

# **Role of USP Monographs and General Chapters**

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# USP Disclosure

- I have served as a USP volunteer in the area of PET drugs for 15 years
- Member of various Expert Committees and Expert Panels involved in USP monographs and general chapters pertinent to nuclear medicine

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# Topics

- Introduction to the USP and how it works
- Public standards for radiopharmaceuticals
  - General chapters
  - Radiopharmaceutical monographs
- Upcoming changes to general chapters and monographs
- Challenges/How to get involved

My goal is to demystify the USP and encourage more active involvement between the nuclear medicine community and the USP

What is the USP?

# Background

- USP is the abbreviation for U.S. Pharmacopeial Convention
- Founded in 1820 by a group of physicians who wanted to standardize the preparation and use of medicinal products
- Today, the USP is a non-profit scientific organization whose mission is to improve public health around the globe
- Develops public standards for identity, strength, quality and purity of medicines, food ingredients, and supplements
- Standards are located in a compendium of monographs and general chapters (“the USP”)

# Food Drug and Cosmetic Act

- Defines “official compendium” as the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary
- States that a drug...
  - is adulterated if the drug is represented as one in the USP, and its strength, quality, and purity differ from the standards in the USP
  - is misbranded if a product does not meet standards for packaging and labeling in the USP

# Food Drug and Cosmetic Act

- If a drug uses the title of the monograph, and it does not meet the monograph requirements, the drug is adulterated
- USP does not enforce standards
  - Enforcement of USP standards falls to the FDA
- It is acceptable to use alternative QC testing methods as long as you have validated the method



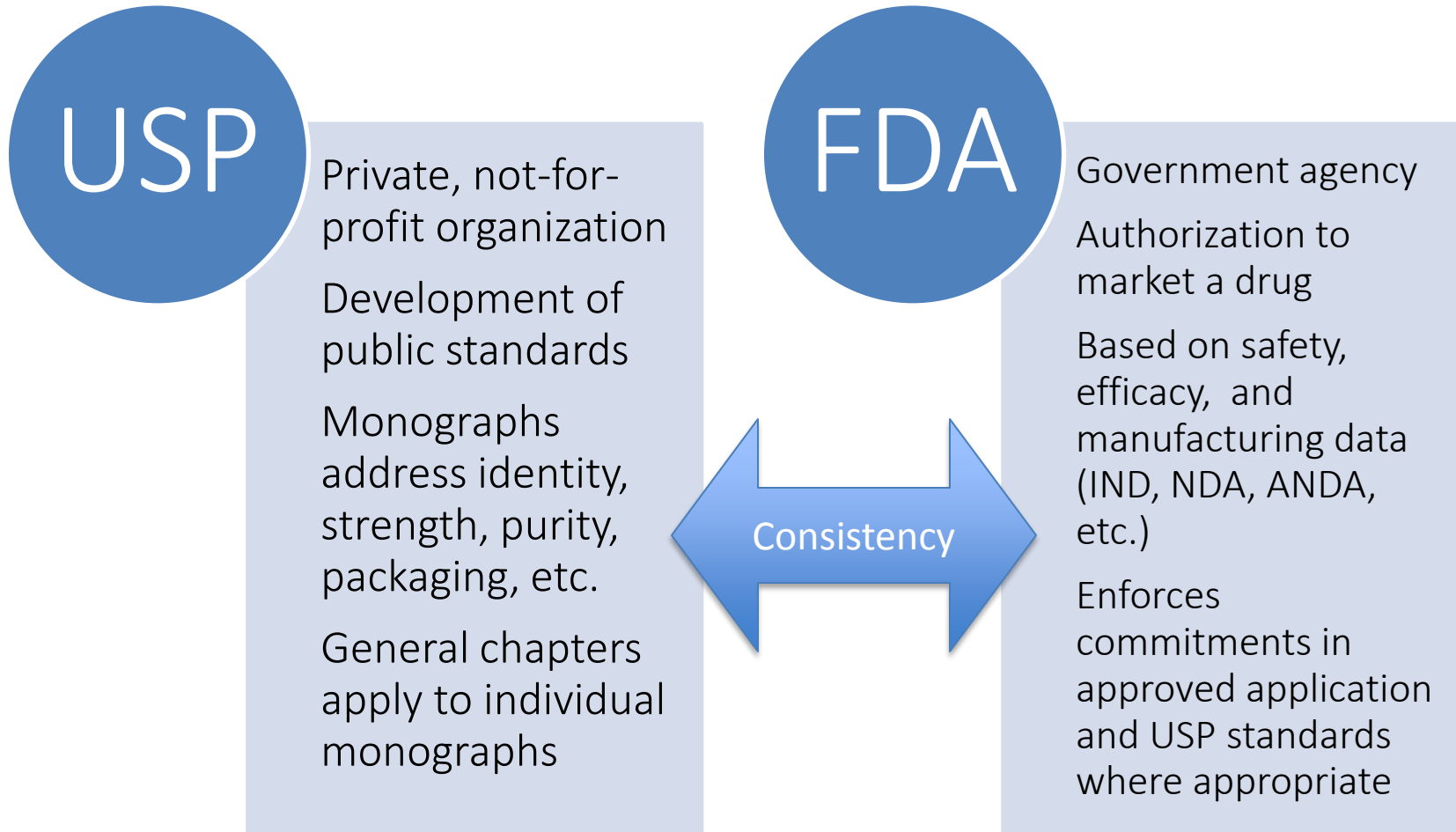
# How does the USP achieve its mission?

- Typically, USP standards are based on data contained in FDA-approved drug applications (NDAs and/or ANDAs)
- Data typically provided to the USP by sponsors who have FDA approval
- USP staff and expert committees (ECs) of volunteers review and assess data to ensure standards comply with contemporary views and science
- USP communicates changes and solicits public comments through a quarterly online journal (*Pharmacopeial Forum* or *PF*)
- Public provides input to USP through:
  - Volunteer service on expert committees
  - Data supplied by sponsors (typically NDA/ANDA holders)
  - Comments on PF articles



This is the  
“public” in USP  
public standards

# The USP is Separate from the FDA



# Interesting Note in 17th Revision of the USP (1965)



## PREFACE

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Despite efforts to gain consistency in nomenclature throughout the volume, some inconsistency will be evident in such groups as the insulins, two of which are named according to the promptness of onset and the duration of action, respectively.

In the interest of typographic simplicity, the titles for the U. S. P. radioactive preparations are of the form "I 131," e.g., Sodium Iodide I 131 Solution. These titles reflect the arbitrary adoption by the Revision Committee of a convention in keeping with a practice thoroughly established in the American pharmaceutical literature but contrary to international usage. The latter was recognized formally by action of the International Union of Pure and Applied Chemistry when it gave sanction to the form  $^{131}\text{I}$  in expressing the mass numbers and symbols of the radioactive nuclides.

## Fludeoxyglucose F 18 Injection

USP Monographs

# Monographs for Radioactive Drugs

- About 100 USP monographs exist radioactive drugs
- Four PET drugs; remainder for SPECT products

## *Current Status:*

- Many monographs have never been updated
- In some cases, monograph content is not consistent with the current practices
- May not be consistent with current regulatory expectations
- Some products no longer on the market

# Current Activities

- Non-approved PET drugs were recently omitted from the USP based on recommendations from PET community and SNMMI
- Monographs for non-PET radioactive drugs are currently under evaluation by an Expert Panel (EP)
- Three possible outcomes for each monograph
  - Maintain as is
  - Maintain with revision
  - Omit

# USP Monograph Development Process

Manufacturer submits proposal



USP initiates development

Monograph development/revision is initiated

Scientific Liaison performs technical review and drafts monograph

USP evaluates procedures requiring RS prior to publication and RS collaborative testing (not applicable to radiopharmaceuticals)

Proposal is published for 90-day public comment period

Scientific Liaison and Expert Committee review comments

Expert Committee votes on the proposal

If approved, the monograph is published in the USP and becomes official six months after publication unless otherwise indicated

# Monograph Development Time Line

- Depends on several factors, including sponsor participation, complexity of the information, etc.
- Typically three to six months for preparation of draft (Steps 1-2)
- Typically 18 to 24 months for a monograph to become official (Steps 1 through Step 7)
- If a revision needs to become official quickly, the Accelerated Revision process may be used



# Monograph Development Challenges

- Some sponsors refuse to share data with USP
- Submissions and/or comments from multiple sponsors
- Receipt of comments after the public review and comment deadline
- Insufficient data to support request for revision
- Long lead times for publication

# Monographs - *Latest Happenings*

- Monographs for PET drugs are also under revision
- The Pharmacopeial Forum (PF) recently published proposed revisions to monographs for:
  - Fludeoxyglucose F 18 Injection
  - Ammonia N 13 Injection
- NDA/ANDA holders strongly encouraged to read and comment to the USP
- Public comment period closes July 31

USP General Chapters

# Overview

- General chapters are referenced in USP monographs
- Each general chapter has a number associated with it
- Chapters numbered less than <1000> are enforceable
- Chapters numbered greater than <1000> are informational
  - Note: a chapter numbered <1000> or greater is enforceable if it is referenced in a chapter with a number below <1000>
- The USP has been updating enforceable chapters to remove content that is informational

# General Chapters related to Radiopharmaceuticals

- <821> *Radioactivity*
- <823> *Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses*
- <1821> *Radioactivity – Theory and Practice*
- <1823> *PET Drugs – Information*
- Others based on requirements of the dosage form
  - <85> *Bacterial Endotoxins*
  - <71> *Sterility*
  - Others

# General Chapters - *Latest Happenings*

- Chapter <823> was revised in 2013 to reflect FDA changes resulting from implementation of FDA Modernization Act
- Chapter <821> was revised in 2016 to update content and clarify enforceable aspects of radioactivity measurements
- Chapters <1821> and <1823> written to provide information on radioactivity measurements and PET drugs
- Chapter <823> is now undergoing a reformat revision to reflect the format in other three chapters
- Chapter <1015> *Automated Radiochemical Synthesis Apparatus* was removed with publication of <1823>

# Revision of General Chapter <821>

- Chapter <821> was revised and divided into two major sections:
  - General Considerations
  - Identification and Assay of Radionuclides
- General information was removed and included in <1821>

# General Chapter <821>

- USP monographs for radioactive drugs include specifications for:
  - Radionuclide identification and purity
  - Radiochemical identification and purity
  - Assay for radioactivity
- Purpose of <821> is to provide standards for these radioactivity measurements
  - Including instrument qualification, calibration, and performance checks



# General Chapter <1821>

- Contains non-enforceable information originally in <821> related to theory and practice of radioactivity measurements
- Describes:
  - Types of radioactive decay and emissions
  - Instrumentation for detection and measurement of radioactive emissions
  - Use of radioactive standards for instrument qualification and calibration

# General Chapter <1823>

- Recently developed to describe general information about PET drugs
- Describes:
  - PET radionuclides
  - Quality assurance, quality control, production and analytical methodologies for PET drugs
  - Quality attributes for PET drug monographs
  - Definitions of common terminology

# Key Concepts in <1823>

- Describes characteristics of PET drugs and why they are a unique class of products
- Recognizes that techniques and requirements may evolve during the development process (i.e., from pre-clinical, to investigational, and ultimately to commercial)
- Contains guidance for quality attributes described in USP monographs for PET drugs

# How to Get Involved

- Comment on proposed revisions
  - e.g., monograph revisions for FDG and ammonia is open for comment until July 31
- Provide data to support comments and recommendations
- Volunteer for membership on Expert Committees and Expert Panels
  - Stay tuned for the possibility of a dedicated EC in 2020
  - Chemistry expertise needed