging pipes or hanging light fixtures. All areas of the production and processing room should be easily accessible for cleaning. Surfaces of the walls, floors, and ceilings in the aseptic work areas should be easily sanitized and capable of withstanding frequent sanitizing. Cleaning and sanitizing should be performed frequently to ensure sufficient and consistent control of the environmental quality. In addition, the aseptic processing area (e.g., LAFW) should be situated in the section of the room with the lowest-traffic and lowest activity. Cartons and boxes should not be stored or opened in the production area to minimize ingress of dust and particulate into the aseptic work area.

C. Equipment

1. Production Equipment

Equipment used in the production, processing, or packaging of a PET drug product should be appropriate for the performance of its intended function and should not contaminate the product. Each piece of equipment should be suitably located to facilitate its use, cleaning, and maintenance. The PET center should establish and follow written procedures that address the following issues, where applicable:

- Assignment of responsibility and frequency for cleaning and maintenance of equipment
- Description of cleaning and maintenance procedures in sufficient detail to include disassembly and reassembly of equipment
- Protection of clean equipment from contamination prior to use
- Inspection of equipment and calibration, if indicated, prior to use.

Each PET center should select suitable cleaning agents and cleaning techniques and ensure that their cleaning operations do not contaminate the drug product.

Newly acquired equipment should be qualified before first use to verify that it was installed correctly and is capable of operating as intended.

449 There should be a preventive maintenance schedule with sufficient
450 frequency to ensure the correct performance of the equipment. Where
451 needed, calibration should be performed prior to the use of the equipment
452 for the intended task. Calibration checks recommended by equipment
453 manufacturers should be followed unless the PET center has determined
454 that more frequent calibrations are needed. Major repairs or upgrades in
455 equipment may warrant requalification. Malfunctioning or incorrectly
456 operating equipment should not be used until repairs or corrective action
457 have been made and the equipment has been found to operate correctly.
458 All qualification, calibration, and maintenance activities should be properly
459 documented, including the date of such performance and who performed
460 them.

461
462 FDA recognizes that a number of PET centers may continue to use
463 existing equipment when they become subject to the requirements of the
464 final CGMP regulations. PET centers should make sure that the existing
465 equipment is working properly and is being maintained and calibrated
466 according to written procedures.

467
468 Representative equipment is discussed below to illustrate how it might be
469 controlled in a PET center.

470
471 a. Automated radiochemical synthesis apparatus

472
473 The apparatus should enable the PET center to carry out the production
474 process reliably and reproducibly. The provisions contained in the USP
475 General Chapter <1015> *Automated Radiochemical Synthesis Apparatus*
476 should be considered to help ensure proper functioning of a synthesis
477 apparatus.

478
479 Prior to the production of a PET drug product batch, the operator should
480 conduct a performance check to ensure the following:

- 481
- 482 • The synthesis apparatus has been cleaned/ flushed according to the
483 established procedures.
 - 484
 - 485 • All the tubing, reaction vessels, purification columns or cartridges, and
486 other materials have been replaced and connected as required.
 - 487
 - 488 • The monitoring and or recording devices (e.g., temperature, pressure,
489 flow rate) are functioning properly.
 - 490
 - 491 • When the process is under microprocessor control, the operator should
492 ensure that the system is functioning and recording correctly and that
493 the correct program and operational parameters are used.
 - 494

495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540

b. Aseptic Workstation

The aseptic workstation provides an appropriate environment for aseptic procedures. Examples of workstations include a laminar air flow workbench (LAFW) or barrier isolator system. An integrity test should be conducted at installation (including after each change of the high-efficiency particulate air (HEPA) filter) to ensure proper performance. Certification of the aseptic workstation should be performed when the unit is initially installed and at least every 6 months thereafter to ensure the desired air quality. More frequent testing may be appropriate if air quality is found to be unacceptable, for example, as part of an investigation into a finding of sterility failure in a PET drug, or if leakage or decrease in optimal airflow is found.

A qualified operator should change the prefilters in the aseptic workstation periodically in accordance with written procedures and preventive maintenance schedules. Some laminar flow hoods are equipped with easily readable static pressure gauges that indicate when the pressure builds up behind the filter because of the clogging of the filter. The filter should be changed when clogging is detected.

Laminar airflow velocities should be monitored periodically at the work surface as well as at the HEPA filter face to ensure adequate uniformity of flow throughout the critical area. Operators should be trained on the importance of minimizing objects and equipment within the critical area so laminar airflow is not disrupted.

c. Electronic or analytical weight balance

Written procedures should be available describing the proper use of the balance, assessment of accuracy, and a schedule for calibration. Performance should be checked by weighing two or more standard weights on each day of use. The calibrated weights used for assessing daily performance should bracket the range of the weights being measured. The balance should be fully calibrated periodically, or upon failure to meet daily performance checks.

d. Dry-heat ovens

If glassware and heat-stable materials are depyrogenated and sterilized on-site, the PET center should validate and document that the depyrogenation cycle will achieve at least a 3-log reduction of an endotoxin challenge, as measured by a bacterial endotoxins test. A suitable challenge study should involve random placement of endotoxin indicators in a representative oven load of materials. Suitable endotoxin indicators include glass vials that contain 1,000 to 10,000 Endotoxin Units.

541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586

e. High performance liquid chromatograph (HPLC)

When an HPLC is used for purification of a PET drug, the operator should ensure that the system is working properly and there is no bleeding of unintended materials (e.g., column material) into the mobile phase.

f. Temperature recording device

The temperature and humidity (where appropriate) of the dry heat oven, refrigerator, freezer, and incubator should be recorded on each workday when in use. Automated recording devices are recommended for ease of documentation and for recording any deviations.

2. Quality Control Equipment

A PET center should have the necessary equipment to adequately perform each quality control function that it intends to perform. Representative quality control equipment can include:

a. Gas chromatograph (GC)

Prior to its use, the analyst should make sure that the GC system is functioning correctly. Appropriate system suitability testing procedures and criteria (see USP General Chapter <621> *Chromatography*) should help ensure the correct performance of the GC system.

b. High performance liquid chromatograph (HPLC)

The HPLC system should have detectors that are suitable for the intended purpose. The detector should be of sufficient sensitivity, and prior to its use, the analyst should make sure that the HPLC system is functioning correctly. System suitability testing procedures and criteria (see USP General Chapter <621> *Chromatography* and FDA reviewer guidance, *Reviewer Guidance — Validation of Chromatographic Methods* (November 1994) should help to ensure the correct performance of the HPLC system.

c. Dose calibrator

A dose calibrator that gives a printout should be used and tested for (1) accuracy at installation and at least annually thereafter using at least two NIST traceable sealed sources in the energy range that covers the energy of the PET radioisotope; (2) linearity in the range of measurement upon installation and at least quarterly thereafter; (3) geometry dependence, over the range of volumes and volume configurations, at installation; and

587 (4) precision on a daily basis. Nuclear Regulatory Commission
588 regulations (under 10 CFR 35.50) should be followed for the procedure
589 and acceptable criteria for the above calibrations.

590
591 d. Radiochromatogram scanner

592
593 A radiochromatogram scanner (or equivalent equipment that provides a
594 radiochromatogram) should be used for the measurement of radioactivity
595 distribution in the developed thin layer chromatography plate (e.g., ITLC,
596 paper or plate). The scanner should have sufficient sensitivity and spatial
597 resolution for the intended discriminatory and quantitative objective.
598 Manufacturers' recommended checks and maintenance should be
599 performed on the radiochromatogram scanner (see USP General Chapter
600 <821> *Radioactivity*).

601
602 e. Multichannel analyzer (MCA)

603
604 A multichannel spectrometer coupled to a calibrated sodium iodide
605 scintillation detector (or preferably with the higher resolution germanium
606 lithium compensated, Ge (Li) detector) should be useful for the
607 determination of radionuclidic purity and for the identification of the
608 radionuclide. The overall system should have sufficient sensitivity and
609 resolution for the intended purpose (see USP General Chapter <821>
610 *Radioactivity*). Adequate calibration using NIST traceable standards and
611 preventive maintenance should be performed at intervals specified in a
612 written procedure and as recommended by the equipment manufacturer.
613 More frequent intervals should be used if problems in the operation of the
614 MCA are encountered.

615
616

617 VI. CONTROL OF COMPONENTS, CONTAINERS AND CLOSURES

618
619

619 A. Regulatory Requirements

620
621

621 Preliminary draft proposed 21 CFR 212.40(a) and (b) would require PET centers to
622 establish, maintain, and follow written procedures for the control of components,
623 containers, and closures. There would have to be appropriate written specifications for
624 components, containers, and closures.

625
626

626 Proposed 21 CFR 212.40(c) would establish the minimum standards for controlling
627 components, containers, and closures from receipt to consumption.

628
629

629 Proposed 21 CFR 212.40(d) would require that components, containers, and closures
630 be handled and stored in a manner that prevents contamination, mix-ups, and
631 deterioration.

630
631
632

633 Proposed 21 CFR 212.40(e) would require that PET centers keep a record of each
634 shipment of each lot of components, containers, and closures that they receive.

635
636
637

B. Control of Components, Containers, and Closures

638 Written procedures should be established specifying how each material (components,
639 containers, and closures) will be selected and controlled in PET centers. Procedures
640 should cover the life cycle of a material, from time of receipt to ultimate consumption.
641 The process for procurement and use of materials should include the following
642 elements, where applicable:

643
644

1. *Vendor Selection*

645
646
647
648
649
650
651
652

Only qualified vendors should be used. A vendor becomes qualified when there is evidence to support its ability to supply a material that consistently meets all quality specifications. PET centers should obtain assurance from a vendor that the vendor will report any major changes in the manufacture of an item. It is preferable to have more than one qualified vendor for a component. A vendor should be replaced if there is an indication that it is supplying unsatisfactory materials.

653
654
655

2. *Receipt of materials*

656
657
658
659
660
661
662
663

Each lot of material should be checked upon receipt to determine that the order was filled correctly and arrived in good condition. Each lot should be logged in and assigned a new identification code number. The code number should be used in the disposition of that lot. Sufficient information should be documented to enable the PET center to have full accountability and traceability of each lot. Before release for use, incoming materials should be segregated and placed under quarantine. A lot can then be inspected, sampled, and tested, if applicable.

664
665
666

3. *Acceptance, release and storage of materials*

667
668
669
670
671
672

Analytical results in the certificate of analysis (COA) for each lot of incoming material should be inspected against the PET center's current specification sheet to ensure that acceptance criteria are met. At a minimum, certain components described below (see Acceptance Testing) should be tested to confirm their identity before they are accepted and released for use in the production of a PET drug product.

673
674
675
676
677
678

Materials that meet a PET center's specifications can be approved and released for use. Such release should be recorded and the examination and testing data maintained. It may be helpful to have a component logbook to record information such as receipt date, quantity of the shipment, supplier's name, lot number, expiration date, results of any

679 testing performed, and person responsible for release.³ Approved
680 materials should be labeled *Approved* with an identifying code number,
681 storage conditions, and expiration date. Materials should be stored under
682 the proper storage conditions and in an area designated for approved
683 materials. If a lot is rejected, it should be labeled *Rejected*, segregated,
684 properly disposed of, and each of these actions should be documented.
685

686 An item should be stored under the conditions recommended by the
687 vendor (e.g., temperature and humidity). Moisture sensitive materials
688 should be stored in desiccated devices in sealed containers. There should
689 be an expiration date for each item. PET centers should have a policy
690 that guides the expiration dating of items, by category. Vendor assigned
691 expiration dates could be used unless the in-house date is sooner.
692

693 4. *Acceptance Testing*

694 a. Reagents, solvents, gases, purification columns, and other auxiliary 695 materials 696

697
698 PET centers should have procedures in place to ensure that only
699 materials meeting applicable specifications from approved reliable sources
700 are used. The COA and container label for each shipment of incoming
701 materials should be examined to ensure that all specifications are met.
702 The use of an identity test is recommended, but not required. Most PET
703 centers currently employ micro-scale chemistry and use relatively small
704 amounts of solvents or reagents in the automated radiochemical
705 synthesis. The amount of solvents or reagents in the finished product is
706 typically reduced or eliminated during production or purification
707 procedures. Residual reagents, process impurities, and solvents can be
708 identified during finished product testing.
709

710 b. Components that yield an active pharmaceutical ingredient (API) 711 and inactive ingredients 712

713
714 Under proposed § 212.40(c), PET centers would have to conduct identity
715 testing on each lot of a component that yields an API and on each lot of
716 inactive ingredient. In addition, each lot of such a component or an
717 inactive ingredient would have to be tested for conformity with written
718 specifications. PET centers that do not perform such testing can accept a
719 lot on the basis of a COA on that lot from the supplier provided that they
720 have established the reliability of the supplier's test results and that they
721 perform at least one identity test on each such lot received. In those
722 cases when specific tests exist, they should be used. The reliability of the

³ A sample format for record keeping of incoming components is available at www.fda.gov/cder/regulatory/pet.

723 supplier's test results can be established by conducting independent
724 testing and confirmation of the testing results for the first three lots of the
725 components received and at appropriate intervals thereafter (e.g.,
726 semiannually or because of a change in specifications).

727
728 Following are examples of testing of components that yield an API:
729

- 730 • For the production of fludeoxyglucose F 18 injection (FDG F 18), the
731 components that yield the API are O 18 water and mannose triflate. A
732 reaction-based identity test for O 18 water is the production of F 18 by
733 nuclear bombardment. Alternatively, the identity of O 18 water can be
734 established by mass spectroscopy. A specific identity test can be
735 performed on mannose triflate using infra red spectroscopy (IR) or
736 nuclear magnetic spectroscopy (NMR) analysis.
737
- 738 • In instances when F 18 fluoride is obtained from outside suppliers, a
739 PET center should establish appropriate acceptance procedures that
740 include examination of the COA to ensure that each lot is acceptable
741 for use in PET drug product production.
742
- 743 • If the target material (O 18 water) is recycled, approved, and validated,
744 procedures on how the reprocessed lot can be accepted for use should
745 be established and used.
746

747 The inactive ingredients in PET drugs usually consist of a diluent, a
748 stabilizer, and/or a preservative. Under proposed § 212.40(c)(1), if a
749 product that is marketed as a finished drug product intended for
750 intravenous administration is used as an inactive ingredient, it would not
751 be necessary to perform a specific identity test for that ingredient.
752 Proposed § 212.40(c)(1) also states that if an inactive ingredient (e.g.,
753 0.9% sodium chloride solution) were prepared on site, an identity test on
754 the components used to make the inactive ingredient would have to be
755 performed before they were released for use.
756

- 757 c. Commercially available ready-to-use sterile, pyrogen-free, sealed
758 container/closure systems for injections, syringes, transfer sets,
759 and filters used in aseptic process
760

761 PET centers should use approved and reliable sources for these items.
762 Under proposed § 212.40(c)(3), a visual identification of each lot of
763 containers and closures would have to be conducted. A COA showing
764 conformance with the established specifications should be obtained before
765 accepting each lot of the container/closure system. The container/closure
766 system should be properly stored under appropriate environmental
767 conditions (e.g., correct temperature, humidity, and sterility).
768

769 If the sterilization and depyrogenation of the container/closure are
770 performed on site, validation of the efficacy of each process should be
771 demonstrated. Validated procedures should be used in such cases.

772
773

5. *Handling of components, containers, and closures*

774
775

When the quality control unit has determined that a lot of material has met all acceptance criteria, the material should be labeled *Approved*. Under proposed § 212.40(d), approved materials would have to be handled and stored in a manner that prevents degradation or contamination. Unacceptable materials would have to be promptly rejected, identified, and segregated to prevent their use prior to appropriate disposal.

776
777

778
779

780
781

6. *Records*

782
783

Under proposed § 212.40(e), records would have to be kept for each shipment of each lot of components, containers, and closures that the PET center receives, including results of any testing performed.

784
785

786
787

788
789

VII. PRODUCTION AND PROCESS CONTROLS

790
791

A. Regulatory Requirements

792
793

Preliminary draft proposed 21 CFR 212.50 would require adequate production and process controls to ensure consistent production of a PET drug product that meets the applicable standards for identity, strength, quality, and purity. Under proposed § 212.50(a), PET centers would be required to have written production and process control procedures to ensure and document that all key process parameters are controlled and that any deviations from the procedures are justified.

794
795

796
797

798
799

Proposed § 212.50(b) would require PET centers to have a master production and control record that documents all steps in the PET drug production process, and specifies what would be required in the master production and control record.

800
801

802
803

Proposed § 212.50(c) would require that a batch production record be generated from the master production record template for each new batch of a PET drug product. Each batch of a PET drug product would be uniquely identified, and its batch record would include each production step, weights, and identification codes of components used, dates of production steps, identification of major equipment, testing results, labeling, names of persons performing or checking each significant step in the operation, and any investigations conducted.

804
805

806
807

808
809

810
811

Proposed § 212.50(f) would require that the process for producing each PET drug product be validated according to established procedures. Validation activities and

812
813

814 results would have to be documented. The quality control unit would have to approve
815 the validation process and the results.

816

817 **B. Master Production and Control Record/Batch Production and Control**
818 **Record**

819

820 A master production and control record is the principal document describing how a
821 product is made. It serves as a template for all batch records, documenting how each
822 batch should be produced. The quality control unit should approve the master
823 production and control record, or any changes to it, before it is implemented.

824

825 Suitable controls should be initiated to consistently produce a product with the desired
826 quality attributes. The master production and control record should present logical,
827 chronological step-by-step instructions that document how the PET drug is to be
828 produced.⁴ Production can be discussed under headings, where applicable, such as
829 accelerator operation, radiochemical synthesis, purification steps, and formulation of the
830 finished product. The entire production process should be pre-established and fully
831 described in the master production and control record, which also should identify the
832 equipment and instrumentation that will be used in a specified and controlled manner as
833 part of the approved production process. The master production and control record
834 should include valid specifications for each critical step. Under proposed § 212.50(b),
835 the master production and control record should include the following:

836

- 837 • The name and strength of the PET drug product in MBq/ml or mCi/ml (strength
838 should be measured at a calibration time immediately after production)
- 839
- 840 • If applicable, the name and weight or measurement of each API per batch or per
841 unit of weight or measure of the drug product and a statement of the total weight
842 or measurement of any dosage unit
- 843
- 844 • A complete list of components designated by names and codes (component
845 code) sufficiently specific to indicate any special quality characteristic
- 846
- 847 • Identification of all major equipment used in production of the drug product
- 848
- 849 • An accurate statement of the weight or measurement of each component (e.g.,
850 batch formula). In the process of producing FDG F 18, for example, multiple
851 components are weighed or measured by volume. The radioactive component
852 should be recorded in terms of radioactivity units
- 853

⁴ A draft guidance for industry, entitled *PET Drug Applications — Content and Format for NDAs and ANDAs*, was published in March 2000. Once finalized, that guidance will represent the Agency's current thinking on this subject. Also, a sample format for a batch production and control record is available at www.fda.gov/cder/regulatory/pet.

Draft — Not for Implementation

- 854
- 855
- 856
- 857
- 858
- 859
- 860
- 861
- 862
- 863
- 864
- 865
- 866
- 867
- 868
- A statement of the action limit on radiochemical yield (i.e., the maximum and minimum percentages of yield beyond which investigation and corrective action are required)
 - Complete instructions for production, control, and testing of the PET drug. The synthesis of certain PET drugs, such as FDG F 18, involves multiple steps including drying, exposure to organic solvents, heating, pH adjustments, passage through purification media, and sterilizing filtration. There should be a description of all in-process steps and their controls so that the operator and quality control unit can confirm that all steps are completed within specified conditions, where feasible. Controls for movement of liquids or gases should also be provided.
 - A description of the PET drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling.

869 A batch of a PET drug product is a predefined quantity of the drug that has been
870 produced to have uniform character and quality. In the case of FDG F 18, a batch
871 normally consists of the PET drug product produced in a single synthesis and
872 purification operation. For ammonia N 13, a batch normally consists of multiple sub-
873 batches having uniform character and quality, and they are produced according to a
874 single preparation order during one succession of multiple irradiation using a synthesis
875 and/or purification operation.

876

877 Proposed § 212.50(c) would require the use of a batch record to document the
878 production and testing of each batch. Information in the batch record should be an
879 accurate reproduction (paper, or electronic copy) of the master production record. The
880 batch record should be a check list documenting, for example, that all processing steps
881 and their controls were carried out, timed events occurred within specifications, heating
882 steps occurred at the specified temperature, and ingredients were properly transferred
883 into the reaction vessel. The batch record also should contain a compilation of tests
884 and printouts that led to acceptance of the final product. The batch production and
885 control record enables an operator to fully document and establish traceability to
886 specific lots of all components, containers/closures, and equipment used in the
887 production of the PET drug.

888

889 Under proposed § 212.50(c), information specific to a batch record would include the
890 following:

- 891
- 892
- 893
- 894
- 895
- 896
- 897
- 898
- 899
- Unique identifier or number for each batch (an identifier or number also should be provided for each sub-batch produced)
 - Dates of production steps
 - Identification of major pieces of equipment used in the manufacturing
 - Actual weights (or measures) and identification codes of components used

900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945

- Labeling (a description of the finished drug product container label and the outer container label should be included)
- Identification of the person(s) performing and checking each significant step of the operation
- Results of any investigations conducted (this should include documentation of any deviations and follow-up investigations)
- Results of finished PET drug product testing

When entries are made in batch records, an entry should be made directly after performing the activity (in the order performed) and should identify the person (signature or initials) making the entry. Corrections to paper entries should be dated and signed or initialed, leaving the original entry still readable. Corrections to electronic records should be recorded according to Part 11 (21 CFR Part 11, Electronic Records; Electronic Signatures), and there should be an audit trail to document the changes. Each batch record should be reviewed and approved for final release (signature/ initials and date).

C. Microbiological Control on Aseptic Processing and Sterilizing Filtration

Most PET drug products are designed for parenteral administration and are produced by aseptic processing. The goal of aseptic processing is to make a product that is free of microorganisms and toxic microbial byproducts, most notably bacterial endotoxins. The use of aseptic technique and control of microbiological impurities in components can eliminate microbial and endotoxin contamination from PET drugs. Aseptic processing of PET drugs should involve microbiological control over various types of components, as discussed below.

1. Water

Production processes that are relatively free of water content or have rigorous chemical processes are unlikely to have microbial or endotoxin contaminants. PET centers often use *water for injection*, USP (WFI), an approved drug product. Using finished packaged WFI eliminates the need for the PET center to maintain and validate a sterile water system.

Nonsterile water can develop significant microbial growth in a matter of days. Production processes that are water-intensive should have sufficient controls to avoid microbial growth and development of biofilm (bacterial colonization). If nonsterile water is allowed to stagnate in a container or tubing, biofilm will develop. Tubing and glassware should be washed, rinsed, and promptly dried to minimize their contact with water.

946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988

2. *Glassware*

Glassware and heat-resistant containers are relatively easy to keep free of microbial growth and pyrogens because they can be appropriately wrapped in foil and terminally sterilized by a suitable dry-heat cycle (see Section V). Control procedures for these items should include prompt cleaning after use, rinsing with purified or WFI water, wrapping in aluminum foil, and depyrogenation by a suitable dry-heat oven cycle.

3. *Transfer Lines*

Transfer lines, which are used for synthesis and transfer of solvents or products, are usually made of durable plastic and are amenable to reuse. Prompt cleaning with organic solvents after use, rinsing with WFI, flushing with a volatile solvent, and drying with nitrogen are measures that help to control microbial contamination. Organic solvents such as ethanol and acetone are useful as a final rinse and are easily dried from containers or lines.

For PET drugs with a very short half-life (e.g., ammonia N 13), sometimes a long fluid line is used to deliver multiple batches of the product solution to a remote area for further processing. These fluid lines should be clean and free of pyrogen contamination for their duration of use.

4. *Resin columns*

Resin columns are a potential source of microbes and pyrogens because they can carry microorganisms. If available, the purchase of low-microbial grade resin material may limit bioburden. Material used for preparing resin columns should be suitably processed and rinsed with a large amount of WFI to control contamination. The prepared column should be appropriately flushed. Refrigerated storage is helpful in controlling contamination. Wet columns should not be stored for a prolonged period of time.

5. *Components*

The selection of a reliable vendor and high-quality materials are effective ways to limit the risk of microbiological contamination. Components that support microbial growth during storage should be kept under controlled conditions and periodically assessed for microbial growth/ contamination.

989 6. *Qualification for aseptic processing*

990
991 Only personnel trained in aseptic techniques should conduct aseptic
992 processing. Personnel performing aseptic processing should be qualified
993 by media fill, which is a simulation of the production process.

994
995 Aseptic processing in PET drug production normally consists of, but is not
996 limited to, (1) the aseptic assembly of the container/closure system
997 (syringe, needle, filter and vial) and (2) sterile filtration of the PET drug
998 product. Prospective operators can qualify for aseptic processing by
999 performing media fill runs using bacterial growth media instead of the
1000 actual drug product. An operator should complete three successful media
1001 fill runs to qualify as a new operator. Each operator should be re-qualified
1002 annually.

1003 7. *Sterilizing filtration*

1004
1005 Even if care is taken to minimize microbiological contamination during
1006 synthesis, a drug is considered to be nonsterile until it is passed through a
1007 sterilizing grade filter. Generally, PET centers can use commercially
1008 available, pre-sterilized filters to sterilize these solutions, provided that the
1009 vendor has been shown to be reliable, the filter is certified as compatible
1010 for the product, and it meets acceptable specifications.

1011
1012 Before using filters from a particular lot, a sample should be tested for
1013 integrity to demonstrate that the membrane has the ability to retain
1014 microorganisms. The manufacturer's recommended method can be used.
1015 In addition, the integrity testing of the membrane filter should be
1016 performed postfiltration to ensure that the filter has performed according to
1017 specifications. This can be accomplished by performing the bubble-point
1018 test to show that the integrity of the filter was not compromised during or
1019 before use.

1020 8. *Environmental and personnel monitoring*

1021
1022 Environmental monitoring is crucial to maintaining aseptic conditions.
1023 Microbiological testing of the aseptic workstation should be performed
1024 periodically. Methods can include using swabs or contact plates for
1025 surfaces, and settling plates or dynamic air samplers for air quality.

1026
1027
1028
1029 **D. Process Validation and Computer Control**

1030
1031 Preliminary draft proposed § 212.50(f) would require that PET drug production
1032 processes be validated to ensure that they are capable of consistently producing a
1033 product that meets all specifications. For a PET center that has an established history
1034 of PET drug production, validation of the production processes can be conducted

1035 retrospectively, provided that the current process is supported by adequate
1036 accumulated data to support a conclusion that the process is normally sufficiently
1037 capable of yielding batches meeting predetermined specifications. Successful
1038 retrospective validation involves a comprehensive review of accumulated production,
1039 testing, and control data according to a written protocol defining the acceptable
1040 conditions. The accumulated data should be sufficient to verify that the process used
1041 was consistent and should consider all changes to and failures of the process.
1042

1043 Ideally, validation of a new process, or a significant change to an already validated
1044 process, would be shown prospectively (i.e., before any batches are distributed). As
1045 with retrospective validation, prospective validation should be conducted according to a
1046 written protocol and generally include at least three consecutive acceptable production
1047 runs.
1048

1049 Due to the short half-lives of PET drugs, a PET producer may decide to validate a new
1050 process or significant change to a validated process **concurrently** with the distribution
1051 of each validation batch. The decision to rely on concurrent validation should be
1052 justified in writing and approved by the quality control unit, and, as with any validation,
1053 performed according to a written protocol. Each batch subject to a concurrent validation
1054 protocol should be processed in strict adherence to the written procedures, fully tested
1055 (except sterility), and found to comply with all procedural and quality test requirements
1056 prior to final release. The PET producer should weigh the risks and benefits carefully in
1057 considering which type of validation scheme to follow, giving preference to validating
1058 prospectively, then retrospectively, and finally concurrently.
1059

1060 Synthesis of some PET drugs can be executed under automated or computer control.
1061 In such cases, the computer program should be validated to demonstrate that it is
1062 suitable for its intended purposes and is capable of producing valid results. For
1063 example, the computer program used in the automated synthesis of FDG F 18 can be
1064 validated by demonstrating that acceptable production criteria for the PET drug product
1065 are met for at least three consecutive production runs. Subsequent changes or
1066 upgrades made to the computer program should be revalidated. PET centers can rely
1067 on a certification by the software or system vendor that the specified software was
1068 validated and verified under its operating conditions.
1069

1070 Computerized systems should have sufficient controls to prevent unauthorized access
1071 or changes to data. There should be a record of any data change made, the previous
1072 entry, who made the change, and when the change was made. A back-up system
1073 should be available in case of system breakdown.
1074

1075

1076 VIII. LABORATORY CONTROLS

1077

1078 A. Regulatory Requirements

1079

Draft — Not for Implementation

1080 Preliminary draft proposed 21 CFR 212.60 would require the establishment and
1081 implementation of procedures for testing components, in-process materials, and
1082 finished PET drug products. All necessary tests of materials and products would have
1083 to be documented. Each laboratory would also be required to have sampling and
1084 testing procedures designed to ensure that components, drug product containers and
1085 closures, in-process materials, and PET drug products conform to appropriate
1086 standards. Analytical methods and test equipment would have to be suitable for their
1087 intended uses. Reagents, solutions, and supplies used in testing procedures would
1088 have to be adequately controlled. The preventive maintenance, calibration, and
1089 procedures to make sure that the equipment is functioning properly would have to be
1090 documented. A complete record of all tests related to the production of a PET drug
1091 product would have to be kept to ensure compliance with established specifications and
1092 standards, including examinations and assays, as follows:

- 1093
- 1094 • A description of the sample (including source, batch or lot number, date, and time
1095 the sample was received for testing)
 - 1096
 - 1097 • A description or reference (e.g., standard operating procedure) to each method,
1098 including any calculations or weight or measurement of the sample used for each
1099 test
 - 1100
 - 1101 • A complete record of all data (including graphs, charts, and spectra)
 - 1102
 - 1103 • A statement of results of the tests and their relation to acceptance criteria
 - 1104
 - 1105 • The initials or signature of the analyst and the date of the test
 - 1106

1107 **B. Laboratory Controls**

1108

1109 Under proposed § 212.60, a PET center would have to have written test procedures
1110 (see FDA recommendations on standard operating procedures (SOP)⁵) that describe
1111 how to conduct each test for components, in-process materials, and finished products.
1112 Appropriate sampling and testing procedures would have to be established to ensure
1113 that PET drug products conform to appropriate standards, including established
1114 standards (e.g., relevant USP monographs) of identity, strength, quality, and purity.
1115 Analytical tests would have to be suitable for their intended purpose and have sufficient
1116 sensitivity, specificity, and accuracy. If a USP analytical test method is used, it should
1117 be verified that the method works under the actual conditions of use.

1118

1119 Alternate testing methods can be used, provided the PET center has demonstrated at
1120 least equivalency to the regulatory method. Analytical test methods should be
1121 validated. The FDA and USP have published information for determining the
1122 appropriate analytical parameters (e.g., accuracy, precision, linearity, ruggedness) that

⁵ Recommendations on SOP are available at www.fda.gov/cder/regulatory/pet.

1123 should be used to validate a method (see ICH Q2A *Text on Validation of Analytical*
1124 *Procedures* and USP General Chapter <1225> *Validation of Compendial Methods*).

1125
1126 Most analyses use reference standards. PET centers should establish the reference
1127 standards identified in the analytical procedure or SOP. When a primary reference
1128 standard is obtained from an officially recognized source (e.g., USP), the material
1129 usually does not need further testing if it is stored under conditions consistent with the
1130 supplier's recommendations. However, if a PET center establishes its own reference
1131 standard, data to fully confirm the material's identity and purity should be established
1132 and documented. Documentation such as reference spectra or other supporting data to
1133 prove the identity and purity of the reference standard may be available from the
1134 supplier.

1135
1136 Under proposed § 212.60(f), equipment would have to be routinely calibrated and
1137 maintained according to the established written procedures (see Section V). PET
1138 centers should verify that the equipment is in good working condition at the time the
1139 samples are analyzed.

1140
1141 Any reagent or solution prepared on-site should be adequately controlled (including
1142 temperature control, if applicable) and properly labeled with respect to identity,
1143 composition, and expiration date.

1144
1145 Raw test data (such as chromatograms, spectra, and printouts) and any calculations
1146 performed should be documented and become part of the batch production and control
1147 record. Records should have information such as the source of the test material, a
1148 description of the appearance of the material, the amount used, test and acceptance
1149 criteria, and an entry for data and interpretation of results. Laboratory controls should
1150 be followed and documented at the time of performance. Deviation from written
1151 procedures should be documented and justified. Any out-of-specification results
1152 obtained should be investigated and documented.

1153

1154

1155 IX. STABILITY TESTING

1156

1157 A. Regulatory Requirements

1158

1159 Preliminary draft proposed 21 CFR 212.61 would require the establishment of a written
1160 stability testing program for each PET drug product. This program would have to be
1161 used to establish suitable storage conditions as well as expiration dates and times.

1162

1163 B. Guidance on Stability

1164

1165 The PET drug molecule should remain stable during the course of storage of the PET
1166 drug product. Appropriate parameters should be evaluated to establish and document
1167 the stability of a PET drug product under proposed storage conditions. Examples of
1168 stability parameters include radiochemical identity and purity, appearance, pH, stabilizer

1169 or preservative effectiveness, and specific activity. Appropriate stability-indicating
1170 methods that can distinguish degradation products and impurities should be used.
1171 Stability testing of the PET drug product should be performed at the highest radioactive
1172 concentration, and the whole batch volume in the intended container/closure should be
1173 stored. At least three production runs of the final product should be studied for a time
1174 period equal to the labeled shelf life of the PET drug product.
1175

1176

1177 X. FINISHED DRUG PRODUCT CONTROLS AND ACCEPTANCE CRITERIA

1178

1179 A. Regulatory Requirements

1180

1181 Preliminary draft proposed 21 CFR 212.70 would require that specifications be
1182 established and met for each PET drug product batch, including identity, strength,
1183 quality, purity, and, if appropriate, sterility. The proposed regulation would require the
1184 implementation of procedures to ensure that a product is not released until appropriate
1185 laboratory testing is completed, reviewed, and approved by an appropriate releasing
1186 authority.
1187

1188 Proposed 21 CFR 212.71 would require a PET center to reject PET drug products that
1189 fail to meet acceptance criteria. The quality control unit would have to identify and
1190 segregate the product. There would have to be predetermined procedures for
1191 investigating the cause of the problem and preparing a timely report on the occurrence,
1192 including a description of the corrective action taken, where appropriate.
1193

1194

1195 B. Finished Product Testing

1196

1197 Methods of PET drug production may differ from one site to another; therefore, there
1198 may be specific impurities to assess depending on the method of production, such as
1199 kryptofix in FDG F 18. Approved NDA specifications, or the IND accepted
1200 specifications, should be used. Under proposed § 212.70, PET centers would have to
1201 ensure that each batch of PET drug product meets its established acceptance criteria,
1202 except for sterility (see Section X.C), before it is given final release.
1203

1204

1205 C. Microbiological Tests for Sterile PET Drugs

1206

1207 The USP General Chapter <85> *Bacterial Endotoxins Test* (BET) should be performed
1208 for a sterile PET drug that is intended for injection. The harmonized BET in Supplement
1209 2 of USP 24 NF 19 contains gel-clot and photometric methods for endotoxin
1210 measurement.
1211

1212

1213 The USP General Chapter <71> *Sterility Tests* provides information about media and
1214 incubation conditions. Sterility testing should be performed within a day after the
completion of PET drug production in a controlled area such as an LAFW with clean-
room apparel. Aseptic techniques should be used for sterility testing. The greatest risk
of false-positive results arises in the sampling and transfer of the test aliquot from the

1215 vial to the media. It may be convenient to apply direct inoculation into commercial
1216 media. The media should be observed after days 3, 7, and 14 after inoculation, but it is
1217 prudent to observe the media more often during the first week of incubation.

1218

1219 If the result of any BET exceeds the acceptance limit, or if a sterility test is positive for
1220 microbial growth, a complete investigation should be conducted immediately and
1221 documented. Corrective actions based on the results of the investigations should be
1222 implemented promptly.

1223

1224

D. Accepting and Releasing a Batch (Lot)

1225

1226 The quality control unit or designate should review all laboratory testing and
1227 documentation from the batch record to determine whether or not the PET drug product
1228 has met all acceptance criteria. If the product has met acceptance criteria, the quality
1229 control unit should sign and date the release sections of the batch record and sign a
1230 release for human administration. In a larger PET center where there is a separate
1231 quality control unit, decisions made by the quality control unit to reject batches should
1232 not be subject to further review or revocation by another organizational unit.

1233

1234 In many cases, modifications to this standard procedure for product release may be
1235 appropriate. For example, transportation deadlines may justify a prerelease for
1236 distribution before all elements of testing and review are finalized. Other than sterility
1237 testing, all end-product tests should be completed or in progress at the time of shipment
1238 or distribution. Under proposed § 212.70, these tests would have to be completed prior
1239 to final release for human administration. When it is determined that all acceptance
1240 criteria have been met, the PET center should then provide a notice of final release to
1241 the receiving facility so that the dose can be given to the patient. There should be
1242 effective procedures for immediate notification of the receiving facility if there is
1243 evidence of an out-of-specification result and for documenting the fate of such a drug
1244 product.

1245

1246 PET drugs that have a very short half-life (e.g., ammonia N 13) can be produced in
1247 multiple sub-batches on the same day. End product testing of the initial sub-batch can
1248 be conducted, provided a sufficient number of sub-batches (beginning, middle, and end)
1249 have been validated. For routine production in this circumstance, the release of
1250 subsequent sub-batches can be qualified if the initial sub-batch meets all acceptance
1251 criteria. In certain cases, testing each sub-batch for certain attributes prior to release
1252 may be appropriate (e.g., for pH determination in ammonia N-13 production method
1253 using Devarda's alloy catalyst).

1254

1255

E. Rejection and Reprocessing

1256

1257 Under proposed § 212.71(a), a batch of a PET drug product that fails to meet
1258 established specifications would have to be rejected, and the quality control unit would
1259 have to identify and segregate the product. Proposed § 212.71(b) would require that

Draft — Not for Implementation

1260 documentation of the investigation of a nonconforming product include the results of the
1261 investigation and final disposition of any rejected product.

1262
1263 Under proposed § 212.70 (d), a drug product may be reprocessed if preestablished
1264 procedures (set forth in production and process controls) are followed and the finished
1265 product conforms to specifications before final release. When the option for
1266 reprocessing is exercised, the event should be documented and conditions described in
1267 a brief deviation report. Examples of reprocessing could include a second passage
1268 through a purification column to remove an impurity, or a second passage through a
1269 filter if the original filter failed the integrity test.

1270

1271

1272 **XI. LABELING AND PACKAGING**

1273

1274 **A. Regulatory Requirements**

1275

1276 Preliminary draft proposed 21 CFR 212.80 would require that:

1277

1278 • A PET drug product be suitably packaged and labeled to ensure that the integrity
1279 of the product is maintained during storage, handling, and shipping.

1280

1281 • Labels and packaging operations be controlled to prevent labeling and product
1282 mix-ups.

1283

1284 • All information stated on each label be contained in each batch production
1285 record.

1286

1287 **B. Recommendations on Labeling and Packaging**

1288

1289 Regardless of the scope of operation of a PET center, appropriate measures should be
1290 taken to handle labels in a way that prevents mix-ups with any other labeling materials.

1291

1292 A PET drug product should be labeled with adequate, legible identifying information to
1293 prevent errors during storage, shipment, and use. Labels can be computer generated
1294 or handwritten.

1295

1296 A string label can be used by PET centers to label the immediate container provided
1297 that there is a way to associate the label with the vial if the label were to come off.

1298 Different approaches can be used as long as the approach ensures that the required

1299 information is available on the label. A label identical to that affixed to the container
1300 shield should be incorporated into the batch production record. A final check should be
1301 made to verify that the correct label has been affixed to the container and the shield.

1302

1303 For PET centers producing and distributing a large volume of PET drugs, the quality
1304 control unit should verify the contents of each label for accuracy and completeness.

1305

1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351

XII. DISTRIBUTION

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.90 would require the development of procedures to ensure that only PET drug products that have been suitably released will be shipped and that the shipment will not adversely affect the product. PET centers would have to maintain distribution records for PET drug products.

B. Recommendations

For PET centers distributing to affiliated institutions, outside clients, or outside pharmacies, information on the method of shipment and the contact person at the final destination should be included. A system should be in place by which the distribution of each batch of PET drug product can be readily determined to permit its recall if necessary. A recall would consist of notifying the receiving facility, pharmacist, and the patient's physician, if known. When the receiving facility disposes of the recalled drug, the PET drug producer should obtain a signed statement from the receiving facility confirming the recalled drug has been disposed of and describing the manner in which it was disposed.

XIII. COMPLAINT HANDLING

A. Regulatory Requirements

Preliminary draft proposed 21 CFR 212.100 would require that procedures be developed and implemented for receipt and handling of all complaints pertaining to a specific PET drug product, including review by the quality control unit to determine compliance with specifications and to initiate an investigation into the problem. A file for drug product complaints would have to be maintained. The file would have to contain a complete record of the drug involved, the complainant, the nature of the occurrence, and the investigation and response to the complaint. A PET drug product implicated in a complaint could not be reprocessed and would have to be destroyed in accordance with applicable Federal and State law.

B. Recommendations

The quality control unit should be responsible for collecting as much information as possible about the drug and the nature of a complaint and for completing an investigation of the matter as soon as possible. Corrective action should be taken immediately if there is any reason to believe that an adulterated drug was implicated in the complaint. Under proposed § 212.100(c), complaints would have to be maintained in a file designated for that purpose. Complaint files should be easily retrievable by the quality control unit for review and trending.

1352

1353

1354 **XIV. RECORDS**

1355

1356

A. Regulatory Requirements

1357

1358

Preliminary draft proposed 21 CFR 212.110(a) would require that all records be maintained at the PET center or another location that is reasonably accessible to responsible officials of the PET center and FDA investigators.

1359

1360

1361

1362

Proposed § 212.110(b) would require that all records referenced in part 212 be kept for at least 1 year from the date of release of a PET drug product.

1363

1364

1365

B. Recommendations

1366

1367

The regulation would require that records be stored at a PET center or another location that is reasonably accessible. A reasonably accessible location is one that would enable the PET center to make requested records available to an FDA investigator in a reasonable period of time during an inspection. The records would have to be legible and stored in a manner that prevents their deterioration and/or loss.

1368

1369

1370

1371

1372

1373

Forms for collecting data should be kept to a minimum by designing multipurpose documents and eliminating redundancy, where possible. It is prudent to have as much of the required information within the batch production record as possible. Records can be kept electronically.

1374

1375

1376

1377

1378

Other records that should be kept include information relating to the composition and quality of the PET drug product and operation of the production processes, such as laboratory records, out-of-specification results, master and batch records, distribution records, and complaint files. Records relevant to materials and PET drug products would have to be kept at least 1 year from the date of final release. Validation reports should be kept as long as the systems are in use.

1379

1380

1381

1382

1383

REFERENCES

- 1384
1385
1386
1387 FDA. *Guide to Inspection of Computerized Systems in Drug Processing*. February
1388 1983.
1389
1390 FDA. *General Principles of Process Validation*. May 1987.
1391
1392 FDA. *Sterile Drug Products Produced by Aseptic Processing*. June 1987.
1393
1394 FDA. *Q2B Validation of Analytical Procedures: Methodology*. May, 1977.
1395
1396 FDA. *Q2A Text on Validation of Analytical Procedures*. March, 1995.
1397
1398 FDA. *Reviewer Guidance — Validation of Chromatographic Methods*, November 1994.
1399
1400 FDA. 21 CFR Part 11; Electronic Records; Electronic Signatures. FR Notice 7/21/99
1401 (64 FR 39146).
1402
1403 U.S. Pharmacopeia. <71> *Sterility Tests*. USP 24 NF 19, 2000
1404
1405 U.S. Pharmacopeia. <85> *Bacterial Endotoxins Test*. USP 24 NF 19, Supplement 2,
1406 2000.
1407
1408 U.S. Pharmacopeia. <823> *Radiopharmaceuticals for Positron Emission Tomography –*
1409 *Compounding*. USP 24 NF 19, 2000.
1410
1411 U.S. Pharmacopeia. <1015> *Automated Radiochemical Synthesis Apparatus*. USP 24
1412 NF 19, 2000.
1413
1414 U.S. Pharmacopeia. <621> *Chromatography*. USP 24 NF 19, 2000.
1415
1416 U.S. Pharmacopeia. <821> *Radioactivity*. USP 24 NF 19, 2000.
1417
1418 U.S. Pharmacopeia. <1225> *Validation of Compendial Methods*. USP 24 NF 19, 2000.
1419
1420