USP Monographs
Revision or Deletion?
…and what about the future?

Steve Zigler, Ph.D.
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Conflict of Interest

- Employee of PETNET Solutions, a Siemens Company
- USP volunteer and member of 2010-2015 Expert Committee Small Molecules 4
- I will mention several approved and investigational agents, but will not discuss any indications or uses
- In addition, I am speaking as a private citizen, not a USP volunteer or a Siemens employee
Objectives

- Discuss regulatory history of PET drugs
- Discuss historical role of USP monographs for PET drugs
- Understand upcoming changes resulting from the FDA’s conclusion of their requirements in the Modernization Act
- Discuss problems with existing PET monographs
- Describe potential future pathways for PET monographs in the USP

Will the role of the USP monographs for PET drugs change on December 12, 2011?
Before the FDA Modernization Act of 1997 (FDAMA)—

- Tumultuous debate started in the late 1980’s about how PET should be regulated in the US
- Centered around practice of pharmacy vs. FDA regulation
- Debate ended with the passage of FDA Modernization Act of 1997
- Section 121 contained provisions for PET
FDA Modernization Act of 1997

Required that compounded PET drugs—

- Be compounded by or on the order of a state-licensed practitioner in accordance with state law (i.e., practice of pharmacy/medicine)
- Be compounded in conformance with USP standards and monographs
  - Must have a USP monograph
  - Must comply with USP general chapter <823> Radiopharmaceuticals for Positron Emission Tomography—Compounding
FDA Modernization Act of 1997

**Required the FDA to develop**—

- Appropriate review procedures for approval of PET drugs
- GMP regulations specifically for PET drugs

**FDA cannot require NDA’s or ANDA’s for PET drugs until two years after completion of these tasks**

**FDAMA enabled a commercial compounded PET drug industry in the US without FDA approvals**
FDA Modernization Act of 1997

Current status—

- Final PET GMP’s published in December 2009
- Created 21 CFR Part 212, “PET Drugs – Current Good Manufacturing Practice (CGMP)”
- PET GMP’s became effective on December 12, 2011
- Therefore, the FDA has completed the required tasks described in FDAMA

On June 12, 2011, commercial PET drugs…

…must be produced under an NDA or ANDA

…(due to FDA’s recent extension of filing deadline)
NDA/ANDA’s for PET Drugs

**FDA Approvals for PET drugs—**

- **[¹⁸F]Fluoride ion**
  - NDA 17-042 (New England Nuclear)*
  - NDA 22-494 (National Cancer Institute)*

- **[¹⁸F]FDG**
  - NDA 20-306 (Methodist Medical Center)*
  - NDA 21-768 (Weill Medical College)
  - NDA 21-870 (The Feinstein Institute)
  - ANDA 79-086 (PETNET Solutions)

- **[¹³N]Ammonia**
  - NDA 21-219 (The Feinstein Institute)

*Withdrawn from sale, but not for reasons of safety or effectiveness.*

Apologies if I’ve missed any!
Non-approved PET Drugs

**Some examples**—

- Non-proprietary products:
  - $[^{18}\text{F}]$FLT, $[^{18}\text{F}]$FMISO, $[^{18}\text{F}]$FDOPA, $[^{11}\text{C}]$acetate, $[^{11}\text{C}]$methionine, $[^{15}\text{O}]$water, $[^{15}\text{O}]$oxygen + many others
- Proprietary products currently in various pipelines
- PET drugs for investigational and research uses may continue to be produced according to an IND or RDRC (Radioactive Drug Research Committee)

**Key question**: Does it make sense to have USP monographs for research or investigational products?
Summary of Upcoming Changes

Until June 12, 2011—

- Commercial PET drugs may be compounded according to a USP monograph
- Investigational PET drugs may be produced according to an IND or RDRC, but do not require a USP monograph

On June 12, 2011—

- Commercial PET drugs must be manufactured according to an NDA/ANDA
- Investigational PET drug requirements unchanged

A USP monograph is not required for either scenario
Monographs for PET Drugs

- Which PET drugs have monographs
- Problems and challenges
- Potential future pathways
PET Monographs

USP monographs exist for these products—

- $^{18}$F]FDG
- $^{[18}F]$Fluoride ion
- $^{18}$F]F-DOPA
- $^{11}$C]Methionine
- $^{11}$C]Raclopride
- $^{11}$C]Mespiperone
- $^{11}$C]Flumazenil
- $^{11}$C]Acetate
- $^{13}$N]Ammonia
- $^{15}$O]Water
- $^{11}$C]Carbon monoxide
- $^{82}$Rb]Rubidium chloride

Already commercially supplied under an approved NDA/ANDA

Will be commercially supplied under NDA/ANDA (after 6/11/12)
Problems with PET Monographs

- Non-radioactive reference standards (e.g., $[^{19}\text{F}]$FDG) from USP may or may not be available to support a particular PET drug monograph
- Some monographs contain outdated analytical methods
- PET drug monographs were published with minimal validation data for analytical test methods
Challenges with PET Monographs

- Sponsors of several existing PET drug monographs are IND holders, not NDA/ANDA applicants as is the case with USP monographs for non-PET drugs
- Several PET drugs with a USP monograph are unlikely to ever be commercialized (i.e., be the subject of an NDA or ANDA)
- It is not clear if all PET drugs with a USP monograph are active (i.e., does anyone produce and use them?)
- Due to the short-half life of PET drugs, it is difficult to independently verify analytical methods
- Potential differences between US and EU markets regarding practice of pharmacy/medicine for the preparation of PET drugs
Potential Future Pathways

- Do nothing? *(Not an option!)*
- **Update** monographs for PET drugs that have an active NDA or ANDA. *(Based on approved applications. This must be done.)*
- **Update** monographs for PET drugs that do not have an active NDA or ANDA. *(Requires validated analytical methods. Who will do the work? Who will verify it?)*
- **Petition USP to remove** monographs for PET drugs that do not have an active NDA or ANDA. *(Is there a hidden downside due to existing standards of care? How would the process get started?)*
- **Going forward**, only consider future monographs for PET drugs that have an active, approved NDA or ANDA. *(Probably a good idea!)*
- Provide reference standards to USP for products with existing monographs *(Who will do this?)*