



U.S. Pharmacopeia  
The Standard of Quality<sup>SM</sup>

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Division of Dockets Management  
U.S. Food and Drug Administration 8769 12 JAN -3 P3:02  
Department of Health and Human Services  
5630 Fishers Lane, rm. 1061  
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**CITIZEN PETITION OF  
UNITED STATES PHARMACOPEIAL CONVENTION (USP)  
TO AMEND FDA POSITRON EMISSION TOMOGRAPHY (PET)  
REGULATIONS TO REPLACE THE EXISTING INCORPORATION BY  
REFERENCE OF USP'S PET-RELATED CHAPTER <823> IN THE 32<sup>ND</sup>  
EDITION OF USP (UNITED STATES PHARMACOPEIA) WITH THE  
UPDATED CHAPTER <823> IN USP 35 PUBLISHED NOVEMBER 1,  
2011**

The United States Pharmacopeial Convention (USP) submits this Citizen Petition under Title 21 of the *Code of Federal Regulations (CFR)* Part 10, § 10.30 and requests that the Commissioner of the United States Food and Drug Administration (FDA) amend the regulation in Title 21 *CFR*, Part 212, § 212.5(b) pertaining to current good manufacturing practices (CGMPs) for positron emission tomography (PET) drugs, which currently incorporates by reference USP *Chapter <823>* of USP 32/NF 27.<sup>1</sup> 21 *CFR* § 212.5(b) permits investigational and research PET drugs to comply either with the federal PET CGMP regulations in Part 212, or with USP's standards for compounding investigational and research PET drugs ("USP CGMP standards") in *Chapter <823>* of USP 32/NF 27, which is incorporated by reference. Specifically, USP requests that Title 21 *CFR* § 212.5(b) be amended to incorporate by reference *Chapter <823>* of USP 35/NF 30, which was published November 1, 2011, and is the most current version of USP's CGMP standards for investigational and research PET drugs. Amending Title 21 *CFR*, Part 212, § 212.5(b) to incorporate by reference the USP CGMP standards in *Chapter <823>* of USP 35/NF 30 will ensure that those producing PET drugs under an Investigational New Drug application (IND) or under the approval of a Radioactive Drug Research Committee (RDRC) will, as intended by FDA, have the option of either conforming to FDA's PET CGMP regulations *or* to the most current version of USP's CGMP standards.

By way of background, PET is a medical diagnostic tool involving imaging of various body organs following injection of radioactive drugs. Because PET images can show biochemical changes of an organ or tissue, they can be more helpful than other scanning technologies (X-ray, CT or MRI) in the diagnosis of such diseases as cancer and heart disease. Originally, PET drug products were produced in academic institutions, but then production of such drugs became more commercialized, particularly as PET scans began to be reimbursed by private insurance plans.

<sup>1</sup> See, 21 *CFR* § 212.5(b) (2011).

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The first USP monograph for a PET drug was published in 1989. 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. The passage of the FDA Modernization Act (FDAMA) in 1997 required that a PET drug be compounded in accordance with *USP* monographs and general chapters to assure under the adulterated drug provisions of the Federal Food, Drug, and Cosmetic Act (FDCA) section 501(a) that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess.<sup>2</sup> FDAMA directed FDA to develop appropriate procedures for the approval of PET drugs as well as appropriate PET CGMPs, and for USP's special statutory role to continue under FDCA 501(a) until two years after the date on which FDA establishes these procedures and requirements, which as detailed below occurred in 2009 and became effective December 12, 2011. This petition is submitted with regard to these FDA regulations, and specifically those pertaining to FDA's authority under FDCA 501(a).<sup>3</sup> It should be noted that the FDAMA authority under which FDA has acted and this petition is submitted, is distinct from the separate role for USP compendial standards under the adulterated drug provisions of FDCA section 501(b); this citizen petition does not pertain to, or affect, the status and federal enforceability of USP standards for drugs the name of which are recognized in *USP/NF*, including standards for strength, quality or purity.<sup>4</sup>

In 2005, FDA issued a proposed rule for PET CGMPs 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.<sup>5</sup> FDA has determined that the USP CGMP standards in *Chapter <823>* are adequate to ensure that investigational and research PET drugs are produced safely under appropriate conditions, consistent with section 501(a)(2)(B) of the [Food, Drug and Cosmetic] Act, and are appropriate CGMP requirements for the investigational and research stage of development.<sup>6</sup>

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<sup>2</sup> FDA Modernization Act § 121(b)(1) (1997).

<sup>3</sup> FDA Modernization Act § 121(c)(1)(A)(i) and (ii) (1997). *See also*, FDA Modernization Act § 121(c)(2).

<sup>4</sup> By the terms of the USP General Notices, and FDCA section 501(b), USP compendial standards do not become official and enforceable until they are deemed official by USP. The updated General Chapter <823> which is the subject of this petition does not become official, as stated in *USP 35/NF 30*, until May 1, 2012. However, the requested action in this Citizen Petition is for FDA to immediately incorporate by reference the updated <823> as published November 1, 2011. FDA may do this because FDA's original incorporation by reference was done with regard to the Agency's CGMP authority in FDCA 501(a), not that pertaining to USP's official compendial role in 501(b); only the latter depends on USP standards as "recognized in an official compendium." FDA has discretion to incorporate by reference these published USP standards whenever it wishes to under its FDCA 501(a) authority. In any case such action would also be consistent with USP *General Notices* section 3.10, which provides for the early adoption of published standards before the official date (i.e. *USP* standards *may* be conformed with upon publication; they *must* be conformed to when they become official). The incorporation by reference here essentially provides those subject to certain PET standards under 21 CFR 212.5(b) with the option of complying with these updated USP GMPs immediately if they wish, as an alternative to FDA's GMP regulations.

<sup>5</sup> 70 *FedReg* 55040 (September 20, 2005).

<sup>6</sup> FDA Guidance PET Drugs – Current Good Manufacturing Practice (CGMP) (Small Entity Compliance Guide) pg. 3 (August 2011).

In 2009, FDA issued final CGMP regulations for PET drugs in Title 21 CFR Part 212 but delayed their implementation for two years.<sup>7</sup> As stated above, 21 CFR § 212.5(b) permits investigational and research PET drugs to comply either with the federal PET CGMP regulations in Part 212, or with the USP CGMP standards in Chapter <823> of USP 32/NF 27, which is incorporated by reference. The federal CGMP regulations in 21 CFR Part 212 for PET drugs became effective on December 12, 2011.<sup>8</sup> Because these regulations are now in effect, the USP CGMP standards in Chapter <823>, published in USP 32/NF 27 and incorporated by reference in 21 CFR § 212.5(b) are likewise effective standards for investigational and research PET drugs. All other PET drugs are now subject to FDA approval as a New Drug Application (NDA) or Amended New Drug Application (ANDA) and all FDA approved PET drugs (those not investigational or research) must specifically comply with the CGMP requirements of 21 CFR Part 212.

In January 2011, USP initiated revisions to the USP CGMP standards in Chapter <823> and after public notice and comment, including comments from FDA, published those revisions in USP 35/NF 30 on November 1, 2011. USP 35/NF 30 will become official on May 1, 2012.<sup>9</sup> As a result, the USP CGMP standards for investigational and research PET drugs in Chapter <823> of USP 32/NF 27 and incorporated by reference in 21 CFR § 212.5(b) are being superseded by the revisions published in USP 35/NF 30. Unless 21 CFR § 212.5(b) is amended to incorporate by reference USP 35/NF 30 as the source of the current USP CGMP standards for investigational and research PET drugs, producers of investigational and research PET drugs that opt to comply with USP Chapter <823> of USP 32/NF 27 in accordance with the regulation will be following and implementing outdated standards.

#### A. ACTION REQUESTED

USP respectfully requests that FDA amend 21 CFR § 212.5(b) to incorporate by reference USP 35/NF 30, which contains the most current version of USP CGMP standards in Chapter <823> that are applicable to compounded, investigational and research PET drugs.

#### B. STATEMENT OF GROUNDS

The USP CGMP standards in Chapter <823> of USP 32/NF 27, have now been superseded by the revisions published in USP 35/NF 30. Continuing to reference USP 32/NF 27 in 21 CFR § 212.5(b) will create confusion among producers as to the appropriate USP CGMP standards to follow going forward as an FDA-provided optional alternative to the agency's CGMP regulations for PET drugs. Additionally, requiring

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<sup>7</sup> 74 FedReg 65409 (December 9, 2009).

<sup>8</sup> On December 9, 2011, FDA issued a press release that it does not intend to take enforcement action for the next six months against a PET facility currently producing PET drugs for clinical use for a failure to submit a NDA by December 12, 2011, provided that the facility is in compliance with all other FDA requirements, including CGMPs. These facilities are not subject to FDA enforcement until after June 12, 2012.

<sup>9</sup> This means the revised USP CGMP standards in Chapter <823> may be complied with beginning November 1, 2011, but they *must* be complied with on and after May 1, 2012.

compliance to outdated USP CGMP standards fosters inconsistency and may lead to a lack of uniformity in the quality of investigational and research PET drugs.

### **C. ENVIRONMENTAL IMPACT STATEMENT**

Under *21 CFR* § 25.30(j), this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore neither an Environmental Assessment (EA) nor Environmental Impact Statement (EIS) is required.

### **D. ECONOMIC IMPACT**

Pursuant to Title *21 CFR* §10.30(b), information on economic impact is only to be submitted when requested by the Commissioner following a review of this petition. USP is not aware of any information that would be likely to occasion a request by the Commissioner for an economic impact statement. Moreover, the incorporation by reference sought by this petition pertains to the provision of optional compliance alternatives in lieu of otherwise applicable federal regulatory requirements, i.e. the incorporation by reference does not result in any mandatory action.

### **E. CERTIFICATION**

The undersigned certifies that, to my best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.



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