

Revision of USP General Chapter Radiopharmaceuticals for Positron Emission Tomography—Compounding <823>

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ABSTRACT This *Stimuli* article presents the reasons for the proposed revision of General Chapter *Radiopharmaceuticals for Positron Emission Tomography—Compounding <823>*, as well as the basis for each of the major changes. The objectives of this *Stimuli* article are four-fold: (1) provide background about the need for the proposed revision, (2) offer rationale for each major change, (3) initiate discussion, and (4) solicit public comments that will be reviewed and considered by USP's Expert Committee.

INTRODUCTION AND HISTORY

The first USP monograph for a positron emission tomography (PET) drug was published in 1989 (1). This monograph described acceptance criteria for identity, strength, quality, and purity characteristics associated with Fludeoxyglucose F 18 Injection. More monographs were published for various PET drugs throughout the 1990s so that the total number of USP monographs for PET drugs now stands at 12. In addition to individual monographs, USP has published two informational general chapters for PET drugs. The first was General Chapter *Automated Radiochemical Synthesis Apparatus <1015>* (2). This chapter described a quality assurance (QA) program for equipment, reagents, documentation, and software used in the production of PET drugs. The second was General Chapter *Radiopharmaceuticals for Positron Emission Tomography—Compounding <823>* (3). This chapter provides an extensive QA program for compounding PET drugs.

The FDA Modernization Act became law in 1997 and required that PET drugs be compounded in accordance with USP monographs and general chapters until FDA established current good manufacturing practice (CGMP) regulations for PET (4). In 2005, FDA issued a proposed rule for PET CGMP and indicated that different CGMP requirements should be applied to investigational and research PET drugs to allow more flexibility during the development of these drugs (5). Because the provisions in <823> are generally less specific and explicit than those proposed by FDA, FDA determined that <823> would be adequate to ensure that investigational and research PET drugs are produced safely. FDA recently published final regulations (the Final Rule) (6) and an accompanying guidance document (the Guidance) (7) for PET CGMP. When this Final Rule becomes effective on 12 December 2011, chapter <823> as published in

USP 32 will officially constitute the minimum CGMP requirements for investigational and research PET drugs used in human subjects under an Investigational New Drug application (IND) or under the approval of a Radioactive Drug Research Committee (RDRC) (8), and all other PET drugs will be subject to FDA's new CGMP requirements. It should be noted that the revisions now being proposed to <823> will not be enforceable as part of the Final Rule unless the reference in the Final Rule to USP 32 is updated to reflect the official publication in which the revised <823> is published.

At the time the monographs and general chapters for PET drugs were published by USP in the 1990s, most PET drugs were produced and used within research or medical institutions. Since then, the environment where PET drugs are produced and used has changed significantly. Today, research and medical institutions continue to produce and use PET drugs for investigational and research purposes. In addition, commercial producers supply most PET drugs used in routine diagnostic imaging procedures. PET imaging agents also have attracted the interest of pharmaceutical companies as potential tools to accelerate and reduce the cost of traditional drug-discovery efforts. Finally, numerous efforts are underway to develop new routine diagnostic imaging agents for use in cardiology, oncology, and neurology. Thus, the use of PET imaging agents today spans discovery, research, clinical development, and routine diagnostic imaging procedures.

RECOMMENDATIONS

The diversification of PET during the past 15 years has resulted in new requirements for the PET environment, including a greater number of PET drugs, higher production levels, shorter synthesis times, shorter quality control (QC) times, more complex syntheses, and increased regulatory oversight. To understand these changes, USP jointly sponsored two symposia with the Society of Nuclear Medicine (SNM) during SNM's annual meetings in 2008 and 2009 (9,10). USP staff and RMI EC members (see *Appendix 1* for membership) presented talks and led discussions about historical trends and changes in the PET environment.

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One goal of these symposia was to describe issues related to *USP* general chapters for PET drugs and to gather feedback from the PET community. The *USP*–SNM joint symposia and current regulatory considerations led RMI EC to conclude that the general chapters for PET drugs must be revised. Deficiencies in the current version of <823> include the following:

- Differences in the organization of <823> compared to the Final Rule (5) and Guidance (6)
- Further enhancement of <823>'s flexible provisions by incorporating items such as periodic quality indicator test (PQIT), a 30-hour initiation time frame for sterility testing, and conditional final release according to FDA's PET CGMP requirements
- Need for consistency with other revision efforts for *USP* general chapters
- Inappropriate methodologies for system suitability and quantitative analysis in current chromatographic tests
- Lack of defined frequency for certain QC tests
- Lack of discussion about the timing of the completion of certain QC tests relative to product release
- Lack of requirements for out-of-specification (OOS) investigations for QC tests.

The Revision Process for <823>

To address these deficiencies, RMI EC proposed the establishment of an Ad Hoc Advisory Panel (Advisory Panel) composed of academic and industrial members of the PET community (see *Appendix 2* for membership). The goal of the Advisory Panel was to advise RMI EC about suitable revisions to <823> in accordance with *USP*'s mission. The formation of the Advisory Panel was completed in late 2008, and beginning in July 2009 the Advisory Panel met numerous times. The outcome of this effort is summarized here.

Differentiation between <823> and <797>

USP General Chapter *Pharmaceutical Compounding—Sterile Preparations* <797> (11) describes procedures and requirements that are designed to reduce the risks associated with the use of compounded sterile preparations (CSPs). Because most PET drugs are sterile solutions intended for intravenous administration, they must be handled in accordance with <797>. The Advisory Panel wishes to differentiate the applicability of <797> and <823>. As noted above, <823> describes requirements for the production and compounding of PET drugs, typically as injectable solutions in a multidose vial or bulk pharmacy package. Once a PET drug has been produced or compounded according to <823>, <797> applies to the handling of the PET drug. The most common example of such handling is the dispensing of the PET drug into unit doses according to the practice of pharmacy or medicine. Based on the nature of the dispensing process and the short half-life of positron-emitting radionuclides, the handling of PET drugs is consistent with the description of low-risk CSPs, and these PET drugs can be handled in a segregated compounding area if a less than 12-hour beyond-use date is assigned.

In summary, <823> when revised supersedes <797> regarding the production and compounding of PET drugs. Once a PET drug has been produced or compounded according to <823>, <797> applies to the drug's dispensing.

ORGANIZATION OF REVISED <823>

To reflect the new role of <823> in the Final Rule on PET CGMP and to uphold PET compounding practice, the title of the proposed revision of <823> has been changed to *Positron Emission Tomography—Drugs for Compounding, Investigational, and Research Uses*. By means of compounding, pharmacists (or other qualified individuals working under the authority and supervision of a physician) fulfill an essential health-care need—providing patients with medications tailored to their needs. In some cases compounding pharmacists provide a drug that is not commercially available. In other cases the patient may be allergic to certain ingredient(s) of the drug, or the dosage form may not be suitable for administration to the patient. In addition to giving patients access to otherwise unavailable or more appropriate PET drugs, compounding may also be used for teaching or QC purposes.

To streamline general chapters related to PET drugs, the Advisory Panel decided to consolidate key standards and requirements stated in <1015> into the proposed revision of <823>. Consequently, <1015> will be deleted from *USP–NF*. In addition, a new general chapter numbered <1823> will be developed to supplement <823>. Although the title of this new general chapter has not been formally established, it will describe concepts, technologies, and procedures for the preparation of PET drugs. These supplemental descriptions are more suitable for an informational general chapter. This is consistent with *USP*'s General Chapter Design Project, which is an effort to exclude nonenforceable information from general chapters numbered less than 1000 (12).

Following are the sections in the proposed revision of <823>:

- Definitions
- Adequate Personnel and Resources
- Quality Assurance
- Facilities and Equipment
- Control of Components, Materials, and Supplies
- Process and Operational Controls
- Stability
- Controls and Acceptance Criteria for Finished PET Drugs
- If a PET Drug Does Not Conform to Specifications
- Reprocessing
- Labeling and Packaging

The remainder of this *Stimuli* article summarizes each section.

Definitions

The proposed revision of <823> contains a definitions section to clarify technical terms. These definitions apply only to words and phrases as they are used in the proposed revision and may not be suitable for other parts

of *USP–NF*. Most of the definitions are self-explanatory and well understood, but some are discussed below to illustrate the rationale for the most important definitions.

Production vs. Compounding—For purposes of the proposed revision of (823), production is defined as the process of synthesis or formulation of a PET drug for investigational or research uses. In addition, *compounding* is defined as the process of synthesis or formulation of a PET drug for use in pharmacy and medicine. These definitions are consistent with FDA's use and the differentiation between drug manufacturing and compounding (13). Because the proposed revision of (823) is intended to support both production and compounding activities, the use of these terms has been carefully controlled to achieve these goals and to avoid confusion.

Batch vs. Lot—The Final Rule (6) uses the terms *batch* and *lot* interchangeably. In addition, the Final Rule appears to use *lot* synonymously with *sub-batch*. These definitions and usages may be confusing to the PET community. To differentiate the specific meaning of each term, the Advisory Panel and RMI EC propose that the definition of *batch* apply explicitly to the PET drug and that the definition of *lot* apply only to components used in the preparation (including QC) of a PET drug.

PET Drug—The definition of *PET drug* in the Final Rule (6) includes "any non-radioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug." The Advisory Panel and RMI EC believe this definition is too broad. Instead, we propose to define *PET drug* as "a finished form of a radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is intended for human administration in diagnosis or therapy." We believe that non-radioactive reagents, reagent kits, ingredients, and target materials are components used to produce a PET drug and that radionuclide generators, accelerators, electronic synthesizers, and computer programs are ancillary items used in the production of PET drugs.

To avoid the use of different terms with the same meaning, the term *PET radiopharmaceutical*, which appears in several places in the current version of (823), has been replaced with *PET drug* in accordance with these definitions.

QA vs. QC—QA and QC are commonly used interchangeably in the PET community even though the terms have fundamental differences. The proposed revision of (823) separately defines QA and QC and outlines the differences in the first paragraph of the section on *Quality Assurance* (see below).

Strength—The Final Rule (6) defines *strength* as radioactivity on a volume or weight basis. The Advisory Panel and RMI EC believe that this definition risks confusing *strength* and *specific activity* because it is not clear if weight refers to the cold mass of the active pharmaceutical ingredient or the overall weight of the solution. In addition, it is common practice in PET to define strength

on a volume basis. Therefore, *strength* is defined in the proposed revision of (823) strictly based on volume (e.g., mCi/mL or MBq/mL).

Validation vs. Verification—The Final Rule (6) does not define the terms *validation* and *verification*. It must be noted that the terms *validate* and *validated* are used in the Guidance (7) without any definition. Validation and verification are essential and complementary elements in the CGMP process. The proposed revision of (823) defines *validation* as the "establishment of documented evidence that a method, process, or system accomplishes its intended requirements." In addition, *verification* is defined as "confirmation that an established method, process, or system meets predetermined acceptance criteria." It is helpful to think of validation as "building the right thing," and verification is "building it right." These definitions are separate from the same terms used for analytical procedures/methods.

Adequate Personnel and Resources

Adequate personnel and resources are addressed in several sections of the current version of (823), including *Compounding Procedure Verification*, *PET Radiopharmaceutical Compounding for Human Use*, and *Quality Control*. The proposed revision includes a separate section titled *Adequate Personnel and Resources*, which requires a sufficient number of personnel with appropriate education and training and indicates that the number of personnel depends on the size and complexity of the facility.

This section of the proposed revision of (823) reflects the layout of the Final Rule (6) addressing personnel and resources as the first topic. Part 212.10 of the Final Rule asks, "What personnel and resources must I have?" In response, the Final Rule states that "the facility must have sufficient personnel with necessary education, background, training, and experience to perform their assigned functions ... with adequate resources to enable personnel to perform these functions" (6). The regulation does not fully define that statement but notes that the responsibilities and assigned duties must be clearly identified in written policies. The Guidance (7) defines personnel qualification requirements more specifically as training in CGMP, ongoing training in new or revised procedures, and maintenance of an employee file that includes CV, copies of diplomas, and certificates of training.

The proposed revision of (823) requires training in synthesis and purification methods used to make and test PET drugs. Training also should address aseptic assembly of all sterile components, including the techniques and equipment used to achieve International Organization for Standardization (ISO) Class 5 environmental conditions. Media fills are required in triplicate to qualify a new operator, but an annual review should be performed to determine if repeat annual simulations are necessary. The Final Rule (6) does not specify the training qualifications, but the Guidance (7) in the section titled *Production and Process Controls* describes the assessment of

aseptic processes by media fills. The Guidance requires the same initial qualification but requalification annually with one media fill (7).

Quality Assurance

This section describes the difference between QA and QC in the production of PET drugs. QA covers all matters that influence the product's identity, strength, purity, and quality. QC is a subset of QA that deals with testing materials and products to determine if they meet acceptance criteria. The QA function typically consists of oversight activities, and the QC function consists of execution activities (14).

Facilities and Equipment

Although the current version of (823) does not have a dedicated section for facility and equipment, it describes requirements for aseptic workstations, automated chemistry modules, QC equipment, and others throughout the chapter. In the proposed revision, these requirements are organized into one section titled *Facilities and Equipment*. The information in this section has been augmented and includes topics that were omitted in the current version of (823), as well as clarifications for some topics such as system suitability, qualification, certification, calibration, cleaning, and maintenance. In addition, this section contains portions of (1015) that have been consolidated during the proposed revision. Some of the important elements in this section are discussed below.

System suitability requirements for chromatography systems—The Guidance states that at least one injection of a standard is required for system suitability (7). The Guidance does not address reproducibility as a part of system suitability but instead references *USP General Chapter Chromatography* (621), which describes system suitability requirements (resolution, replicate injections, and tailing factor) (15). Although these requirements are important for chromatography systems used in PET, the number of injections required for replicate injections in (621) may not be appropriate because of the nature (i.e., half-life) and number of different PET drugs and/or the number of batches prepared at a typical academic or commercial PET facility. Consequently, the proposed revision of (823) describes two acceptable system suitability approaches that can be used for chromatographic systems.

The first approach is the construction of a calibration curve that can be used for an extended period of time. In routine use, the injection of a known standard is used to verify that the calibration curve is appropriate for use in subsequent sample injections. The second approach is the use of a single-point calibration created from two injections of a known standard at the beginning of each testing cycle. In each case, the requirement for replicate injections is met by comparison of multiple injections, either within a single testing cycle or over an extended period of time. Together, the approaches described in the proposed revision of (823) provide more flexibility and clarity than does the Guidance.

Cleaning of equipment—The current version of (823) describes the cleaning of equipment but does not specifically address cleaning between batches of PET drugs. As a result, there has been confusion about the acceptability of cleaning between batches. The proposed revision of (823) addresses this deficiency by describing requirements for cleaning equipment between multiple batches of one or more PET drugs. This approach is consistent with the equipment cleaning requirements described in the Guidance for PET CGMP (7).

Control of Components, Materials, and Supplies

The proposed revision of (823) requires that components, materials, and supplies used in the preparation of PET drugs must be controlled to avoid problems. A designated person must be responsible for these activities. Written specifications for all components, materials, and supplies must be established, including appropriate storage conditions. These items must be stored in a controlled-access area according to specifications. Each shipment of these items must be logged in and examined to ensure that they meet established specifications. This compliance can be accomplished by a procedure, a test, or a manufacturer's Certificate of Analysis (COA) that includes actual test results for the lot. For precursors, a COA and an identity test such as melting point are required. Alternatively, a COA can be used as the sole acceptance criterion for the precursor if finished-product testing is performed to ensure the correct precursor has been used. Membrane filters used for end-product sterilization must have a COA or a certificate of conformance that certifies the product complies with the manufacturer's written specifications. If sterile filter testing is performed only on a skip-lot basis, a COA may not be available for every lot. These receipt requirements are less prescriptive and are more flexible than the Guidance (7) and are suitable for the investigational and research environment for PET drug production.

The current version of (823) does not specify how long receipt records for components, containers, and closures must be retained. The proposed revision requires that receipt records of completed examinations and tests should be maintained for one year after the expiration of the item or one year after the release of any batch produced from the items, whichever is longer. This is in line with the minimum storage period of all records and documentation referenced in the Final Rule (6).

The proposed revision of (823) describes a simplified growth-promotion test to ensure the viability of media used for sterility testing. In this test, a single microorganism is used to demonstrate that the media are capable of supporting microbial growth. The proposed revision includes an alternative to the simplified growth-promotion test wherein positive controls can instead be used during routine sterility testing.

Process and Operational Controls

Process controls—A master formula must be established for each PET drug, and designated person(s) must be responsible for ensuring the activities summarized in the master formula are conducted properly. Acceptance criteria must be established in the master formula for each PET drug, and if a *USP* monograph exists, *USP* standards are the minimum acceptable requirements unless there are acceptance criteria specified in an FDA-approved IND or RDRC protocol. The master formula for each PET drug must include final sterile 0.22- μm membrane filtration (for parenteral dosage forms) and 0.45- μm particle filtration (for products administered by inhalation). The master formula also must include a description of routine cleaning, components and materials, synthetic process, formulation process including stabilizers and buffers, calculations used in key parameters, and QC tests and their frequency. This approach is consistent with the master production and control record described in the Final Rule (6) and Guidance (7).

Documented studies must be performed to ensure that the process described in the master formula yields a PET drug that meets the defined acceptance criteria. The testing must be completed on three batches that cannot be consecutive. This allowance was added to account for a batch that may not be completed because of factors that are not relevant to the quality characteristics of the PET drug (e.g., cyclotron malfunction, hardware malfunction, and so on). This allows the completion of process validation without the potential losses that could occur with three *consecutive* batches. All processes described in the master formula should be reviewed annually and updated as needed.

Appropriate controls must exist for computer-controlled equipment that is described in the master formula to ensure that changes are instituted only by authorized personnel and that these changes are documented and verified.

The current version of (823) states that “a minimum of one verification study that shows the product meets acceptance criteria must be conducted on an annual basis.” This annual verification batch is not required in the Final Rule (6) for PET drugs “for which each entire batch undergoes full finished-product testing to ensure that the product meets all specifications.” The requirement for an annual verification batch has been removed in the proposed revision of (823).

Operational controls—A batch record must be completed to document each batch of a PET drug. A batch record is a subset of the master formula and is used primarily for record-keeping purposes. This approach lends itself to the repetitive nature of the PET drug environment and is consistent with the batch production and control record described in the Final Rule (6) and Guidance (7). The batch record must contain the lot numbers for all components, materials, and supplies used, a description of the procedures followed, raw analytical data, and results from QC tests. Entries in the batch record should be made directly after analysts perform the activity. Completed batch records and associated docu-

mentation must be maintained for one year after batch release. This corresponds to the record retention described in the Final Rule (6).

Aseptic operations—The proposed revision of (823) requires the use of aseptic technique in the preparation of the PET drug vial assembly and all components downstream of the membrane sterilizing filter in an ISO Class 5 environment. After the PET drug vial is assembled, it can be removed to a noncontrolled environment. During aseptic operations, operators are required to wear clean laboratory clothing, forearm sleeves, hair cover, beard and moustache covers (as appropriate), and sanitized gloves (rather than “sterile” gloves specified in (797)) that cover the wrist. This is consistent with the Guidance in *Facilities and Equipment* (7). The proposed revision of (823) also allows the preparation of multiple PET drug vial assemblies in a single aseptic operation cycle.

For sterility test inoculations, the proposed revision of (823) requires that inoculation of sterility test media must be performed in a manner that is consistent with personnel radiation exposure requirements. If media tubes have a screw-cap opening inoculations must be performed in the aseptic workstation, but if the media tubes have a septum cap inoculation can occur in a shielded area that does not contain a HEPA (high-efficiency particulate air) filter. The Guidance does not differentiate inoculation requirements for screw-cap or septum-cap media tubes.

Stability

The proposed revision of (823) is consistent with the Guidance regarding stability evaluation for PET drugs. In each case, the PET drug must meet acceptance criteria for stability-indicating QC tests at the beginning of the shelf-life period and at expiry. The stability-indicating QC tests include: radiochemical purity, appearance, pH, and stabilizer content (or preservative effectiveness).

The proposed revision of (823) also adopts two of FDA’s conditions for stability testing that are not addressed in the current version of (823), including:

- Stability testing must be performed at the highest strength (see *Definitions*) in the intended final product container-closure, and
- At least three batches of the final PET drug should be stored according to proposed conditions and should be studied for a time equal to the proposed shelf life.

Controls and Acceptance Criteria for Finished PET Drugs

Flexible requirements for QC testing—To provide a more flexible environment for QC testing of PET drugs, the proposed revision of (823) contains the following changes:

- If a QC test procedure is described in *USP–NF*, the accuracy and reliability of this procedure does not require validation (16). The suitability of the testing procedure requires verification only under the actual conditions of use.

- Noncompendial QC tests for PET drugs must be reliable and specific. In addition, this is consistent with the guidance for analytical methods validation (17), which states that “analytical procedures should be fully developed and validation completed when the NDA [New Drug Application] or ANDA [Abbreviated New Drug Application] ... is submitted.”
- In addition to finished-product QC testing, the revised (823) includes in-process testing and continuous process monitoring of an attribute by means of statistical process controls. These two options are new items added to the Guidance (7).

Must and should QC tests—The proposed revision of (823) divides QC tests into two categories: those that must be performed and those that should be performed.

Must QC tests must be performed on each batch before release for human administration. These tests include:

- Determination of radiochemical purity and identity for all dosage forms
- Determination of pH for parenteral dosage forms
- Bacterial endotoxin test (BET) for parenteral dosage forms
- Sterility test for parenteral dosage forms.

The current version of (823) permits a reduction in the frequency of sterility tests after a record of successful sterility tests is established for a particular PET drug. The revision states that the first batch “prepared each day shall be subject to a sterility test using cultivation methods.” Because sterility testing and BET are both biological assessments, the proposed revision of (823) includes a reduction in the frequency of the BET. Like the sterility test, the BET must be performed on the first batch of each PET drug prepared each day.

Should QC tests are recommended at intervals sufficient to ensure the consistent production of PET drugs that meet acceptance criteria for quality and purity. This stipulation allows PET drug producers the flexibility to determine QC testing frequency based on scientific rationale. This approach is consistent with the Guidance, which introduces the concept of PQIT (7). With PQIT, FDA recognizes that certain noncritical attributes (e.g., radionuclidic purity, low-level nontoxic impurities, class 3 residual solvents, and others) are not as significant as the final acceptance specifications of a finished PET drug. For a noncritical QC attribute, FDA allows a PET drug producer to conduct PQIT at predetermined intervals rather than on a batch-to-batch basis.

Removal of in-process 20-minute endotoxin limit test—The current version of (823) describes an in-process 20-minute endotoxin test. The Advisory Panel and RMI EC believe that this test is out of date and is too prescriptive (i.e., a 20-minute process and “incorporating positive controls in the range of 5 EU per mL to 175 EU/V, where V is the maximum volume of injection”). Therefore the proposed revision of (823) does not include the 20-minute in-process test.

Extended time for inoculation of sterility test media—The current version of (823) requires that sterility tests should be initiated within 24 hours of sterile filtration. The proposed revision of (823) extends this time to “within 30 hours” to allow additional flexibility and to

better accommodate the daily cycle of production and testing for PET drugs. This is consistent with the Final Rule (6), which also requires that sterility testing be started within 30 hours after the completion of PET drug production [see 212.70(e)]. The proposed revision of (823) allows the extension of this time period beyond 30 hours provided that the extended period does not significantly reduce the viability of a USP indicator organism (e.g., *E. coli*) in the decayed PET drug. This provision, which is consistent with the Guidance (7), was included to address staffing issues that could result from weekends and holidays.

Conditional final release—The current version of (823) does not allow the conditional release of PET drugs in the event of a QC equipment malfunction. This concept was first introduced by FDA in the proposed rule for PET CGMP (5) and is also included in the Final Rule (6). The proposed revision of (823) includes provision for conditional release and includes requirements that are consistent with the FDA documents (6,7). Conditional release of PET drugs should be rare if equipment is properly maintained, but this provision is important because of the short half-life of PET drugs.

If a PET Drug Does Not Conform to Specifications

If a PET drug does not conform to specifications the first action generally is to investigate the QC process. Such investigations typically are known as out-of-specification (OOS) investigations. OOS investigations are not addressed in the current version of (823).

The Guidance for OOS investigations of traditional pharmaceuticals (19) does not apply well to short-lived PET drugs. Section 212.71 of the Final Rule (6) addresses the question, “What actions must I take if a batch of PET drug does not conform to specifications?” This section requires the rejection of PET drugs that do not meet specifications but does not discuss OOS investigations and the possibility of analytical error as a cause of OOS results. The result is that none of the FDA documents adequately address OOS investigations for PET drugs. To resolve these shortcomings, the proposed revision includes a description of OOS investigations.

The focus of an OOS investigation is to determine if the OOS QC finding is the result of an analytical error or a true product failure. If the investigation determines that the OOS result is caused by analytical error, the original test results are invalidated. Thus, an OOS result does not necessarily mean that the batch fails and must be rejected. However, if the investigation determines that the OOS result indicates a true product failure, the batch must be rejected, and the cause of the failure must be investigated. Rejected batches may be reprocessed.

Reprocessing

Batch reprocessing is not addressed in the current version of (823). Section 212.71 of the Final Rule (6) permits the reprocessing of rejected batches, and a section about reprocessing has been added to the proposed revision of (823). This section describes requirements for the repro-

cessing of PET drugs that do not conform to established specifications, including examples of possible reprocessing operations and the testing requirements for reprocessed PET drugs. Key requirements are that reprocessing must be described in established procedures and that the reprocessed batch must be tested to ensure it meets the acceptance criteria for the PET drug.

Labeling and Packaging

Labeling requirements for PET drugs are not described in the current version of <823> but are included in a separate section in the proposed revision. The section has been divided into information required on the immediate container for PET drugs and on the immediate shielding during storage and use.

CONCLUSION

This article has described the process and rationale for RMI EC's revision of <823>. Since the original publication of this chapter, technological, marketplace, and regulatory changes have necessitated this chapter's revision. This article has also reviewed the most important changes in the proposed revision of <823>. These changes will serve the needs of patients, research subjects, medical institutions, clinical researchers, pharmaceutical companies, commercial PET drug producers, and all members of the PET community.

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APPENDIX 1. RMI EC MEMBERS

Members of the RMI EC include: Thomas E. Boothe, PhD, Patricia E. Cole, MD, PhD, Ravindra K. Kasliwal, PhD (FDA Liaison), Jerome M. Lewis, MD, PhD, Sally W. Schwarz, RPh, MS, Steve S. Zigler, PhD, and Joseph C. Hung, PhD (acting chair).

APPENDIX 2. ADVISORY PANEL MEMBERS

Members of the Advisory Panel include: Marc S. Berridge, PhD, Joseph C. Hung, PhD, Donald Kinney, BCNP, Maxim Kiselev, PhD, Scott Mason, PhD, Steve Mattmuller, MS, Sally W. Schwarz, MS, Jean-Luc Vanderheyden, PhD, and Steve S. Zigler, PhD (chair).