

# **Harmonizing FDA Regulation and the Practice of Pharmacy: Challenges and Opportunities**

**Plus an update on PET Drug User Fees**

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# Disclosures

- Employee of PETNET Solutions, Inc.
- Will not discuss usages or indications for any approved and investigational agents

# Learning Objectives

- Overview of FDA Draft Guidance documents related to pharmacy practice
- Overview of the changes of Board of Pharmacy Regulations related to USP 797
- Overview of the challenges and opportunities in harmonizing FDA Regulation and the Practice of Pharmacy
- Review specific examples from certain States
- Overview of recent changes to PET Drug User Fee Structure

# FDA Regulation of Pharmacy Practice

- Unless a 503(b) Outsourcing Facility then the FDA does not routinely inspect pharmacies – they defer to individual State Boards of Pharmacy (BOPs)
  - However, FDA has enforcement authority all the way to the patient. FDA will exercise enforcement discretion.
- BOPs review FDA Guidance Documents on compounding and some attempt to enforce (Example: Insanitary Conditions Draft Guidance Document)

# FDA Regulation of Pharmacy Practice

## Draft Guidance Documents released by FDA

- Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act (July 2016)
- Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act (July 2016)
- Insanitary Conditions at Compounding Facilities (August 2016)
- Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities (December 2016)
- Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities (December 2016)
- Mixing, Diluting, and Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (Revised Draft Guidance) (January 2017)

# USP Chapter <797> : focus on prevention

- Microbial Contamination
- Excessive bacterial endotoxins
- Variability in intended strength that exceed monograph limits
- Use of ingredients of inappropriate quality
- Unintended physical and chemical contaminants

# USP Chapter <797>

- Enforceable by the FDA and most State Boards of Pharmacy
  - (some States seem very eager to enforce the proposed USP 797 revision)
- Based on best sterile compounding practices and current scientific information
- Recognized as the national standard of practice
- Minimum practice and quality standards for compounding sterile preparations

# Purpose of Proposed 797 Revision

- Reorganized existing chapter to group similar topics together, eliminate redundancies, and clarify requirements. Key procedural information is placed in boxes so that it can be easily referenced and followed.
- Collapsed compounded sterile preparations (CSP) microbial risk categories from three to two and changed terminology. No sterile compounding is inherently “low risk” and preparation of all CSPs must be done carefully.
- Removed specific information on handling of hazardous drugs and added references to Hazardous Drugs—Handling in Healthcare Settings (USP800)
- Introduced terminology for “in-use time” to refer to the time before which a conventionally manufactured product used to make a CSP must be used after it has been opened or punctured, or a CSP must be used after it has been opened or punctured.



# Proposed USP <797>

## Summary of Major Changes:

3 risk levels changed to 2 categories distinguished by conditions under which they are made and time within which used	Removal of HD handling section and cross reference to USP 800
Quarterly requirement for Personnel Monitoring (visual observation of hand hygiene and garbing, MFT and ongoing GFS).	Quarterly requirement for Viable Air sampling and Surface sampling
BUD and Storage times changed with a maximum BUD of 45 days regardless of sterility testing	Introduction of “In-Use time” (time before which conventionally manufactured product or compounded dilution bag must be used after it is punctured)
Master formulation and compounding records will be required for all batch and non-sterile compounding	New guidance for sterility testing of CSP prepared in batch sizes of less than 40 (10% rule)
New placement requirements on use of isolators	Requirement of sterile wipes and cleaning tools that need to be re-sterilized but not sterile disinfectants

# Summary of Major Changes for PET Pharmacy Operation

CURRENT CHAPTER	PROPOSED CHANGES/NEW REQUIREMENTS
3 Risk Levels (Low, Medium & High)	2 Categories (1 & 2) – Based on Conditions Under which they are Made and Time in which they Will be Used
Yearly Low Risk Gloving/Gowning/Fingertip Qualification	Quarterly Operator Challenge on this Process
Yearly Low-Risk Operator Media-Fills	Quarterly Challenge
–	Introduction of “In-Use Time” for Conventionally Manufactured Products
–	Introduction of Sterile Sleeves

# Summary of Major Changes for PET Pharmacy Operation

CURRENT CHAPTER	PROPOSED CHANGES/NEW REQUIREMENTS
Semiannual Viable Air Sampling	Quarterly
Periodic Viable Surface Sampling	Quarterly
Suggested 20 <sup>0</sup> C or Cooler Temp	Must be 20 <sup>0</sup> C or Cooler Temp
–	Humidity Below 60% at All Times

\*Note: 20<sup>0</sup> C or cooler requirement is for worker comfort

# Impact to the PET Industry

- Dispensed PET doses are sterile injections of the radiopharmaceutical product
- Though all PET drug product manufacturing takes place under GMP conditions (21 CFR Part 212), the fact that the dispensed doses are sterile injections makes the small pharmacy practice component of the operation subject to USP 797 guidelines
- Net Impact: Increased Workload for Pharmacy Employees & Increased Overall Expense to all PET Pharmacies

# Board of Pharmacy Compounding Regulations

- Many States have Incorporated USP 797 by Reference into their Laws
- Other States Have Written their own Sterile Compounding Regulations (e.g. California, Texas & Massachusetts)
- The Expectations can be Quite Different than those in 797 (more stringent, more lenient)
- State Regulations Also Tend to Change on a More Frequent Basis – Requiring Continued Reassessment to Remain in Compliance
- Difficult to Maintain Uniform Procedures Across Numerous States
- Decreases the Flexibility of a Company and Increases Operational Costs

# Board of Pharmacy Update

## New Sterile Compounding Regulations and Expectations



- Most if not all 50 States have now drafted Sterile Compounding Regulations or Incorporated USP 797 (by Reference) into their Laws.
- The expectations can vary significantly from State to State and by Inspector to Inspector

# Board of Pharmacy Update

## New Sterile Compounding Regulations and Expectations



The most comprehensive new regulations for 2017 originated in three states:

- Texas
- California
- Massachusetts\*

\*Drafted and approved by the MA BOP and awaiting final approval from the state.

# Board of Pharmacy Update

## New Sterile Compounding Regulations and Expectations



### Oversight Crossing State Lines

- TX is Requiring all Non-Resident Pharmacies to Meet the Standards set for those Pharmacies Located within their State
- Required to have Third-Party Inspections for non-resident permits



# Board of Pharmacy Update

## New Sterile Compounding Regulations and Expectations



### 2017 California Sterile Compounding Revision

- More Comprehensive than the Previous CA Regulation Revision

### Areas of Focus impacting PET:

- Proper Attire in Segregated Compounding Area
- Demarcating the Segregated Compounding Area
- Covering CA & CETA Expectations for the ISO-5, CFU Certification

# Board of Pharmacy Update

## New Sterile Compounding Regulations and Expectations



### New MA Sterile Compounding Regulation

- Expected to be Implemented in Early 2018
- A 47 Page Document – Possibly the Most Comprehensive & Prescriptive Pharmacy Law Ever Released
- Many potential implications for PET (Classified Air, New Device Certification Demands, Increased Qualification Frequency)

# Board of Pharmacy Update

## New Sterile Compounding Regulations and Expectations



### Further Implications in MA

- MA is the last State not requiring non-resident pharmacies to be licensed
- A draft regulation currently exists for this process to begin
- Included: Inspections by MA Agents and/or Third-Party Vendors to Assure MA Laws are Followed
- Repercussions for all PET Pharmacies Shipping into the State

# Board of Pharmacy Update

## New Sterile Compounding Regulations and Expectations

SUMMARY



### Key Message

- New Sterile Compounding Regulations and Expectations continue to emerge and evolve
- PET Pharmacies may struggle to meet some of these expectations which will result in process and procedural changes
- Announcement of the creation of a separate USP Compounding Chapter for radiopharmaceuticals is a great opportunity to “right-size” the requirements

# Challenges

- PET Drug Manufacturing and Pharmacy co-located Model
- Some BOPs encroaching on manufacturing
- BOP inspections going further upstream into manufacturing activities
- BOPs struggle with where manufacturing ends and Pharmacy begins
- Environmental Monitoring (differences between USP 797 expectations and FDA expectations)
- Access to manufacturing area and pharmacy area

# Opportunities

- New USP Chapter <825> Compounding—  
Radiopharmaceuticals
- Get states to realize new chapter takes  
precedence (What do we do in the interim?)
- Federal Pharmacy standards (align all States)
- PET Drug Community must get involved

# User Fees for PET Drugs: Overview

# PET Drug User Fees (current state FY2017)

- In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA).
  - This was reauthorized by the Food and Drug Modernization Act of 1997 and again by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and in 2007.
- PDUFA authorized FDA to collect fees from companies that produce certain human drug and biological products.
  - Any time a company wants the FDA to approve a new drug or biologic prior to marketing, it must submit an application along with a fee to support the review process.
  - In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed.
- Previously, taxpayers alone paid for product reviews through budgets provided by Congress. In the new program, industry provides the funding in exchange for FDA agreement to meet drug-review performance goals, which emphasize timeliness.



# PET Drug User Fees (current state FY17)

## Basic PDUFA Construct

- Fee funds are added to non-fee funds and are intended to increase staffing and other resources to speed and enhance review process
- User fees pay for services that directly benefit fee payers\*
- Fee discussions with industry focus on desired enhancements in terms of specific aspects of activities in “process for the review of human drugs”

\*OMB Circular A-25; direct benefit distinguishes user fees from tax

# PET Drug User Fees (current state FY17): Performance Commitments and Fee Funding Have Evolved Since 1992

- **PDUFA I: 1993-1997**

- Added funds for pre-market review; reduce backlog and set predictable timelines (goals) for review action

- **PDUFA II (FDAMA): 1998-2002**

- Shorten review timelines; add review goals; add process and procedure goals; some added funding

- **PDUFA III (BT Preparedness & Response Act): 2003-2007**

- Significant added funding; increase interaction in first review cycle (GRMPs); allow limited support for post-market safety

- **PDUFA IV (FDAAA): 2008-2012**

- Increased and stabilized base funding; enhanced pre-market review; modernize post-market safety system

- **PDUFA V (FDASIA): 2013-2017**

- Small increase to base funding; review enhancements increase communication with sponsors; strengthen regulatory science & post-market safety; electronic data standards

# PET Drug User Fees (current state FY2017)

- User Fees for new drugs fall into 3 categories
  - Application Fees – one time fee per NDA
  - Establishment Fees – per manufacturing site per year
  - Product Fees – per product (annual)
  
- Application Fees specifically waived for FDG, NaF, and Ammonia

# PET Drug User Fees

## ■ Waivers and Fee Reductions

- Necessary to protect the public health
- Fee presents a “significant” barrier to innovation
- Fee exceeds FDA’s cost of the review process
- Fee would be inequitable because the product is similar to certain generic drugs that are not part of the user fee program

# PET Drug User Fees

In 2007 successful in lobbying Congress and FDA to achieve significant reduction in Est. Fee(1/6 for PET Drugs).  
~\$97,500

Background

## ■ 2016 User Fees

- Application Fee (w/clinical data) = \$2,374,200
- Establishment Fee = ~~\$585,200~~
- Product Fee = \$114,450

■ aNDA route resolved issue for FDG, Ammonia and NaF for currently approved indications

■ aNDA route does not solve problem for new indications of FDG, Ammonia and NaF or for other PET drugs

# PET Drug User Fees

## Fee Rates for FY 2016

- ~30% increase in application fee and product fee from 2012
- ~25% increase in establishment fee from 2012

**New biomarkers require clinical data**

TABLE 7—FEE SCHEDULE FOR FY 2016

Fee category	Fee rates for FY 2016
Applications:	
Requiring clinical data .....	\$2,374,200
Not requiring clinical data .....	1,187,100
Supplements requiring clinical data .....	1,187,100
Establishments .....	585,200
Products .....	114,450

**Biomarkers with existing notices of safety and efficacy by FDA or existing clinical data do not require clinical data**

**In accordance with Section 103(a)(3) of the FDA Amendments Act of 2012, the FY 2016 establishment fee for PET drug establishments is 1/6 of the ordinary fee, or \$97,533.**

# PET Drug User Fees – Example (current state FY17)

- Establishment Fees for 24 manufacturing sites = ~~\$14,044,800~~ per year (based on FY 2016 rates – before 1/6 reduction)
- Establishment fees alone present a barrier to PET drug innovation
- Relief from establishment fees is essential to the development of new PET drugs
- This relief was achieved in FY07 via Industry lobbying efforts

Actual Establishment Fee based on 1/6 reduction = \$2,340,792  
Fee Reduction Savings = \$11,704,008

# PET Drug User Fees 2017 Reauthorization (future state 2018-22)

- On April 14, 2017, leaders from the Senate HELP Committee and the House Energy & Commerce Committee released the first discussion draft of the 2017 FDA user fee reauthorization bill.
- The draft “FDA Reauthorization Act of 2017” would establish the framework for the next five years of these programs, from FY2018, which begins on October 1st of this year, through FY2022.
- The draft tracks the four individual user fee commitment letters negotiated between FDA and industry in 2016 and submitted to the Congressional Record, including important changes to the structure of all four user fee programs.



# PET Drug User Fees 2017 Reauthorization (future state 2018-22)

- Upon reviewing Congress' discussion draft, it appears the draft eliminates the reduced establishment registration fees for PET Drugs but replaces it with “program” fees.
  - For this reauthorization it appears the fees for NDA supplements and establishment fees are removed by section 102(a)(1)(C) and (G), respectively.
  - Establishment fees and product fees are replaced by “program fees,” with **no relief** provision for PET drugs.
- The exemption for PET drug applications from generic user fees is preserved (section 302(1)).

# PET Drug User Fees 2017 Reauthorization (future state 2018-22)

## How to calculate the “program” fee (approximation):

- Number of 2016 FDA NDA submissions – 2646
- Approximate 2018 total fees to be collected - \$900 million
- 80% (program fees) of \$900 million - \$720,000,000
- 20% (applications fees) of \$900 million - \$180,000,000
- 80% total divided by 2646 – approximately \$274,000 per NDA strength, or the “program” fee.

# PET Drug User Fees 2017 Reauthorization (future state 2018-22) Discussions with FDA (CORAR, MITA)

## FDA Response:

- “Based on our analysis, most PET sponsors would have reduced fees under PDUFA VI relative to PDUFA V.
- Currently, the sponsor of an approved PET product under an NDA would be invoiced for 1/6 of the establishment fee for each establishment as well as product fees for each approved product:
  - FY16 Product fees = \$114,450
  - FY16 Establishment fee at 1/6 PET rate = \$97,533

# PET Drug User Fees 2017 Reauthorization (future state 2018-22) Discussions with FDA (CORAR, MITA)

## FDA Response:

- Under the PDUFA VI fee structure, there would be no establishment fee(s). The sponsor of a PET product would only be invoiced for a program fee for each approved product:
  - Program fee (if PDUFA VI structure applied to FY16 revenue levels) = \$274,671
- Based on FY16 invoicing data, there are an average of 7.6 establishments per approved PET product.
- PET product sponsors may also qualify for PDUFA fee waivers , such as public health and barrier to innovation, and exemptions -- which would remain unchanged in the PDUFA VI agreement.

# PET Drug User Fees – Example (Current state FY2017 vs. Future state FY2018-22)

## Current State

Payment Example  
FY 2016 @ 24 sites

- Establishment Fee =  
\$2,340,792
- Product Fee =  
\$114,450
- Total User Fees =  
**\$2,455,242**

## Future State

Proposed Annual Payment Example  
FY2018-22

- Proposed “Program Fee”  
for 24 manufacturing sites =  
\$274,671 (based on PDUFA VI  
estimates)
- Potential Savings with  
“Program Fee” model =  
**\$ 2,180,571**

# PET Drug User Fees 2017 Reauthorization (future state 2018-22): **Key Takeaways**

- In PDUFA VI, establishment fees and product fees will be replaced by a single “program fee.”
  - Like product fees, program fees will be payable for each product
- For ANDAs, PDUFA VI preserves the exemption for PET drugs from all fees – application, supplement, drug master file, and facility fees.
- New “Program” Fee Structure may lead to a significant cost savings to NDA Sponsors
- Not penalized for multiple manufacturing sites
- Waivers may be possible for small entities

**Thank You!**

**Questions?**