HOUSEKEEPING SLIDES

In-Person Attendees

- Please submit your lunch order before 9:30 AM at the kiosk (located in the main hall) and pick-up during lunch break.
  - Lunch can be eaten within the room, or any tables in the main hallway.
  - Coffees and assorted beverages can be purchased at the kiosk throughout the day.
- Bathrooms are located behind the kiosk in the main hall.
- Any phone calls should be taken in the main hall, outside of the presentation room. Please ensure they are silenced throughout the presentations.
- There will be an opportunity to ask questions:
  - Please hold comments for the Open Discussion sections of the meeting.
  - Microphones will be available for use located in the room.

Wifi Network:
FDA-PUBLIC ACCESS
Password:
publicaccess

POSITRON EMISSION TOMOGRAPHY DRUGS: PRODUCT QUALITY, REGULATORY SUBMISSIONS, FACILITY INSPECTIONS, AND BENEFIT-RISK CONSIDERATIONS (MONDAY, NOVEMBER 13, 2023)

Welcome and Introductory Remarks

COALITION OF PET DRUG MANUFACTURERS

MITA MEDICAL IMAGING & TECHNOLOGY ALLIANCE

SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

FDA U.S. FOOD & DRUG ADMINISTRATION

Welcome

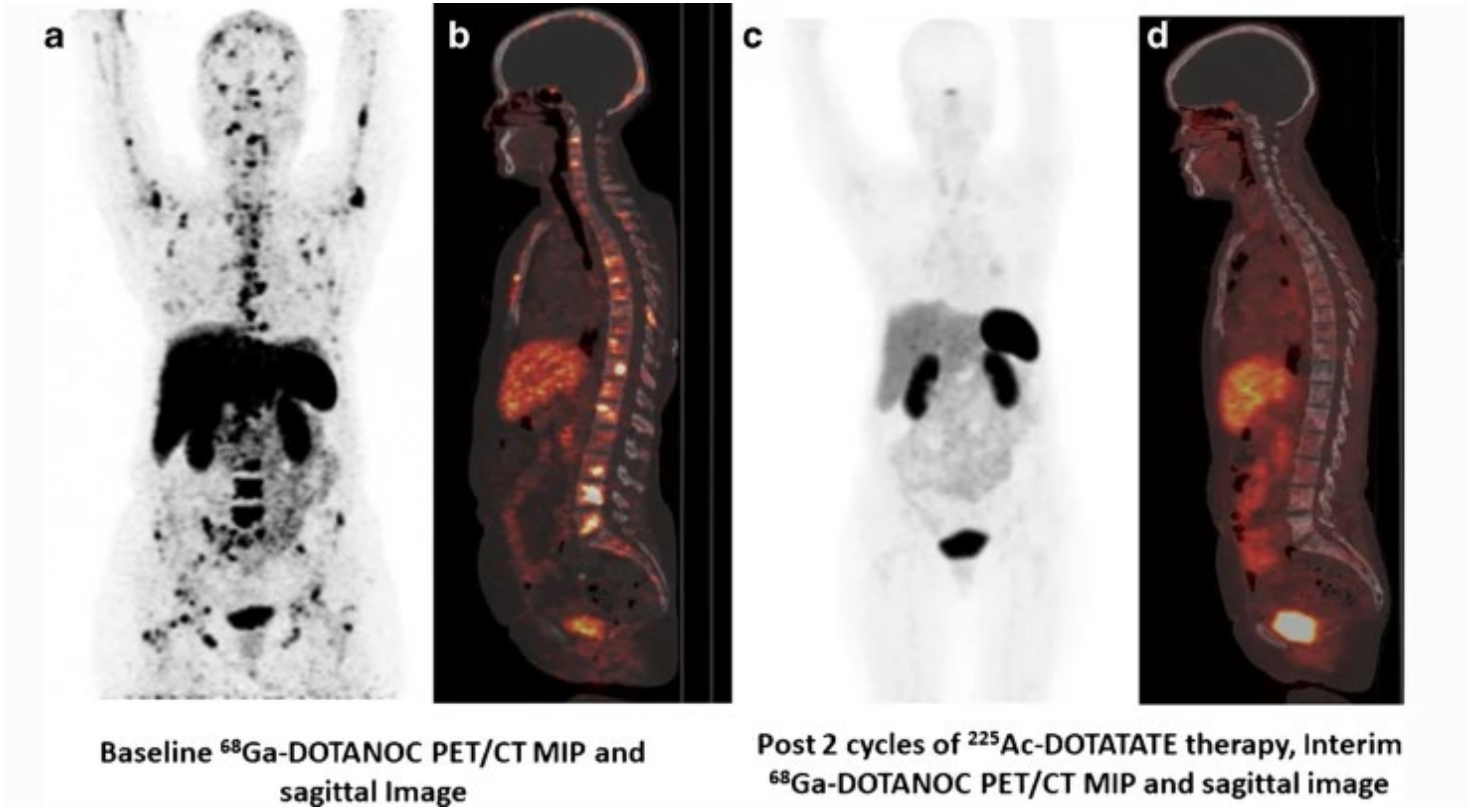
Cathy S. Cutler, PhD

President Elect
Society of Nuclear Medicine and Molecular Imaging

November 13, 2023

Overarching Mission: Working together we advance healthcare for patients

- Ensure safety and quality of radiopharmaceuticals
- Patient access to radiopharmaceuticals
  - Diagnoses
  - Inform patient management
  - Monitor response
  - Change management



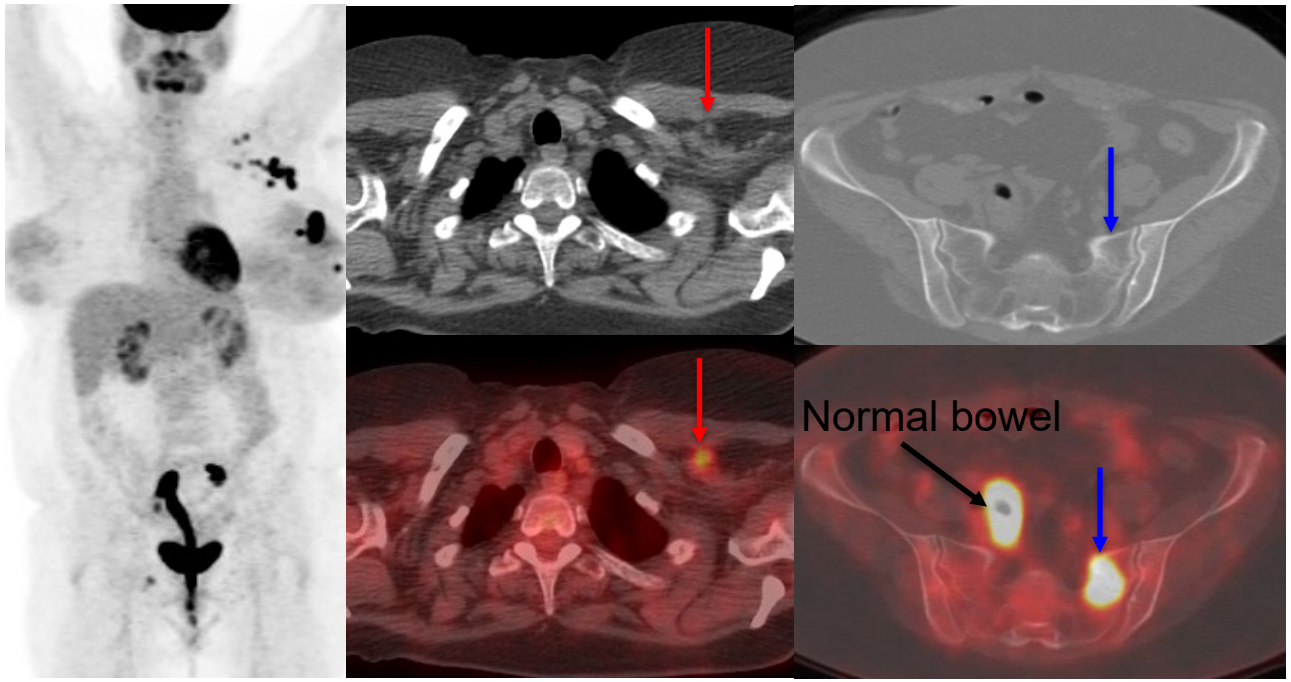
Baseline ^{68}Ga-DOTANOC PET/CT MIP and sagittal Image

Post 2 cycles of ^{225}Ac-DOTATATE therapy, Interim ^{68}Ga-DOTANOC PET/CT MIP and sagittal image

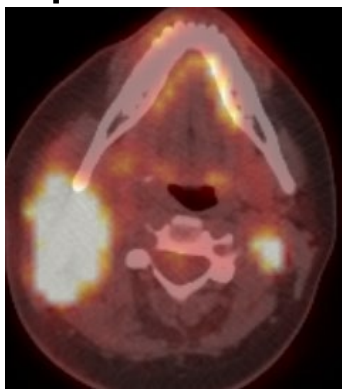
Balla S., et al., Eur J Nucl Med Mol Imaging: 2020 47(4) 934-946
doi: 10.1007/s00259-019-04567-2

Clinical Impact

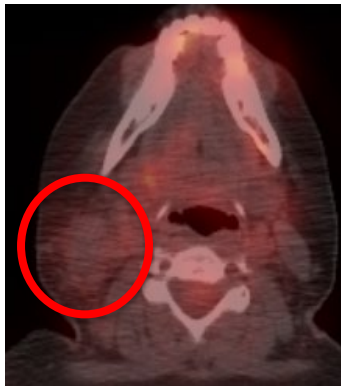
Initial staging of breast cancer



Aggressive lymphoma before treatment

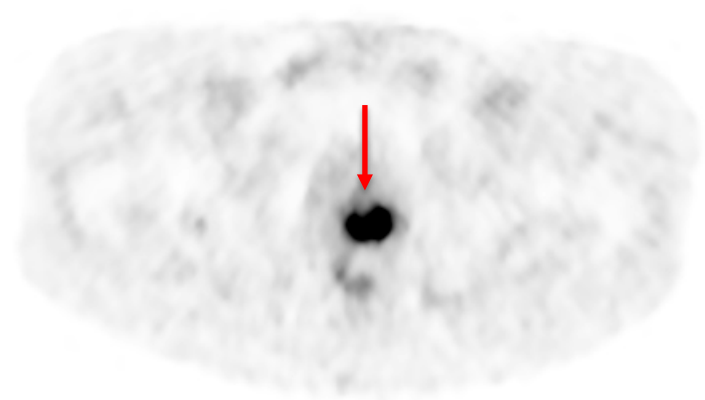


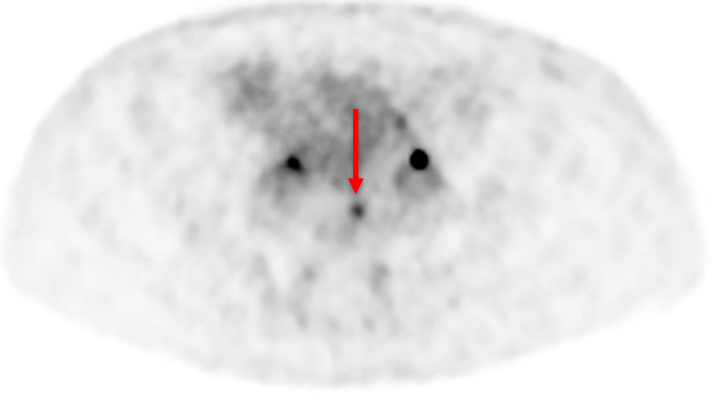
After treatment

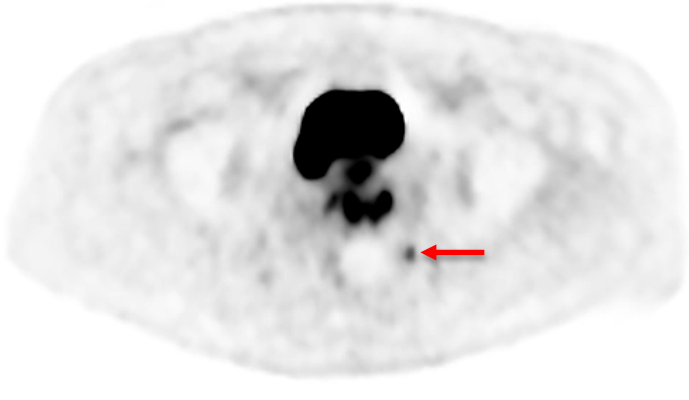


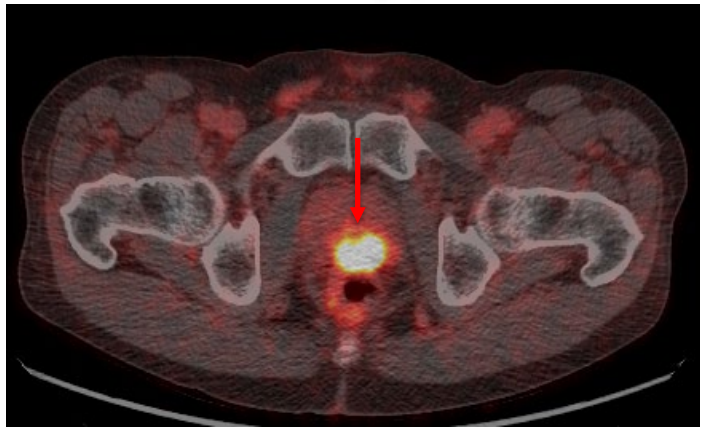
PSMA-PET/CT
Known Prostate Cancer

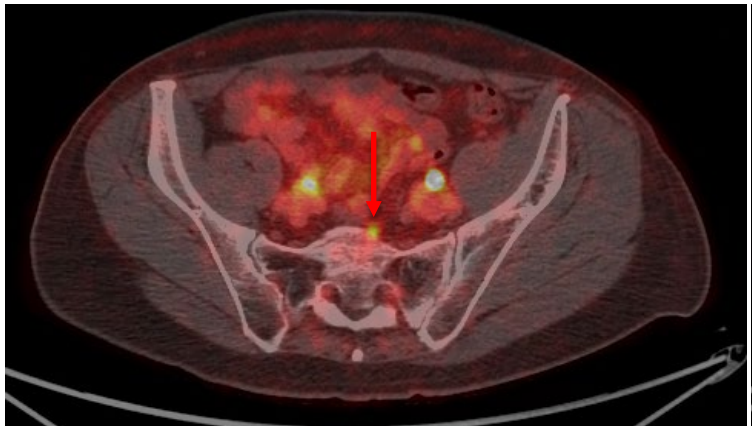
Unknown presacral and peri rectal lymph nodes outside the standard surgical field

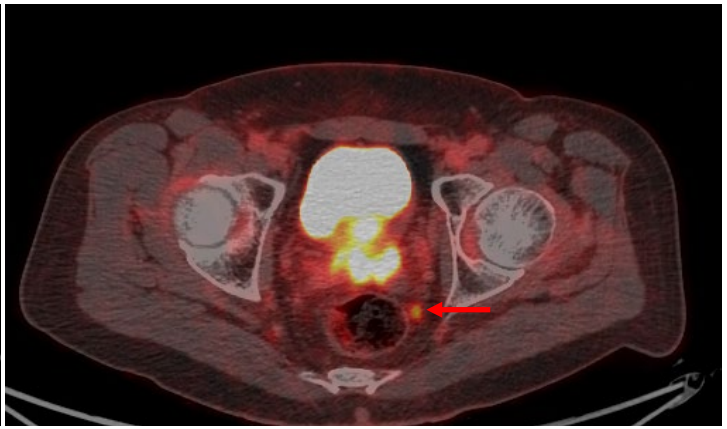












Surgery canceled → Radiation, hormones and androgen receptor pathway blocker

Demographics of PET Drugs

As of October 27, 2023–

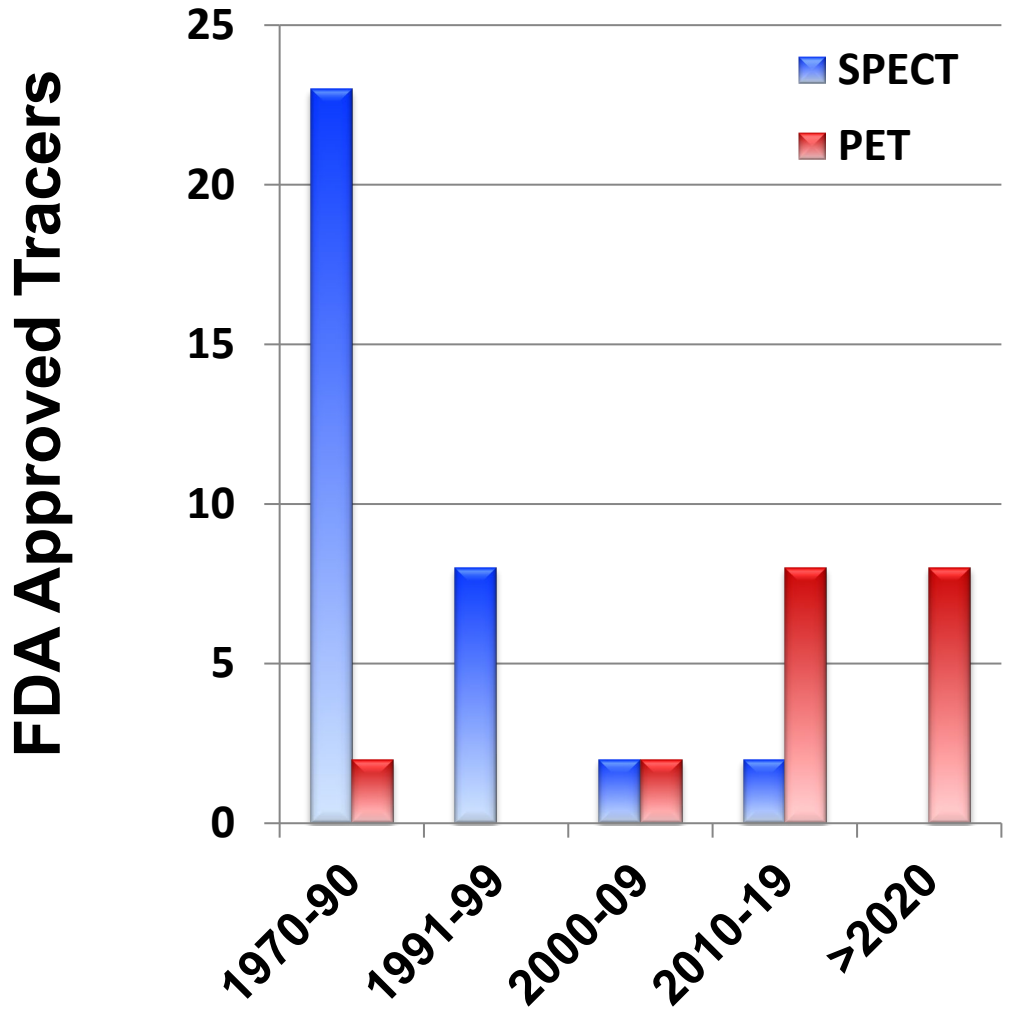
- There are 21 PET drugs currently approved by the FDA in the US (up from 12 in 2020)
- There are approximately 50 NDA/ANDA holders for PET drugs in the US
- Approved PET drugs are labeled with a variety of isotopes including F-18, Ga-68, Cu-64, Rb-82, C-11 and N-13
- Over 50 new PET drugs are in development as companion imaging agents for theranostic agents

Other demographic data for PET drugs –

- An estimated 2.495 million PET scans were performed in the US in 2022; FDG accounted for about 82% of these scans.[1]
- Estimated sales of **all** PET drugs in the US in 2022 is $461.1M[1]

[1]PET Imaging Market Summary Report 2023, IMV Market Research

Approved Tracers and Future Pipeline



The future depends on a sustainable supply of PET drugs and adequate reimbursement.

* includes 2 approved kits for Ga-PSMA-11

Questions Submitted to the FDA

The FDA offered to answer questions from the PET manufacturing/nuclear medicine community.

A request for questions was sent to approximately 15,000 individuals in the PET manufacturing/nuclear medicine community in advance of the Workshop. Questions were grouped into:

- Facility Inspections and Compliance
- Product Quality and Regulatory Submissions
- Product Safety and Risk Assessment
- Management of the PET Drug Lifecyle
- Other

We want to thank the FDA for reviewing and researching the questions and look forward to discussing the answers today and tomorrow.

Welcome

Sue Bunning

Managing Director, Positron Emission Tomography
Medical Imaging & Technology Alliance

Welcome

Charles Metzger

Executive Director
Coalition of PET Drug Manufacturers

November 13, 2023

Acknowledgements

- FDA and other sponsors
- Non-FDA speakers are here to represent *all* academic and commercial PET drug manufacturers
- The content and views expressed in their presentations are the result of a consensus by the authors with input from other PET drug manufacturers and are not necessarily views of the organizations they represent

Background

- The Coalition helped organize the February 2020 workshop “PET Drugs: A workshop on inspections management and regulatory issues”
- Published proceedings of the workshop in JNM

WORKSHOP

PET Drugs: A Workshop on Inspections Management and Regulatory Considerations

FEBRUARY 21, 2020

Share Tweet Linkedin Email Print

https://www.fda.gov/drugs/pet-drugs-workshop-inspections-management-and-regulatory-considerations-02212020-02212020

SPECIAL CONTRIBUTION

Proceedings: PET Drugs—A Workshop on Inspections Management and Regulatory Considerations

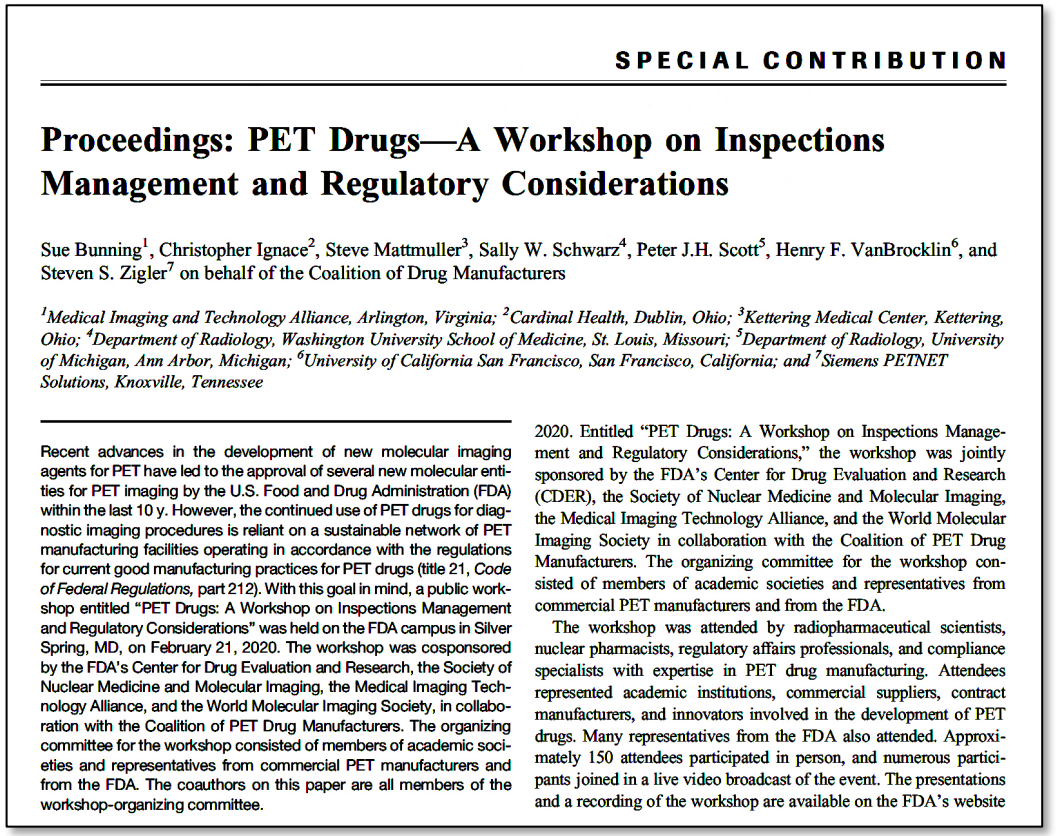
Sue Bunning[1], Christopher Ignace[2], Steve Mattmuller[3], Sally W. Schwarz[4], Peter J.H. Scott[5], Henry F. VanBrocklin[6], and Steven S. Zigler[7] on behalf of the Coalition of Drug Manufacturers

[1]Medical Imaging and Technology Alliance, Arlington, Virginia; [2]Cardinal Health, Dublin, Ohio; [3]Kettering Medical Center, Kettering, Ohio; [4]Department of Radiology, Washington University School of Medicine, St. Louis, Missouri; [5]Department of Radiology, University of Michigan, Ann Arbor, Michigan; [6]University of California San Francisco, San Francisco, California; and [7]Siemens PETNET Solutions, Knoxville, Tennessee

J Nucl Med 2022; 63:1117–1123.

Predominant Workshop Themes from 2020

1. Need for uniformity in FDA inspections of PET facilities
2. Need for a science-based risk profile for PET drugs
3. Improvements to training for FDA investigators and the regulated community
4. The need for continued dialog between the FDA and the PET community



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Recent advances in the development of new molecular imaging agents for PET have led to the approval of several new molecular entities for PET imaging by the U.S. Food and Drug Administration (FDA) within the last 10 y. However, the continued use of PET drugs for diagnostic imaging procedures is reliant on a sustainable network of PET manufacturing facilities operating in accordance with the regulations for current good manufacturing practices for PET drugs (title 21, *Code of Federal Regulations*, part 212). With this goal in mind, a public workshop entitled "PET Drugs: A Workshop on Inspections Management and Regulatory Considerations" was held on the FDA campus in Silver Spring, MD, on February 21, 2020. The workshop was cosponsored by the FDA's Center for Drug Evaluation and Research, the Society of Nuclear Medicine and Molecular Imaging, the Medical Imaging Technology Alliance, and the World Molecular Imaging Society, in collaboration with the Coalition of PET Drug Manufacturers. The organizing committee for the workshop consisted of members of academic societies and representatives from commercial PET manufacturers and from the FDA. The coauthors on this paper are all members of the workshop-organizing committee.

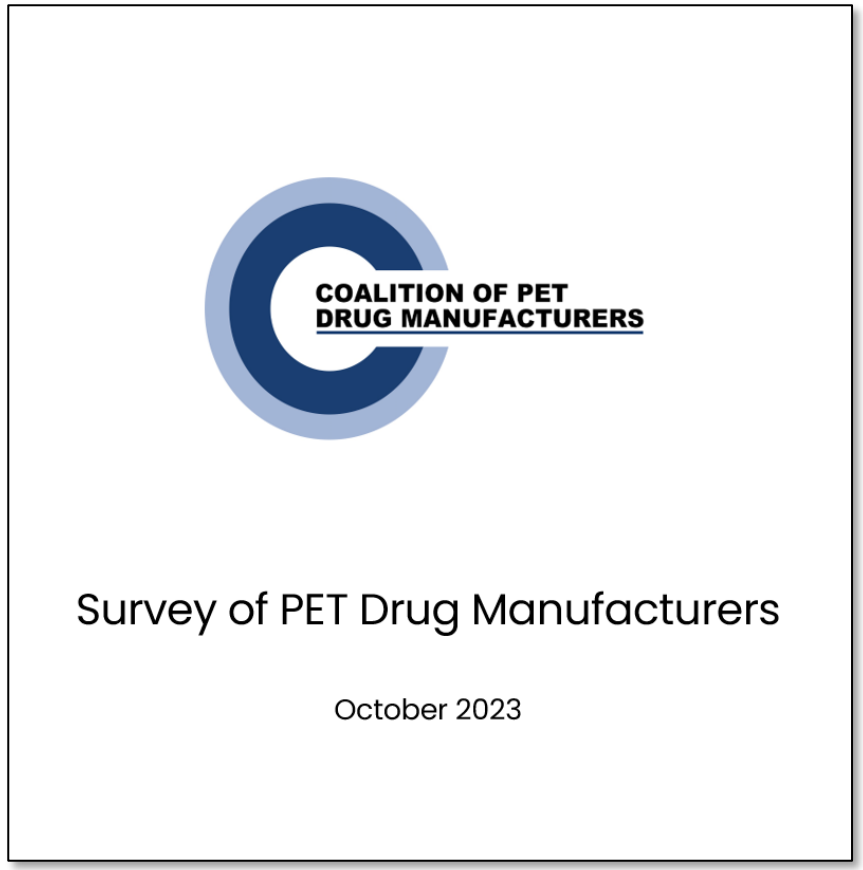
2020. Entitled "PET Drugs: A Workshop on Inspections Management and Regulatory Considerations," the workshop was jointly sponsored by the FDA's Center for Drug Evaluation and Research (CDER), the Society of Nuclear Medicine and Molecular Imaging, the Medical Imaging Technology Alliance, and the World Molecular Imaging Society in collaboration with the Coalition of PET Drug Manufacturers. The organizing committee for the workshop consisted of members of academic societies and representatives from commercial PET manufacturers and from the FDA.

The workshop was attended by radiopharmaceutical scientists, nuclear pharmacists, regulatory affairs professionals, and compliance specialists with expertise in PET drug manufacturing. Attendees represented academic institutions, commercial suppliers, contract manufacturers, and innovators involved in the development of PET drugs. Many representatives from the FDA also attended. Approximately 150 attendees participated in person, and numerous participants joined in a live video broadcast of the event. The presentations and a recording of the workshop are available on the FDA's website

J Nucl Med 2022; 63:1117–1123.

2023 Survey of PET Drug Manufacturers

- Survey of academic and commercial PET drug manufacturers conducted by the Coalition in Sep 2023
- Sent to all known PET drug manufacturers in the US and responses were anonymously compiled by the Coalition
- Eighteen (18) responses were received - 68,819 batches under NDA and/or ANDA applications
- Coalition believes data sources are reliable but does not warrant the results and does not assume any liability for the accuracy or comprehensiveness of the information
- Email Charles to participate in this anonymous survey



SESSION 1: CONSIDERATIONS AND TRENDS IN FACILILITY INSPECTIONS AND COMPLIANCE

Facility Evaluations in Applications and Pre-approval Inspections

Krishna Ghosh, Ph.D.

Food and Drug Administration

Office of Process and Manufacturing Assessment

Center for Drug Evaluation and Research

Disclaimer

This presentation reflects the views of the speaker and should not be construed to represent FDA's views or policies

Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

COALITION OF PET DRUG MANUFACTURERS

MITA

SNMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

FDA U.S. FOOD & DRUG ADMINISTRATION

Presentation Outline

- **New *draft* Guidance**
  - Use of Alternate tools for Facilities Assessment, *September 2023*
  - Use of Remote Interactive Evaluation for application, *October 2023*

- **Key Topics with recommendations:**
  - Application vs Post Market Stability study requirements and reporting
  - Identity Testing requirements for PET drug Precursors and drug substance
  - Data Integrity topics and recommendations

NEW *DRAFT* GUIDANCE

Risk-based facility assessment for Application Approvals

Facility Risks

- Compliance history/status
- Competency to manufacture the product under evaluation
- FDA 483 Observational Trends

Process Risk - *Risks with execution of manufacturing process design and control strategy?*

- Inherent process complexities
- Unique process characteristics
- Application concerns – Manufacturing and Micro

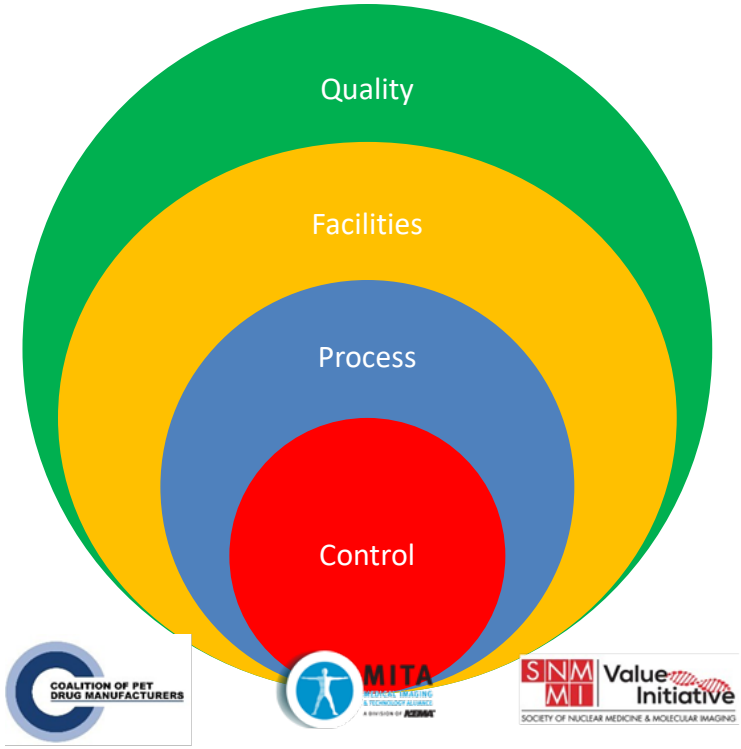
Product-specific Risk Factors - *Risks related to drug product characteristics*

- Radiopharmaceuticals/ PET Drugs

PET Drug Facility Assessment
Application Approvals during COVID-19

- **Same Quality Standards** using **risk-based** assessment of product, process and facility risks to determine inspection need

- **Successful use of "Alternative Tools" used during facility assessment of PET drug applications during COVID -19**
  - Relying on Mutual Recognition Agreement (MRA) (EU and UK)- For Identification of risks
  - Information using 704(a)(4) of the FD&C Act in lieu of inspection
  - Remote Interactive Evaluations (RIEs) - ***No PET drug RIE's were conducted***
- **Four (4) 704(a)(4) desk reviews** were conducted between 2020 March to 2021 Dec for application approvals
- **We completed 12 Pre-approval inspections** of PET drugs between 2020 March and mid 2023 for application approvals



Use of Alternate tools
Assessment of Manufacturing Facilities

Draft Guidance issued **September 2023** describing how facility assessments will be conducted utilizing alternate tools for original and supplemental applications

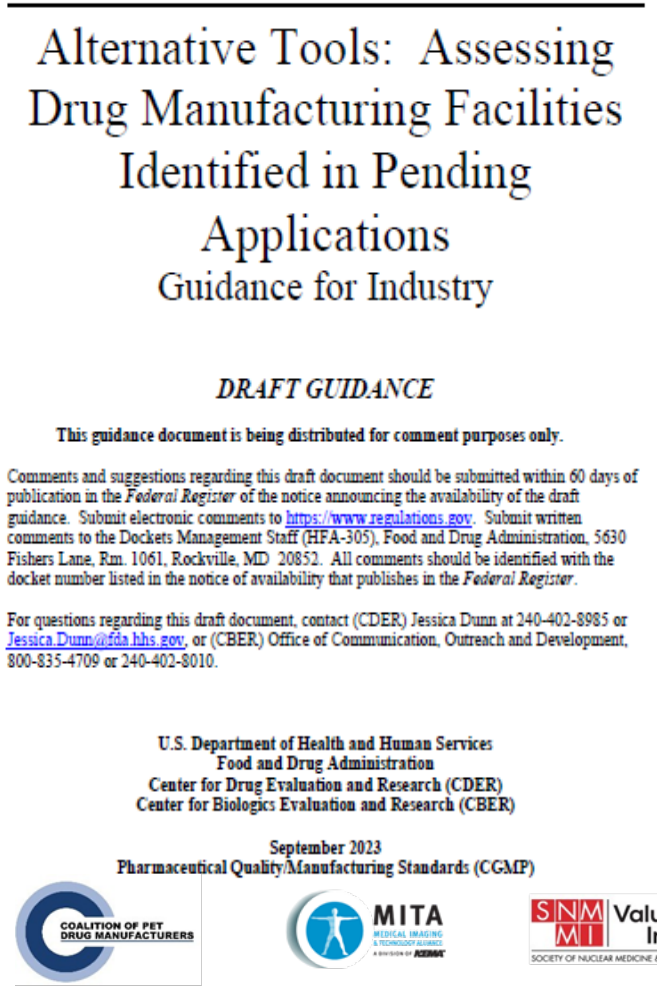
a. NDA

b. ANDA

c. BLA

This guidance does not apply to other drug inspection programs:

- ✓ Post Approval Inspection
- ✓ Surveillance Inspection
- ✓ Follow up and compliance inspection
- ✓ Bioresearch Monitoring facilities



Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

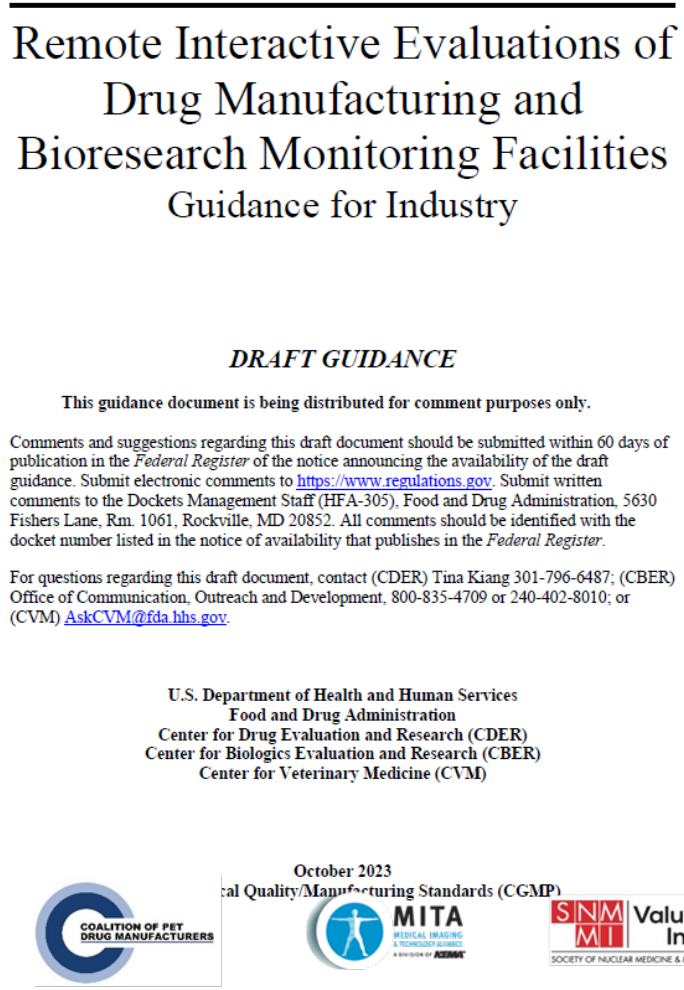
For questions regarding this draft document, contact (CDER) Jessica Dunn at 240-402-8985 or Jessica.Dunn@fda.hhs.gov, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2023
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Use of Remote Interactive Evaluation

- Draft Guidance issued **October 2023** describing what to expect when FDA performs “remote interactive evaluation”
- RIE means any interaction with a facility other than inspection or a record request (704(a)(4) of the FD&C Act)
- T-cons, livestreaming video of facility/ops, screen-sharing of records/info, disclosing records, etc.
- Records Requests and RIEs may be used in lieu of inspections **to make application decisions**
- **Voluntary**: a facility is not obligated to participate
- RIE will **support an application approval**



Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Tina Kiang 301-796-6487; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CVM) AskCVM@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

October 2023
...al Quality/Manufacturing Standards (CGMP)

1. Stability study requirements and reporting

Product Stability Requirements For Application Approval

- The stability protocol and post market stability commitment in an original NDA/ANDA is reviewed as described in FDA's Manual of Policy and Procedures (MAPP) 5200.14 *Filing Review of Abbreviated New Drug Applications*

- Stability studies should be performed at the highest radioactive concentration, and the whole batch volume should be stored in the intended container/closure

- At least **3 batches for each configuration (vials, syringes etc.) and each process (e.g., Cyclotron vs Generator or different synthesizers)** should be tested for a period equal to the labeled shelf life of the PET drug product

- Stability studies performed at one of the PET drug facility is acceptable with PET producers with a network of facilities submitted in the 356h form for ***application approval only***

- **Network of facilities should be under the same Quality system (e.g., same procedures, equipment's, methods and manufacturing processes etc.)**

Product Stability Requirements For Application Approval

- Appropriate parameters should be evaluated to establish and document the stability of PET drug under proposed storage conditions.
  - ✓Examples of stability parameters: radiochemical identity and purity, appearance, pH, stabilizer or preservative effectiveness, and chemical purity (impurities)
  - ✓Use stability–indicating methods that can distinguish degradation products and impurities (e.g., radiolysis phenomenon generates byproduct, and detection mechanisms will vary based on chemistry, being unique to each product and approved in the application)

Importance of Post Approval Stability Studies

There may be continued variations in the PET Drug production process after an application approval:

- Personnel
- Raw material lots/controls
- Change in Suppliers
- Manufacturing and testing equipment/ upgrades
- Software/firmware upgrades
- Facility related controls- Environmental factors

It is imperative that **stability studies are not limited only to initial three production batches produced to support application approval**, but a portion of annual production batches are to be subjected to an ongoing stability program at **each production facility**.

This is consistent with FDA's recommendation to manufacturers of drug products regulated under 21 CFR 211 described in **FDA's inspection technical guide *Expiration Dating and Stability Testing for Human Drug Products* (2014).**

Stability Program and CGMP requirement

- 21 CFR Part 212 CGMP requirements are applicable to all finished dosage PET drug **production facilities listed and approved in an application**
- **Establishment of a stability program at each production facility is a requirement under 21 CFR Part 212.61**
- FDA requires a PET drug producer to establish, follow, and maintain a written testing program to outline how it will implement the stability protocol and any post approval stability commitment they submit to FDA in each PET drug application (21 CFR 212.61(a))
- Annual stability studies aligned to post market stability protocol should be conducted at each PET drug production facility including PET producers with a network of facilities
- PQIT tests submitted and approved in an application should be included as part of annual stability testing program

Post Market Stability Study Execution and Reporting

- **Regulatory Application Requirement-** FDA requires that PET drug producers submit the stability test results in an annual report (21 CFR 314.81(b)(2)(viii)) from all manufacturing sites
- **Applications with one facility:** Acceptable executing and reporting

  Annual Stability study is executed and annually reported on a minimum of one batch based on the Post Approval Stability Protocol for each packaging configuration and process as applicable
- **Some applications with multiple production facilities**: ***Gaps identified*** in annual study execution and reporting:
  - Post approval annual stability study is ***executed only at* one *facility*** and ***stability report from one facility*** is submitted in annual report
  - ***PET drug producers need to conduct annual stability study from at least one batch for each of the PET Drug production facilities*** listed in the 356h form in the application
  - Sponsors may choose to adopt an abbreviated format of annual stability studies data reporting for **large number of additional facilities only**

Post Market Stability Study Reporting

Example of an Abbreviated format for annual stability results from network of facilities:

- Name/location and FEI#
- Confirmation regarding date of annual stability study execution at each listed facility
- Confirmation of meeting all approved specifications in the application
- Any failure of stability studies should be reported with full test results, failure investigation details and root cause identification

Each PET drug producer should store the stability study results, reports, data etc. at the respective facilities and make it available during inspections.

Stability Testing Program
Example: FDA 483

21 CFR 212.61(a)

There is **no written testing program designed to assess the stability characteristics of drug products.** Specifically,

You failed to establish a formal written stability program including reliable, meaningful, and specific test methods with approved protocols, reports, and raw data to support stability conclusions in your final report

2. Precursor and drug substance IDENTITY (ID) testing

Control of Components – 21 CFR 212.40(c)

- **21 CFR 212.40(c)(1)(ii)**
  - **If finished product testing** of a PET drug product can not ensure **that the correct components have been used**, you **must conduct identity testing on each lot** of a component **that yields an active ingredient** and **each lot of an inactive ingredient** used in that PET drug product.
    - (e.g., this is applicable for **precursors**)

    This testing **must be conducted** using **tests that are specific** to each component that yields an active ingredient and each inactive ingredient.

Why a precursor will require ID Testing

- **Precursor** is the last intermediate that can be tested directly for correct structure and quality of the API
  - TLC or HPLC based identity tests are not specific to the precursors/API and do not conclusively confirm that the correct precursor has been used (e.g., identity of the precursor).
  - A precursor may have stereochemical center, which may have an impact on safety or efficacy – simple TLC or HPLC is unlikely to confirm this.
  - Since API is produced in-situ, upstream control of the precursor is necessary.
  - Only approved suppliers (as filed in application) should be used.
  - Precursor/API manufacturers are inspected under ICH Q7 standards

Control of Components – 21 CFR 212.40(c)

- **21 CFR 212.40(c)(1)(ii)**
  - ***For any other component, such as a solvent or reagent, that is not the subject of finished-product testing, you must determine that each lot complies with written specifications by examining a certificate of analysis provided by the supplier; if you use such a component to prepare an inactive ingredient on site, you must perform an identity test on the components used to make the inactive ingredient before the components are released for use.***
    - [E.g., preparation of sodium chloride solution instead of purchasing 0.9% Sodium Chloride Injection, USP, would require an identity test on components used to make sodium chloride]
  - ***However, if you use as an inactive ingredient in a product that is approved under section 505 of the act (21 U.S.C. 355) and is marketed as a finished drug product intended for intravenous administration, you need not perform a specific identity test on that ingredient.***
    - [E.g., purchasing commercially available 0.9% Sodium Chloride Injection, USP or Ascorbic Acid Injection, USP, an identity test would not be required]

Identity Testing Summary

A specific identity test is not required for:

- Components that are themselves finished products
- Components whose identity is confirmed through finished product testing
- Components that are not active or inactive ingredients

Regardless of whether a specific identity test is required for a component, the producer must confirm that the component meets written specifications.

3. Data Integrity Topics

Data Integrity and PAI Objectives

1. Determine whether the establishment has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations

2. Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the Exhibit batches (and other clinical batches, when applicable)

3. Audit the raw data in analytical and manufacturing equipment, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, Exhibit batch data) were submitted in the CMC section

4. **Commitment to Quality in Pharmaceutical Development (New Objective)**

Data Integrity and PET Drug Manufacturing

"Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry" ***December 2018***

- Access controls for computer systems **[212.60(a) – 212.60(g), 212.30(b)]**
  - ❖Changes to programs and methods must be controlled
- Shared login unacceptable – **[212.50(c)10]**
  - ❖Actions must be attributable to individuals
  - ❖Deficiencies may be found in Electronic Batch Records where steps are executed electronically
- Production and testing areas must have restricted access controls to authorized personnel – **[212.40(d), 212.50]**
- Document Control system **[212.50, 212.60 & 212.70]**
  - ❖Lack of control of blank forms can result in data manipulation
  - ❖Issuance of electronic batch record should be restricted to limited individuals

Data Integrity and PET Drug Manufacturing

- Audit trails and review **[212.60(g)(3) "complete records"; 212.50(a)]**
  - ❖ Activation of all audit trails is required (exceptions for legacy systems)
  - ❖ Frequency of review should be based on risk
- Maintenance and storage of electronic records **[212.110(b) "stored to prevent deterioration or loss"]**
  - ❖ Metadata must be secured
  - ❖ Dynamic records must be maintained as originally obtained (e.g., HPLC and accompanying metadata)
  - ❖ Static records (e.g., printout from a balance)
- Raw test data (e.g., chromatograms, spectra) and any calculations need to be preserved **[212.60(g)(3)]**
- Personnel should be trained to prevent and detect data integrity issues **[212.10]**

- Reference: FDA Guidance for Industry — Reference: Data Integrity and Compliance With Drug CGMP, Questions and Answers, Dated December 2018

Audit Trail Review
21 CFR 212.60(a)

- Audit trails are considered part of the associated records.

- Audit trails that capture changes to critical data…should be reviewed by firms:
  - A reasonable frequency of review for audit trails should be based on risk
  - This review should be ideally be performed by someone other than the person capturing the data

- Not every batch release requires audit trail review. Firms may be able to demonstrate a reasonable frequency of review

- Equipment exemptions for audit trails are applicable for legacy systems
  - Without an audit trail for legacy systems, operational and procedural controls should be established to ensure the reliability of the electronic data
  - Electronic data should still be reviewed for unexplained retesting, unjustified reprocessing, or unreported data

Raw Data Access Controls
FDA 483

21 CFR 212.60(a)

Each laboratory used to conduct testing of PET drug products **does not have and follow written procedures for the conduct of each test and the documentation of the results. Controls have not been established to restrict user access and data file access** for the following:

- The Microsoft Excel spreadsheet is used for raw data entry (half-life parameters) and calculations. This spreadsheet is accessible to anyone with access to the network drive and has no restrictions to prevent alteration of cells containing formulas.

- The radionuclidic purity data generated by HPGe detector, has no controls. In addition to QC personnel, the equipment and software are used by university students with no access controls established.

Loss of Raw Data
FDA 483

21 CFR 212.110(b)

All records including those not stored at your inspected establishment are **not stored to prevent deterioration or loss. Electronic records are used, but there is no assurance they are complete.** Specifically:

- When computers were updated from Windows 7 operating system to Windows 10, electronic data from the #### and #### software, which captured endotoxin test data for several batches of final drug product Injection, were lost.

- Additionally, the ##### software is incompatible with the Windows 10 operating system, so it can no longer be used.

Some Closing Remarks…

- We are in a post COVID-19 era and the successful implementation of flexible regulatory frameworks during COVID-19 phase has helped us to evolve rapidly
- Alternate tools and best practices published as draft guidance will help the agency to facilitate efficient facility evaluations and approvals during application review
- We have observed great improvements in implementation of 21 CFR Part 212 regulations, but the changing landscape with newer PET drugs (e.g., PET drug kits and generators) may need additional controls and standards to ensure product quality
- Lack of Identity testing as an incoming acceptance test has been identified during pre-approval inspections in several PET drug facilities and it requires immediate corrective action by PET producers
- Clarifications on application related stability study requirements vs post approval annual stability studies and meeting CGMP requirements at each production facility will help PET drug producers to address the existing compliance gaps
- Data Integrity principles and its applicability during any manufacturing operations is one of the key objectives for pre-approval as well as surveillance inspections


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
bedankt
dziękuję
sukriya
kop khun krap
go raibh maith agat
mochchakkeram
arigatô
dakujem
grazie
terima kasih
감사합니다
спасибо
мерси
tapadh leat
dank je
takk
hvala
sagolun
tack
Баярлалаа
рахмат
хвала
ありがとう
ευχαριστώ

U.S. FOOD & DRUG ADMINISTRATION

SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

COALITION OF PET DRUG MANUFACTURERS

MITA MEDICAL IMAGING & TECHNOLOGY ALLIANCE A DIVISION OF NEMA

FDA Inspections: Commercial Perspective

Speaker: Keith Bowen, Avid@ Lilly

Industry Perspective on Commercial Site Inspections In Relation to cGMPs

&

Discuss Opportunities to Clarify GMP Expectations For Manufacturer & Inspection Success

PURPOSE

A proactive approach to clarify GMP expectations for manufacturer and inspection success

&

FDA and PET Drug Manufacturing Industry Partnership

ACHIEVE

REFERENCES

1. Federal Register Notice Dec 3, 2009, Published Dec 10, 2009 [Docket No. FDA2004N0449] (formerly Docket No. 2004N0439) Current Good Manufacturing Practice for Positron Emission Tomography Drugs
2. FDA Public Meeting – PET Drugs: Submitting An Application for PET Drugs Currently in Clinical Use, March 2, 2011
3. FDA 21 CFR PART 212 - CURRENT GOOD MANUFACTURING PRACTICE FOR POSITRON EMISSION TOMOGRAPHY DRUGS
4. FDA 21 CFR PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS
5. FDA POSITRON EMISSION TOMOGRAPHY (PET) CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/ INVESTIGATIONS PROGRAM 7356.002P; 11 Sep 2015.
6. FDA Oversight of PET Products – Questions and Answers; Dec 2012
7. FDA Guidance - PET Drugs - Current Good Manufacturing Practices; Aug 2011
8. FDA Guidance – Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs; Apr 2012
9. FDA Sterile Drug Products Produced by Aseptic Processing; Sep 2004

REFERENCES

10. FDA Inspection Observations Inspection Observations | FDA; FY 2022 Excel File
11. USP-NF 40, <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
12. Eudralex Vol 4 GMP, Annex 1 – Manufacture of Sterile Medicinal Products Brussels, 22.8.2022 C(2022) 5938 final; Effective 25 August 2023
13. ISO14644-7:2004; Cleanrooms and associated controlled environments. Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini environments)

14. **PET Drugs: A Workshop on Inspections Management and Regulatory Considerations;** FEBRUARY 21, 2020. WEB LINK: PET Drugs: A Workshop on Inspections Management and Regulatory Considerations - 02/21/2020 - 02/21/2020 | FDA

15. **Product Quality Assurance: Microbiological Regulatory Perspective;** Laura R. Wasil, Ph.D. WEB LINK: PET Drugs Workshop Presentations Part II (fda.gov)

16. **Microbiological Safety of Positron Emission Tomography Drugs**; David Hussong, PhD and Henry VanBrocklin, PhD. WEB LINK: PET Drugs Workshop Presentations Part II (fda.gov)

OTHER REFERENCES

What is a PET Drug?

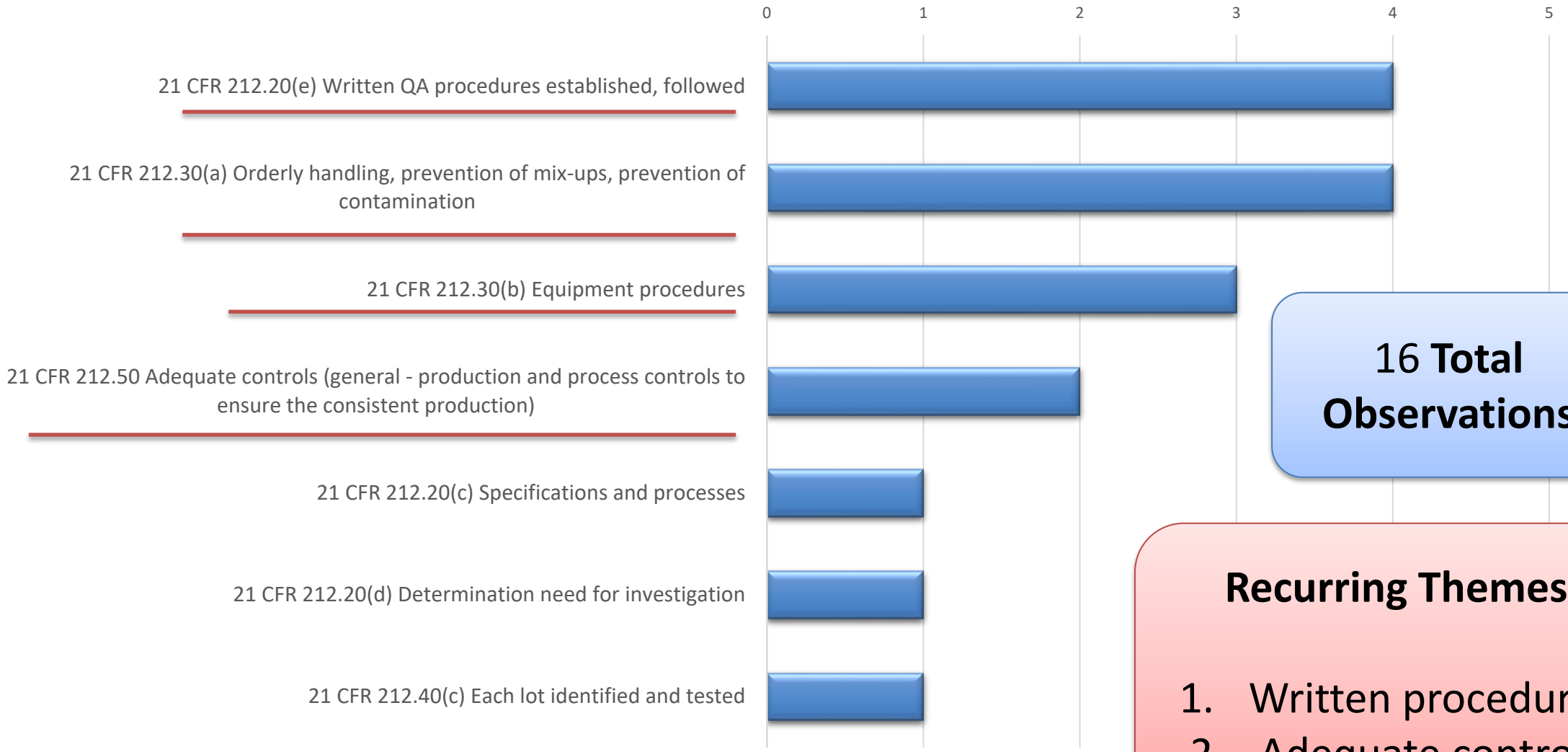
- A medical imaging modality involving the use of a unique type of radiopharmaceutical drug product that contains a positron emitting isotope[5]

- Intended for diagnostic use and are not intended to provide a therapeutic effect; however, many PET drugs provide their diagnostic effect by binding to receptors, which is a type of pharmacological activity. [5]

PET Drug GMP Scope

- All operations to the point of final release of a finished dosage form (commonly a single multi-dose vial). [5]
- Not covered,
  - Dispensing of the patient unit doses from a multidose vial[5]
    - *Does not apply if manufacturer's marketed product is a unit dose vial*[5]
  - Use of a PET drug product after receipt by a receiving facility[5]

COMMERCIAL SITE INSPECTION OBSERVATION METRICS

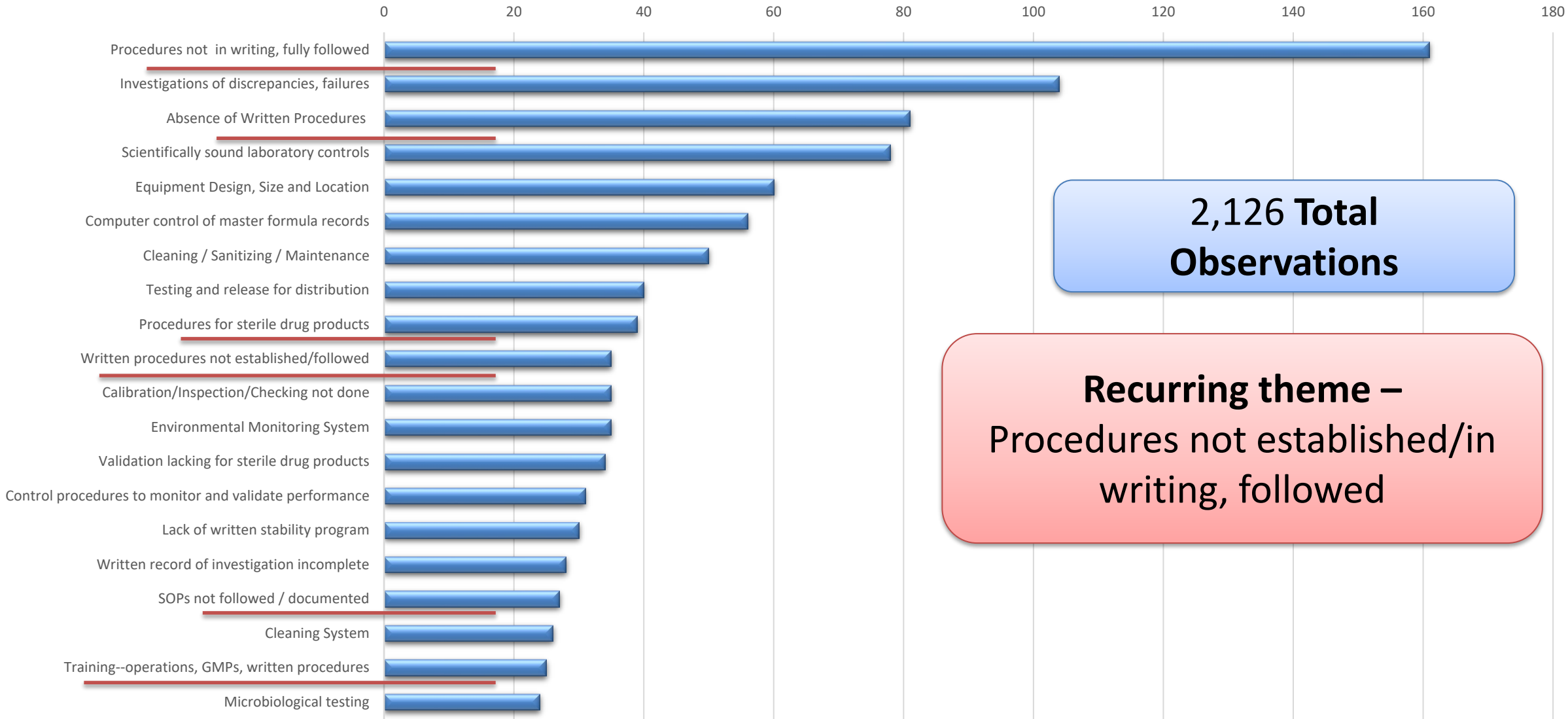


16 **Total Observations**

Recurring Themes

1. Written procedures
2. Adequate controls

21 CFR PART 212 - FDA INSPECTION OBSERVATIONS - FY22 [10]



2,126 **Total Observations**

Recurring theme – Procedures not established/in writing, followed

ALL DRUG INSPECTIONS – FY22 [10]

INDUSTRY INSPECTION PERSPECTIVES

Industry Inspection Perspectives

- Mostly pre-announced
- *Manufacturing sites have "**fewer personnel**[1,2,3,5]" to manufacture product. Requires Admin/Corporate resources to host inspections.*

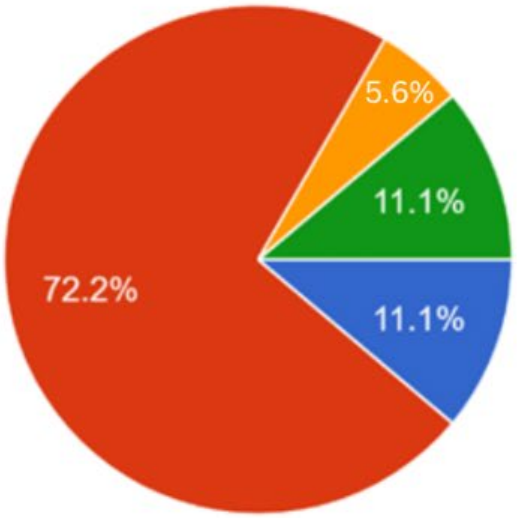
Industry Inspection Perspectives

- 7356.002P - POSITRON EMISSION TOMOGRAPHY (PET) CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/INVESTIGATIONS was established for PET Drug Manufacturing inspections, Impl. 09/2015
- Additional guides employed,
    1. 7346.832 - Preapproval Inspections, Impl. 2010
    2. 7356.002A - Sterile Drug Process Inspections (N/A for PET manufacturing). Rev. Impl. 2015

Industry Perspectives Survey

11. Based on your experience, do FDA inspectors understand the differences between traditional GMP regulations (part 211) and the PET GMP regulations (part 212)?

18 responses



N/A - never been inspected

A change could also mean a difference in interpretation

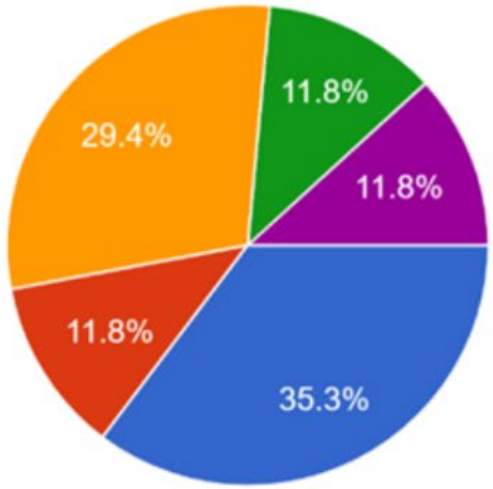
There are several unique features of PET drug products, and many common GMP expectations

Source: Academic and commercial PET drug manufacturers conducted by the Coalition of PET Drug Manufacturers (the Coalition) in September 2023 (18 Responders)

Various Industry Interpretations

17. What is the action level for the number of microbial CFU in ISO 5 areas?

17 responses



Why would almost 12% believe there are no Action Limits?

PET Drug cGMPs state “ISO 5”, “Class 100”

What risk-based expectations should apply to “Closed Vial Systems”?

Alert/Action Limits stated in
FDA Sterile Drug Products Produced by Aseptic Processing; Sep 2004

Scope: 21 CFR 210 and 211, Supplementary to 21 CFR Parts 600, 680

Turbulent airflow can be allowed for “Closed Isolator Systems”[9]

Source: Academic and commercial PET drug manufacturers conducted by the Coalition of PET Drug Manufacturers (the Coalition) in September 2023 (18 Responders)

Industry Inspection Perspectives

- A [PET drug] Recall consists of,
  - *notifying the receiving facility, the pharmacist, and the patient's physician, if known.*
  - *When the receiving facility disposes of the recalled drug, the PET drug producer can obtain a notification from the receiving facility confirming the recalled drug has been disposed of and describing the manner in which it was disposed.* [5]

If no inventory exists, should a recall checklist per current guidance & 21 CFR 7.40 be employed?

Industry Inspection Perspectives

- **Annual Product Reviews** - strongly recommended

Industry Inspection Perspectives

Annual stability testing strategy

…under discussion

FDA Public Meeting – March 2, 2011

PET Drugs: Submitting An Application for PET Drugs Currently in Clinical Use

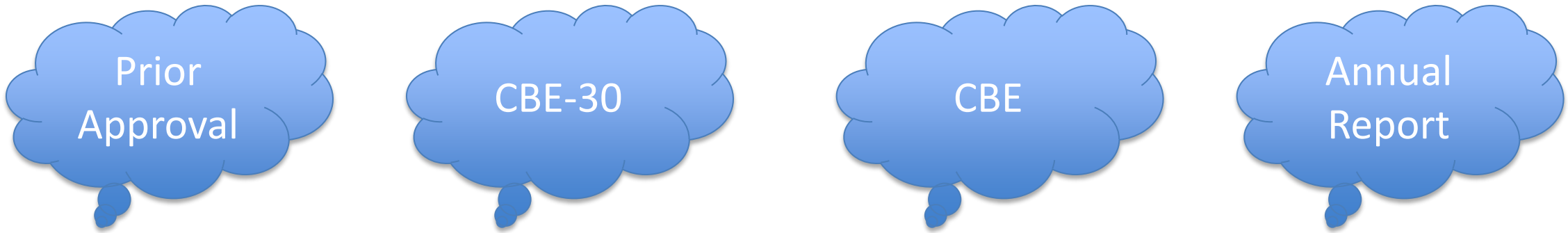
Stability. Release and stability, three batches at the upper range of proposed radio concentration should be provided. We are not looking for site-specific stability. So as long as your manufacturing process is the same, uses the same synthesizer, the data from that site should be okay. You don't need to generate stability data at each site.

Industry Perspective Application Reviews

– *a Phase 1 Laboratory investigation cannot be initiated to evaluate/invalidate original test results. Any OOS result should result in a rejected batch.*

Industry Perspective Application Reviews

- Differing ***facility/product change mgmt. filing strategy*** recommendations



Industry Perspectives

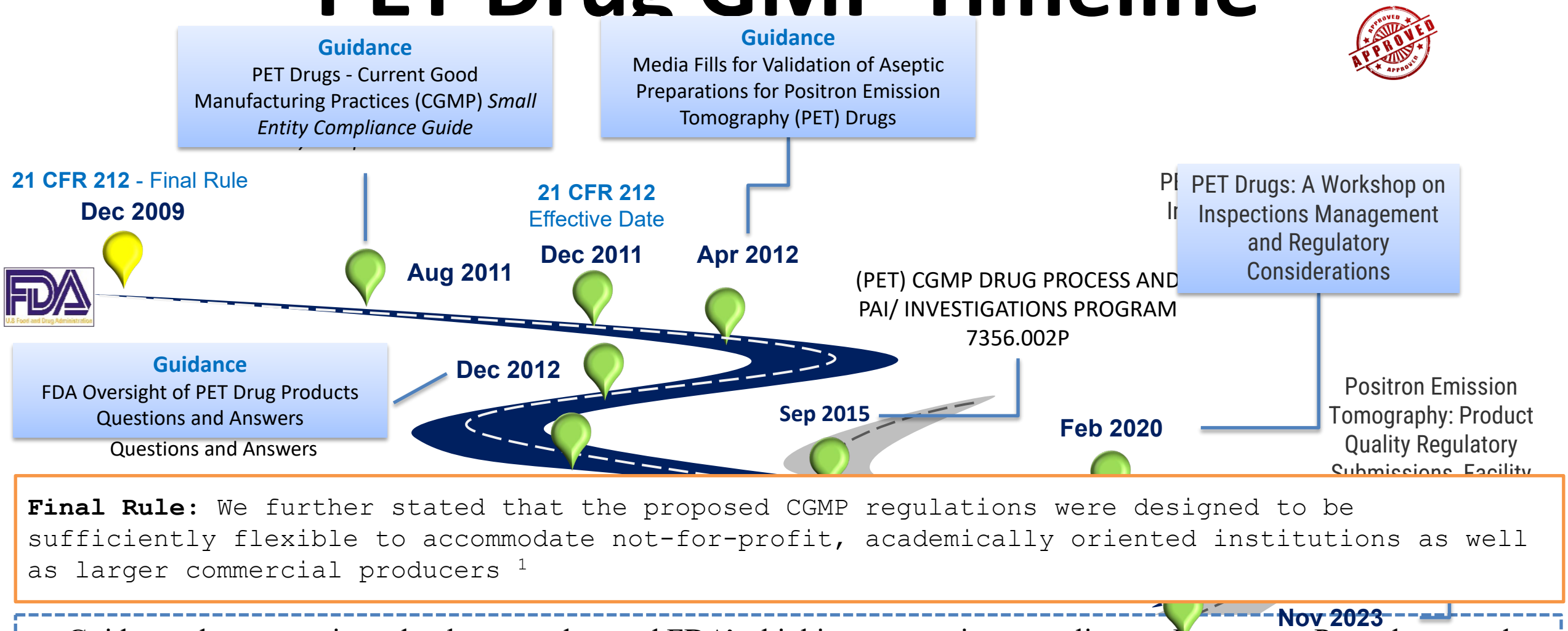
- Feb 2020 - **PET Industry & FDA Workshop on Inspections Management and Regulatory Considerations**
  - Highlighting differences in cGMP interpretations
  - Action to develop training materials for site inspectors. *SNMMI drafted material issued*

What Could be Causing This?

INDUSTRY LED CGMP ASSESSMENT

References: #1, 2, 3, 4, 5, 6

PET Drug GMP Timeline



Final Rule: We further stated that the proposed CGMP regulations were designed to be sufficiently flexible to accommodate not-for-profit, academically oriented institutions as well as larger commercial producers [1]

Guidance documents issued to better understand FDA's thinking concerning compliance - Resources, Procedures, and Documentation for production facilities, academic and commercial[5]

PET Drug GMP Origins

FDA Public Meeting (Dec. 2009)

Current Good Manufacturing Practice for Positron Emission Tomography Drugs

- In consideration of the unique nature of PET drugs and PET drug production, the proposed CGMP requirements for **PET drugs differed in many significant ways from the CGMP requirements for non-PET drugs found in our regulations in parts 210 and 211** (21 CFR parts 210 and 211). [1]
- The proposed PET CGMP requirements included differences concerning **personnel; aseptic processing; quality control of components; self-verification of production steps; same-person oversight of production, batch record review, and authorization of product release; and labeling requirements.**[1]

Industry Feedback on the New Regulation

How can they allow these different requirements?

Differences of PET Drug Product Manufacturing Potentially Enabling Risk Based GMPs

- Mostly ***single use materials and components, many pre-sterilized***
- Very small or No ***production hold times***
- ***Identical automated equipment, electronic manufacturing sequences, & procedures across manufacturing networks***
- Single produced batch vial ***("100% batch QC sampling")***
- Patient dose administration ***within minutes, hours, to a few days***

Closed isolator systems

- Exclude external contamination from the isolator's interior by accomplishing

Should the Laminar Flow Hood require ISO 5 / Class 100 & Non-Turbulent conditions?

Should the GMPs focus on guidance for aseptic practices, LFH sanitization, Sanitization and aseptic handling of the pre-sterilized vial

9. FDA Sterile Drug Products Produced by Aseptic Processing; Sep 2004

What Should We Do?

Industry led cGMP Assessment Initiative

- MITA Quality and Regulatory Team

Team Members	Organization	Job Title
Stacie Aman	Novartis	Director, Federal Policy, Global Public Affairs
Keith Bowen	Eli Lilly	Associate Vice President, Quality Assurance, Avid @Lilly
Sue Bunning	Medical Imaging & Technology Alliance (MITA)	Managing Director, Positron Emission Tomography
Anne Butterworth	Lantheus	Vice President, Quality Assurance
Christopher Ignace	Cardinal Health	Vice President, Scientific Affairs and Strategic Partner Management, Nuclear & Precision Health Solutions
Lynn C. Mendonca	Lantheus	Associate Director, Regulatory Affairs
Ashley Mishoe	PharmaLogic	Vice President, Regulatory Affairs and Quality Assurance
Michael Nazerias	PETNET Solutions	Vice President, Regulatory Affairs and Quality Assurance
Artur Shchukin	GE HealthCare	Senior Manager, USCAN Regulatory Affairs
Jill Wilson	Ionetix	Vice President of Regulatory Affairs & Quality Assurance
Daniel Yokell	Telix Pharmaceuticals (US) Inc.	Head of Global Commercialization – TLX101CDx

Industry Led PET cGMP Assessment

	GMP Area	Examples of Clarity Needed
1	Annual Stability Strategy	Manufacturer's producing the same product on the same automated radiosynthesizer, same manufacturing sequence at different manufacturing sites
2	Aseptic Processing	EM alert/action limits, Risk based approach when using closed vial systems
3	Annual Product Reviews	Strongly recommended
4	Electronic/Computer Systems and CSV, Data Integrity/True Copy	What parts of the PET Drug manufacturing operation are in scope?
5	Recalls	Should a Recall be conducted when there is no finished product inventory?
6	Handling OOS investigations (sterility and analytical QC)	Currently discussed for sterility testing and non-conforming rejected product. Can PET manufacturers conduct Phase 1 Laboratory investigations?
7	GMP/Scienced Based Principals to Risk Management	What standards are needed, What details are missing for PET drug manufacturers? How should it be applied in PET drug manufacturing environments?

Industry Perspective on 21 CFR Part 212 & PET Guidance

- “Relatively new”
- Fundamental (common) GMP Expectations across product types
- Unique Features designed into cGMPs
- Possible to enhance cGMPs using scientific and risk-based principals?

Conclusion

- An enhanced risk-based approach could result in an opportunity to clarify GMP expectations

A partnership with FDA could create a balanced approach to applying risk management principles leading to manufacturer and site investigator success

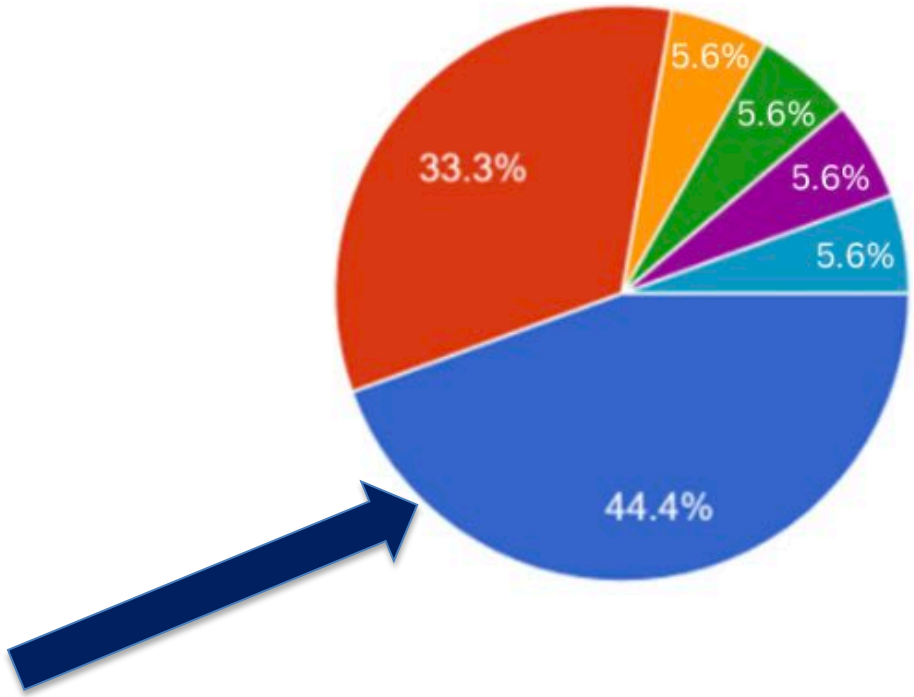
FDA Inspections: Academic Perspective

Robin Ippisch, PhD
University of California San Francisco
Director, Radiopharmaceutical Facility
Director, Radiology Research Development

DISCLAIMER

Data presented and discussed does not represent University of California San Francisco. Data from this talk was provided by the Coalition of PET Drug Manufacturers through a survey of PET drug manufactures, as well as through verbal communication with academic PET drug manufacturing facility personnel.

SURVEY PARTICIPANTS: MAJORITY ACADEMIC



- Academic
- Commercial
- Both
- Provider of solution (machines, raw material, starting material,..) for Pet drug manufacturers.
- National lab
- Drug Sponsor

MANUFACTURING LANDSCAPE

- Since PET has been regulated, landscape has changed from initially academic centers to current commercially dominated supply.

PET drug	NDA #	Institution	Approval year	No. of active ANDAs
Fludeoxyglucose F-18	020306	Downstate Clinical PET Center	1994	38
Fludeoxyglucose F-18	021768	Cornell University	2004	38
Ammonia N-13	022119	Feinstein Institutes for Medical Research	2007	26
Fludeoxyglucose F-18	021870	Feinstein Institutes for Medical Research	2008	38
Sodium fluoride F-18	022494	NIH National Cancer Institute	2011	21
Choline C-11	203155	Mayo Clinic	2012	4
Florbetapir F-18	202008	Avid Radiopharmaceuticals	2012	0[a]
Flutametamol F-18	203137	GE Healthcare	2013	0[b]
Florbetaben F-18	204677	Life Molecular Imaging	2014	0[c]
Dotatate Ga-68	208547	Advanced Accelerator Applications	2016	0[d]
Fluciclovine F-18	208054	Blue Earth Diagnostics	2016	0[e]
Dotatoc Ga-68	210828	University of Iowa	2019	0[f]
Fluorodopa F-18	200655	Feinstein Institutes for Medical Research	2019	0[f]
Flortaucipir F-18	212123	Avid Radiopharmaceuticals	2020	0[g]
Fluoroestradiol F-18	212155	Zionexa US Corp	2020	0[h]

Dick, Handbook of Radiopharmaceuticals, page 499, 2021

MANUFACTURING LANDSCAPE

- Since PET was been regulated, landscape has changed from initially academic centers to current commercially dominated supply.
  - Manufacturing currently a mix of academic and commercial
  - >100 commercial and ~30 academic manufacturing sites

- Still major differences between academic and industry

- The PET Manufacturing community must work together for a **uniform** set of procedures to enable manufacturing to continue safely and provide patient care
  - *Need to work with the FDA to ensure that the regulations are **consistently applied across all sites** and are consistent with the risk and needs in order provide patient access*

ACADEMIC OPPORTUNITIES

- Distribution
  - Academic facilities often do not distribute beyond their own clinic
    - Supplying fewer doses
    - Overall reduced risk
  - Often fill critical gaps in PET drug availability
- Ability to collaborate with cross-functional experts
  - In-house expertise
- *Crucial for innovation*
  - *Work collaboratively with industry partners*
  - *Goal is to continue to work with the FDA to ensure regulations and policies* ***do not present barriers to innovation***

ACADEMIC CHALLENGES

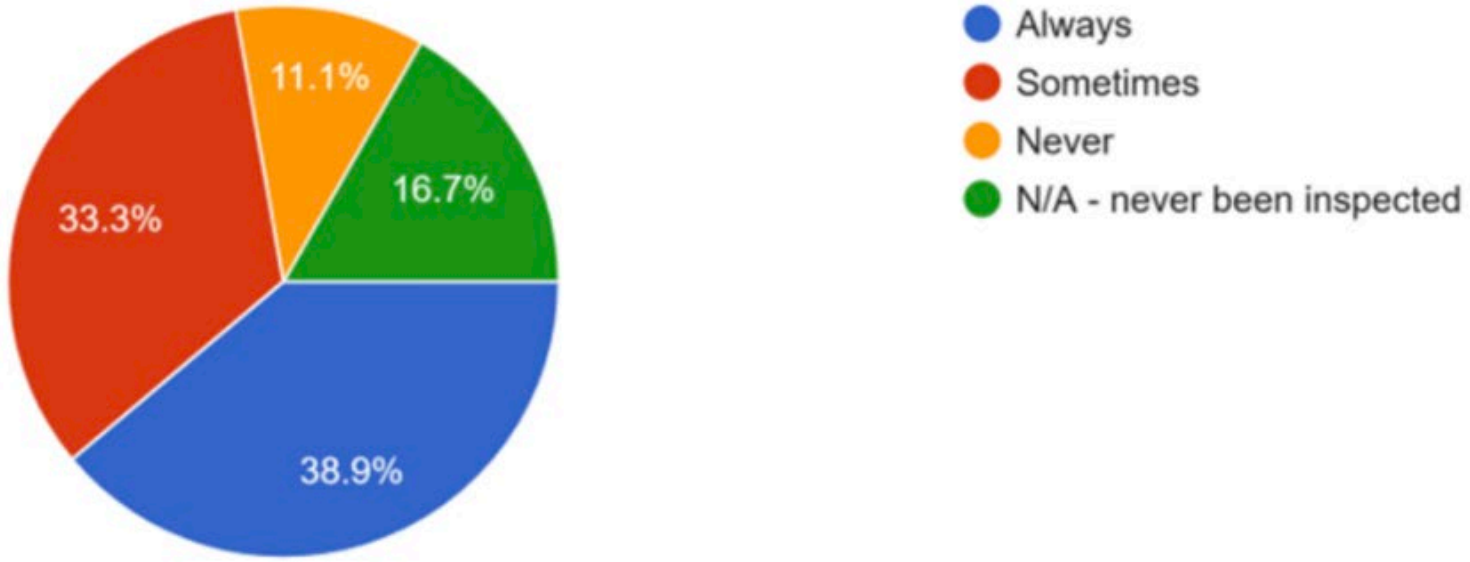
- Vendor auditing
  - Academic institutions lack the infrastructure and resources for vendor audits
  - Potential to leverage Coalition for vendors of commonly used components
    - ALK vials, ABX precursors
  - Establishment of SOP is essential for academics to qualify vendors
- Supplies and Purchasing
  - Central purchasing through University
    - Limited vendors
    - Long timelines to add a new vendor into system
  - Shipping of incoming components
    - Often ship to a central receiving location on campus
      - Chain of custody often difficult to impossible

ACADEMIC CHALLENGES

- Organizational Structure
  - Top level (Board of Trustees, etc) often very removed from radiopharmaceutical facilities
    - Important to contact regulatory personnel for support
- IT challenges
  - Hardware and software updates often mandatory
  - If no update, no institutional support
  - Potential loss of electronic data – perceived data integrity issues
- Facility constraints for existing facilities
  - Resources for altering infrastructure very limited
  - Lengthy timelines to complete upgrades/changes
    - *Potential to prohibit patient access*

5. Do FDA inspectors pre-announce inspections?

18 responses



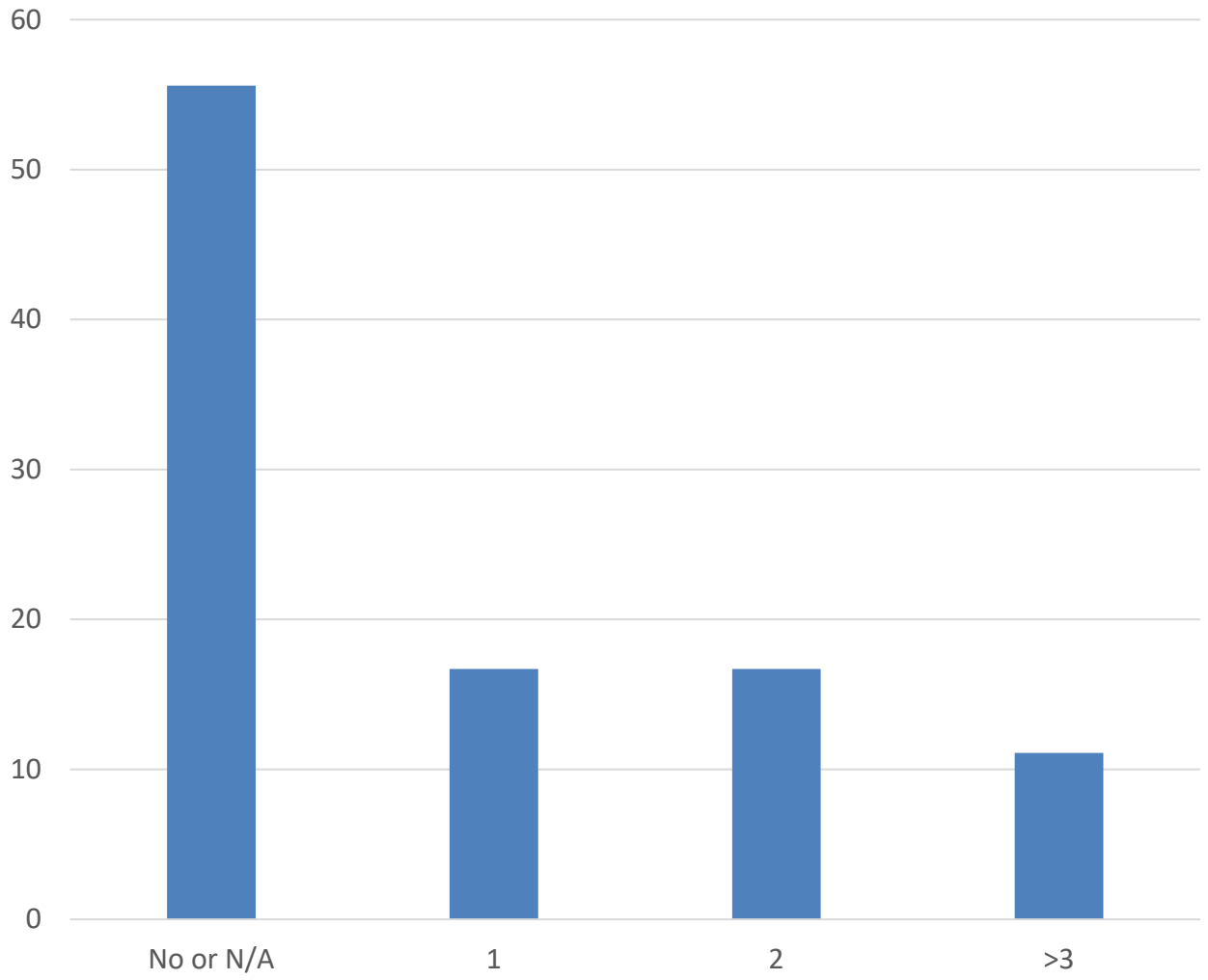
1	• Organization Chart • Identify the personnel associated and trained for PET drug manufacturing with roles and responsibilities	
2	Batch Release procedure(s)- Final QA release • Include the procedure for conditional final release for PET drugs if a separate procedure	
3	Procedure(s) related to agency communication (e.g. FARs)	
4	SOP for Recalls	
5	Change Control or Change Management procedure(s)	

6	Please explain UCSF's history with PET manufacturing
	• How long have you been working with PET?
	  ○ Provide a list of IND and RDRC drugs currently being produced in the laboratory
	• What other approved PET products do you have experience with?
	  ○ Please list	

7	List of procedures specific to PET production • Procedure for sample retention plan for PET drugs for (conditional release) • Provide procedure for sterility investigations • Procedure for PET stability program and protocol for PSMA 11- Ga^{68}Injection	
8	Change Controls to introduce PSMA 11- Ga^{68}Injection into the facility	
9	List of all material suppliers for the PSMA 11- Ga^{68}Injection	

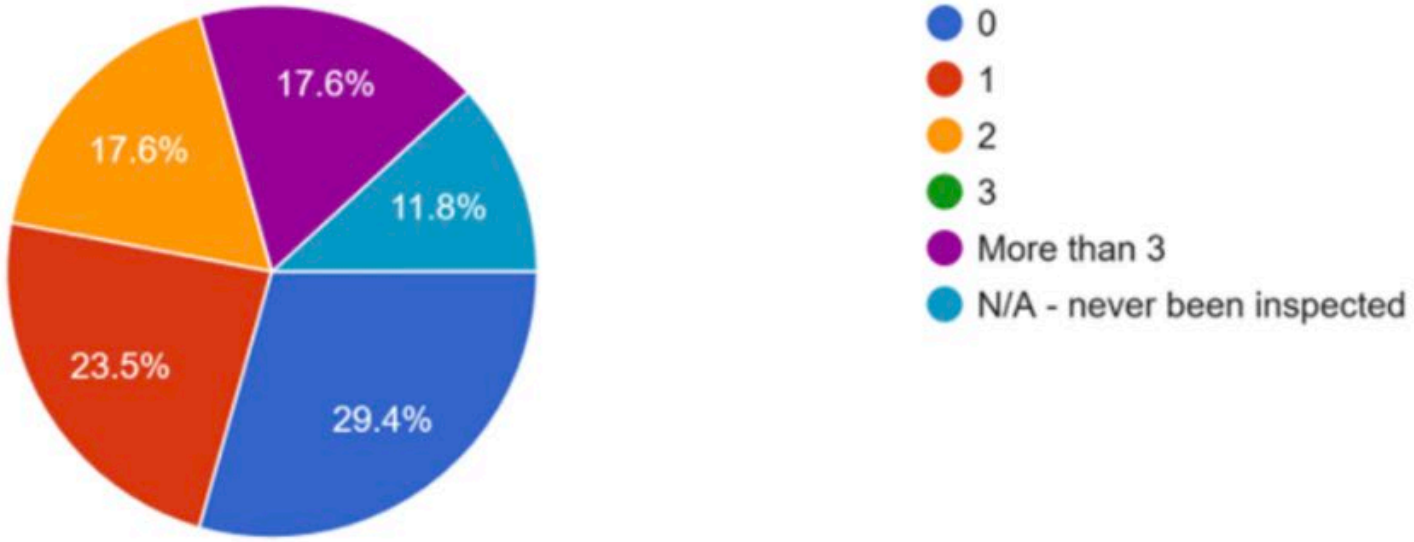
Survey results: *Number of 483s related to an observation of a QC test method or manufacturing process that you were following without deviation according to approved NDA or ANDA*

- Invalid Endotox test result- SOP indicated to retest sample
  - 483 given for not reporting as OOS and for releasing upon retesting
- Mandatory use of sterile gloves and wipes



9. How many times have you received an FDA 483 observation due to a change in the interpretation of existing FDA regulations that you were not aware of until the issuance of the 483?

17 responses



PRECURSOR ACCEPTANCE TESTING

(1)(i) If you conduct finished-product testing of a PET drug product that includes testing to ensure that the correct components have been used, you must determine that each lot of incoming components used in that PET drug product complies with written specifications by examining a certificate of analysis provided by the supplier. You are not required to perform a specific identity test on any of those components.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=212&showFR=1&subpartNode=21:4.0.1.1.12.5

- 2 separate institutions received 483 observations for not doing additional identity testing (beyond CoA) on precursor from known and trusted vendor (ABX)

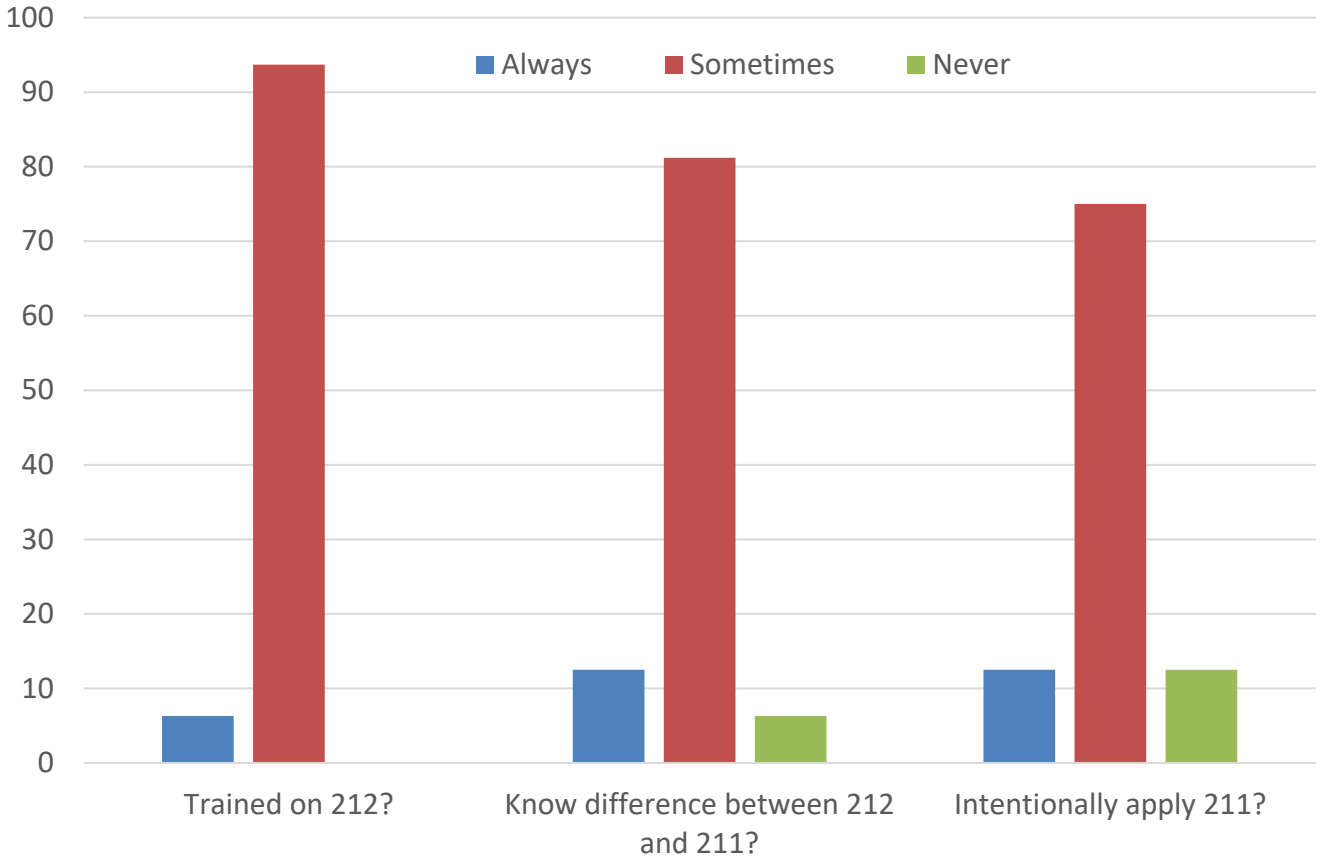
- Difference in the way regulation is being interpreted
  - CoA for precursor was not deemed sufficient for identity testing

- PET community needs to understand the **expectation** from the FDA
  - Appropriate SOPs based on the FDA expectations

EXAMPLES OF ACADEMIC 483

- IT software upgrade caused loss of electronic data
  - A unique challenge for academic institutions
- Observations to monitor non-classified areas (syntheses hotcells, non-classified rooms)
  - Regulations do not specify this is required
- Quality Systems
  - Need for implementation of a robust quality management system
    - Can be lacking in academic setting
  - Typically no dedicated QA group
    - Industry has central QA team for multiple sites

SURVEY RESULTS: FDA INSPECTOR TRAINING



- Critical that FDA inspectors are trained in 21CFR212 prior to inspections
  - Consistency amongst all sites
- Work with the Coalition to develop and implement uniform manufacturing practices (and inspections) across all PET manufacturers

SUMMARY

- Academic institutions represent an important portion of PET Drug Manufacturers in the United States
  - Academics face unique challenges
    - Infrastructure and resources
  - ***Academics are essential for innovation and patient care***

- Appropriate regulatory environment that supports the **breadth** of manufacturing sites

- It is critical that we achieve manufacturing and **inspection uniformity** to maintain the **patient access** to critical imaging agents

BREAK


COALITION OF PET
DRUG MANUFACTURERS


SNMMI
Value
Initiative


FDA
U.S. FOOD & DRUG
ADMINISTRATION

PET Surveillance Inspections and Training Update

Nicholas Violand
Drug National Expert
Pharmaceutical Quality Programs Branch
Division of Pharmaceutical Quality Programs
Office of Pharmaceutical Quality Operations
Office of Regulatory Affairs

Positron Emission Tomography Product Quality Regulatory Submissions, Facility Inspections, and Benefit-Risk Considerations

November 13, 2023

Outline

- Surveillance Inspections
- Recent 483 Examples
- Investigator Training
- Inspection Protocol

Surveillance Inspections

PET Drug Surveillance inspections monitor conformance to 21 CFR 212 Regulations, which represent the minimum CGMP requirements.

These systems-based inspections follow Compliance Program(CP) 7356.002P and will always include coverage of Quality System with Aseptic Sterility Controls, with additional system(s) as described in the CP for abbreviated and full inspections.

Some Key Points on Surveillance Inspections

- Compliance Program and electronic Inspection Protocol are based on conformance with 21 CFR 212 Regulations.
- Inspections are generally scheduled with a firm in advance due to limited operational staff, except in the case of “For Cause” assignments.
- The cyclotron is not typically physically inspected due to potential hazards, but maintenance records may be encompassed in the inspection (e.g., target maintenance, frequency of window replacement)

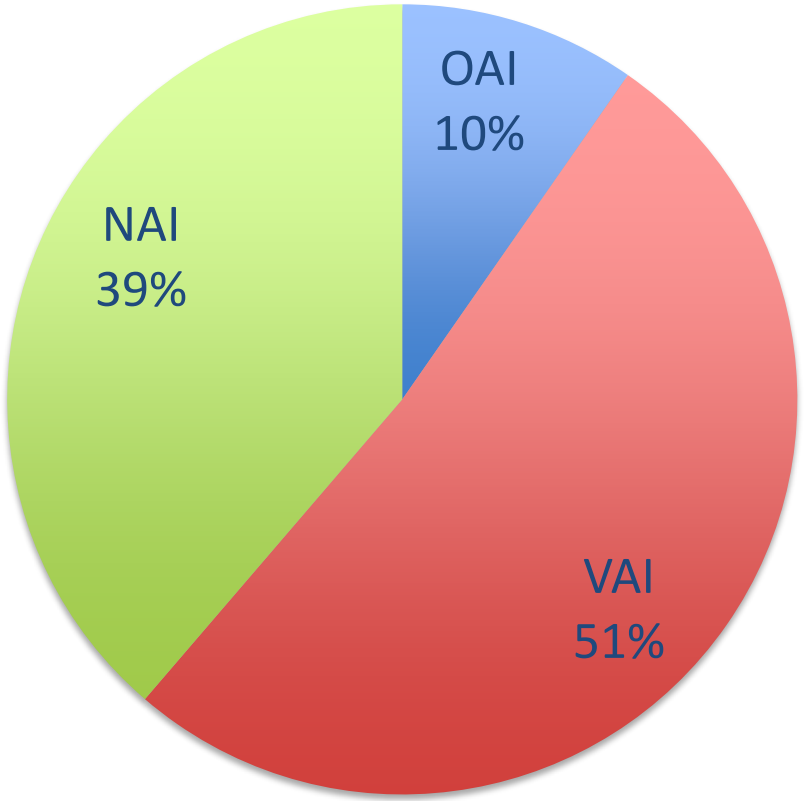
Some Key Points on Surveillance Inspections

- As with other inspection types, the collection of electronic records to facilitate faster, more thorough data review may be performed and is outlined in the Investigations Operations Manual.
- Collection of photographs has routinely been utilized on FDA inspections to document deficiencies or better describe an operation and is supported by case law.
- The FDA-483 is not a final Agency determination and voluntary firm response is considered if received within 15 business days.

PET Surveillance Inspections 2020-2023

- 31 Total Surveillance Inspections:
  - 2020: 10 inspections
    - (5 VAI, 5 NAI)
  - 2021: 11 inspections
    - (2 OAI, 4 VAI, 5 NAI)
  - 2022: 4 inspections
    - (2 VAI, 1 NAI)
  - 2023: 7 inspections
    - (1 OAI, 5 VAI, 1 NAI)

Final Inspection Classifications



704(a)(4) Record Requests 2020-2023

- Approximately 19 record requests conducted for surveillance of PET facilities since 2020 under FD&C Act Section 704(a)(4)
- Starting July 2021 and going forward, findings are being communicated to firms in writing

Recent 483 Examples

The following summarizes the Top FDA 483 Citations utilized for inspections of PET Facilities between 2020 and 2023, among both Surveillance and Pre-Approval assignments.

Top PET 483 Citations – 2020-2023

CFR Citation	Short Description	Number of Obsevations
212.30(b)	Equipment procedures	10
212.20(d)	Determination need for investigation	8
212.20(e)	Written QA procedures established, followed	8
212.50	Adequate controls (general)	8
212.30(a)	Orderly handling, prevention of mix-ups, prevention of contamination	8
212.60(b)	Lab sampling and test procedures	3
212.60(c)	Analytical methods	3
212.70(b)	Before implementing new procedure establish and document accuracy etc.	3
212.30(c)	Contact surfaces	2
212.71(c)	Correction of problems	2
212.40(a)	Written procedures for control of components, containers, and closures	2

Most Common 483 Citations – 212.30(b) Equipment Procedures

You did not [implement procedures] [document your activities in accordance with your procedures] to ensure that all equipment is [cleaned] [suitable for its intended purposes] [properly installed, maintained, and capable of repeatedly producing valid results] that could reasonably be expected to adversely affect the identity, strength, quality, or purity of a PET drug, or give erroneous or invalid test results when improperly used or maintained. Specifically, ***

Most Common 483 Citations – 212.30(b) Equipment Procedures

- "[Nuclear Pharmacist placed] his head, which included his exposed neck and facial skin, directly within the ISO 5 vertical Laminar Flow Hood (LAFH) during cleaning…immediately prior to sterile preparation and assembly of empty product vials"
- "…failed to apply the appropriate contact time for a sporicidal cleaning agent…as outlined by the manufacturer's instructions"
- "…do not disinfect the ISO 5 rated hot cell with sporicidal agents on a routine basis…[and there] is no documented cleaning procedure for the ISO 5 rated hot cell or the non-rated QC lab where the hot cell is located."

Most Common 483 Citations – 212.20(d) Determination Need for Investigation

When errors occurred or a production batch or any component of the batch, failed to meet specifications, you did not [determine the need for an investigation] [conduct an investigation] [take appropriate corrective actions] when necessary. Specifically, ***

Most Common 483 Citations – 212.20(d) Determination Need for Investigation

- “Two operators…continued to manufacture sterile drugs…when their media fill re-qualification was expired.”
- “…failed to adequately investigate and assess potential product impact…from the failure of the container closure system…”
- “(OOS) results…obtained during endotoxin analysis of five (5) batches…retested a single time and the passing result was considered valid…no detailed investigations to determine the root cause(s) of these events.”

Most Common 483 Citations – 212.20(e) Written QA Procedures Established/Followed

You did not [establish] [follow] written quality assurance procedures. Specifically,***

Most Common 483 Citations – 212.20(e) Written QA Procedures Established/Followed

- "Pharmacy Technician quickly and lightly touched the agar plates…as opposed to slowly rolling each fingertip and thumb on the agar surface with adequate pressure to ensure recovery of potential microbes as per SOP…"
- "QA personnel did not ensure all GMP records are complete and accurate" (e.g., facility maintenance and sanitization log not documented, glove fingertip testing, environmental monitoring results not reviewed)
- "…failed to establish procedures…in the event that there are system suitability failures of the…(TLC) instrument…"

Most Common 483 Citations – 212.50 Adequate Controls (General)

Your firm lacks adequate production and process controls to ensure the consistent production of a PET drug that meets the applicable standards of identity, strength, quality and purity. Specifically,***

Most Common 483 Citations – 212.50 Adequate Controls (General)

- “Operator replaced the dirty mop head…and did not sanitize their gloved hands before taking out a sterile clean mop head from the packet…”
- “…gloves used during aseptic manipulation of components, in-process materials, and finished drug products…within the ISO 5 rated hot cell were non-sterile.”
- “non-sterile [mop] covers [are used for] cleaning the inside ISO 5 surfaces of the Hot Cell.”

Most Common 483 Citations – 212.30(a) Orderly Handling, Prevention of Mix-Ups, Prevention of Contamination

Your facilities are not adequate to ensure [the orderly handling of materials and equipment] [the prevention of mix-ups] [the prevention of contamination of equipment or product by substances, personnel, or environmental conditions] that could reasonably be expected to have an adverse effect on product quality. Specifically, ***

Most Common 483 Citations – 212.30(a) Orderly Handling, Prevention of Mix-Ups, Prevention of Contamination

- "…sterility test failure classified as a 'false positive'… attributed to a contaminated septum…consistent recovery of microorganisms from the ISO 5 laminar flow hood, gloves, and…inside Hot Cell [above alert and action levels that include] spore-forming bacteria…and multiple too numerous to count (TNTC) results."
- "…failed to label the mini cell housings containing chemistry modules with on-going batch manufacturing status and cleanliness status to avoid…contamination, errors, and mix-ups…"
- "robotic arm grabbers [not included] in your environmental monitoring program…come into direct contact with final product vials when performing aseptic manipulations"

PET-Specific Investigator Training

Updated comprehensive training was delivered in 2021 to FDA Investigators focusing on the 21 CFR 212 Regulations for PET Drug Manufacturing, highlighting differences from the 211 Regulations.

Training targeted to Investigators already performing inspections of sterile drug manufacturers, to elucidate key differences in PET products and their associated controls. Also encompassed use of PET Inspection Protocol and Basic Radiation Safety.

PET Inspection
High-Level Training Topics

- Introduction to PET Drugs, Brief History of Production, and 21 CFR 212 Regulations
- Unique Aspects of PET Drug Production and Regulations
- Manufacturing Traditional PET Drugs & Production Technologies
- Systems-Based Surveillance and Pre-Approval Inspectional Coverage as Outlined in CP 7356.002P
- Emphasis of Differences Between 21 CFR 211 and 21 CFR 212 Regulations Throughout

PET Inspection Protocol

Inspection Protocol specifically designed for PET Drug facilities is currently being used for Surveillance Inspections conducted under Compliance Program 7356.002P.

The protocol may be executed on a tablet or laptop computer by FDA Investigators and was specifically created for systems-based coverage and aligns with 21 CFR 212 Regulations.

PET Inspection Protocol

- Leads to more efficient and consistent inspections that align with 21 CFR 212 Regulations
- Modernize inspections through collection of structured data that can be analyzed over time:
  - Quantitate the state of pharmaceutical quality
  - Accelerate the pace of making informed, data-driven decisions supporting areas such as:
    - Application approvals
    - Resource allocation
  - Identify policy and outreach opportunities across the industry

Thank You!

Nicholas Violand

Drug National Expert

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Overview of the SNMMI Quality Systems Personal Training Program (QSPTP)

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Emeritus Professor of Radiology
Washington University Medical School
St. Louis, MO

PURPOSE & SCOPE

The Society of Nuclear Medicine & Molecular Imaging (SNMMI) Qualified Systems Personnel Training Program (QSPTP) has been developed to define the competencies of a Qualified Person in the release of manufactured radiopharmaceuticals, providing experts in the field of radiopharmaceutical science guidance in program development

DEFINITION OF NEED

- The manufacture of radiopharmaceuticals and the ongoing production of radiopharmaceuticals is dependent on skilled personnel cross-trained in several disciplines. There is a need to educate, train and develop individuals with a pharmacy or chemistry background in production and release of radiopharmaceuticals.

- At the current time there are insufficient individuals with this type of training, and it would benefit both academic and commercial entities by providing these trained individuals


SNMMI Qualified Systems Personnel Training Program
ENHANCE YOUR EXPERTISE IN RADIOPHARMACEUTICAL SCIENCES
Defining the competencies of a qualified person in the release of manufactured radiopharmaceuticals.
BUILD COMPETENCIES TO:
• Manufacture radiopharmaceuticals
• Comply with production and development regulations
• Assume responsibility for small-scale radiopharmaceutical manufacturing
• Promote standards of practice in radiopharmaceutical production and development
• Individual and group registration available.
LEARN MORE
SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

OVERVIEW

- Provide theoretical knowledge and practical experience needed to assume responsibility for small scale manufacture, quality control and release of radiopharmaceuticals.
- Cross-training chemists and radiopharmacists
- Provide training in manufacturing and quality assurance of radiopharmaceuticals for both the academic and commercial settings
- Training in synthesis and pharmaceutical formulation of radiopharmaceuticals—PET, SPECT and radiotherapeutics, especially from cyclotron produced radionuclides
- Understand compliance with regulatory requirements associated with radiopharmaceutical manufacturing
- Application of radiopharmaceuticals in biomedical research and clinical nuclear medicine
- Research applications including IND and RDRC processes

TARGET LEARNERS

- Prior training: PharmD, B.S. or M.S. Pharmacists or M.S. in Chemistry prior to beginning QSPTP Program
- Lectures can be taken independently for the training

COURSE FEES

The SNMMI QSPTP course fee includes all Part One/Two learning modules. *No CE credit is available for this program.*

- SNMMI Members: $1,495 | Nonmembers: $2,195
- Institutions (up to 5 personnel): $2,495

Part Three Hands-on/Experiential Learning program fee will be determined by the participating site.

PROGRAM OVERVIEW
PART ONE - REGULATORY

- Quality Systems (Procedures and Operations: Basic concept, QA Management and Structure)
- Pet Drugs - Current Good Manufacturing Practice (CGMP)
- Overview of 21 CFR Part 211
- Overview of 21 CFR Part 212 and USP Chapter 823
- Historical Overview USP
- USP Chapters 797 and 825
- NDA and ANDA Submission
- Reporting Requirements
- IND submission
- Contract Manufacturing
- 21 CFR 212 Subpart C: Quality Assurance (212.20)
- 21 CFR part 212 Subpart D: Facilities and Equipment (212.30)
- 21 CFR Part 212, Subpart E: Control of Components, Containers and Closures (212.40)

PROGRAM OVERVIEW
PART ONE - CONTINUED

- 21 CFR Part 212 Subpart F: Production and Process Controls (212.50) and Subpart G: Laboratory Controls (212.60) PART 1
- 21 CFR Part 212 Subpart F: Production and Process Controls (212.50) and Subpart G: Laboratory Controls (212.60) PART 2
- 21 CFR Part 212 Subpart H: Finished Drug Product Controls and Acceptance
- 21 CFR Part 212 Subpart I: Packaging and Labeling (212.80) & Subpart J: Distribution (212.90) Subpart K: Complaints (212.100) & Subpart L: Records (212.110)
- Quality Assurance
- Cyclotron and PET Chemistry Synthesis Modules; Maintenance and Calibration
- Microbiology

PROGRAM OVERVIEW
PART TWO –SCIENCE

- Nuclear Physics and Instrumentation: Atomic Structure and Radioactive Decay
- Nuclear Physics and Instrumentation: Interaction of Radiation with Matter and Radiation Detection
- Nuclear Physics and Instrumentation: Nuclear Counting Statistics
- Nuclear Physics and Instrumentation: Nuclear Counting Systems
- Radiation Dosimetry for Radiopharmaceuticals
- Radionuclide Production Devices
    1. Radionuclide Production - Reactors
    2. Radionuclide Production - Cyclotrons
    3. Radionuclide Production Radionuclide - Generators
- Substrate Specific radiopharmaceutical Localization
- Substrate Non-Specific radiopharmaceutical Localization
- Pharmacology of radiopharmaceuticals "Radiopharmacology" PART 1
- Pharmacology of radiopharmaceuticals "Radiopharmacology" PART 2
- Pharmacology of radiopharmaceuticals "Radiopharmacology" PART 3

PROGRAM OVERVIEW
PART TWO - CONTINUED

- Introduction to Radiopharmaceuticals
- Basic Nuclear and Radiochemistry
- Radiochemical Syntheses - Automated
- Non Metal Radionuclides General Concepts and ^{18}F
- Non Metal Radionuclides ^{11}C, ^{13}N, ^{15}O, ^{124}I
- Non Meta SPECT Radionuclides, Imaging & Therapy
- Radiometals - General concepts
- Radiometals - Single Photon Radiometals ^{99m}Tc, ^{111}In, other
- Radiometals - Positron-Emitting radiometals
- Radiometals - Therapeutic Radiometals
- Quality Control Techniques - Visual, pH, Methods, TLC
- Quality Control Techniques - HPLC
- Quality Control Techniques - GC
- Quality Control Techniques - Dose Calibrator and MCA
- Quality Control Techniques - PET Quality Control & Analytic Methods Transfer
- Quality Control of Radiopharmaceuticals

PROGRAM OVERVIEW PART THREE
EXPERIENTIAL LEARNING--FDA MANUFACTURING SITES

Applicants will take part in an experiential learning program at a participating institution for ~4-6 weeks. A separate fee (determined by the participating site) will apply for this component.

Institutions:

1. University of California San Francisco
2. Massachusetts General
3. Washington University School Medicine in St. Louis
4. Sloan Kettering
5. University of Michigan
6. MD Anderson Cancer Center
7. University of Alabama
8. University of Iowa
9. University of Michigan
10. University of Pennsylvania

Hands on Training Topics

1. Aseptic Training
2. Media Fill Testing
3. Laminar Flow Cleaning
4. Assembly of Final Product Vial
5. Environmental Monitoring
6. Facility Cleaning
7. Production procedures
8. Quality Control Instrumentation and Procedures
    a. HPLC (standard curves, development and maintenance)
    b. GC (standard curves, development and maintenance)
    c. TLC Scanner
    d. Filter Integrity testing
9. Dose Calibrator
    a. Gamma
    b. Beta
10. System Suitability
11. Standard Operating Procedures (SOPs)

QUALIFIED PERSON (QP) CERTIFICATE

- Based on prior training, candidates can test out of course areas
- Certificate of Training will be issued on completion of the Didactic Program
- Certificate of Program Completion will be issued on completion of the Hands on Program

SNMMI QSPTP Committee

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Conclusion

- There are insufficient individuals with this type of training, and it would benefit both academic and commercial entities by providing this training opportunity.

- It could also offer training for potential investigators who will be inspecting in the field of radiopharmaceuticals.

Thank You!

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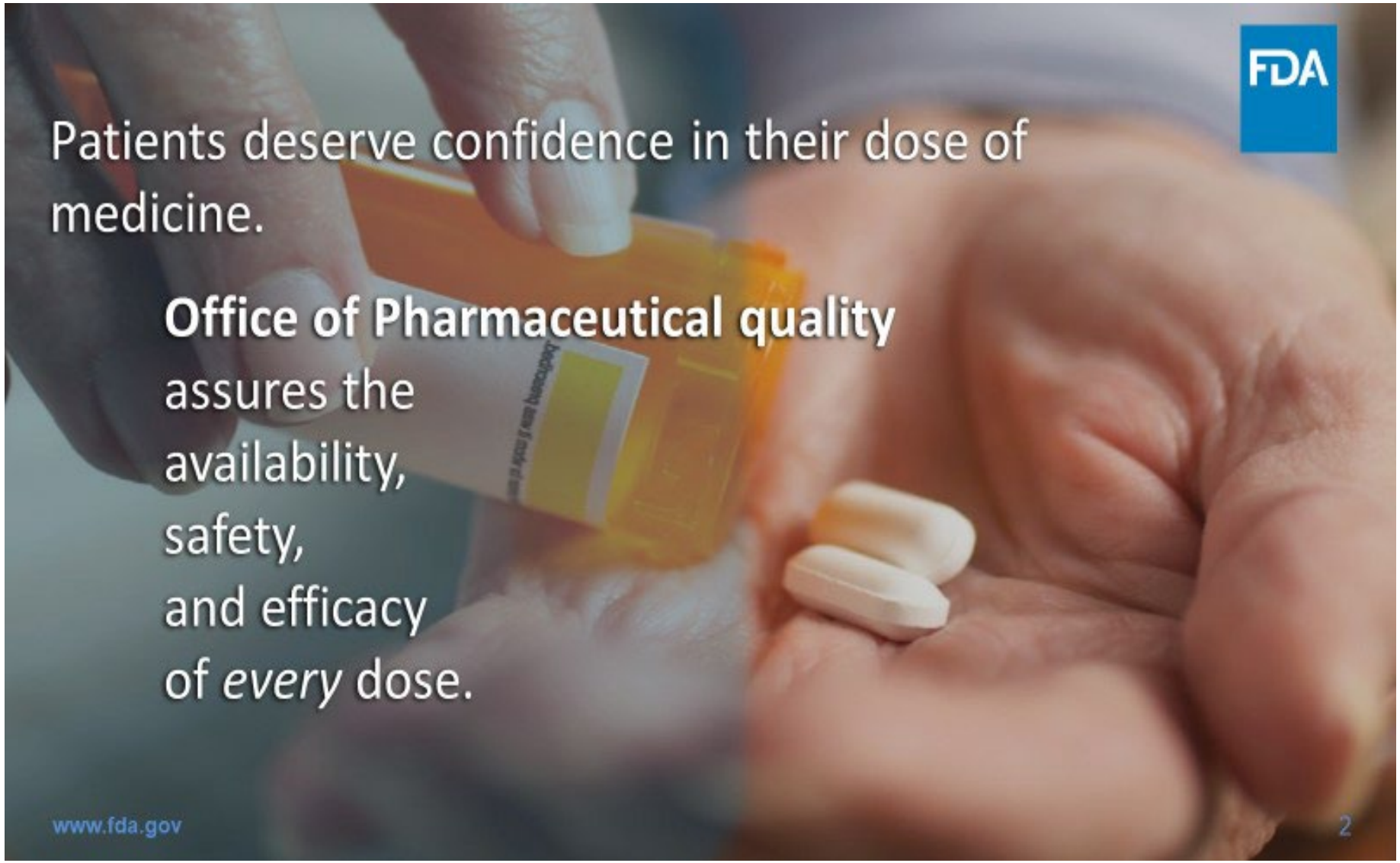
PANEL DISCUSSION/AUDIENCE Q&A

SESSION 2: PRODUCT QUALITY AND REGULATORY SUBMISSIONS

Product Quality Considerations for PET Regulatory Applications

Danae Christodoulou, Ph.D.
Branch Chief, Office of New Drug Products
FDA/CDER/OPQ



COALITION OF PET DRUG MANUFACTURERS

MITA MEDICAL IMAGING & TECHNOLOGY ALLIANCE

SNMMI Value Initiative

FDA U.S. FOOD & DRUG ADMINISTRATION

Outline

- Highlights of Critical Quality Considerations/Format in PET INDs
- Highlights of critical Quality Considerations/Format in PET NDAs
- Comparability protocols in PET Radiopharmaceutical NDAs

Quality data in an IND submission

- As required per 312.23 (a)(7)

Drug product quantitative composition, controls to ensure the identity, potency, purity and quality, stability data, controls of raw materials, manufacturers.

PET Radiopharmaceuticals:

Three qualification batches at each site of manufacture

with tabulated batch analysis results

At least one executed batch record

Certificates of analysis and expiry dates for chemical precursor, radionuclide and reference standard

Repeat Gaps in PET IND Submissions

- "Empty" CMC Section: No information as to who supplies PET drug for the IND study
- Lack of accurate Letters of Authorization (LoAs) or location of LoAs (e.g., state where submitted in previous protocol)
- Lack of identification of the production site that will supply the clinical site with PET drug
- Lack of qualification data for PET drug produced at the sponsor's site, even though cross-referenced to another sp[illegible]r's IND

Outcomes

Unsuccessful

- Insufficient quality information to assess risk to subjects may lead to a recommendation for clinical hold per 21 CFR 312.42(b)(1)(iv) for the clinical protocol

Successful

- A complete application at the time of submission that includes a complete quality and microbiology package

Multicenter Trials

- Identify product manufacturing sites that supply the clinical centers
- Opening trial: The qualification batches at the site of manufacture in the original submission, amend the IND with qualification batch data from subsequent sites
- Across sites/centers: Same range of specific activity, same formulation, same manufacturing process
- Accurate Letters of Authorization (LoA) and CMC data from the opening site(s) at the time of submission

Quality Content and Format

- *"IND Applications for Clinical Investigations: Chemistry, Manufacturing, and Control (CMC) Information"*
- *"Providing Regulatory Submissions in Alternate Electronic Format"*
- *"Guidance for Industry M4Q: The CTD — Quality"*

Refer to the FDA Guidance(s) at www.fda.gov

Drug Substance – CTD

(Precursor and Radioactive Drug Substance)

- S.1 General Information: Nomenclature, Structure, General Properties
- S.2 Manufacture
  - Manufacturers
  - Description of Manufacturing Process and Process Controls
    - Flow Diagram
    - Process Narrative
    - Process Controls
  - Control of Materials
    - Starting Materials
    - Reagents, Solvents, Auxiliary Materials
  - Control of Critical Steps and Intermediates
  - Manufacturing Process Development
- S.3 Characterization
  - Elucidation of Structure
  - Other Characteristics
    - Physicochemical properties
    - Solid State Forms
  - Impurities
    - Types (organic, inorganic, residual solvents)
    - Classification (specified/unspecified, identified/unidentified)
    - Reporting, Identification and Qualification Thresholds
    - Acceptance Criteria
    - Qualification
- S.4 Control of the Drug Substance
  - Specifications
  - Analytical Procedures
  - Validation of Analytical Procedures
  - Batch Analyses
  - Justification for Specifications
- S.5 Reference Standards
- S.6 Container Closure System
- S.7 Stability
  - Stability Protocol and Data Evaluation
  - Forced Degradation/Stress Testing
  - Photo stability
  - Stability Summary and Conclusion
  - Post-approval Stability Protocol and Commitment
  - Stability Data

Drug Product – CTD

- Drug Product
- P.1 Description and Composition
- P.2 Pharmaceutical Development
  - Drug Substance
  - Excipients
  - Formulation Development
  - Manufacturing Process Development
  - Container Closure Suitability
  - Other
- P.3 Manufacture
  - Manufacturer
  - Batch Formula
  - Description of Manufacturing Process and Process Controls
  - Control of Critical Steps and Intermediates
- P.4 Control of Excipients
- P.5 Control of the Drug Product
  - Specifications (release, stability, in-house)
  - Analytical Procedures
  - Validation of Analytical Procedures
  - Batch Analyses
  - Justification of Specifications
- P.6 Reference Standards
- P.7 Container Closure Systems
  - Primary, Secondary, Functional and Non-Functional Secondary Packaging
- P.8 Stability
  - Stability Protocol and Data Evaluation
  - Forced Degradation/Stress Testing
  - Photo stability
  - Stability Summary and Conclusion
  - Post-approval Stability Protocol and Commitment
  - Stability Data
- Appendices (3.2.A)
  - Facilities and Equipment (3.2.A.1)
  - Adventitious Agents Safety Evaluation (3.2.A.2)
- Regional Information (3.2.R)
  - Executed batch records, comparability protocols, methods validation package

Phase 3 studies

- Transfer of production sites from earlier stages
- Clear identification of suppliers of critical components, e.g., precursors (peptides, ligands), radionuclides (sources, e.g., generator, accelerator, and production methods), Letters of Authorization (LoA) to Drug Master Files (DMF), sterile components

Phase 3 studies

- Final drug product formulation or bridge pivotal clinical trial formulation to commercial product
- Drug Product Specification
- Presentation (single dose, multidose)

NDA submission

- Successful updates to the IND until Phase 3 lead to a successful NDA submission
- PET Diagnostic radiopharmaceutical: May be produced in a PET production facility, or the kit formulation may be radiolabeled at the radiopharmacy

NDA submission

- All manufacturing facilities ready for inspection current GMP compliance, listed accurately in 356h form
- All DMFs identified with LoAs
- Is the drug product formulation the same as used in Phase 3 clinical studies? Otherwise bridging information in the NDA 21 CFR 320.24
- Drug Product Release specifications and batch results for at least 3 exhibit batches

NDA submission

- Diagnostic radiopharmaceutical: A kit formulation should be demonstrated to radiolabel successfully by a radiochemical sourced from available different sources, e.g., generator, cyclotron, etc.
- Complete drug product specification should be included in the application with batch analysis test results

Labeling Considerations

- For a New Molecular Entity, what is the USAN name and has it been accepted by the USAN council?
- Strength: What is the radioactivity concentration or radioactivity amount?
- Radiolabeling instructions in the PI should be supported by CMC data submitted in the application, e.g., manipulations, reaction conditions, volumes etc.
- User Manuals: Safe use of complex products and accurate dose dispensing by the end user/operator

Comparability Protocols (CP)

- CP can be submitted in an original NDA application or in a Prior Approval Supplement (PAS) per 21 CFR 314.70(e)

- Effective knowledge of the product and manufacturing process
- Robust control strategy
- Robust pharmaceutical quality system
- Risk management activities over a product's life cycle

Comparability Protocols in PET Radiopharmaceuticals

- PET drugs or radiopharmaceuticals with short half-lives are often produced by a large network of manufacturing sites to dispense to hospitals and radiology facilities in proximal geographic locations

- Multiple drug product manufacturing sites in the NDA application and/or expanded after approval and launch to market –Large number of sites in an application, supported by compliant GMP status and production data

- Alternate manufacturing sites with acceptable inspectional history and GMP requirements using the same validated manufacturing process to ensure the same drug product composition and purity profile may be submitted in a "Changes Being Effected" (CBE-30) supplement. The GMP status of a facility is a "live" system and the category of supplement may be re-assessed to **PAS** at the time of submission of the supplement if the facility is not cGMP compliant.

Successful Comparability Protocol Assessments

- Effective use of knowledge of the product and manufacturing process:
- Radiosynthesis has been validated in a defined range of specific activities
- Formulation of the drug product remains the same

These are considered major changes per 21 CFR 314.70:

Change(s) in the precursor (different leaving group, different protecting group) or its manufacturer

- Change of equipment, e.g., synthesizer type and model, purification
- Change(s) of critical process parameters of the radiosynthesis and deprotection reaction
- Change of the purification method relating to the radiosynthesizer, e.g., HPLC to SPE
- Major change(s) in the analytical method analyzing impurities in the drug product (e.g., column, mobile phase, elution method (gradient-isocratic), run time)

Conclusions

- Product Quality (CMC) data are critical to successful NDA assessments and IND studies.

- FDA encourages innovation and engages with stakeholders and other government agencies working towards availability of new PET drugs and nuclear medicine technologies to patients

U.S. FOOD & DRUG ADMINISTRATION

THANK YOU

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COALITION OF PET DRUG MANUFACTURERS

MITA MEDICAL IMAGING & TECHNOLOGY ALLIANCE

SNMMI Value Initiative

SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

U.S. FOOD & DRUG ADMINISTRATION

Microbiological Quality Considerations for PET Regulatory Applications

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

- The comments expressed today are those of the presenter only and do not necessarily represent the official positions or policies of the FDA

Microbiological Considerations

- PET drug products are broadly defined as radioactive solutions, nonradioactive kits, nuclide generators, etc. (21 CFR 212.1)

- The microbiological information needed to support sterility assurance for an NDA/ANDA submission for a PET drug product is determined by the product type

- The following slides provide submission considerations for finished injection PET drug products and nonradioactive “cold” kit PET products

Presentation Outline

- Finished injection PET drug products
  - Manufacturing process overview
  - NDA/ANDA submission considerations
- Nonradioactive “Cold” kit PET drug products
  - Manufacturing process overview
  - NDA/ANDA submission considerations
- Review Case Studies

Finished Injection PET Drug Products

Manufacture of Finished Injection PET Drugs

- Finished injection PET drugs are manufactured as ready-to-use solutions with short shelf life (same day administration, usually within a couple hours of manufacture)
- Manufacturing process is fast and includes aseptic operations (bold font)

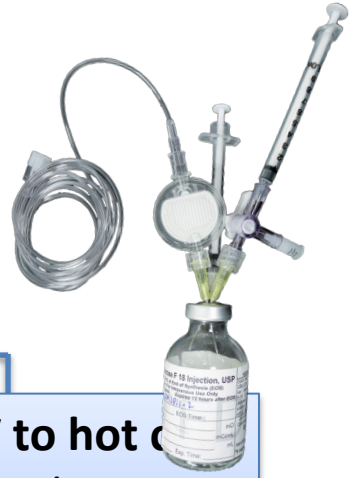
Empty pre-sealed, pre-sterilized vial with septum

Final product vial assembly in ISO 5 LFH

Pre-sterilized membrane filter, syringes

Unfiltered product (~10-50 mL)

Closed tubing



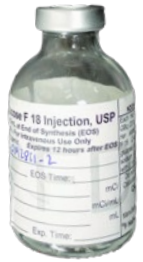
Transfer FPV to hot c tubing attached upstream of membrane filter, **sterile filtration**

QC testing, product dilution and transfer

Micro release tests:
Filter integrity
Bacterial endotoxins
Sterility (post-release)

Administered same day (within a few hours)
Batch size: 1-2 vials

Finished Product



NDA/ANDA Submission Considerations
Manufacturing Facility and Controls

- Facility floor maps, relevant equipment (i.e., laminar air flow hood (LFH), hot cell, etc.) for each manufacturing site
  - Aseptic operations (i.e., product vial assembly, sterility testing, etc.) should be performed in ISO 5 (Class 100) environments

- Description of the environmental monitoring program for ISO 5/critical areas
  - Type of monitoring, locations, frequency, alert/action levels, actions when levels exceeded
  - Performed routinely and during execution of aseptic operations
  - Environmental monitoring program also assessed during facility inspections

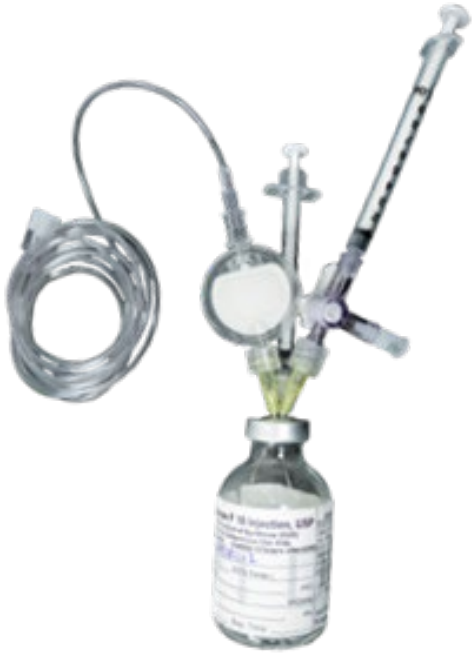
NDA/ANDA Submission Considerations
Container Closure System

- Pre-sealed, sterile, pyrogen-free container/closure consisting of glass vial, rubber stopper and seal from commercial source
  - Provide supplier info: CoA or DMF#/LOA, if applicable, for sterility and depyrogenation info
  - Container closure integrity testing generally not needed

- Container closure system depyrogenated and sterilized at PET production site
  - Provide validation information for depyrogenation and sterilization processes
  - Principles outlined in 2004 FDA guidance *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, Section IX.C.*

NDA/ANDA Submission Considerations
Manufacturing Process

- Product vial assembly
  - Assembly performed in ISO 5 LFH
  - Storage conditions and maximum hold time for assembled vials described
  - All components in direct contact with the sterilized drug product solution must be sterile (i.e., QC syringes, filter, etc.)
    - CoAs or DMF#/LOA must be provided



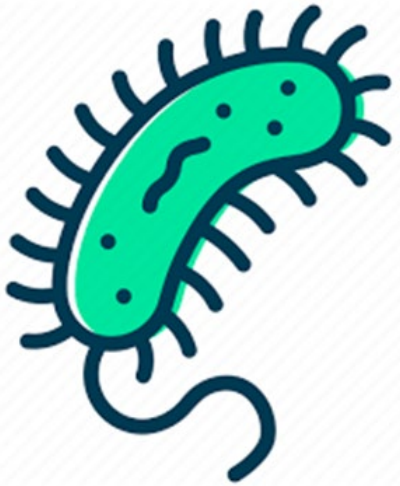
- Sterilizing Filtration
  - Following synthesis, finished injection PET drugs are passed through a sterile 0.22 µm or 0.2 µm sterilizing filter into the pre-sealed vial (closed system)
  - Filter validation studies are not generally required

NDA/ANDA Submission Considerations
Media Fills

- Provide description of the media fill program
  - Include product vial assembly/transfer to hot cell and all aseptic operations downstream of product filtration step up to product release
  - Represent worst-case conditions for aseptic operations
  - Use same rooms/critical equipment used during commercial production
  - Include positive control
  - Performed in triplicate for new operator qualification; annual requalification for each operator; performed when procedures/equipment are changed significantly
- Provide results for a minimum of 3 media fills
- Describe actions taken following media fill failure
  - Failed media fills should result in operator re-training and repeat media fill(s)
- 2012 FDA guidance *Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs*

NDA/ANDA Submission Considerations
Finished Product Release Testing

- Microbiological tests included in release specification:
  - Filter integrity
  - Bacterial endotoxins
  - Sterility



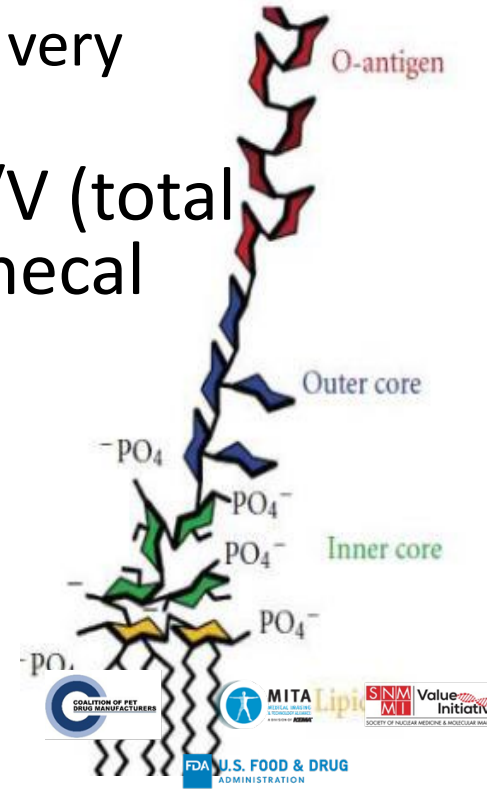
- No microbiological testing required for stability for PET products administered the same day they are manufactured
  - May be necessary on stability for finished injection products with longer shelf-life

Filter Integrity

- Performed after completion of filtration but prior to release of the PET drug product
  - Ensures integrity of filter not compromised during or before use
  - Per manufacturer's recommended test (i.e., bubble point test)
- Test method, wetting agent and acceptance criteria included in release specification
- CoA from filter manufacturer should be provided

Bacterial Endotoxins

- Testing should be performed in accordance with USP <85> recommendations
  - Initiated promptly after product manufacture is complete but prior to product release
    - Can be performed on QC-sub batches for radionuclides with very short half-lives (e.g., ^{15}O, ^{13}N)
  - Endotoxins specification for PET drug products: 175 EU/V (total volume injected) in one hour period; 14 EU/V for intrathecal administration
- Test method and acceptance criteria should be included in release specification
- Method suitability studies and results provided in submission



Sterility

- Testing should be performed in accordance with USP <71> recommendations
- Initiated within 30 hours of the completion of production
  - If initiated after 30 hours, perform additional studies to demonstrate that extended time period in drug product does not adversely affect viability of contaminating microorganisms and cause false negative results
- Test method and acceptance criteria should be included in release specification
- Method suitability studies and results provided in submission
- Describe actions following sterility test failure

Nonradioactive “Cold” Kit PET Drug Products

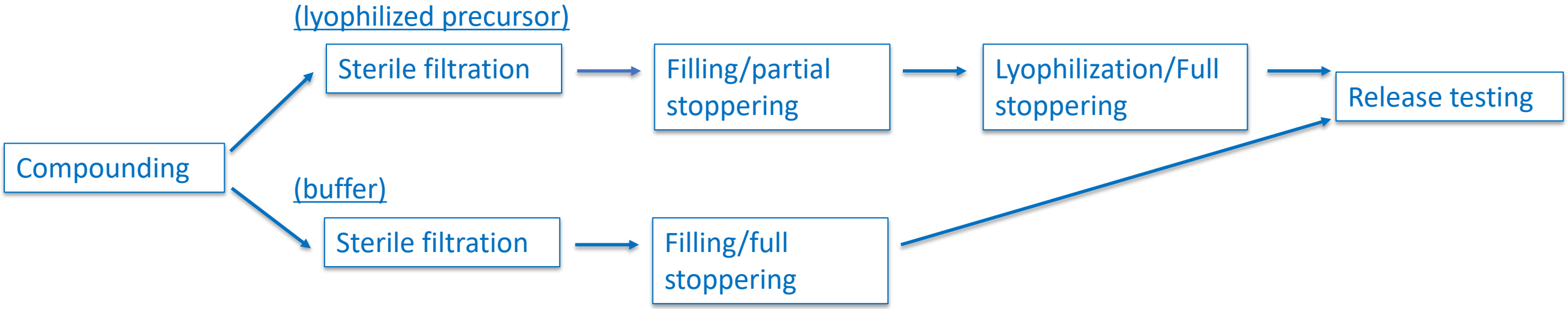
Nonradioactive "Cold" Kit Products

- All items included in the kit must be sterile (e.g., precursor, buffer(s), accessory items like empty vials, syringes, etc.)
- Manufacturing process(es) more complex than traditional finished injection PET products (i.e., lyophilization, larger batch sizes, long shelf life)
  - Sterility assurance is similar to nonradioactive, sterile pharmaceuticals
  - Principles outlined in the following guidances are applicable to kit products:
    - 2004 FDA guidance *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*
    - 1994 FDA *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*
- Sterility assurance reviewed for sterile kit components, associated sterile generator(s) and radiolabeling procedure (performed at radiopharmacy)

Overall Manufacturing Process Examples for Nonradioactive "Cold" Kit Products

Cold kits may include items that are manufactured by aseptic processing (e.g., lyophilized precursor, buffers) and/or terminal sterilization (e.g., buffers, accessory items)

Aseptic Processing Example



Terminal Sterilization Example

NDA/ANDA Submission Considerations for "Cold" Kits

Aseptic Processing

Compounding → Sterile filtration → Filling/partial stoppering → Lyophilization/Full stoppering → Release testing

Terminal Sterilization

Compounding → Bioburden-reducing filtration (if applicable) → Filling/full stoppering → Terminal sterilization → Release testing

Product Development

- Container closure integrity testing for each vial/container

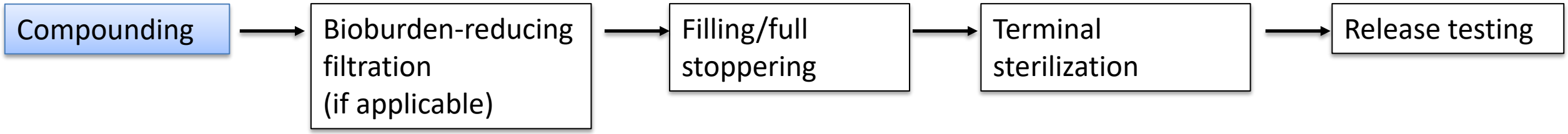
Facility Information

- Equipment/floor plans
- Description of environmental monitoring program
- Air quality/classifications for critical areas/operations

NDA/ANDA Submission Considerations for "Cold" Kits

Aseptic Processing

Terminal Sterilization



- Pre-filtration/pre-sterilization bioburden testing should be performed for bulk solutions (precursor and buffer, if applicable)
- Critical hold times (e.g., pre-filtration hold) should be described
  - Supporting microbiological data may be needed for extended hold times

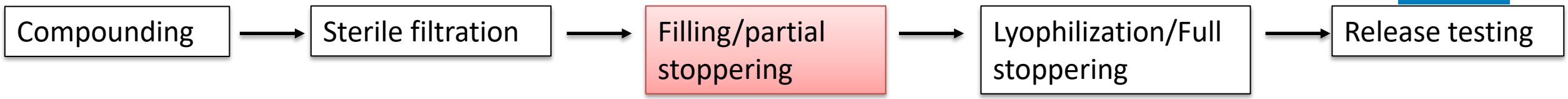
NDA/ANDA Submission Considerations for "Cold" Kits

Aseptic Processing

- Post-filtration integrity testing should be performed – test method, wetting agent, acceptance criteria described
  - If using drug product as wetting agent, bubble point determination studies
- Bacterial retention studies for bulk solutions (precursor, buffer, etc.)
- Sterilization validation information for filter/filtration equipment

NDA/ANDA Submission Considerations for "Cold" Kits

Aseptic Processing



- Sterilization validation information for filling equipment/product contact parts
- Depyrogenation and sterilization validation information for container closure system
- Media fill data to support aseptic filling process

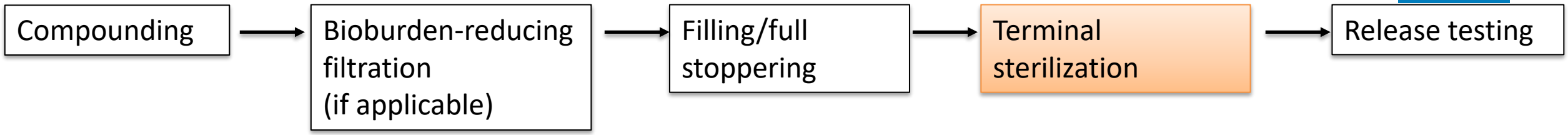
NDA/ANDA Submission Considerations for "Cold" Kits

Aseptic Process

- Sterilization validation information for lyophilizer chamber/trays

NDA/ANDA Submission Considerations for "Cold" Kits

Terminal Sterilization



- Sterilization validation information
- Pre-sterilization hold time (and supporting data, if applicable)

NDA/ANDA Submission Considerations for "Cold" Kits

Aseptic Process

Compounding → Sterile filtration → Filling/partial stoppering → Lyophilization/Full stoppering → Release testing

Terminal Sterilization

Compounding → Bioburden-reducing filtration (if applicable) → Filling/full stoppering → Terminal sterilization → Release testing

- Sterility and endotoxins testing for each kit component – test method and acceptance criteria described
- Method suitability studies included
- Endotoxins specification should account for all items included as part of the kit and endotoxins contribution from generator eluate
  - The sum of the endotoxins limits should not exceed 175 EU/V (total volume injected)

Stability

- Testing to demonstrate the maintenance of sterility required for each kit component (i.e., annual sterility testing or container closure integrity testing)

Review Case Study 1
Finished Injection Product – Media Fills

- Application indicated that commercial production of the subject PET drug product includes the addition of sterile saline to the sterile drug product solution (for tonicity adjustment). The addition of the sterile saline was not simulated during the media fill.

- **FDA Response:** Inadequate. All aseptic operations downstream of the sterile filtration step, including dilution or repackaging of the sterile drug product solution should be included in the media fill simulation.

Review Case Study 2
Kit Product – Sterilization Validation

- Application included validation information for sterilization processes for filtration/filling equipment and container closure components. The applicant noted that the lyophilizer chamber and trays are not sterilized.

- **FDA Response:** Inadequate. All product contact parts/equipment must be sterilized and validation information to support the sterilization processes must be included in the NDA/ANDA submission. The product vials are only partially stoppered during lyophilization, so the chamber and trays are considered product contact parts/equipment.

In Conclusion

- Sterility assurance information needed for NDA/ANDA determined by the type of PET drug product (i.e., finished injection, nonradioactive “cold” kit, etc.)

- Additional validation data needed to support sterility assurance for nonradioactive “cold” kit PET products
  - 1994 FDA *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

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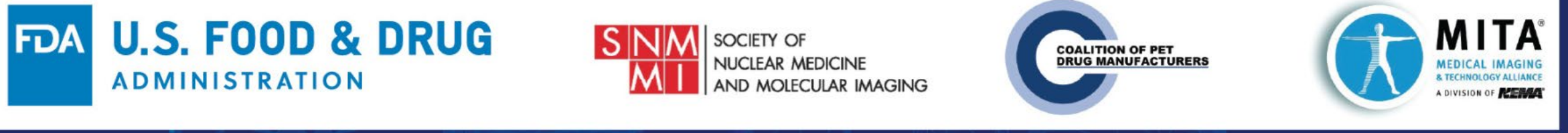
U.S. FOOD & DRUG ADMINISTRATION



Chemistry, Manufacturing and Control Issues

Peter J H Scott, PhD (University of Michigan)

Daniel L Yokell, Pharm.D. (Telix Pharmaceuticals (US) Inc)

SPEAKER DISCLOSURES

Dr. Daniel Yokell is an employee of Telix Pharmaceuticals (US), Inc. The views he expresses in this presentation are his own and do not reflect the views and positions of Telix Pharmaceuticals (US), Inc. or its affiliates.

Dr. Peter Scott has no relevant disclosures.

STABILITY TESTING: HOW ARE INSPECTORS TRAINED TO ASSESS ADEQUACY OF STABILITY PROGRAMS? FOR PET MULTI-SITES/NETWORKS, SUBMITTING STABILITY DATA PER PRODUCT FROM ONE REPRESENTATIVE SITE IS CONSIDERED COMPLIANT.

CAN FDA PROVIDE SPECIFIC EXAMPLES WHERE SINGLE SITE STABILITY ANNUAL SUBMISSION ARE CONSIDERED INADEQUATE?

Perspective: For PET drugs which are made on the same synthesis platform and validated via comparability protocol under an application which demonstrates "equivalence" of the processes at the different manufacturing sites, single site annual stability is believed to be adequate.

PET drugs are manufactured on a daily (or multiple times per day) and having each site perform stability can interfere with doses being available to patients as stability runs often use a patient batch manufacturing slot.

CAN THE FDA COMMENT UPON INCONSISTENCIES IN APPLICATION OF GUIDELINES AROUND, FOR EXAMPLE, RESIDUAL SOLVENTS. WHEN A SITE FILED THEIR IND THEY WERE ASKED FOR A 10 PPM TFA LIMIT, DESPITE THE OTHER TWO SITES ON THE STUDY NOT TESTING FOR RESIDUAL TFA. THE PROCESS GAVE TFA IN THE 100s OF PPM, ALTHOUGH THE pH WAS FINE. THE FDA HAD SAID THAT THEY KNEW IT WAS POSSIBLE SINCE OTHER PLACES HAD DONE IT, BUT PROVIDED NO DETAILS. CLINICAL WORK IS SEVERELY DELAYED NOW BECAUSE SITE IS STILL REDESIGNING THE SYNTHESIS TO TRY AND GET THE TFA NMT 10 PPM

Perspective: Inconsistent application of regulations between sites, especially multiple sites on the same study like in this case, causes confusion and frustration amongst the community. Moreover, setting overly conservative release criteria without rationale (e.g. TFA is not a Class I solvent, so why request residual limits akin to benzene (2 ppm) or carbon tetrachloride (4 ppm)?), is making it extremely difficult for academic PET Centers to develop and translate new PET tracers on short grant timelines, while also managing busy production schedules, and is ultimately slowing progress, stifling innovation and reducing the competitiveness of the United States PET Community compared to other nations (e.g. Germany, where PSMA and DOTATATE were developed).

WHAT REQUIREMENTS MAY BE USED BY PET DRUG DEVELOPERS IN SUPPORT OF IMPURITIES, SUCH AS IDENTIFICATION, CHARACTERIZATION AND QUALIFICATION? DOES ICH Q3A AND ICH Q3B APPLY TO RADIOPHARMACEUTICALS? HOW CAN PET DEVELOPERS BEST LEVERAGE SUCH GUIDANCE DOCUMENTS?

Perspective: Applying commercial standards to IND products which most likely will never be commercial (e.g. C-11 compounds) is overly burdensome and hampering translation of new radiotracers to first-in-human studies. Moreover, there are general issues around expectations of literature compounds, and the fact that manufacturing under <823> guidelines are sometimes scrutinized like commercial 212 products.

PET drugs are inherently safe and have an excellent track record of safety – millions of doses are administered each year without adverse events. Microdosing of C-11 compounds, however, and particularly literature compounds such as C-11 acetate that have been used for decades, appear to be under enhanced scrutiny of late. In one instance, a group was told the impurity profile using the established SPE purification was no longer acceptable, despite having been used around the world for a long time, and needed to develop an HPLC purification. This can be done, but again takes time away from other activities and appears to be unnecessary given the small numbers of research subjects (10s) and the well-established low risk profile of radiopharmaceuticals.

CAN THE FDA PROVIDE GUIDANCE ON WHEN A QC TEST CAN MOVE FROM PER BATCH TO A PQIT, HOW A COMPANY SHOULD EVALUATE AND JUSTIFY, AND ALSO IS THERE ANY GUIDANCE ON THIS TRANSITION PROCESS?

Perspective: The guidance "*Changes to an Approved NDA or ANDA*" notes that changes in product specifications to comply with compendial changes can be a CBE-30 – for example the FDG and NH_3 USP monographs have been updated since many sites had initial application approval.

For sites which seek to move a compendial test from per batch to PQIT or to move to a longer PQIT test frequency i.e. quarterly to annual, this could be justified with data and appropriate risk assessment of the change according to the guidance, with submission potentially as a PAS.

FOR CMC, IF THE EQUIPMENT CHANGES, BUT THE TESTING AND SPECIFICATIONS DO NOT CHANGE, CAN THIS BE SUBMITTED AS PART OF THE PRODUCT'S ANNUAL REPORT?

Perspective: The guidance "*Changes to an Approved NDA or ANDA*" notes that changes to equipment which produces an equivalent product can be submitted in the annual report.

There is lack of clarity in the community around FDA expectations here – some sites are submitting CBE's for this, while others are submitting in the annual report. For example, if a synthesis module is replaced with a new manufacturer and/or model can this change be documented in the next annual report?

WHAT IS FDA'S EXPECTATION REGARDING VENDOR QUALIFICATION FOR PET MANUFACTURERS? ARE ONSITE AUDITS REQUIRED FOR CRITICAL VENDORS OR CAN THEY BE QUALIFIED BY ALTERNATIVE MEANS?

Perspective: PET cGMPs provide for reliance on vendor performance and COAs since many firms are academics or networks with multiple sites which may require use of local vendors. Onsite audits of critical vendors has been raised during inspections and the industry believes this is will be a challenge for many firms, especially academic sites to comply with.

A more acceptable approach is continued reliance on the vendor history and COAs and documentation of key vendor qualifications in local QMS.

WHAT ARE THE EXPECTATIONS FOR TRENDING NO/LOW SYNTHESIZER YIELDS FOR MANUFACTURING EQUIPMENT?

Commerical Perspective (NDA/ANDA): Applications may not have yield specifications, in the event of no specification for yield in an approved application, trending of yields is not required.

Trending of no yield batches should occur in the local QMS with CAPA investigations as no yield is most likely considered under a site QMS as a quality event to identify root cause and remediate if possible. Since the PET industry relies in CMOs and equipment manufacturers for synthesis sequences and cassettes which are "locked", manufacturers may not have ability to immediately remediate the root cause if related to consumable/synthesis sequence. This requires working with suppliers to remediate the cause while tolerating an acceptable failure rate due to daily production requirements which does not impact quality or safety of the PET drug since no product was manufactured.

IND Perspective: Given that even multi-center IND studies frequently involve low numbers of research subjects at a given site (10s), n values are typically too low to meaningfully track / trend.

PRECURSORS ISSUES

i) TESTING BEYOND THE COA ACCEPTANCE

ii) STANDARDS FOR PRECURSOR SYNTHESIZED IN HOUSE TO VERIFY NEW PRECURSOR, UPON RECEIPT, MEETS TEST/RELEASE SPECIFICATIONS

Perspective: There is ongoing ambiguity and confusion over what standards are required to receive components intended for manufacture of PET radiopharmaceuticals. 21CFR212 states *"If you conduct finished-product testing of a PET drug product that includes testing to ensure that the correct components have been used, you must determine that each lot of incoming components used in that PET drug product complies with written specifications by examining a certificate of analysis provided by the supplier. You are not required to perform a specific identity test on any of those components."*

However, sites have been requested to synthesize samples of precursor themselves to confirm identity of incoming lots ((A)NDA), while more stringent GMP criteria are even being asked for precursors in Phase 0/1 IND applications. These inconsistencies between the regulations and site experience are complicated translation of radiopharamceuticals.

WHY IS FDA MANDATING THROUGH INSPECTION THAT HOT-CELLS ARE WIPED DOWN WITH STERILE IPA WHEN IT IS A CLOSED SYSTEM WITH TERMINAL STERILIZATION?

Perspective: A number of sites have reported this issue arising. There is no requirement to have ISO 5 for synthesis in 21CFR212 and EM is not conducted. Hot-cells themselves are not LAFs, and synthesis modules themselves are not sterile, or necessarily even compatible with solvents like IPA. Syntheses frequently involve a closed-system and all PET drugs are terminally sterilized. Indeed, given this latter point, use of non-sterile reagents is also typical/necessary for some radiosyntheses.

There is ambiguity around this point, and it is unclear to the community what expectations are. Clarity about the FDA's thinking would be helpful.

CLARIFICATION IS REQUESTED ON ISSUES SURROUNDING RADIONUCLIDIC IDENTITY AND PURITY TESTING:

I) TWO SOURCES ON CONSTANCY FOR DOSE CALIBRATORS WITH Co-57 AND Cs-137?

II) NEED FOR 2 METHODS OF RADIONUCLIDIC PURITY FOR SHORT- AND LONG-LIVED IMPURITIES?

III) HPGE FOR RNP FOR DECAYED SAMPLE; NEED FOR SPECTRUM?

Perspective: These issues are not clearly delineated in 21CFR212 but have cropped up for multiple sites during inspections and application reviews. It is unclear what issues the FDA is trying to solve for with all of this added work, expense and need for additional complex / expensive equipment such as HPGE detectors. Use of 2 sources for daily constancy not in alignment with NRC regs that require 1.

PET drugs are inherently safe and have an excellent track record of safety – millions of doses are administered each year without adverse events. The PET community is unaware of a single batch of radiopharmaceutical that has failed RNP testing.

DUAL TEMP INCUBATION FOR EM MEDIA?

Perspective: Environmental monitoring (EM) remains an essential detection tool for clean environments within radiopharmaceutical-manufacturing facilities. During monitoring, plates are incubated at a specific temperature for a set time. There appears to be no single approach to incubation currently used, and some industry partners have begun asking for dual temperature incubation (TSA) or dual media (TSA/SDA).

Clarity from FDA on their thinking around this issue would be helpful as we aspire for some level of standardization throughout the industry.

LABELING ISSUES

I) **ACTUAL STRENGTH (mCi/mL) AND EXPIRATION (TIME/DATE) SHOULD APPEAR ON THE DOSE VIAL LABEL**

II) **REPLACE THE WORD "MUTIPLE-DOSE VIAL" WITH "SINGLE-DOSE VIAL"**

Academic Perspective: Strength and expiration information is not available until after the vial has been filled, and that is the reason we use Outer Container labels in PET. It is not industry practice to edit labels on vials containing radioactivity as it violates ALARA principles. Moreover, expecting PET Technologists to read expiration information on a radioactive vial and irradiate their eyes is also an egregious violation of ALARA principles. There are provisions for outer container labels in both FDA and USP regulations.

With regards to multi-dose vs single-dose vials, while it is true that most research vials are for a single subject, it is not always the case.

Perspective from FDA on what issues they are trying to solve for with these repeated requests would be helpful.

LABELING ISSUES

I) ACTUAL STRENGTH (mCi/mL) AND EXPIRATION (TIME/DATE) SHOULD APPEAR ON THE DOSE VIAL LABEL

Industry Perspective: Strength and expiration information is not available until after the vial has been filled. Some sponsors have a reduced format label approved for the vial with drug name, strength range, batch number and firm information/caution statement.

An outer shield label with full batch information (total activity, EOS, strength at EOS, expiration date/time, etc.) have been accepted as a balance between batch information on the dose and ALARA, since the drug product is stored and transported inside of a radiation shield.

INSPECTIONS FINDING ISSUE WITH SPONSOR'S CMC DURING INSPECTION AT CMOs AND ISSUING 483s

Industry Perspective: The Sponsor's CMC is reviewed by the Agency review division(s) during application or supplement approval. CMOs are not responsible for the content in the Sponsor's application and are often not privileged to have access to this information.

It would be helpful to clarify why CMC issues are being identified during CMO inspection and resulting in 483s when the CMO has no control over the content in the application.

Are there alternative mechanisms for the Agency to review and communicate the concerns inspectors may raise which would not result in 483s issued to the CMO?

REGULATION OF BIOLOGICS LABELLED WITH PET ISOTOPES FOR IMAGING

Perspective: There are several biologic based diagnostics in late stage development which are labelled with PET isotopes intended for imaging purposes.

There is a novel combination from a regulatory prospective; there have been no biologic imaging agents approved labelled with PET isotopes

While it is acknowledged the drug would be regulated under the Public Health Service Act(PHS)/BLA under 21 CFR 610, there is no clear reference to 21 CFR 212 in the PHS or biologic CFRs.

21 CFR 212 definition of a "PET drug":

> *PET drug* means a *radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images*. The definition includes any nonradioactive 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. “PET drug” includes a “PET drug product” as defined in this section.

QUESTIONS / DISCUSSION?

U.S. FOOD & DRUG ADMINISTRATION

SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

COALITION OF PET DRUG MANUFACTURERS

MITA MEDICAL IMAGING & TECHNOLOGY ALLIANCE A DIVISION OF NEMA

Aseptic Controls in PET Manufacturing

Ashley Mishoe, PharmD, RPh
Reiko Oyama, MS, RPh, BCNP

EXPECTATIONS FOR ASEPTIC CONTROLS IN PET DRUG MANUFACTURING

There is **no difference** between academic and commercial manufacturing in 21 CFR 212

PET DRUG MANUFACTURING IS LOW RISK

Characteristics that define the risk profile of PET drugs

Primary

- Use of closed containers during the automated synthesis process for a typical PET drug
- Short shelf-life
- Small volume batches in one product vial and quality control testing of the whole batch

Secondary

- Use of microbiologically hostile and often lethal synthesis steps
- Synthesis is often completed in minutes
- Pre-sterilized components, aseptic component assemblies and manipulations, and the use of closed containers during the automated synthesis process for a typical PET drug
- Characteristics result in an extremely low – typically zero – bioburden process stream before sterile membrane filtration in the final production step

SURVEY RESULTS OF PET DRUG MANUFACTURERS

2020 AND 2023 SURVEYS

2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Number of FDA Approved PET Drug batches produced										
51,603	50,771	50,658	52,925	51,973	59,194	58,550*	57,676*	61,880*	66,193*	69,655*
Number of out-of-specification (OOS) sterility test results										
4	2	9	12	5	13	2	7	13	12	8
Number of FARs filed for the OOS sterility test results										
**	**	**	**	**	11	2	5	8	11	7
Number of confirmed/presumed product sterility failure										
**	**	**	**	**	**0**	**0**	**0**	**0**	**0**	**0**

*Data based on 2023 survey results as of 10-Oct-2023

**Data not available

SURVEY RESULTS OF PET DRUG MANUFACTURERS

2020 AND 2023 SURVEYS

- Sterility OOS rate is 0.014 % for 11 years (2013 and 2023)
- No confirmed/presumed product sterility failures for at least 6 years (373,148 batches)
- **Controls for PET Drug manufacturing should be set based on the risk**

Comments from the Community

Controls based on risk management

- Inspectors have expressed concerns about longstanding processes for which firms have substantial in-house performance and safety records.
- Can FDA discuss the **need** for additional controls that increase regulatory burden and cost in light of historical documented evidence for substantial safety and compliance?
- What can PET manufacturers do to help the FDA recognize such evidence as part of a Sponsor risk management program?

FACILITY EXPECTATIONS

- Clean room not required
- ISO Class 5 PECs required to be in a segregated area
- ISO Class 5 PEC certifications every 6 months
- Dynamic smoke studies
  - No requirement in 21 CFR 212 to video record smoke study testing

Comments from the Community

Facility

- What standards does FDA enforce regarding rooms that contain laminar flow hood/cabinet, especially regarding ISO 5 LAFW positively pressured inside a controlled room?
- Can FDA specifically point to applicable Guidance and reference standards (such as USP) that apply to room classification and recommended minimum standards?

FACILITY EXAMPLE

ISO Class 5 PECs located
in a segregated area

ISO Class 5 PECs located
in ISO Class 7 area

CLEANING OF ISO 5 AREAS

- Sterile 70% IPA required
- Sterile sporicidal not required
- Sterile wipes required
- Validating hold time of cleaning agents not required
  - Manufacturer's hold time can be followed

Comment from the Community

Validation for Cleaning

- What are FDA’s expectations around Disinfectant Efficacy Studies (DES) and cleaning validation studies for PET manufacturers?

ENVIRONMENTAL MONITORING

- Action vs alert levels
  - Alert levels not required in 21 CFR 212
  - No guidance in 21 CFR 212 regarding action level limit
    - FDA Aseptic Processing guidance references 21 CFR 210 and 211
  - Multi-use facilities may benefit from using USP 825 action limits
    - USP 825 compendially applicable November 1, 2023
- Active air sampling not required for routine monitoring in 21 CFR 212

Viable Air and Surface Sampling (USP Chapter <825>)		
ISO Class	Air Sampling Action Levels (cfu/m^3 of air per plate)	Surface Sampling Action Levels (cfu/device or swab)
5	>1	>3
7	>10	>5
8	>100	>50

ENVIRONMENTAL MONITORING

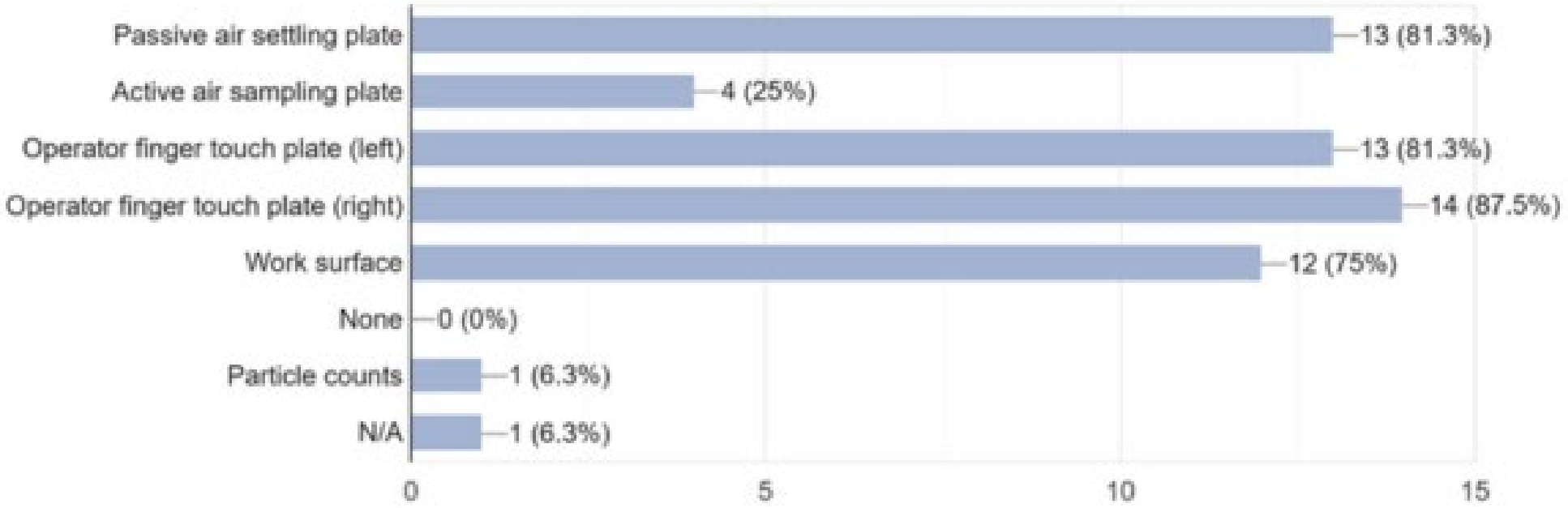
Comments from the Community

- What are the FDA's expectations of house flora testing given the low risk of PET manufacturing compared to the cost of these tests?
- Identification of EM results
  - What benefit has FDA seen from this?
  - Costs associated with this
  - Quarterly EM trend reports not required in 21 CFR 212 but frequently expected/requested in inspections
- Qualification of materials
  - What is the expectation for growth promotion of plates/tubes if growth promotion is included on the CoA?

2023 SURVEY RESULTS
EM DURING FPV ASSEMBLY

14. Please identify the areas typically sampled for environment microbial monitoring as part of the assembly of the final product vial in an ISO 5 area. If you select "other," please describe.

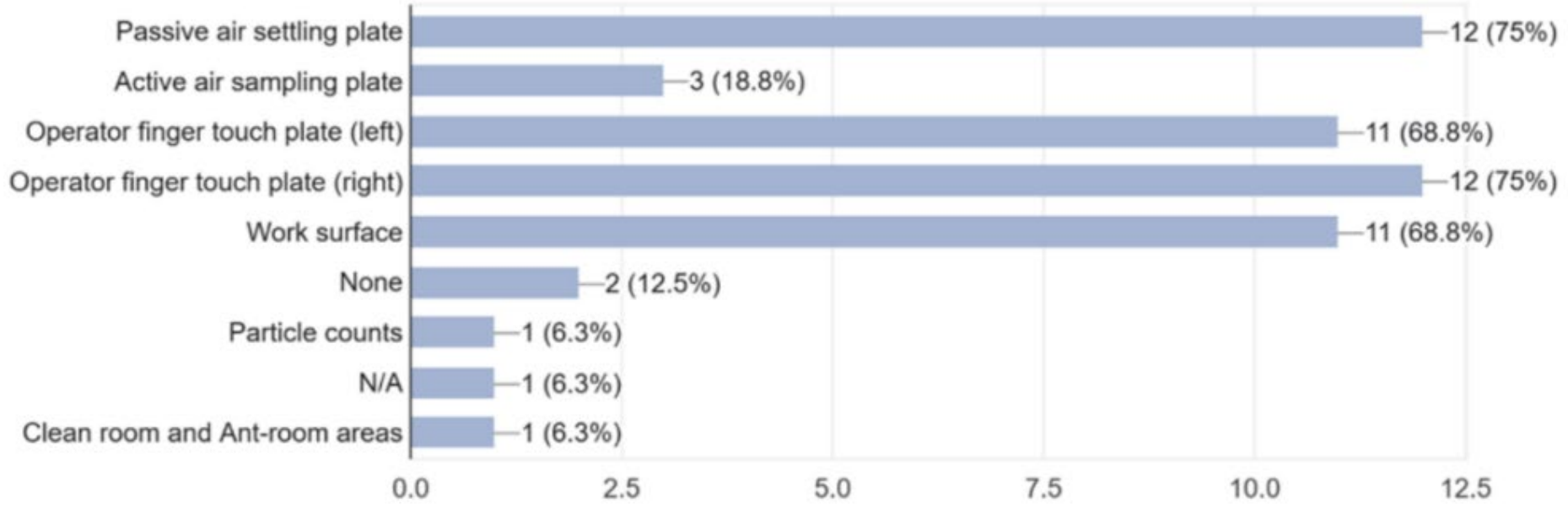
16 responses



2023 SURVEY RESULTS
EM DURING STERILITY TESTING

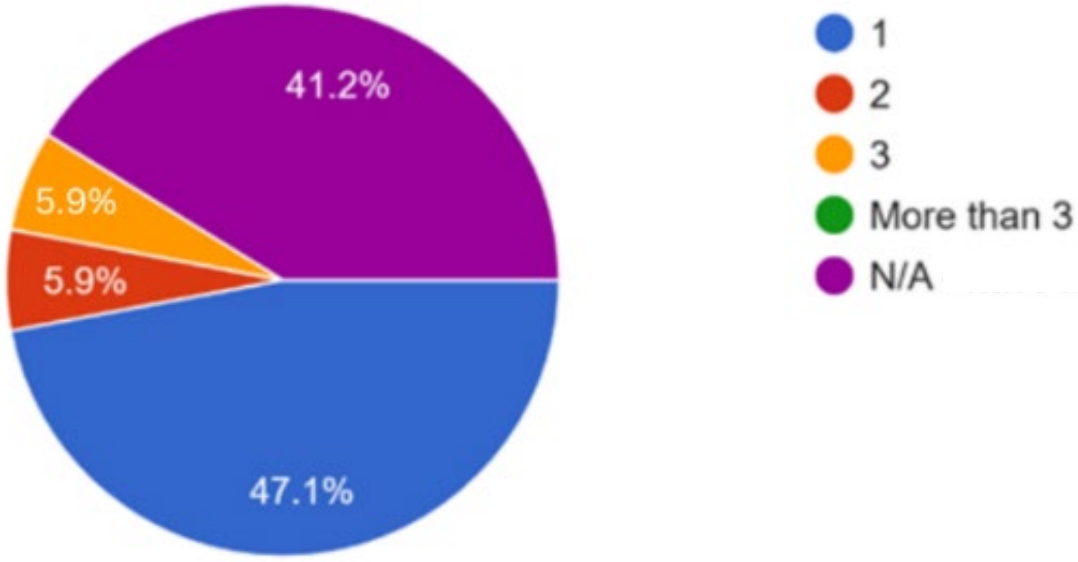
15. Please identify the areas typically sampled for environment microbial monitoring as part of the sterility test inoculation in an ISO 5 area. If you select "other," please describe.

16 responses

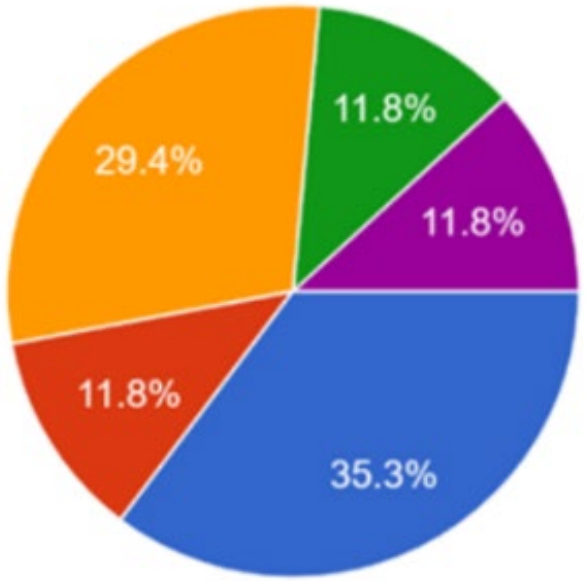


2023 SURVEY RESULTS
ALERT VS ACTION LIMITS

What is the **alert level** for the number of microbial CFUs in ISO 5 areas?



What is the **action level** for the number of microbial CFUs in ISO 5 areas?



MEDIA FILL EXPECTATIONS

Comments from the Community

- PET manufacturers often encompass multiple products/processes into one media fill to justify worst-case scenario
- What are the expectations for MF in each room and ISO 5 area vs risk-based approach?
- What are FDA's expectations regarding the MF for product vs for operators?
- Product vial assembly hold time should be tested
  - Can hold time be tested separately from other MF?

COMMENTS FROM COMMUNITY

Guidance Documents

- Will the FDA be updating and/or issuing new media fill guidance for PET drug manufacturers?
- When will the PET guidance document be updated and when will sterility assurance guidance for PET, as discussed in the last PET Drug Workshop with FDA, be released?
- Inspectors have recently referenced “the new 212” when making justifications for new standards/expectations. When were inspectors trained on new expectations? Can the industry have a copy of this training?

REFERENCES

- 21 CFR 212-Current Good Manufacturing Practice For Positron Emission Tomography Drugs
- Guidance, PET Drugs – Current Good Manufacturing Practice (CGMP), FDA, December 2009
- Guidance, PET Drugs – Current Good Manufacturing Practice (CGMP) (Small Entity Compliance Guide), FDA, August 2011
- Guidance, Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs, FDA, April 2012
- Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, FDA, September 2004
- USP Chapter <825> Radiopharmaceuticals-Preparation, Compounding, Dispensing, and Repackaging, Official as of 01-Dec-2020
- PET Drug Manufactures Survey Results, conducted by Coalition of PET Drug Manufactures in 2023
- PET Drug Manufactures Survey Results, conducted by Coalition of PET Drug Manufactures in 2020

PANEL DISCUSSION/AUDIENCE Q&A

LUNCH BREAK

SESSION 3: PRODUCT SAFETY AND RISK ASSESSMENT

Safety and Benefit/Risk Considerations at Various Stages of Product Development
November 13, 2023
Positron Emission Tomography Drugs: Product Quality, Regulatory Submissions, Facility Inspections, and Benefit-Risk Considerations

Jonathan E. Cohen, PhD

Supervisory Pharmacologist

Division of Pharm/Tox, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (DPT-RDPURM)

Division of Imaging and Radiation Medicine (DIRM)

Center for Drug Evaluation and Research (CDER), FDA

Disclaimer

The views expressed are those of the speaker and do not necessarily reflect the official policy of the US FDA.

No official endorsement by the US FDA is intended or should be inferred.

No Conflicts of Interest.

Focus

Nonclinical study recommendations to support radio-pharmaceutical diagnostic or PET drug development from pre-IND stage, to INDs and future marketing applications

- ❑ What nonclinical and clinical data can be relied upon to support development of PET drugs?
- ❑ How to optimize nonclinical studies to ensure efficiency of clinical development program without jeopardizing safety for FIH studies?
- ❑ PET drug quality attributes (impurities and degradants, excipients) and safety throughout development

Statement on Guidance Documents

"FDA guidance documents do not establish legally enforceable responsibilities. Instead, a guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited"

Regulatory Flexibility

- Current regulations allow for flexibility in nonclinical study requirements
- Sponsors are encouraged to meet with the FDA early in product development phase
- The FDA view is that there is value in early communication and agreement on IND enabling studies

Request a pre-IND meeting with the Review Division to ensure adequacy of the nonclinical package for future IND submissions

PET Drugs

Administered at low mass dose, 1/100th of a dose that elicits a pharmacologic effect, "sub-pharmacologic"

Mass dose ≤ 100 µg for small molecules or ≤ 30 nmol for protein products

Nonclinical study recommendations are more limited based on products' *unique characteristics* and Division *experience*:

- Microdose and radiolabeled
- Single or infrequent use
- Clinical use setting

FDA guidance and regulations include eIND guidance, ICH M3(R2), RDRC (21 CFR 361.1) and implementing the 3 R's

Recommended Nonclinical Studies Prior to Phase 1

Proof-of-concept studies:

- In vitro and in vivo characterization (receptor/target- and off-target profiling
- Evidence that radiolabeling does not significantly alter pharmacologic characteristics
- Biodistribution, imaging and radiation dosimetry

Pharmacokinetics (PK) studies:

- PK information in a test species (exposure, $t_{1/2}$)
- Biochemical information relevant to potential drug interactions

Recommended Nonclinical Studies Prior to Phase 1

Single-dose toxicity study

- Conducted in a single mammalian species (typically a rodent)
- Both sexes (unless justification provided)
- Clinical route of administration
- Doses evaluated should provide an adequate safety margin

Studies Not Recommended

- Safety pharmacology
- Repeat-dose toxicity
- Genotoxicity
- DART studies (CFR 312.10 with adequate justification

Comment on Toxicity Study Requirements

- Nonclinical guidance for diagnostic imaging agents differs from that of oncology drug products
- Consideration of the study design for the single dose toxicity study:
  - Adequate number of healthy animals per treatment group and controls
  - Extended, single dose toxicity studies should include interim and recovery groups with evaluation of clinical signs, hematology, clinical chemistry, body/organ weight, macroscopic and histopathology analysis
- Please provide all pivotal nonclinical safety study reports in your submissions

GLP Study Requirements

- ICH M3(R2) recommends that general toxicity studies supporting safety of an IND be conducted according to GLP regulations (21 CFR Part 58)
- GLP regulations ensure data quality and integrity
- However, if scientifically justified, deviations that would not have significant impact on the quality and integrity of studies may be acceptable on a case-by-case basis

Please Note!

- If a Sponsor determines that nonclinical pharmacology or toxicology studies are not needed, at any stage of development, FDA will consider request for not conducting studies if adequate justification is provided (21 CFR § 312.10)

What is considered adequate justification?

- Leveraging existing data and literature to support an IND
  - Close structural analogs with a toxicology assessment
  - Letters of Authorization to cross-reference IND for nonclinical support (same drug or theranostic pair)
- Please provide key cited literature in your submissions

Exceptions to Microdose Guidance

- Scenarios where additional nonclinical studies may be recommended
  - PET drug with pharmacologic activity at microdose levels (e.g., high affinity ligands or toxins)
  - PET drug clinical dose level exceeds a microdose
  - Presence of drug impurities that may be a greater safety concern than the investigational agent
  - Change in product formulation (e.g., excipient)

Meeting with the Review Division early to determine recommended studies

PET Drug Quality

- Impurities controlled according to ICH guidelines, e.g., ICH Q3A and Q3B
  - For microdose: reporting at 0.1%, identification at 1% (or 5 mcg), qualification at 1% (or 50 mcg)
  - Higher thresholds should be scientifically justified
  - Qualification may require conduct of new toxicity study or published literature (when appropriate)
  - Specifications should be supported by available data and ALARA principle

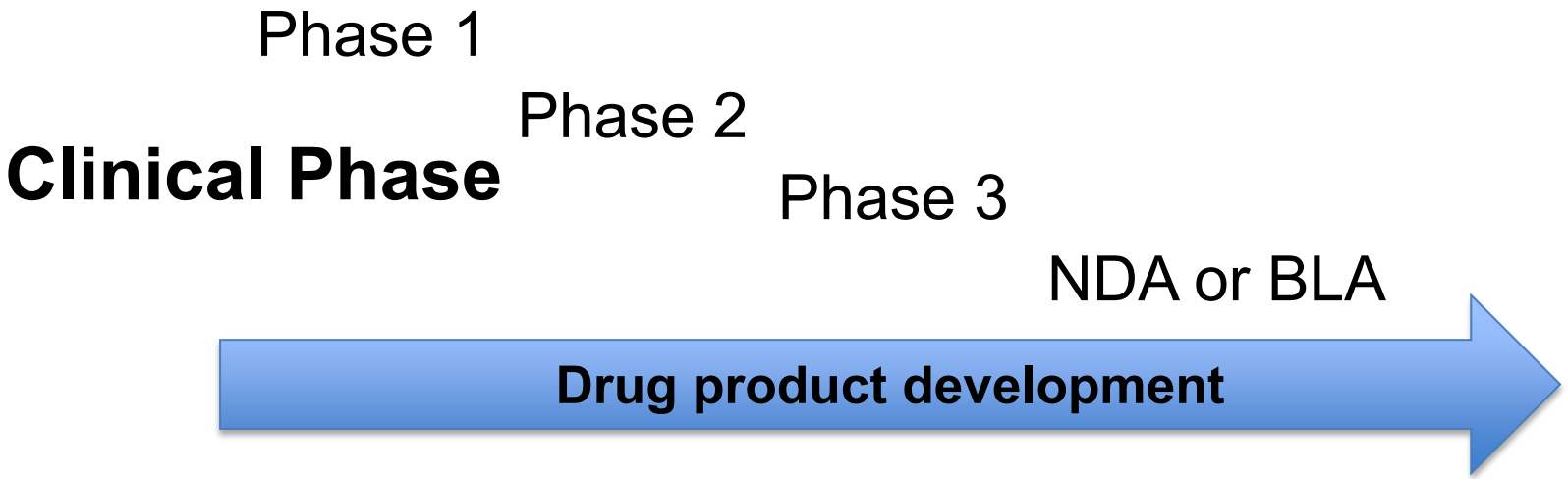
CMC and Pharm/Tox will evaluate PET drug throughout clinical development

PET Drug Quality cont.

- Radionuclide Generators
  - Examples include Rb-82 (from Sr-82) and Ga-68 (from Ge-68)
  - Safety concern with breakthrough
  - Presence of radionuclide impurities and other impurities
- F-18 PET Drugs
  - F-18 AIF radiochemistry; elemental impurities
  - Change in purification methodologies

CMC and Pharm/Tox will evaluate PET drug throughout clinical development

Lifecycle of PET Drug



- ❑ Control of impurities, qualification for later clinical phase
- ❑ Change in method, formulation, radionuclide
- ❑ Any safety or efficacy concern? (toxicological risk assessment, bridging studies)

Significant changes in PET drug quality may require additional data to support an NDA/BLA

Summary

- ❑ A more focused nonclinical safety evaluation
- ❑ Early communication with the Review Division to optimize the nonclinical program
- ❑ A flexible approach that allows innovative products to move safely and quickly though nonclinical development
- ❑ Control of PET drug quality specifications, supported by nonclinical studies and literature (when appropriate)

Thank You!

Guidance Documents:

ICH Q3A Impurities in New Drug Substances: https://www.fda.gov/media/71727/download

ICH Q3B Impurities in New Drug Products: https://www.fda.gov/media/71733/download

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: https://www.fda.gov/media/71542/download

Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations: https://www.fda.gov/media/107641/download

FDA Redbook: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivb1-general-guidelines-designing-and-conducting-toxicity-studies

Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry: https://www.fda.gov/media/129547/download

Safety and Risk Management of PET Drugs

Coalition Co-Chairs

Henry VanBrocklin, Ph.D.

University of California San Francisco

Steve Zigler, Ph.D.

PETNET Solutions, a Siemens Healthineers Company

13 November 2023

The 2020 workshop

WORKSHOP

PET Drugs: A Workshop on Inspections Management and Regulatory Considerations

FEBRUARY 21, 2020

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On This Page

- Meeting Information
- Event Materials

Date: February 21, 2020

Location

FDA White Oak Campus
Building 31, Conference Center, The Great Room
10903 New Hampshire Ave.
Silver Spring, MD 20993
FDA Campus Information

https://www.fda.gov/drugs/pet-drugs-workshop-inspections-management-and-regulatory-considerations-02212020-02212020

See also: "Proceedings: PET Drugs—A Workshop on Inspections Management and Regulatory Considerations, J Nucl Med 2022; 63:1117–1123.

Last slide from the 2020 workshop

Closing Remarks

The PET Community and the FDA aim to:

- Enhance the effectiveness of inspections. This will ensure the uniformity of PET drugs in the US.
- Reach consensus for a science-based risk profile for PET drugs.
- Create and implement training that is intended to enhance consistency of inspections.
- Hold a workshop periodically to continue the dialog between FDA and PET drug stakeholders.
- Hold interim informational meetings between FDA and PET drug stakeholders to discuss ongoing issues associated with inspection of PET drug manufacturing facilities.

Risk Management

- Risk is inherent in the pharmaceutical sciences
- Risk can never be eliminated but only managed
- Gained attention in the 2000s when FDA undertook a variety of initiatives focused on risk management

Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century[1]

- One component was to “encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas”
- Ultimately led to a risk-based model for prioritization of surveillance inspections
- Also catalyzed the application of quality systems in the pharmaceutical industry and within the FDA

[1]Pharmaceutical CGMPS for the 21st Century — A Risk-based Approach (Final Report) (2004).

PDUFA V and VI: Structured approach to benefit-risk assessment in regulatory decision-making[1,2]

- Aimed to develop a more systematic and transparent approach to the benefit-risk framework employed in review and approval of drug marketing applications
- Summarized in a series of white papers, workshops, guidance documents, and other publications[3-6]

[1]Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making - PDUFA V (2013).
[2]Benefit-Risk Assessment in Drug Regulatory Decision-Making - PDUFA VI (2018).
[3]Enhancing Benefit-Risk Assessment in Regulatory Decision-Making - Draft Guidance - PDUFA VI (2022).
[4]FDA Public Workshops on Benefit-Risk Considerations (2017).
[5]www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/pharmaceutical-quality-21st-century-risk-based-approach-progress-report (2018).
[6]Q9(R1) Quality Risk Management; International Council for Harmonisation; Guidance for Industry (2023).

None of these initiatives specifically address risk from the perspective of the manufacturing techniques used for PET drugs

Notable documents dedicated to PET drugs have minimal information regarding risk management

- A keyword search of PET GMP regulations and guidance documents reveals that “risk” occurs four times[1-4]
- Manual for inspection of PET drug facilities uses “risk” twice[5]
- Publicly-available (redacted) review of the most recently approved PET drug evaluates risk from a clinical perspective[6]
- Non-redacted portions of the review do not discuss risk in the context of the microbiology, chemistry, CMC, facilities sections[6]

[1]21 CFR Part 212, Current Good Manufacturing Practice for Positron Emission Tomography Drugs.
[2]CDER. PET Drugs--Current Good Manufacturing Practice (CGMP); Small Entity Compliance Guide (2020).
[3]CDER. PET Drug Products - Current Good Manufacturing Practice (CGMP) (2020).
[4]CDER. Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (2012).
[5]FDA Compliance Policy Guide 7356.002P Drug Process Inspections - PET Domestic (compliance program 7356.002P—PET CGMP Drug Process and Pre-Approval Inspections/Investigations) (2016).
[6]Drug Approval Package: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216023Orig1s000TOC.cfm.

Clarity and transparency

- The goals of the benefit-risk framework[1] are:

  1. Improve clarity and consistency in communicating regulatory decisions
  2. Ensure assessments can be readily understood in the larger patient care and public health context

[1]Benefit-Risk Assessment in Drug Regulatory Decision-Making - PDUFA VI, March 2018, p.3.

Conclusion

Scarcity of publicly-available data suggests that a structured, science-based risk assessment focused on manufacturing techniques for PET drugs has not been elaborated either by the PET community or FDA

Moving forward

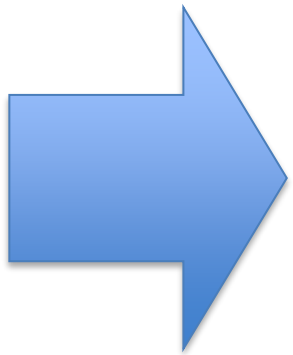
- To fill this gap, we have initiated a risk assessment focused on manufacturing techniques for PET drugs
- Based on a modified Failure Mode Effects Analysis (FMEA)[1]
- Adapted for the characteristics of PET drugs and prototypical manufacturing techniques
- Not intended as guidance or policy, only to present a method for risk assessment of manufacturing techniques with the goal of improved risk-based decision-making

[1]Quality Risk Management for Aseptic Processes, Parenteral Drug Association, Technical Report 44; (2008).

Challenges and methodologies

Challenges–

- Subjectivity
- Uncertainty
- Complexity
- Importance
- Relevance



Methodologies–

- Acknowledge and manage bias
- Multi-disciplinary stakeholders
- Initially limit scope to one process
- Initially focus on sterility assurance
- Corroborate with independent data, e.g., surveys, adverse events

Step 1: Define the process

Prototypical process (Fludeoxyglucose F 18)

Radionuclide Production

Radiochemical Synthesis/ Purification

Membrane Filtration

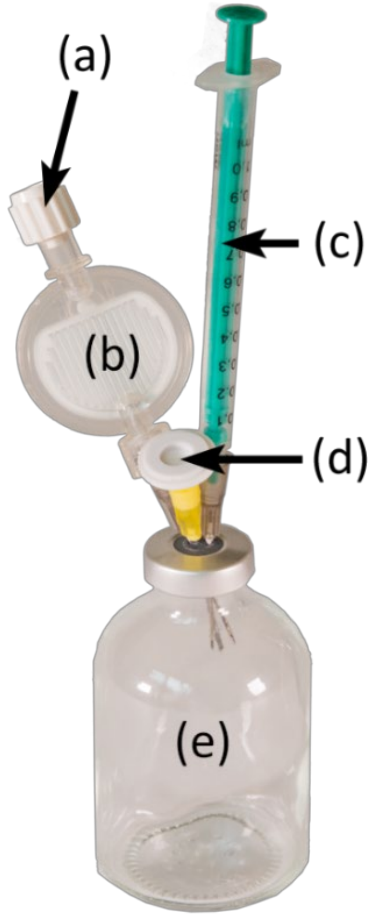
Quality Control

Released Product

Focus on sterility assurance: the final product vial

Critical Design Elements

- Membrane filtration, but not traditional aseptic processing
- Closed system downstream of filter
- Commercially sterilized components assembled aseptically
- Small batch scale, typically one batch = one vial
- 100% sampling plan for QC



Components

(a) Product inlet

(b) Membrane filter

(c) QC sampling syringe

(d) Filtered vent

(e) Product vial

Step 2: Identify failure modes and sources of contamination

Two failure modes for product non-sterility

Contaminated final product vial

Sources of contamination:

1. Personnel
2. Aseptic techniques
3. LFH/BSC
4. Materials/components
5. Process design

Ineffective membrane filtration

Sources of contamination:

1. During routine operations
2. Process design

Step 3: For each contamination source, define failure mechanisms and controls

Example: Personnel

- Failure mechanisms include:
  - Operator touch contamination
  - Airborne contamination from operator and non-operators
  - Poor operator technique
- Controls include:
  - Hygiene, garb, disinfection, etc.

Step 4: Calculate risk levels

Risk level calculation

- For each failure mechanism and existing control, assess the following (H/M/L):
  - Severity of a potential failure
  - Likelihood of failure (occurrence)
  - Probability of detection
- Determine overall risk level from sum of S/L/P

Step 5: Evaluate acceptability of resulting risk level

Work in progress

Failure Mode	Microbial Contamination Sources	ID	Failure Mechanism	Existing Controls	Severity	Occurrence (Likelihood that the process step will fail)	Probability of Detection (Likelihood that a failure of this process step will be known)	Risk Level (H/M/L)	Risk Accepted? (Y/N)
Non-sterile product due to contaminated Final Product Vial (FPV)	1. Personnel	*A*	Touch contamination from operator	Hygiene practices (proper hand washing, no jewelry, etc.)					
				Garb (powder-free gloves)					
				Disinfection (effective disinfectant, proper coverage and contact time)					
		B	Airborne contamination from operator	Hygiene practices (no jewelry, no make-up, no respiratory illness, no sunburn, etc.)					
				Garb (hair/beard covers, face mask, low particulate jacket/forearm cover, shoe covers)					
				Disinfection (effective disinfectant, proper coverage and contact time)					
		C	Airborne contamination from non-operators	Reduce personnel traffic and activities in vicinity of LFH/BSC					
				Minimize sources of particulate matter within LFH/BSC and in the vicinity of LFH/BSC					
		D	Poor aseptic techniques	Training in aseptic techniques and qualification using media simulations					
	2. Aseptic Techniques	*A*	Microbial contamination during assembly of final product vial	Perform critical assembly steps and septum punctures in defined critical zone within LFH/BSC					
				Avoidance of turbulent air exposure (i.e., shadowing) on critical surfaces					
				Training in aseptic techniques and qualification using media simulations					
				Comply with written procedures for aseptic techniques					
		B	Microbial contamination during storage of final product vial assemblies	Place completed final product vials in plastic bags					
				Store and handle assembled final product vials according to written procedures					
	3. Laminar flow hood (LFH)/ Biological Safety Cabinet (BSC)	*A*	Airborne contamination from ineffective air filtration	Operate LFH/BSC for minimum time before cleaning, disinfection, and use					
				Routine use of critical and non-critical zones within LFH/BSC					
				Routine microbial monitoring with air settle plates					
				Routine certification of LFH/BSC					
		B	Surface contamination from walls/ceiling of LFH/BSC	Clean and disinfect walls and ceiling at beginning of each operational					
		C	Surface contamination from work surface of LFH/BSC	Clean and disinfect work at beginning of					
				Routine microbial monit					
		D	Airborne contamination from vicinity of LFH/BSC	Reduce					
	4. Materials and Components (M/C)	*A*	Airborne conta	, of LFH/BSC before placement in the non-critical zone of the LFH/BSC					
				ging in the non-critical zone of LFH/BSC					
		B	Operator touch	Frequently disinfect gloved hands during each operational cycle					
		C	Microbial contamination from individual components in the final product vial assembly	Use of specified components for the final product vial					
	5. Process Design and Engineering	*A*	Microbial contamination due to poorly designed/engineered aseptic techniques	Specify closed system for filtration of product into the final product vial		N/A			
				Specify commercial, pre-sterilized final product vial, syringes, needles, and other components		N/A			
				Validation of critical steps (e.g., exposure of critical surfaces, disinfection of critical surfaces, septum/needle punctures, etc.) using media simulations		N/A			
				Define critical and non-critical zones within LFH/BSC based on size of work space		N/A			
				Assess laminar air flow for critical steps using smoke studies		N/A			
				Define limits on number of steps during each operational cycle		N/A			
		B	Microbial contamination due to poorly implemented aseptic techniques	Develop and control written procedures for aseptic techniques		N/A			
				Develop operations training in aseptic techniques and user qualification procedures using media simulations		N/A			
		C	Microbial contamination during storage of final product vial assemblies	Validation of storage conditions for final product vial assemblies using media simulations		N/A			
				Validation of aseptic integrity of the final product vial assembly design using media simulations		N/A			
				Develop storage conditions (e.g., plastic bags) for completed final product vials to minimize accidental movement of components and to prevent airborne microbial contamination		N/A			

Work in progress

How effective are existing control mechanisms for sterility quality assurance?

Approved PET drug applications[1]

PET Drug Product (Generic Name)	*Date First Approved*	*Approved Applications*
Sodium Fluoride F 18	February 24, 1972	27
Rubidium Chloride Rb 82	December 29, 1989	2
Fludeoxyglucose F 18	August 19, 1994	47
Ammonia N 13	August 23, 2007	31
Florbetapir F 18	April 6, 2012	3
Choline C 11	September 12, 2012	5
Flutemetamol F 18	October 25, 2013	2
Florbetaben F 18	March 19, 2014	1
Fluciclovine F 18	May 27, 2016	1
Gallium Ga 68 Dotatate	June 1, 2016	1
Gallium Ga 68 Dotatoc	August 21, 2019	1
Fluorodopa F 18	October 10, 2019	1
Fluoroestradiol F 18	May 20, 2020	1
Flortaucipir F 18	May 28, 2020	4
Copper Cu 64 Dotatate	September 3, 2020	1
Gallium Ga 68 Gozetotide	December 1, 2020	4
Piflufolastat F 18	May 26, 2021	1
Flotufolastat F 18 Gallium	May 25, 2023	1
	Total:	134

[1]FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm (accessed August 2023).

Silberstein and the SNM Pharmacopeia Committee

SPECIAL CONTRIBUTION

Prevalence of Adverse Reactions in Nuclear Medicine

Edward B. Silberstein, Janet Ryan and the Pharmacopeia Committee of the Society of Nuclear Medicine
The Eugene L. Saenger Radioisotope Laboratory, Division of Nuclear Medicine, Department of Radiology, University of Cincinnati Hospital, Cincinnati, Ohio

JNM 1996

SPECIAL CONTRIBUTION

Prevalence of Adverse Reactions to Positron Emitting Radiopharmaceuticals in Nuclear Medicine

Edward B. Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine
Eugene L. Saenger Radioisotope Laboratory, Division of Nuclear Medicine, Department of Radiology, University of Cincinnati Hospital, Cincinnati, Ohio

JNM 1998

BRIEF COMMUNICATION

Prevalence of Adverse Events to Radiopharmaceuticals from 2007 to 2011

JNM 2014

Edward B. Silberstein

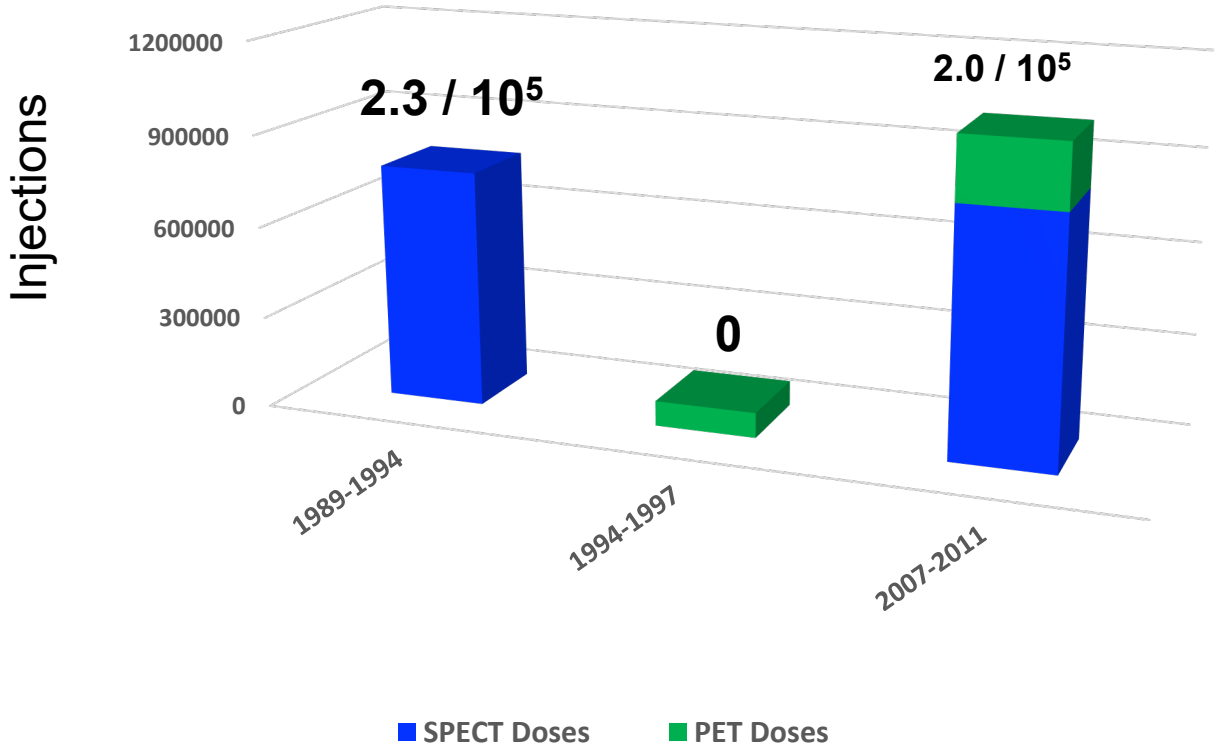
Departments of Radiology and Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio

Pharmacopeia Committee Operational Definition of AE[1]

1. The reaction is a noxious and unintended clinical manifestation (symptoms, signs, laboratory data abnormalities) following the administration of a radiopharmaceutical or nonradioactive adjunct pharmaceutical.
2. The reaction is unanticipated from the known pharmacologic action of the nonradioactive pharmaceutical.
3. The reaction is not the result of an overdose (which is a misadministration).
4. The reaction is not the result of injury caused by poor injection technique.
5. The reaction is not caused by a vasovagal response (slow pulse and low blood pressure).
6. The reaction is not caused by deterministic effects of radiopharmaceuticals intended for therapeutic uses.
7. The definition excludes altered biodistribution which causes no symptoms, signs or laboratory abnormalities.

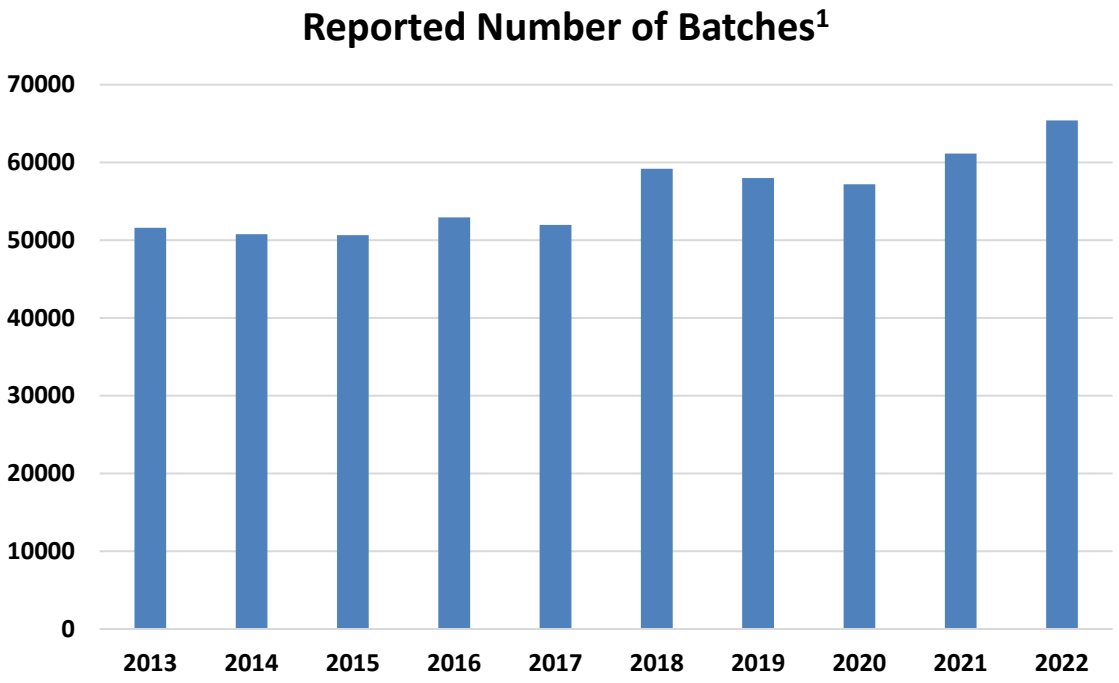
[1]Silberstein, EB, et al. Prevalence of Adverse Reactions in Nuclear Medicine. J Nucl Med. 1996:37, 185-192.

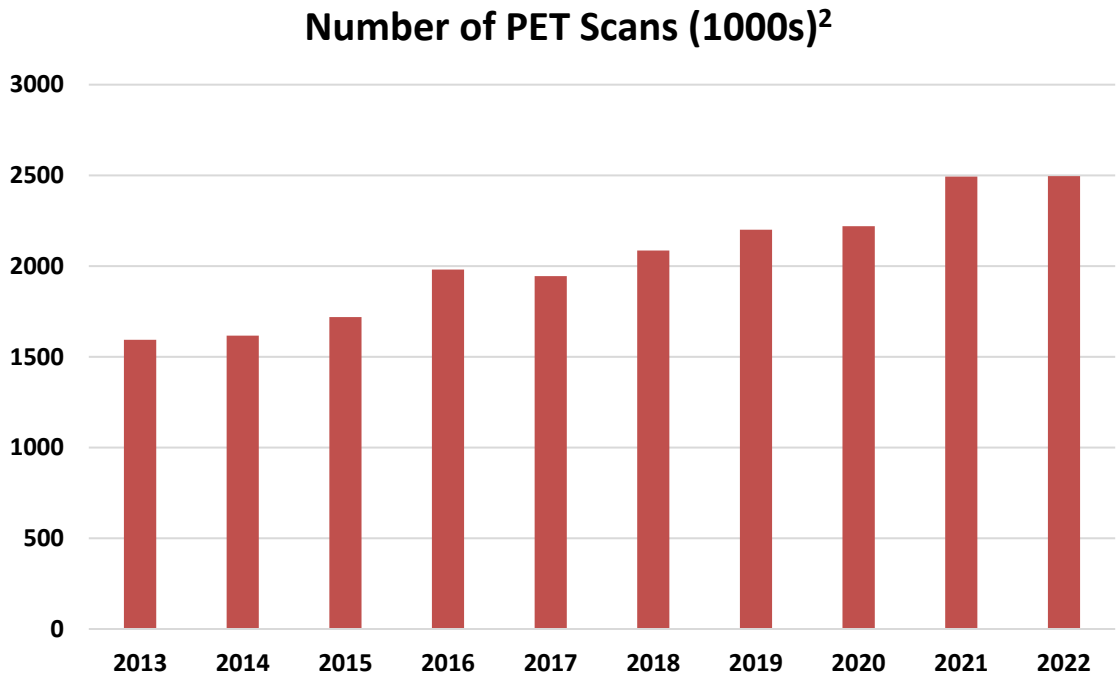
AE Prevalence for PET and non-PET Radiopharmaceuticals[1-3]



[1]Silberstein, EB. Prevalence of Adverse Reactions in Nuclear Medicine. J Nucl Med. 1996:37, 185-192.
[2]Silberstein, EB. Prevalence of Adverse Reactions to Positron Emitting Radiopharmaceuticals in Nuclear Medicine. J Nucl Med. 1998:39, 2190-2192.
[3]Silberstein, EB. Prevalence of Adverse Events to Radiopharmaceuticals from 2007 to 2011, J Nucl Med. 2014: 55, 1308-1310.

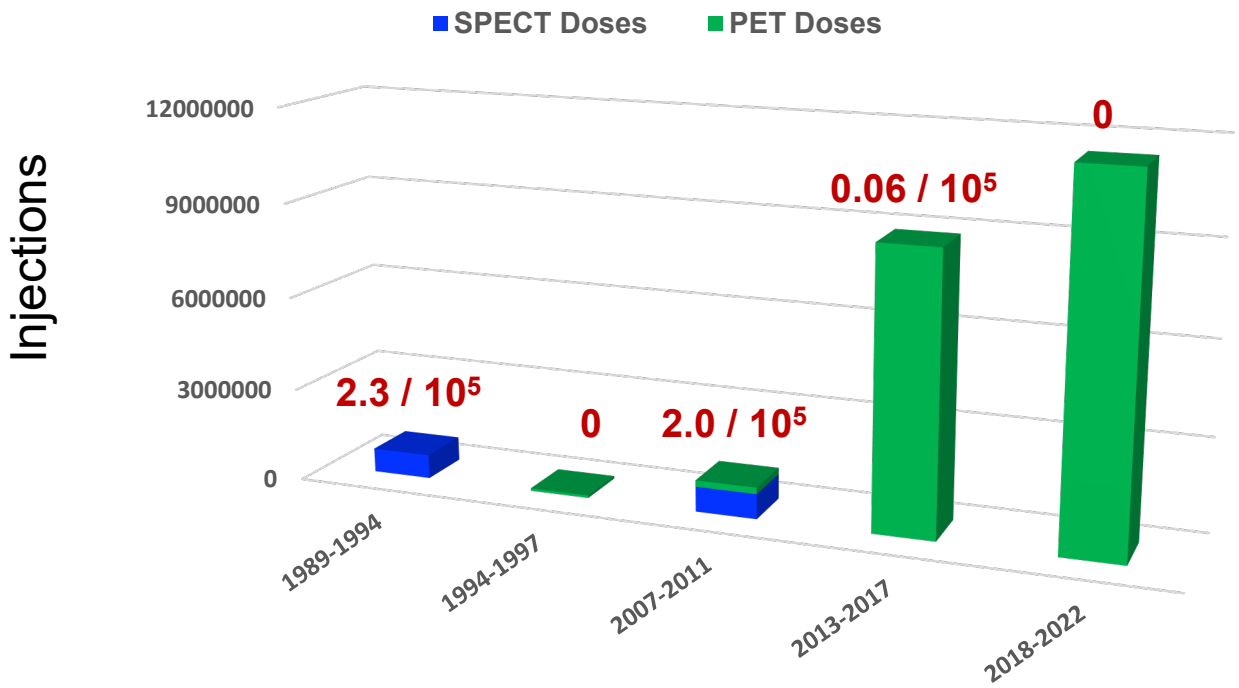
Reported batches and PET scans



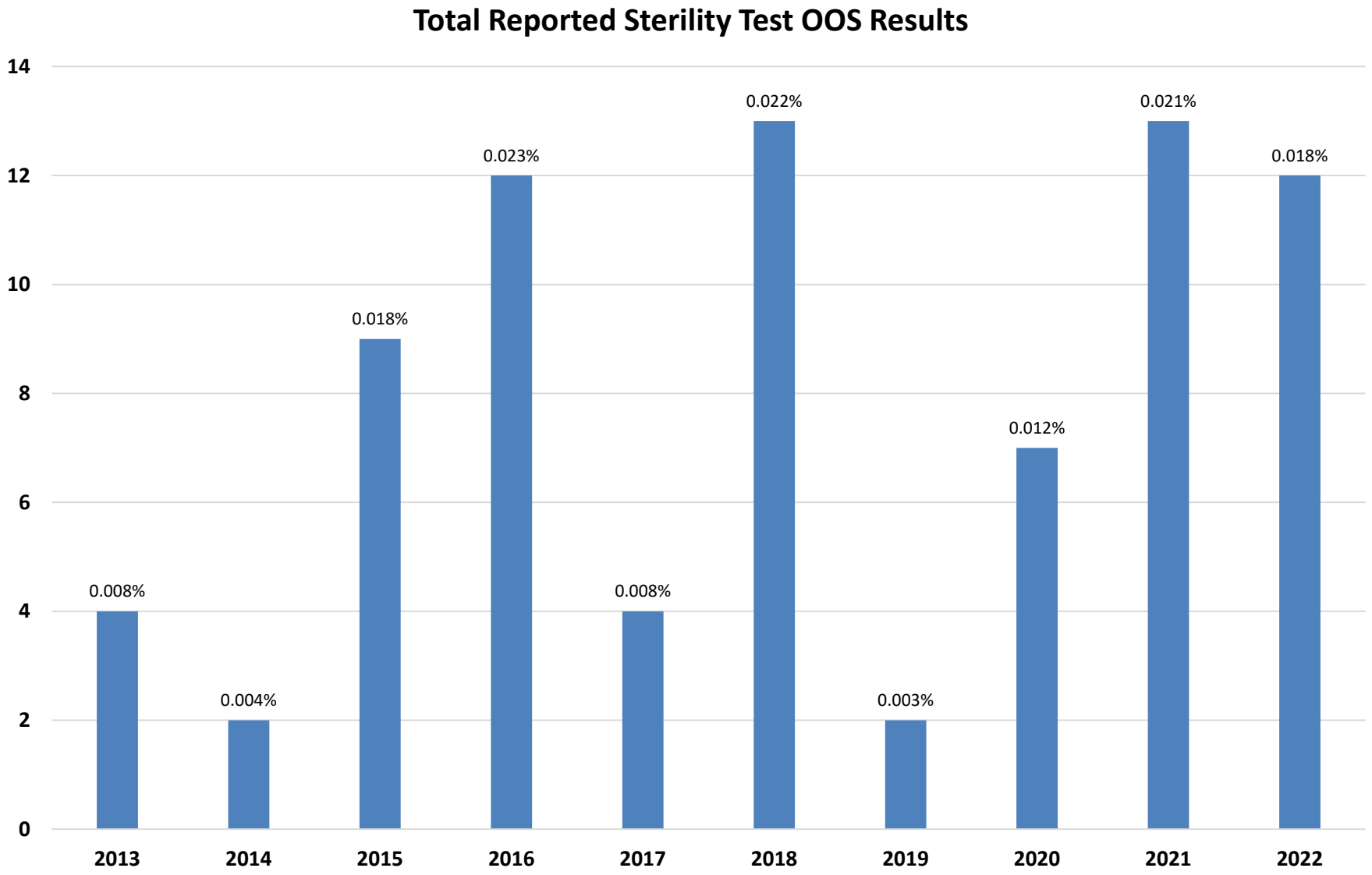


[1]PET Drug Manufacturers Surveys, SNMMI/MITA/Coalition, 2020/2023.
[2]IMV 2023 PET Imaging Market Summary Report, 2023.

AE Prevalence for PET and non-PET Radiopharmaceuticals[1-4]



[1]Silberstein, EB. Prevalence of Adverse Reactions in Nuclear Medicine. J Nucl Med. 1996:37, 185-192.
[2]Silberstein, EB. Prevalence of Adverse Reactions to Positron Emitting Radiopharmaceuticals in Nuclear Medicine. J Nucl Med. 1998:39, 2190-2192.
[3]Silberstein, EB. Prevalence of Adverse Events to Radiopharmaceuticals from 2007 to 2011, J Nucl Med. 2014: 55, 1308-1310.
[4]Coalition for PET Drug Manufacturing Surveys 2020, 2023.

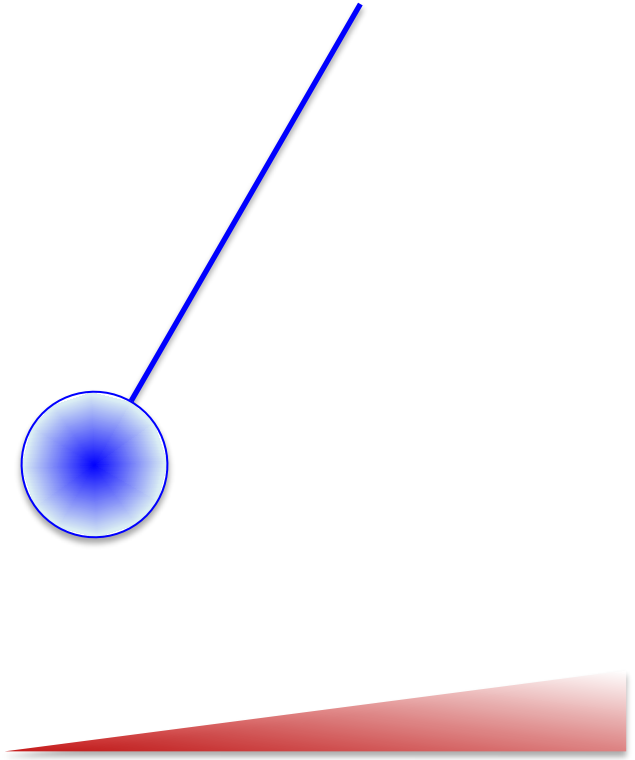

Total Reported Sterility Test OOS Results
14
12
10
8
6
4
2
0
0.008%
0.004%
0.018%
0.023%
0.008%
0.022%
0.003%
0.012%
0.021%
0.018%
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022

Ten-year Summary

- 20.4 million PET scans[1]
- 559,000 reported[2] batches of PET drugs produced
- 78 sterility test OOS results (0.014% of batches)
  - Nearly all OOS investigations conclude accidental contamination (laboratory error; false positives)
  - Compares favorably to expected 0.05% sterility test failure (not OOS)[3]

[1]IMV 2023 PET Imaging Market Summary Report, 2023.
[2]Does not represent all batches produced in US due to non-respondents.
[3]PET GMP Final rule, Federal Register, vol. 74, no. 236, December 10, 2009.

Existing Control Mechanisms are Effective



Current

Adverse Events

0 – 0.06/ 10^5 doses

Future

Decreased Supply Chain

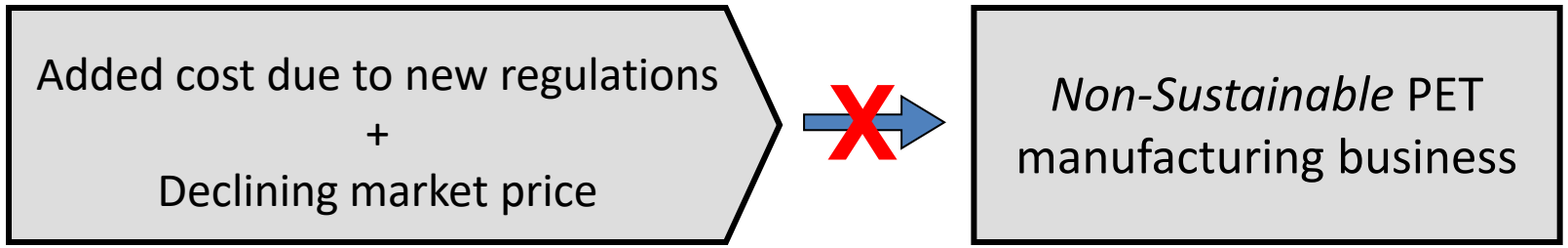
Limits Patient Access

Increased Regulatory Burden

through inspection or regulations without risk assessment

Closing Thoughts

- PET drugs have a proven track record under existing standards and regulations
- Current standards and regulations
  - Can safely maintain existing supply chain of PET drugs
  - Accommodate expansion of new PET drugs as they come onto the market
- Increased costs associated with new regulatory requirements will place pressure on PET drug manufacturers and threaten new product implementation
- The PET community is concerned that potential increased costs with no change in CMS reimbursement could lead some PET drug manufacturers to exit the market, resulting in reduced patient access



Open Questions

- Can the PET community and the FDA work together to develop an effective framework for collecting and assessing AE and sterility OOS data?
- Can the PET community work with the FDA to maintain compliance without increased regulatory burden?
- Can the PET community and the FDA work together to develop an effective risk management framework for PET drug manufacturing?
- Can we accept the conclusions of the resulting risk assessments?

Postmarketing Safety and Risk Management Positron Emission Tomography Workshop November 13, 2023

Samantha Cotter, PharmD, BCPS, FISMP Safety Evaluator
Division of Pharmacovigilance (DPV) II
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER), FDA

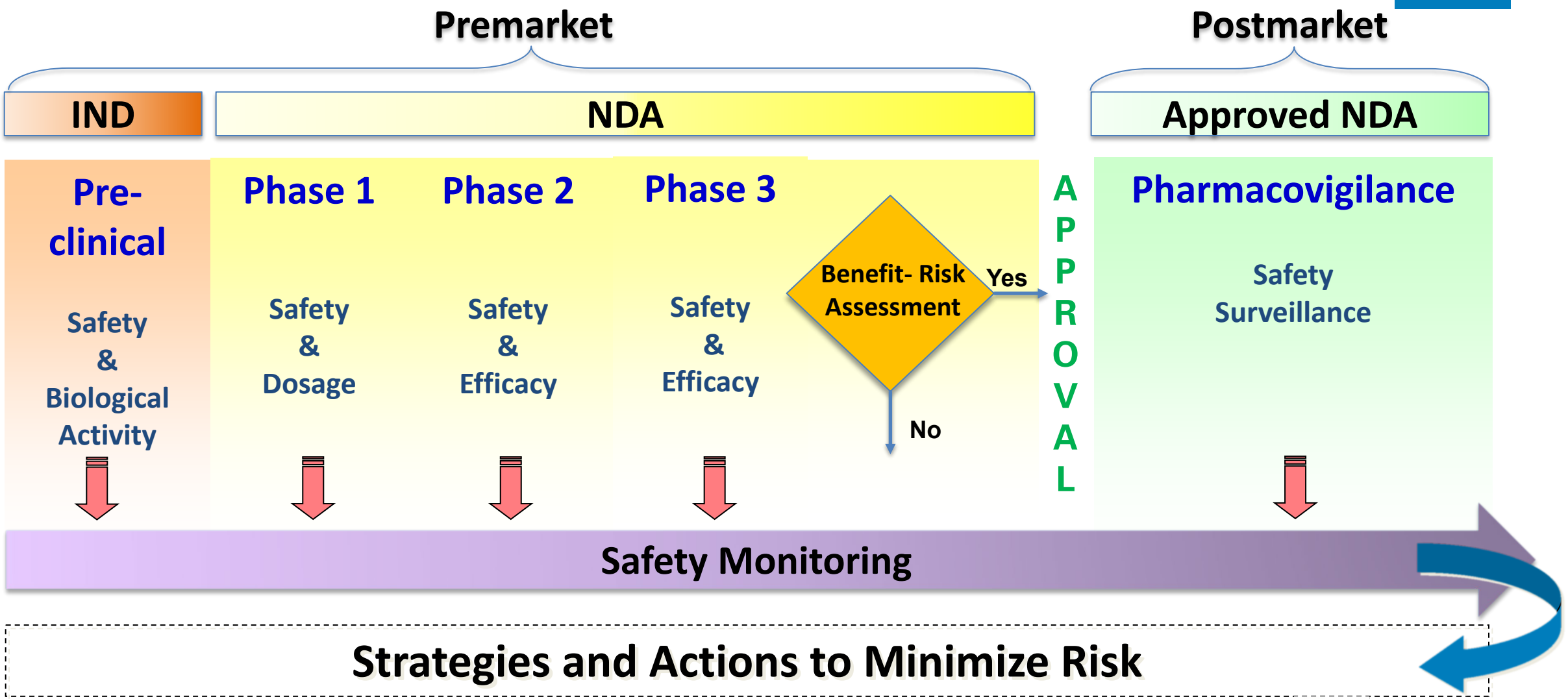
Objectives

- Discuss the lifecycle approach to tracking and acting on safety data
- Review how to report adverse events to FDA
- Explain how the agency uses adverse event report information to monitor the safety of marketed products
- Introduce FDA Adverse Event Reporting System (FAERS)
- Delve into reporting trends for positron emission tomography (PET) drugs
- Provide examples of PET drug adverse events and risk mitigation including safety labeling changes, and other communications

U.S. FOOD & DRUG ADMINISTRATION

Lifecycle Approach to Product Safety Monitoring

Lifecycle Approach to Safety Assessment

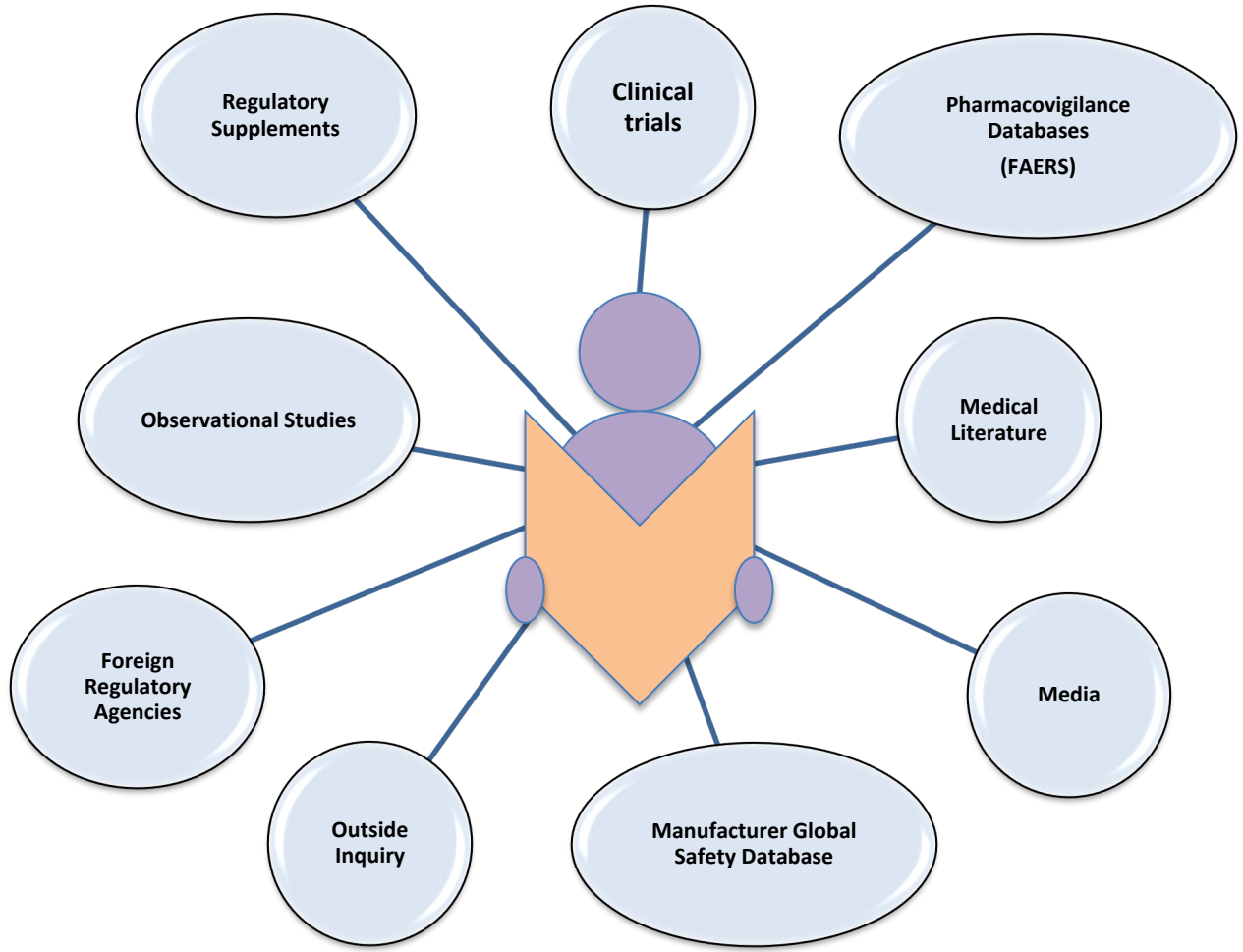


IND – investigational new drug; NDA – new drug application

The Void That Pharmacovigilance Fills

Limitations of Clinical Trials

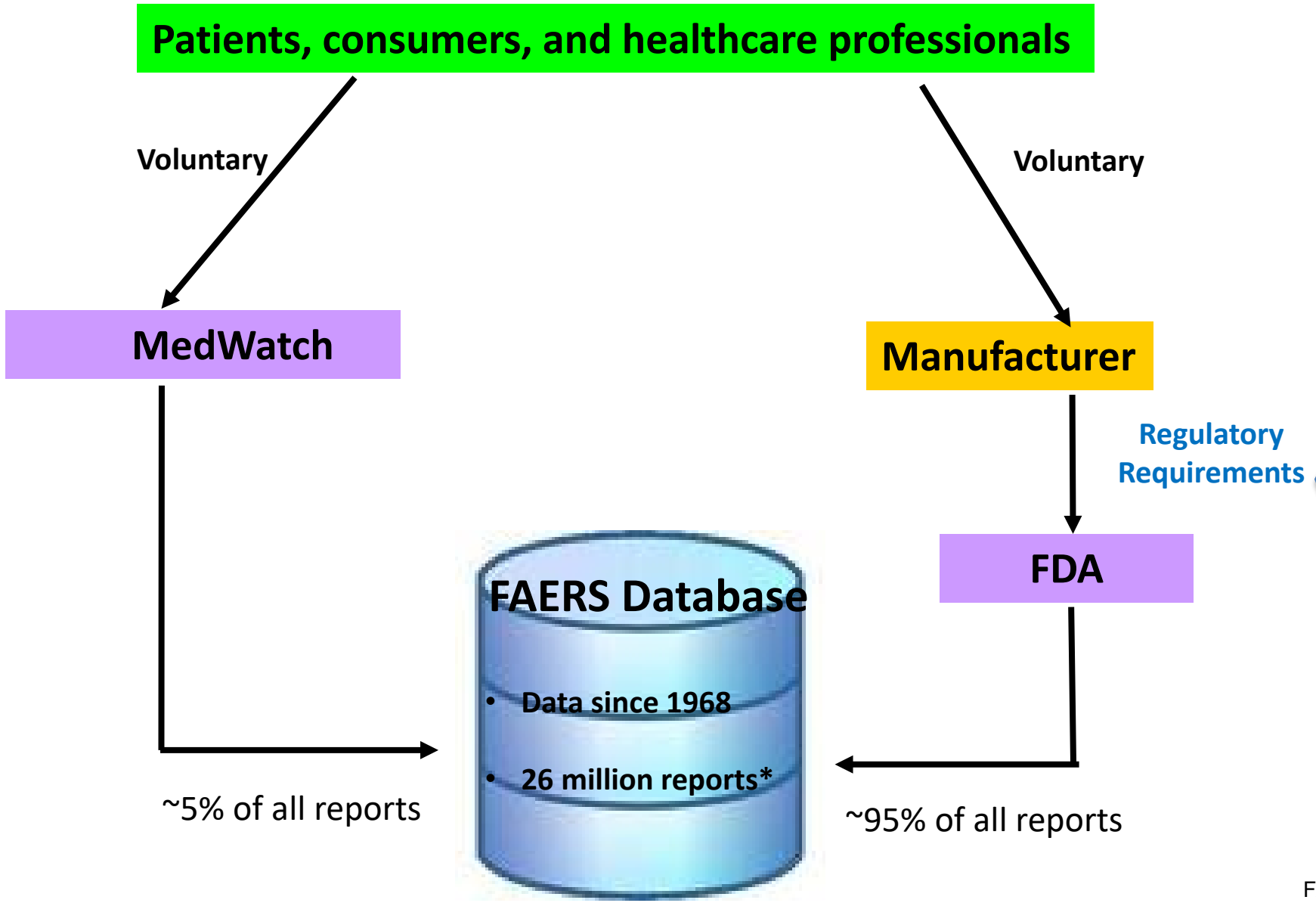
- While completion of phase 1, 2, and 3 trials are the standard for generating evidence to evaluate efficacy and safety, not all potential safety outcomes will be known at the time of approval
- Because trials are limited in size, duration, and may not always reflect real world use of the drug, it is not uncommon for safety events to emerge after a drug is approved
- FDA relies on a robust postmarketing surveillance program to detect and evaluate new safety signals. These signals come from a variety of sources



FAERS - FDA Adverse Event Reporting System

U.S. Food and Drug Administration. Guidance for Industry – E2E Pharmacovigila[illegible]ning, M 2005. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Postmarketing Adverse Events & FAERS Submission



Under 21 CFR 314.80 individual case safety reports must be submitted to FDA for:

- **Expedited reports**: Both **serious*** and **unexpected**† adverse events from all sources (domestic and foreign)
- **Non-expedited reports**: Domestic spontaneous adverse events that are:

-Serious and expected‡
-Non-serious and unexpected
-Non-serious and expected
-Quarterly for the first 3 years then annually

***Serious adverse events are those that result in any of these outcomes:** Death, Life-threatening adverse experience, Inpatient hospitalization – new or prolonged, Persistent/significant disability or incapacity, Congenital birth defect, Other serious

†**Unexpected**: not listed in product's current labeling

‡ **Expected**: listed in product's current labeling

FAERS - FDA Adverse Ev orting System
CFR - Code of Federal Re s

www.fda.gov

* N=25,998,916 ICSRs from 1/1/1968 to 12/31/2022

How to Directly Report Adverse Events to FDA

- How to report:
  - Online (www.fda.gov/medwatch)
  - Download the form
    - Mail
    - Fax 1–800–332–0178
- For questions about the form:
  - 1–800–332–1088

21CFR201.57

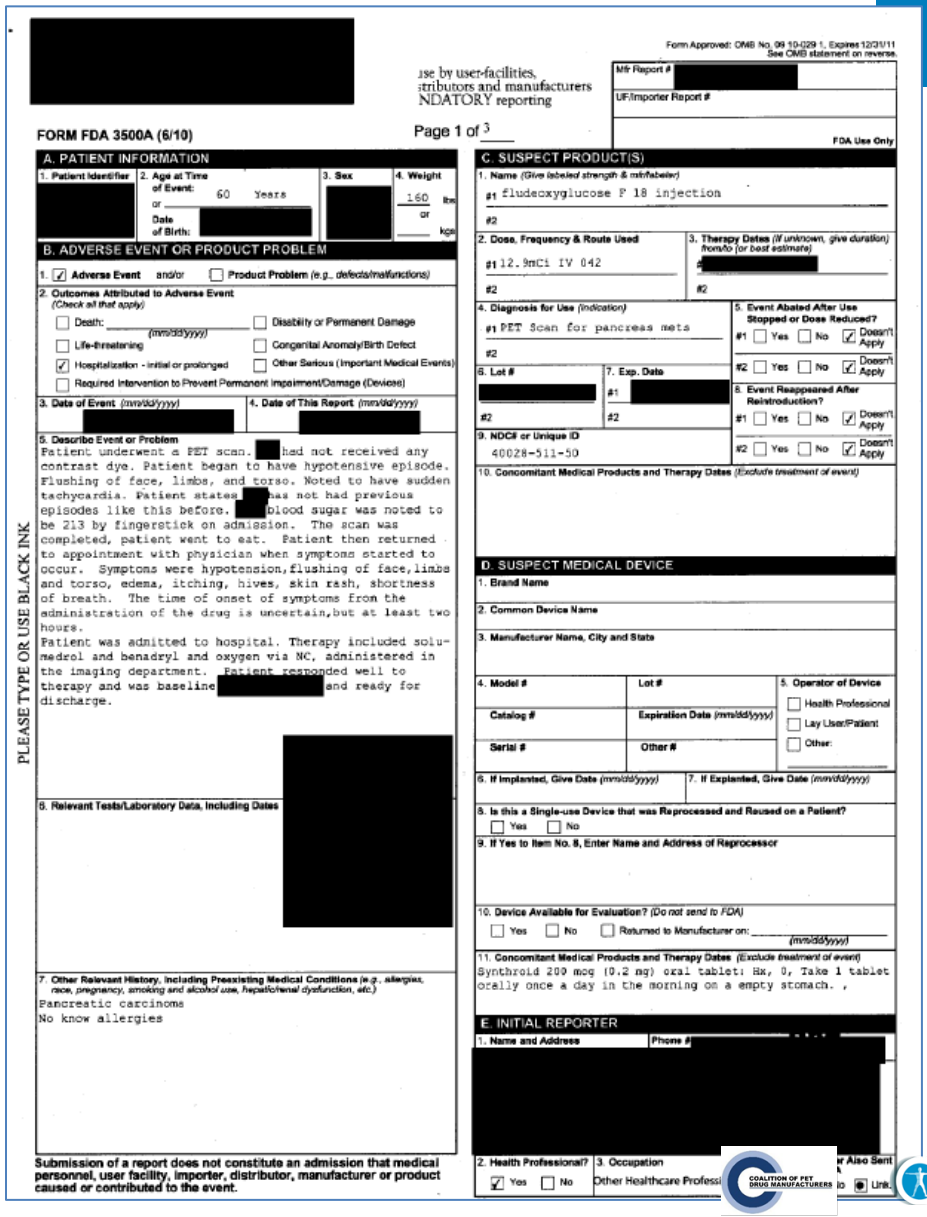
> (ii) For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (*insert name of manufacturer*) at (*insert manufacturer's phone number*) or FDA at (*insert current FDA phone number and Web address for voluntary reporting of adverse reactions*)."

www.fda.gov

U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available at: https://www.fda.gov/Safety/MedWatch/default.htm

How Does FDA Use FAERS Reports?

- Pharmacovigilance staff review FAERS reports and medical literature reporting a safety concern with a drug
- We consult the prescribing information of the drug to determine if the adverse event reported is already known or is new information
- If a new safety signal is identified, we work with DIRM to open a newly identified safety signal (NISS) and may ask the company to assess the issue too
  - NISS are posted to a public FDA website
- If we determine that a new safety concern should be labeled or communicated to the public, then we work to make that happen



FORM FDA 3500A (6/10)

Page 1 of 3

A. PATIENT INFORMATION

1. Patient Identifier [redacted]
2. Age at Time of Event: 60 Years
Date of Birth: [redacted]
3. Sex [redacted]
4. Weight 160 lbs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: (mm/dd/yyyy)
☐ Life-threatening
☑ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☐ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)
3. Date of Event (mm/dd/yyyy) [redacted]
4. Date of This Report (mm/dd/yyyy) [redacted]
5. Describe Event or Problem
Patient underwent a PET scan. [redacted] had not received any contrast dye. Patient began to have hypotensive episode. Flushing of face, limbs, and torso. Noted to have sudden tachycardia. Patient states [redacted] has not had previous episodes like this before. [redacted] blood sugar was noted to be 213 by fingerstick on admission. The scan was completed, patient went to eat. Patient then returned to appointment with physician when symptoms started to occur. Symptoms were hypotension, flushing of face, limbs and torso, edema, itching, hives, skin rash, shortness of breath. The time of onset of symptoms from the administration of the drug is uncertain, but at least two hours.
Patient was admitted to hospital. Therapy included solu-medrol and benadryl and oxygen via NC, administered in the imaging department. Patient responded well to therapy and was baseline [redacted] and ready for discharge.
6. Relevant Tests/Laboratory Data, Including Dates [redacted]
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
Pancreatic carcinoma
No know allergies

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & manufacturer)
#1 fludeoxyglucose F 18 injection
#2
2. Dose, Frequency & Route Used
#1 12.9mCi IV 042
#2
3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 [redacted]
#2
4. Diagnosis for Use (Indication)
#1 PET Scan for pancreas mets
#2
5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply
6. Lot # [redacted]
7. Exp. Date
#1 [redacted]
#2
8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply
9. NDC# or Unique ID
00028-511-50
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # / Lot # / 5. Operator of Device
Catalog # / Expiration Date (mm/dd/yyyy)
Serial # / Other #
☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: (mm/dd/yyyy)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
Synthroid 200 mcg (0.2 mg) oral tablet: Hx, 0, Take 1 tablet orally once a day in the morning on a empty stomach. ,

E. INITIAL REPORTER

1. Name and Address [redacted]
Phone # [redacted]
2. Health Professional? ☑ Yes ☐ No
3. Occupation

PLEASE TYPE OR USE BLACK INK

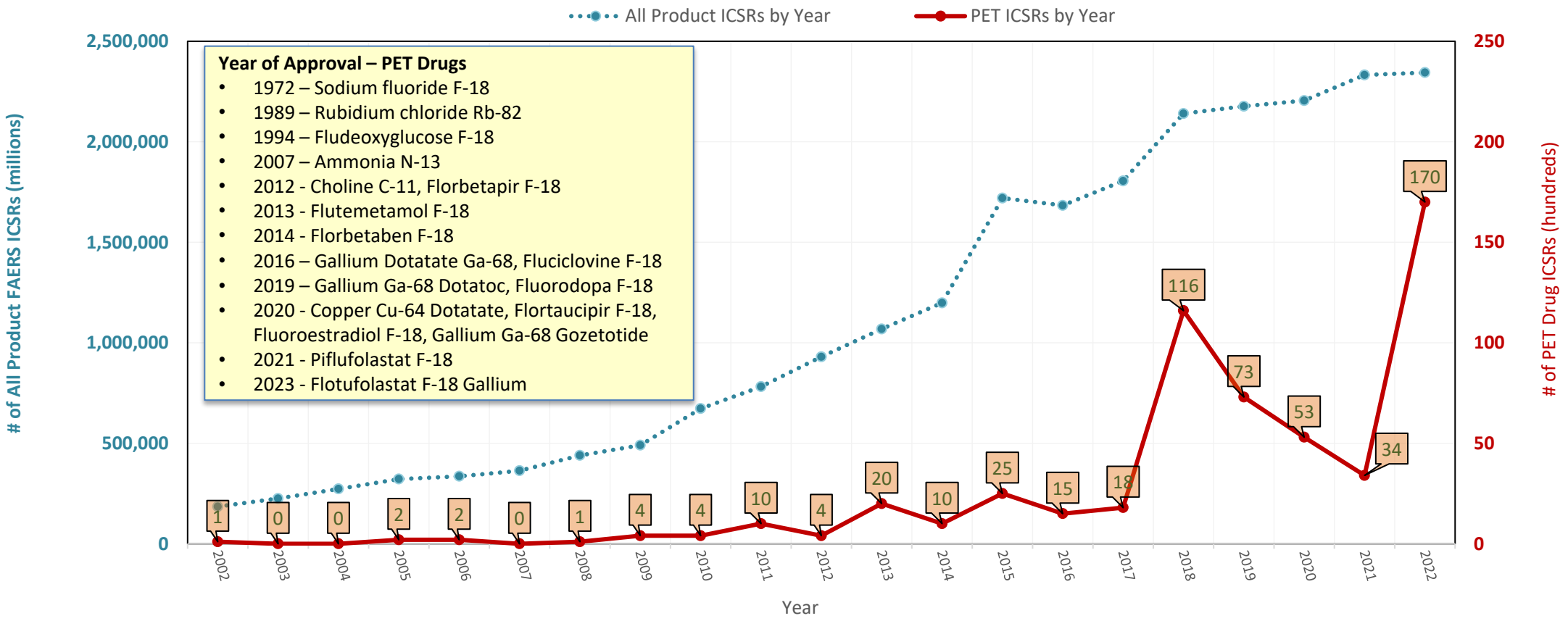
Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

FDA

Form Approved: OMB No. 09 10-029 1, Expires 12/31/11
See OMB statement on reverse.

Mfr Report # [redacted]
UF/Importer Report #
FDA Use Only

Number of Adverse Event Reports in FAERS for All Products Compared to PET Drugs (N=562) by Year 1/1/2002 – 12/31/2022



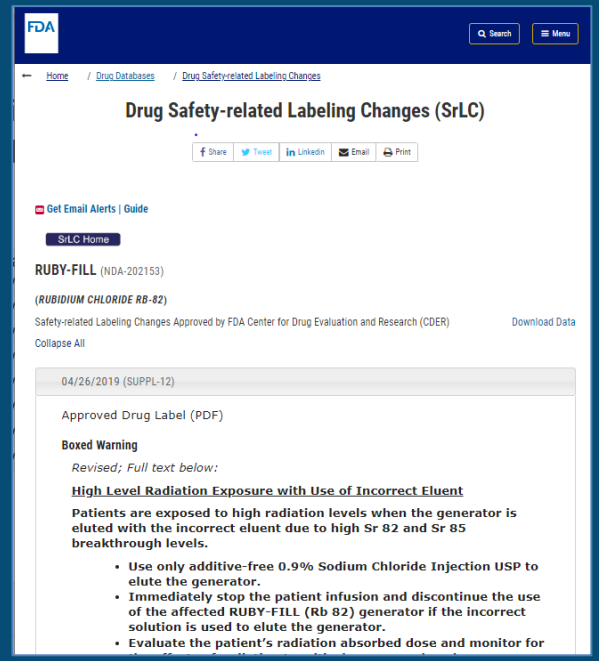
- Slide adapted from FAERS Public Dashboard displaying all report types (direct, expedited and periodic) received by the FDA for drugs and therapeutic biologic products.
- FAERS database contains 25,998,916 ICSRs from 1/1/1968 to 12/31/2022
- A case-level analysis was not performed on all reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, healthcare provider), miscoded related

C – carbon; Cu – copper; F – fluorine; FAERS – FDA Adverse Event Reporting System; Ga – gallium; ICSR – Individual Case Safety Report; N – nitrogen; PET – Positron emission tomography; Rb – rubidium; SrLC – safety-related labeling change

Other Public Communications for PET Radiopharmaceutical Drug Safety-Related Labeling Changes (SrLC)

Active Ingredient	Event	SrLC Date
Rubidium Chloride Rb-82	High level radiation exposure with incorrect eluent; quality control testing procedure	04/26/2019
Rubidium Chloride Rb-82	Patient Counseling Information - pregnancy, lactation, post study voiding	10/15/2020
Fluciclovine F-18	Patient Counseling Information – voiding	05/21/2021
Gallium Dotatate Ga-68	Radiation exposures – infants, pregnancy; drug-drug interaction of false negative image with glucocorticoid	6/22/2021
Copper Cu-64 Dotatate	Hypersensitivity reactions	12/22/2021
Gallium Dotatate Ga-68	Hypersensitivity reactions	12/22/2021

SrLC Database [1]



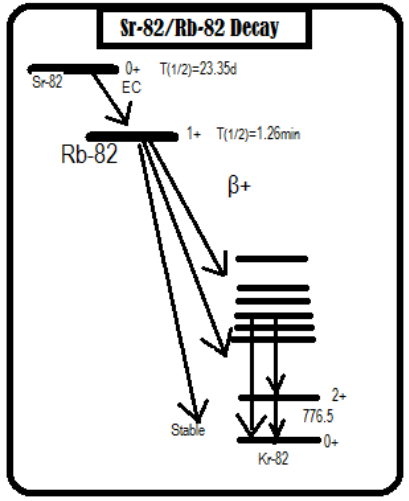
Provides updates to safety information in labeling for regulated NDAs and BLAs.

1. https://www.accessdata.fda.gov/scripts/cder/ eling anges/
NDA – new drug application; BLA - biologics licen ation

U.S. FOOD & DRUG ADMINISTRATION

An Example of FDA's Risk Mitigation Response

Excess Radiation Exposure Secondary to Incorrect Eluent Use with Rubidium Chloride Rb-82 Generators



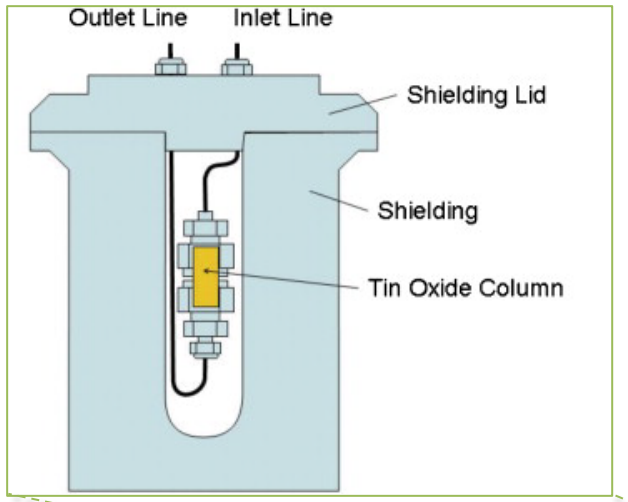
https://science.osti.gov/np/Benefits-of-NP/Applications-of-Nuclear-Science/Archives/Precise-Measurement-of-82Sr-Radioactivity-in-the-Sr-Rb-PET-generator

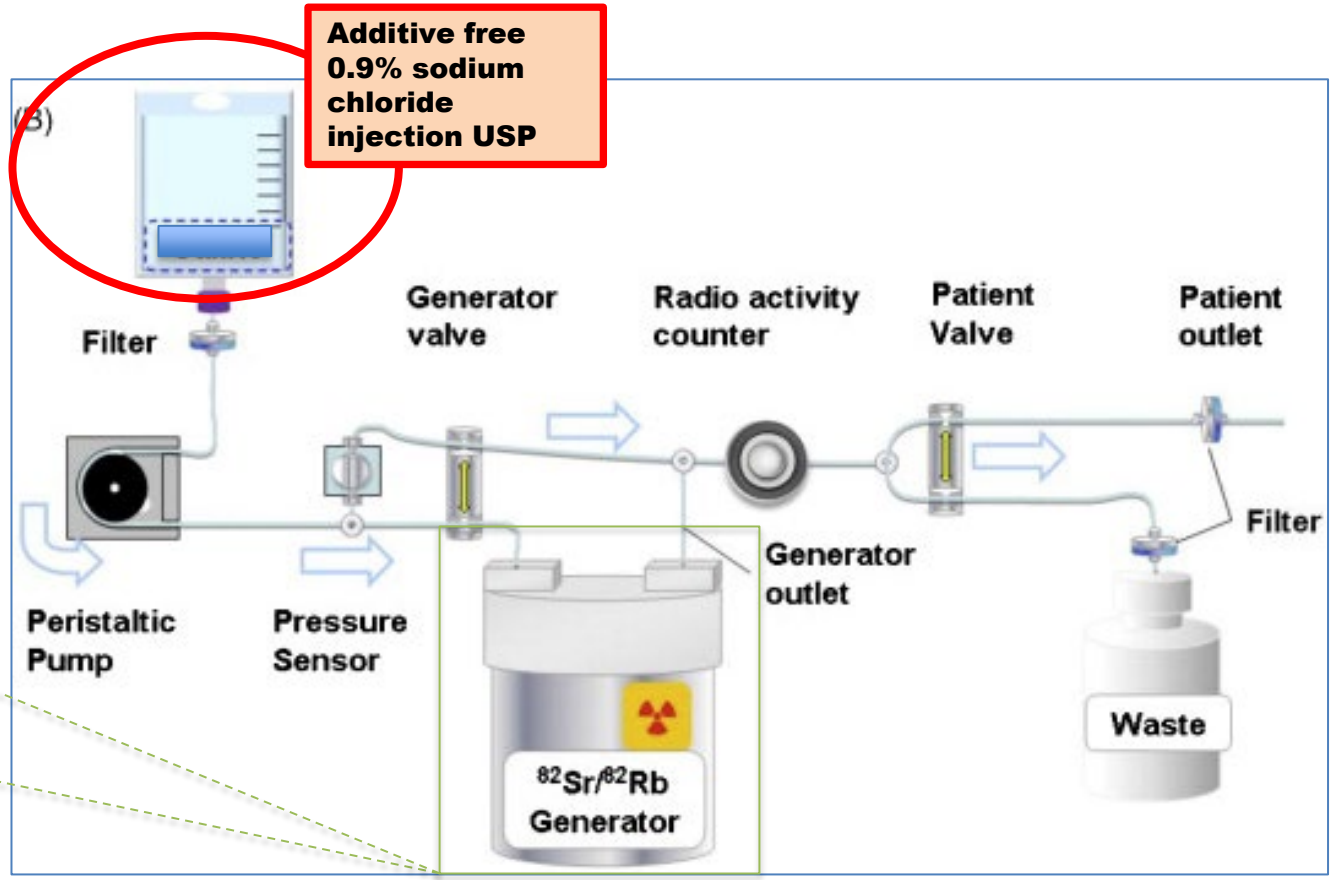
Rubidium Chloride Rb-82 Generators
Incorrect Eluent and Excess Radiation Exposure

- **Background**
  - Rubidium chloride Rb-82 generator systems produce the Rb-82 chloride tracer on-demand from the parent radioisotope strontium-82 (Sr-82) and are used for PET myocardial perfusion imaging
  - Use only additive free 0.9% sodium chloride injection USP to elute the generator
- **Event**
  - FDA received FAERS reports of events resulting in excess radiation exposure following use of incorrect eluent, including calcium-containing solutions such as Lactated Ringer's, with the generators that produce rubidium chloride Rb-82
  - When calcium is present in a solution, the calcium cation (Ca^{+2}) will displace more strontium ion (Sr^{+2}) than desired. As a result, the eluate will contain a higher fraction of Sr-82 and Sr-85. This eluate is infused into the patient with higher radioactive exposure from extended half-life of Sr-82 (~25 days) compared to Rb-82 (75 seconds)
    - Long-term health effects are unknown
      - Strontium isotopes can deposit high levels of radioactivity in organs including the bone, potentially leading to suppressed bone marrow function, suppression of the immune system, and increased risk of radiation-induced cancers

USP – United States Pharmacopeia
https://www.fda.gov/drugs/drug-safety-and-availability/fda-reminds-imaging-facilities-follow-safety-procedures-rubidium-82-generators-used-positron
Ahmadi A, et al.J Nucl Cardiol. 2020 Oct;27(5):1728-1738.

Rubidium Chloride Rb-82 Generator and Infusion System
(Yoshinaga et al.)





Yoshinaga K, Klein R, Tamaki N. Generator-produced rubidium-82 positron emission tomography myocardial perfusion imaging—From basic aspects to clinical applications. Journal of Cardiology, 2010;55:163-173. https://www.sciencedirect.com/science/article/pii/S0914508710000109

Risk Mitigation Measures and Response
Rubidium Chloride Rb-82 Generators
Incorrect Eluent and Excess Radiation Exposure

- Safety Labeling Changes to rubidium chloride Rb-82 labels reflecting high level radiation exposure with use of incorrect eluent
- Communication to the public and healthcare providers
  - Urged patients who need these imaging scans to continue to get them and to talk to their healthcare providers regarding any concerns about use of these systems
  - Dear Healthcare Provider Letters directed to imaging centers and clinicians
- Additional risk mitigation measures
  - Saline Confirmation Label and Saline Tag applied to the additive free 0.9% sodium chloride injection USP

USP – United States Pharmacopeia

1. https://www.fda.gov/drugs/drug-safety-and-availability/fda-reminds-imaging-facilities-follow-safety-procedures-rubidium-82-generators-used-positron
2. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/

U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / Drugs / Drug Safety and Availability / FDA reminds imaging facilities to follow safety procedures for rubidium 82 generators used in Positron Emission Tomography (PET) myocardial perfusion imaging

FDA reminds imaging facilities to follow safety procedures for rubidium 82 generators used in Positron Emission Tomography (PET) myocardial perfusion imaging

Share Tweet Linkedin Email Print

Drug Safety and Availability

Drug Alerts and Statements

Information about Nitrosamine Impurities in Medications

Medication Guides

Drug Safety Communications

Recent incidents due to use of incorrect solutions resulted in excess radiation exposure to patients

[4/29/2019] FDA is aware of recent incidents that caused excess radiation exposure to patients due to user error with certain systems used to produce rubidium Rb 82 injection for use with Positron Emission Tomography (PET) myocardial (heart) perfusion imaging scans. As a result, the agency is requiring Safety Labeling Changes, including a Boxed Warning, on the labels of rubidium 82 generators, reminding systems users to use the correct solution to elute the generator (solution to extract Rubidium 82 from the generator) and carefully follow safety procedures for the system.

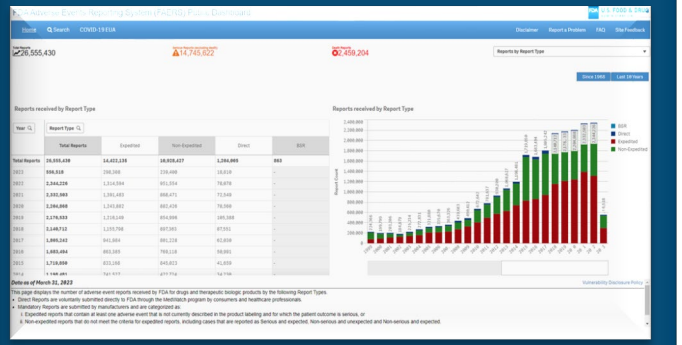
The two systems used in these imaging scans, CardioGen-82 and Ruby-Fill (rubidium Rb 82 generator) require additive- free 0.9% Sodium Chloride Injection USP to safely elute the system. Incidents have been reported to FDA where an incorrect solution was used to elute the generator, including

Content current as of:
04/26/2019

1. https://www.fda.gov/drugs/drug-safety-and-availability/fda-reminds-imaging-facilities-follow-safety-procedures-rubidium-82-generators-used-positron

FDA: Drug Safety Information for the Public

FAERS Public Dashboard [1]

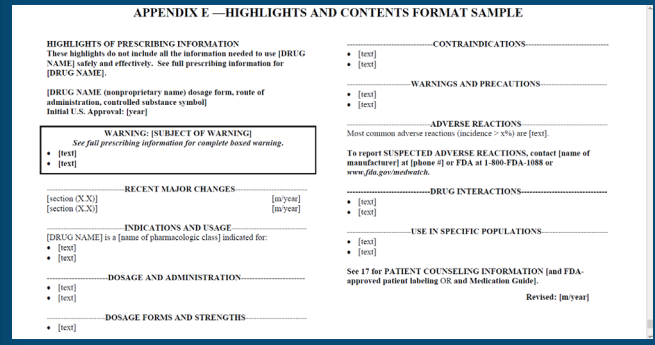


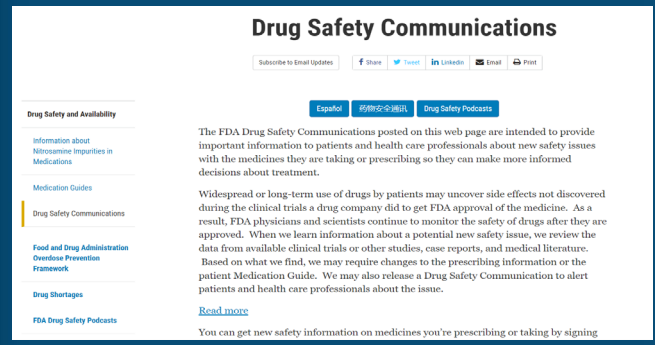
An interactive web-based tool that allows for the querying of FAERS data

Potential Signals [2]

FDA shares early safety signals or potential signals identified through FAERS

Communications [3, 4]





U.S. Prescribing Information, Drug Safety Communications, and other communication tools

[1] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard
[2] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system
[3] https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications
[4] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Overall Summary

- FDA continues to monitor all products, including PET drugs, throughout the lifecycle utilizing pharmacovigilance data sources, multidisciplinary teams and a risk-based approach to surveillance
- Voluntary reporting of adverse events associated with drug products, including PET drugs, by healthcare professionals and patients, is an important activity to support the safe use of FDA-approved drugs
- We encourage continued reporting of drug related adverse events through MedWatch: the FDA Safety Information and Adverse Event Reporting Program (https://www.fda.gov/Safety/MedWatch/default.htm)

FDA U.S. FOOD & DRUG ADMINISTRATION

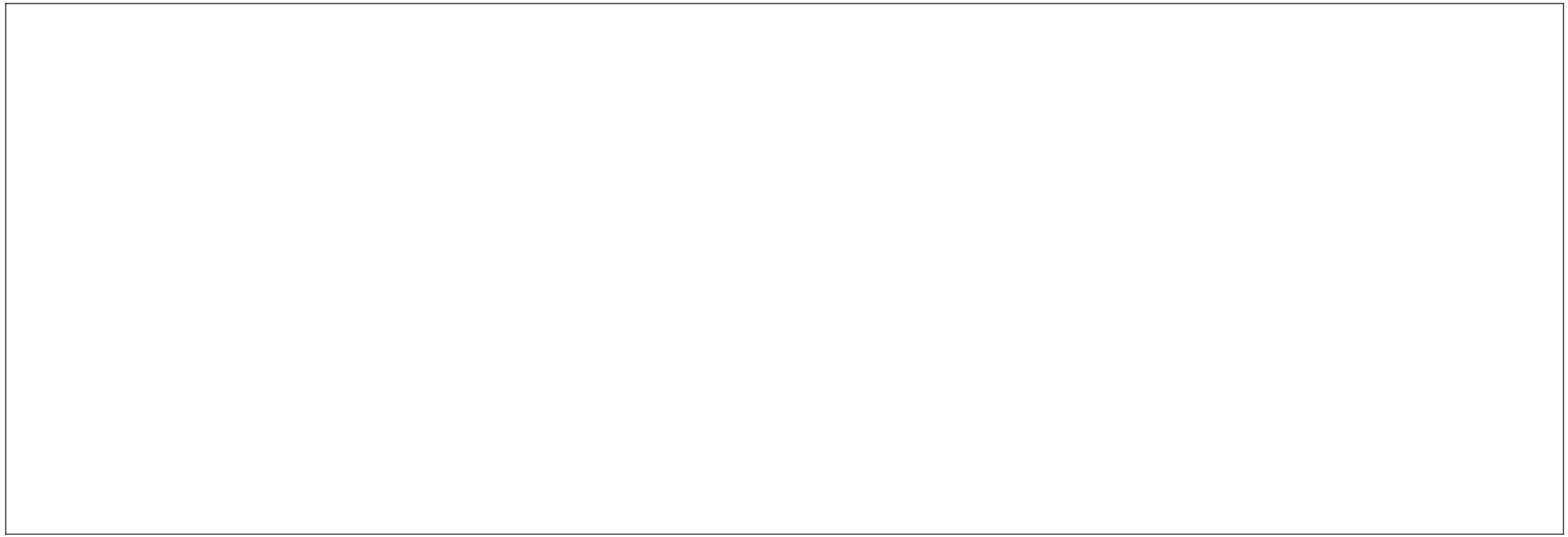
PANEL DISCUSSION/AUDIENCE Q&A

We have seen 483 issued by inspectors related to perceived risk levels of manufacturing processes for which the applicant had generated internal data within a risk assessment approach that supported low to negligible risk. How can the manufacturer receive recognition for the objective evidence (data) generated rather than the inspector fact-free concern?

When an OOS for sterility is detected; at what point should a FAR be raised? Is it immediate upon detection? After assessments on test validity? After investigating the potential causes? After receiving the microbial identification and completing the investigation?

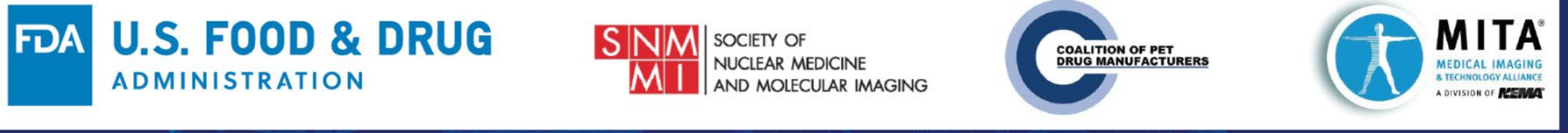
The agency has confirmed the notion that the FAR system can be updated to enhance the value of quality event reporting within the context of a product already administered to a patient. Can the Agenda provide current thoughts and considerations regarding the filing of FARs within the process of initial discovery, investigation and root cause determination?

What are the provisions for a sterility retest; and how is the data interpreted? What level of validation is required to perform a retest? If the second result passes, what is the overall disposition of the batch? What level of validation is required to perform a retest? If the second result passes, what is the overall disposition of the batch?



BREAK

SESSION 4: MANAGEMENT OF PET DRUG LIFECYCLE



Recalls and FARs: the PET Community Perspective

David Dick, University of Iowa

Chris Ignace, Cardinal Health

Recalls in PET

Academic Sites and Recalls

- With rare exceptions, academic sites are not distributing PET drugs outside of their institution.
- Academic PET drug manufacturers keep possession of the PET drug product until it has passed all release specifications.
- Academic PET drug manufacturers rarely, if ever, have a recall.

Commercial Sites and Recalls

- < 1 event per year for all PET drugs produced
- 1 event/3 years for cyclotron-based products
- Insufficient to support data mining, or any analysis
- No apparent trend
- Questions regarding objective and substantive informational value

Regulatory Background about Recalls

- 21.CFR.314 cross-referencing 21.CFR.7.3
- 21.CFR.7.46
- MAPP 7348.002P (“Inspection Manual”)
- FDA PET Drugs - CGMP Guidance (Aug 2011)

- PET Community Survey on Recalls:
  - Most PET Manufacturers never performed recalls
    - Drug product can be retrieved as “stock recovery” prior to change of custody (internal)
    - Drug product has been dispensed to patient

- The PET Community feels a need for stronger alignment around recalls to better assess the regulatory compliance exposure.

Governing Documents	Notes	Key differences Non PET/PET	
21.CFR 7.3 (g)/(l)/(m) Recall	Recalls apply to marketed products believed to be violative, performed according to strategy and classification agreed to with FDA.	No difference in definition and applicability	Clarify applicability of recall process for PET as follows: • **Promote the development of company policy or procedure that addresses stock recovery and recall**. • Recommend that policy/procedure **references the inspection manual 7356.002P and specific CFR areas such as 7.3, 7.46, 7.49, 7.53 and 7.55**. • Recommend that the recall procedure **cross-references the firm's FAR policy/procedure**. • **Propose FDA clarify (e.g. via website) that compliance with the 8/2011 Guidance is sufficient to meet compliance requirements (and if needed address FDA's submissions expectations).** • **Propose FDA further articulate the role and relevance of recalls within its internal risk assessment and profiling of PET manufacturers**. • **Propose FDA clarify language in inspection manual, including C.1.i to confirm that unreleased products are subject to stock recovery and not recalls.**
21.CFR 7.3.(k) Stock recovery	Applies to product not marketed or that has not left the direct control of the firm and not released for sale or use.	No difference in definition and applicability	
21.CFR 7.46 (a)/(b)	When a product (a) "believed to be violative" is recalled, (b) FDA makes recommendations on the firm's strategy and advise on recall classification and places on weekly FDA enforcement report.	PET products typically expired and/or not confirmed to be violative at recall time. **FDA cannot meet the requirements of 21.CFR.46(b) on advising firm on recall strategy and recall classification**.	
Inspection Manual 7356.002P	Section B2 of 7356.002P describes the frequency of recalls to impact a company risk profile. Section C.1.i mentions "**recalling** a product that has been **shipped before final release** if it fails to conform to established specifications". Part V acknowledges that "**recall of small batches of short-lived radioactive products will not be feasible because they are dispensed so quickly"**.	Confusing/loose language; an **unreleased product is under a firm's control and subject to stock recovery.** Profiling of PET recalls vs Pharma(6/2012-2/2023): • **Non-PET pharmaceuticals: 82,009** • **PET: 7** (3 cyclotron based) (internal/informal feedback suggests PET recalls were conducted as excessive caution within a lack of regulatory clarity)	
Guidance: PET Drugs – CGMP - 8/2011	Section XIII.B. "A recall consists of notifying **the receiving facility, the pharmacist and the patient's physician** if known".	Guidance is silent on the need to submit to FDA (no CFR cross-reference).	

PET Community Proposals

- Acknowledge the recall process as “impractical/not feasible” for PET cyclotron drug products
  - Product “stock recovery” is the typical option prior to change of custody (product is still within the manufacturer network).
  - When a PET product has reached the hospital, it has typically been dispensed (i.e. product recovery is not an option).
- Documentation Update Proposals
  - FDA: clarify recall/stock recovery language in MAPP 7356.002P.
  - FDA: reinforce/highlight the lack of materiality of recalls for cyclotron produced PET drug products
  - FDA-PET Community: PET Manufacturers develop/strengthen company policy/procedure
    - Aligned with (revised) Guidance
    - Aligned on Stock Recovery vs Recall concept
    - Cross-referenced to the FAR internal policy/procedure
- General request to FDA from PET Community
  - Since PET recalls are so rare:
    - How does FDA use recall information as part of FDA’s compliance risk management (e.g. inspection priorities, sterility assurance risk assessment)
    - How do recalls contribute to FDA’s overall PET industry risk assessment (e.g. “high risk/low risk” overall categorization of PET).

FARs in PET

Academic sites and FARs

- While infrequent, academic PET drug manufacturers have submitted FARs.
  - These submitted FARs are almost always related to sterility.
- The initial FAR is almost always submitted before the investigation results have been obtained.
- Final FARs are not always submitted after the investigation has been concluded.

Commercial sites and FARs

A real-life FAR-driven inspection scenario

- PET Product sterility testing performed on-site
- First time point shows gross contamination (microbial growth), communicated to Sponsor, initial FAR submitted.
- FAR filing triggers rapid FDA on-site inspection
- Inspector learns that on-going micro-OOS investigation recently identified operator glove contamination as source (“lab error”)
  - Inspector dissatisfied with use of inspection resources/time and questions FAR filing usefulness
  - Inspector states “We have things to do too, you know” and felt it was a waste of time for him to have come.

Topic:

  - Are we making best use of FARs for short-lived drugs, especially PET?
  - What can be done to maintain public/patients safety goals and yet create value added data?

Commercial sites and FARs

- Most FARs for PET are related to potential sterility failures or missing sterility data
  - True status often unknow within 3 working days
  - Product quality failure typically not confirmed, and root cause assigned to Micro Lab error
- The PET Community believes that the following factors impact FARs efficiency:
  - The 3-day reporting timelines create a disproportionately high administrative burden for products with very short shelf lives, such as PET, that are expired, stock recovered or administered by day 3.
  - A high level of FARs follow-up and closure compliance (which is optional) would be required to provide actionable FARs information for risk assessment purpose, as most PET FARs initial findings are not confirmed.
  - Relatively minor changes and upgrades can significantly improve the informational value of FARs for PET.

Regulatory Background around FARs

- 21 CFR.314.81 requires FARs submission for product quality failures that would create a potential patient safety threat.
  - Critical system provides valuable feedback information on quality while serving HCP/patients.
  - A risk is typically potential/unconfirmed at initial filing (3rd working day)
  - FDA uses FARs records to assess risk, institutional compliance and prioritize inspections
  - Submission should be electronic (paper accepted) using FDA Form 3331a

FARs: Improvement Opportunities for PET

FAR Purpose: quickly identify quality defects in distributed drug products that may present a potential safety threat.

Governing Documents	Notes	Key differences 211/212	Recommendations
21 CFR 314.81(b)(1) (Other post marketing reports; NDA FAR)	Reporting within 3 days of receiving information concerning significant quality problem. Includes bacterial contamination and failure to meet spec.	None for PET/non-PET	The PET Community recognizes FARs purpose towards product quality and patient safety. However, there are opportunities to minimize the administrative burden for all parties of non-closed and unconfirmed FARs, while increasing the overall informational value of FARs for PET. A> PET Community FARs Status • Survey PET Community for most common type of FARs (chemistry, micro, container, other) • Assess rate of FARS follow-up/closure • Assess rate of issue confirmation at investigation closure (internal) • Estimate current overall informational value of FARs B> Proposed enhancing FARS informational value • Workshop **validation of historical PET FARs use** findings • Recognize that **PET products are either used, expired and/or stock recovered within 3 days**. • Propose adjusting FDA FAR Guidance - or issue Web supplemental information - to recommend that PET institutions FAR SOP/Policy explicitly 1) maintain immediate HCP communication of potential product quality issue, and (2) remove initial FAR reporting requirement at 3 days, and (3) **set a reporting timeline post investigation (≈21 days)**. This will ensure that nearly all FARs filed are **vetted, meaningful and actionable**.
21 CHR 314.98 (Post-marketing reports)	Links ANDA holders to requirements to 314.81 (FARs).		
Guidance: Field Alert Report Submission Questions and Answers Guidance for Industry 7/2021 On-line https://www.fda.gov/media/114549/download (Field alert submission Q&A) https://www.fda.gov/drugs/surveillance/field-alert-reports (FARs, Webpage)	II.1.c. references **212.71** and **212.100** in support of ID rationale behind findings. "**If determination is preliminary in the initial FAR, you should update** the investigation in a follow-up or final FAR". III.3. and III.4.f defines day 0 as the day of awareness of problem (vis a vis 314.81). III.6 recommends follow-up and closure as **FDA uses FARs to assess problem, risk** to public health and status of adequacy of corrective action, or your **determination that there was no actual defect as initially suspected**. […] This is **used to determine the need for inspection** […] " FDA encourages holders to **submit a follow-up when** […]"(2) you learn that **information submitted in a previous FAR is incorrect**" (III.6.a).	• FAR filing requirement is a **Regulatory compliance issue, not a Quality compliance** issue. Hence, it is neither in 21 CFR.211/212, but in 21.CFR.314.81. • The **FDA Guidance on FAR** (7/2021) cross-references investigations conducted under 21 CFR.211 and **212 (section III.1.c), hence covers PET.** • FDA uses FARs similarly between PET and non-PET to assess risk (Guidance III.6)	

PET Community Proposals

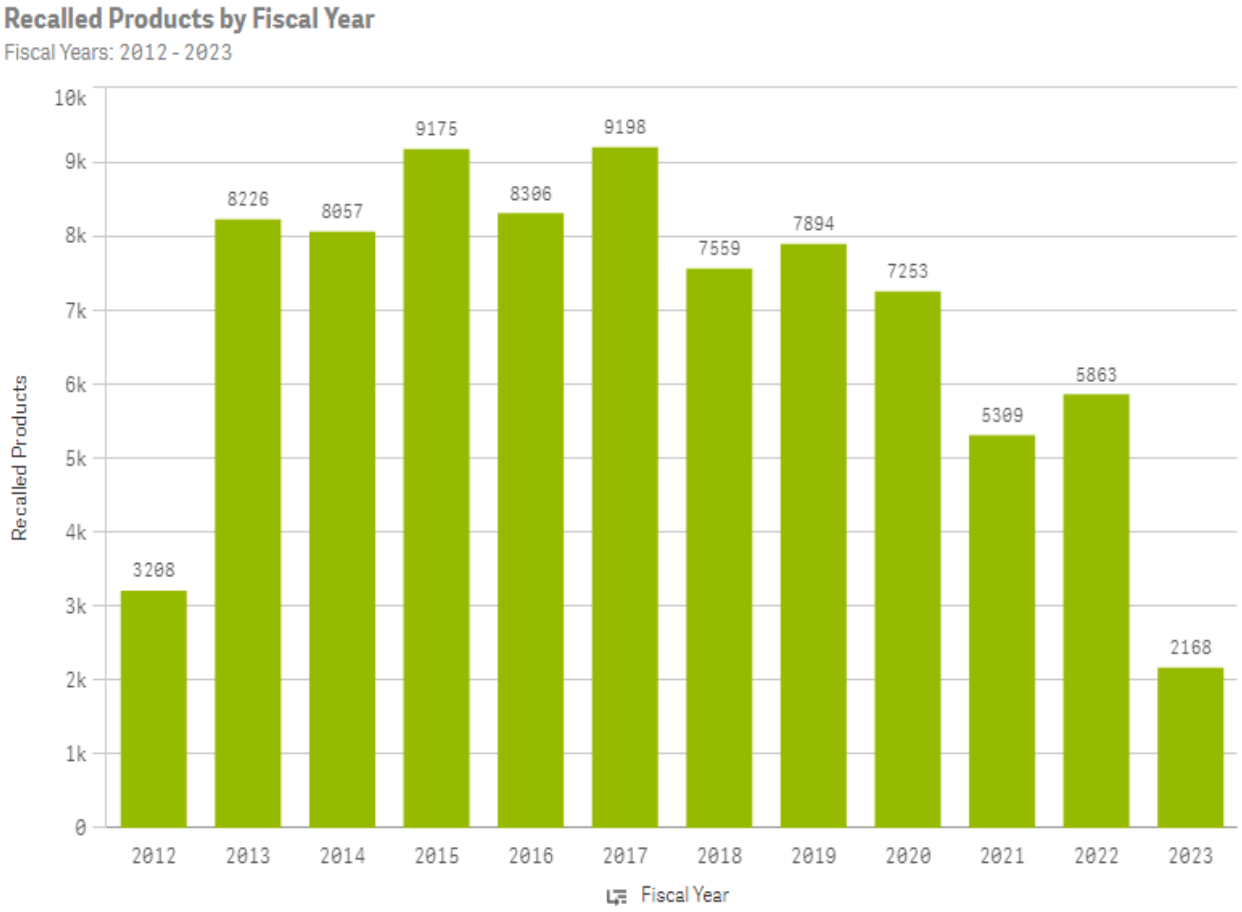
Goal: Improve FAR Informational Value for PET while reducing administrative burden

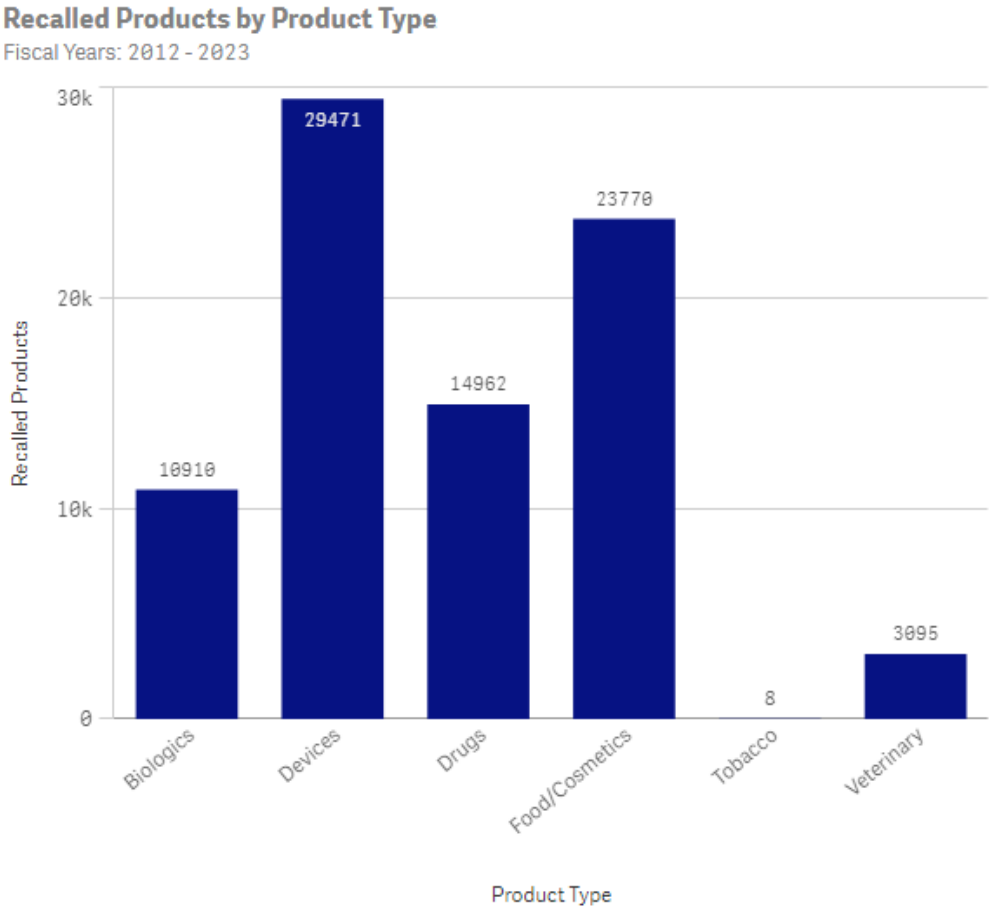
- FDA Background Action
  - Internal review of rate of FARs with no filed follow-up/closure and/or inconclusive outcome
  - Assess administrative burden of unnecessary for-cause inspections triggered by unconfirmed FARs
- PET Community
  - Communicate internal review of non-confirmed findings and/or inconclusive investigations
  - Ensures PET Manufacturer quality system informs HCP of potential safety issue for patient follow-up
- Proposal: Administrative Burden Reduction
  - FDA to set a 3-day FAR filing requirement following confirmation of product quality failure, e.g. post Micro investigation (e.g. via Guidance)

Thank you!

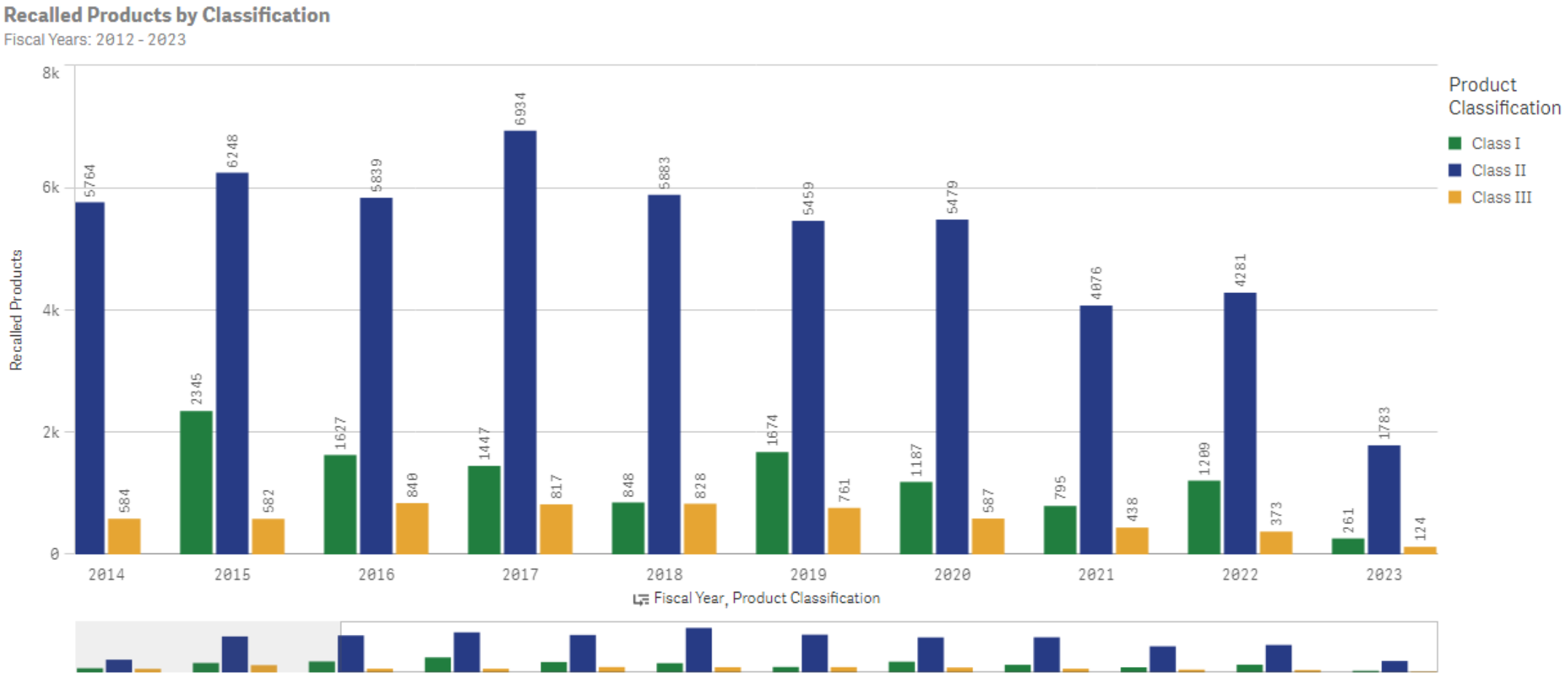
Appendices
(Internal purpose)

All Pharmaceutical Recalls (2012-2022)

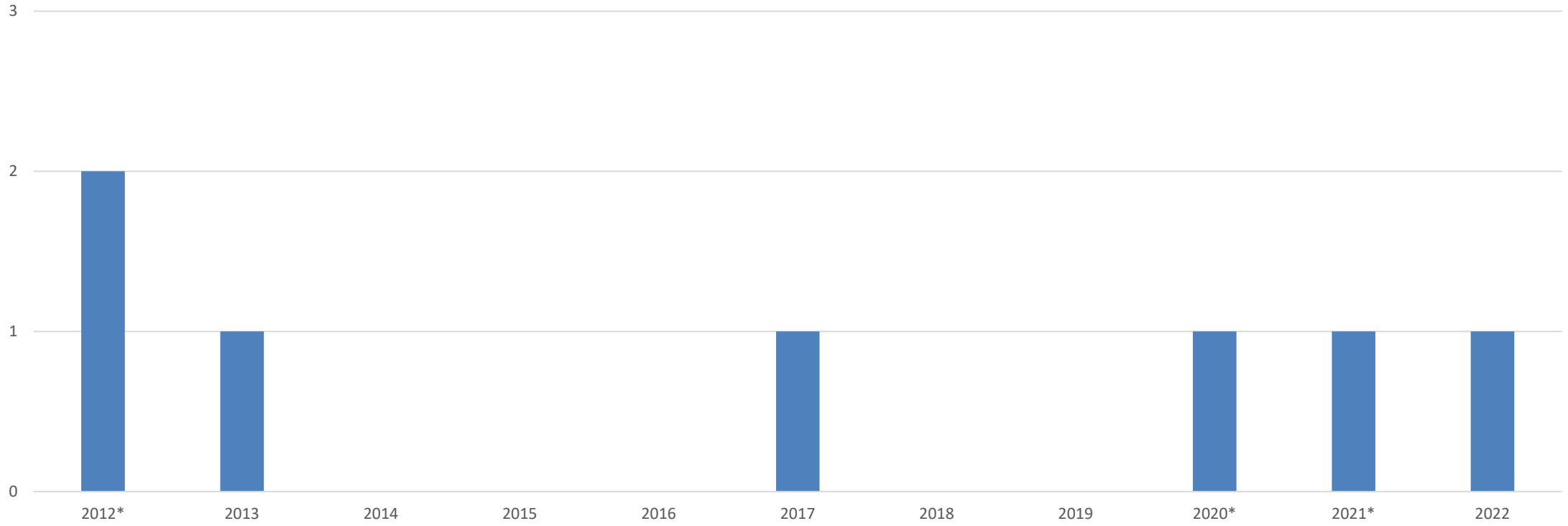




All Pharmaceutical Recalls (2012-2022)



PET Recalls (2012-2022)

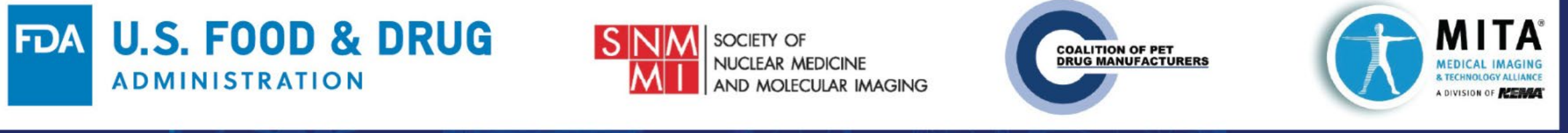


*= non cyclotron products

PET Recalls (2012-2022)

FDA-Approved PET Radiopharmaceuticals (as of 2/2023)	Recalls 6/12-2/23	Year(s)	Root cause	Percent of Drug Recalls
Carbon-11 choline	0	N/A	N/A	0.0000%
Cu-64 dotatate (Detectnet™)	0	N/A	N/A	0.0000%
Fluorine-18 florbetaben (Neuraceq™)	0	N/A	N/A	0.0000%
Fluorine-18 florbetapir (Amyvid™)	0	N/A	N/A	0.0000%
Fluorine-18 flortaucipir (Tauvid™)	0	N/A	N/A	0.0000%
Fluorine-18 fluciclovine (Axumin™)	0	N/A	N/A	0.0000%
Fluorine-18 fludeoxyglucose (FDG)	3	2013, 2017, 2021	Sterility Assurance Degradation/Impurities cGMP failure	0.0037%
Fluorine-18 fluorodopa	0	N/A	N/A	0.0000%
Fluorine-18 fluoroestradiol (Cerianna™)	0	N/A	N/A	0.0000%
Fluorine-18 flutemetamol (Vizamyl™)	0	N/A	N/A	0.0000%
Fluorine-18 piflufolastat (PYLARIFY®)	0	N/A	N/A	0.0000%
Fluorine-18 sodium fluoride	0	N/A	N/A	0.0000%
Gallium-68 DOTATATE (Netspot™)	2	2020, 2022	Subpotent Drug Container closure failure	0.0024%
Gallium-68 DOTATOC	0	N/A	N/A	0.0000%
Ga-68 gozetotide (Illuccix®, Locametz®)	0	N/A	N/A	0.0000%
Nitrogen-13 ammonia	0	N/A	N/A	0.0000%
Rubidium-82 chloride (Cardiogen-82®)	2	2012	cGMP Deviation Sterility Asurance	0.0024%
TOTAL PET	7	N/A	N/A	0.0085%
TOTAL PET CYCLOTRON	3	N/A	N/A	0.0037%
All other pharmaceuticals	82009	various		99.9902%

Note: updated numbers are consistent with the 2020 FDA-PET community Workshop (0.01%)



Introduction of New Manufacturing Sites in a Regulatory Submission

Jill Wilson, Ionetix

Julian Nwoko, SOFIE

Then and Now – Some History

December 12, 2011 (which was later extended to June 12, 2012), if the PET drug is produced for commercial distribution and used in humans for clinical practice to diagnose a patient, the maker of the PET drug must have submitted a new drug or abbreviated new drug application for that drug. **A PET drug marketed prior to December 12, 2011 can continue to be marketed after the application is submitted.**

All PET producers must be operating under an approved NDA or ANDA, (or an effective IND) by December 12, 2015.

What does this mean for the introduction of a brand new site into an ANDA or NDA?

If a company submitted an ANDA **for a new site that was manufacturing before June 12, 2012, the facility was allowed to manufacture while awaiting approval.**

After that date, the company had to await approval before manufacturing, which had no specific timeframe. It could take as long as 3-4 years before approval.

With GDUFA, the FDA has assigned a 10 month clock for review and approval of a new drug and a PAS (vs. CBE-30) if it's a new facility that hasn't been inspected. If the site is inspected and has satisfactory history, the clock can be 6 months.

Example text from a PAS acknowledgment letter from FDA:

This prior approval supplement is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). **The GDUFA goal date for review of this standard supplement is August 21, 2023. If FDA determines that this standard supplement requires an inspection or the use of a time- and resource-intensive alternate facility assessment tool, the goal date will be December 21, 2023. Two possible goal dates are provided because FDA is unable to determine if a supplement requires an inspection or the use of a time- and resource-intensive alternate facility assessment tool at the time of submission.** FDA will make this determination during the assessment of the supplement. For information, see FDA's guidance for industry, *ANDA Submissions– Amendments to Abbreviated New Drug Applications Under GDUFA*.

THE NEED FOR ADDITIONAL SITES

- PET manufacturing generates products with short-lived radionuclides.
- Product shelf-life ranges from 4 to 12 hrs for most Ga-68 and F-18 based PET agents. N-13 products are limited to 45 - 70 mins shelf life. Access is restricted by limitations of conventional transport (auto, air, or co-located).
- Ensuring access to diagnostic agents nationally and globally requires PET manufacturers to invest in the development and qualification of a broad networks of manufacturing facilities.
- Commercial PET manufacturing faces two major risks on a daily basis:
  - Manufacturing Failure prior to product release.
  - Breakdown of logistics and transportation beyond product release.
- Without a broad network of manufacturing sites, patients are forced to travel for diagnostic access.

REGULATORY SUBMISSIONS

Pharmaceutical NDA and ANDA amendments to introduce new facilities fall under two supplement submissions:

- CBE-30
  - Utilized when the additional pharmaceutical manufacturing facility (PMF) is functionally identical in quality, operational structure and aseptic operations to comparator site, in addition to having a satisfactory FDA inspection history.
  - Response typically granted within 30 days of supplement submission. Full approval decision provided 6 months from initial submission.
- PAS
  - Utilized for initial NDA or ANDA submissions of first PMF or a new facility.
  - Utilized when additional PMF is discernibly different in quality, operational structure or aseptic operations from the initial comparator facility.
  - Utilized if the PMF has no recent FDA inspection history.
  - Approval decision generally granted within 6 months of submission. This timeline is extended to 10 months if Inspection is required prior to approval. Priority review can expedite these timelines significantly.

TIMELINE OF SITE PREPARATION – GAP ASSESSMENT

- Facility Gap Assessment
  - Personnel
  - Quality system
    - Exception Report Management (DEV, OOS, CAPAs, etc.)
    - Material Specifications and Equipment Qualification Plans
    - Data Integrity Governance
  - Administration and Operational systems
    - Recent History of Inspections & Audits
  - Aseptic Practices & Environmental Monitoring
- Any gaps identified must be addressed via CAPA plans or applicable remediations prior to submissions.

TIMELINE OF SITE PREPARATION – EQUIP. QUALIFICATION

- Equipment Qualification & Analytical Method Verification
  - All critical equipment must be installed with applicable IQ/OQ & PQ documentation.
  - All analytical methods must be validated or verified according to ICH Guidance and USP <1225> or USP <1226>. Demonstration of method suitability for final product and final product formulation.
    - Chemical Purity & Radiochemical Purity Methods (HPLC, TLC)
    - Residual Solvent Methods (Gas Chromatograph)
    - Endotoxin Methods
    - Impurity Limit Methods

TIMELINE OF SITE PREPARATION – TECH TRANSFER & VALIDATION

- Technology Transfer
  - Demonstrates feasibility and robustness of manufacturing and batch analysis procedures.
  - Demonstrates proficiency of onsite personnel and effective transfer of all processes from comparator site
  - Identify areas of concern prior to formal validation
- Validation (vary by product and Industry vs. Academic)
  - Replicates of demonstrative process validation batches
  - Validation of Sterility test methods and suitability of test media
  - Stability Studies – Product Shelf-life evaluation
  - Bioburden Studies – process sterility by design

TIMELINE OF SITE PREPARATION – SUBMISSION

- Submission (Comparability Protocol, if applicable)
  - Introduction of NDA or ANDA Holder
  - Executive Summary of new PMF and General Facility Information/Overview
  - Description of Quality Systems
  - Process Comparisons to Comparator Site
  - Evaluation of manufacturing components and materials
  - Executed Validation and Stability Records
  - Aseptic Practices Summary
  - Analytical Method Validation/Verifications
  - Deviations

WHAT TO INCLUDE IN ADDING THE NEW SITE

- Form 356h Application to Market a New or Abbreviated New Drug or Biologic for Human Use
- Form 3794 GDUFA Cover Sheet or… Form 3397 PDUFA Cover Sheet
- Cover Letter
- 2.3.P (drug product summary)
- 2.3.S (drug substance summary)
- 3.2.S.2.1 (manufacturer, drug substance)
- 3.2.P.3.1 (manufacturer, drug product)
- 3.2.P.3.3 (manufacturing, process and controls)
- 3.2.P.3.5 (process validation and/or evaluation)
- 3.2.P.8.1 (stability summary)
- 3.2.P.8.3 (stability data)
- 3.2.A.1 (Facilities & Equipment) (Appendices as needed)
- 3.2.P.5 (Control of Drug Product) (As needed)

Note: these are the common submission components within the commercial manufacturing space. Additional items may be added/removed for different spaces depending on the nature of the product, any process changes or classification of regulatory submitter. Further changes could occur to this list in the future at FDA's discretion. See the most recent FDA guidance on the assembly of the Common Technical Document for additional information.

NEXT STEPS AFTER SUBMISSION

- CBE-30 or PAS is submitted through the Electronic Submissions Gateway (ESG) – 3 receipts generated
    - Receive Letter within 30 days of submission
        - Acknowledgment letter with GDUFA or PDUFA dates listed (with and without inspection)
        - Refuse to Receive (ANDA) or Refusal to File (NDA) if application deficiencies are found

QUESTIONS FROM THE PET INDUSTRY

What is FDA's current thinking regarding adding a new manufacturing site (that manufactures currently approved PET drugs) to an ANDA or NDA post approval under an agreed upon comparability protocol as CBE-30?

Are there any instances where a **brand new** manufacturing site can be added to an approved NDA or ANDA under a comparability protocol as a CBE-30 if the company has good inspectional history?

What are FDA's expectations when providing a complete response 6 months after a CBE-30 is approved?

For networks considering a novel NDA or ANDA submission, is it the FDA's preference that an initial meeting be scheduled to discuss the details of the initial and subsequent submissions?

REFERENCES

https://www.fda.gov/files/drugs/published/FDA-Oversight-of-PET-Drug-Products----Questions-and-Answers.pdf

https://www.fda.gov/media/89258/download

https://www.fda.gov/media/162263/download

https://www.fda.gov/media/82370/download

https://www.fda.gov/files/drugs/published/Changes-to-an-Approved-NDA-or-ANDA.pdf

Clarifying 21 CFR 212 and 211 – the Evolving Regulatory Landscape

Serge Lyashchenko

Michael Nazerias

November 13, 2023

Clarifying 21 CFR 212 and 211 – the Evolving Regulatory Landscape

- Background for differences
- Historical perspective - What did FDA say?
- Other differences needing clarification
- Where are we going?

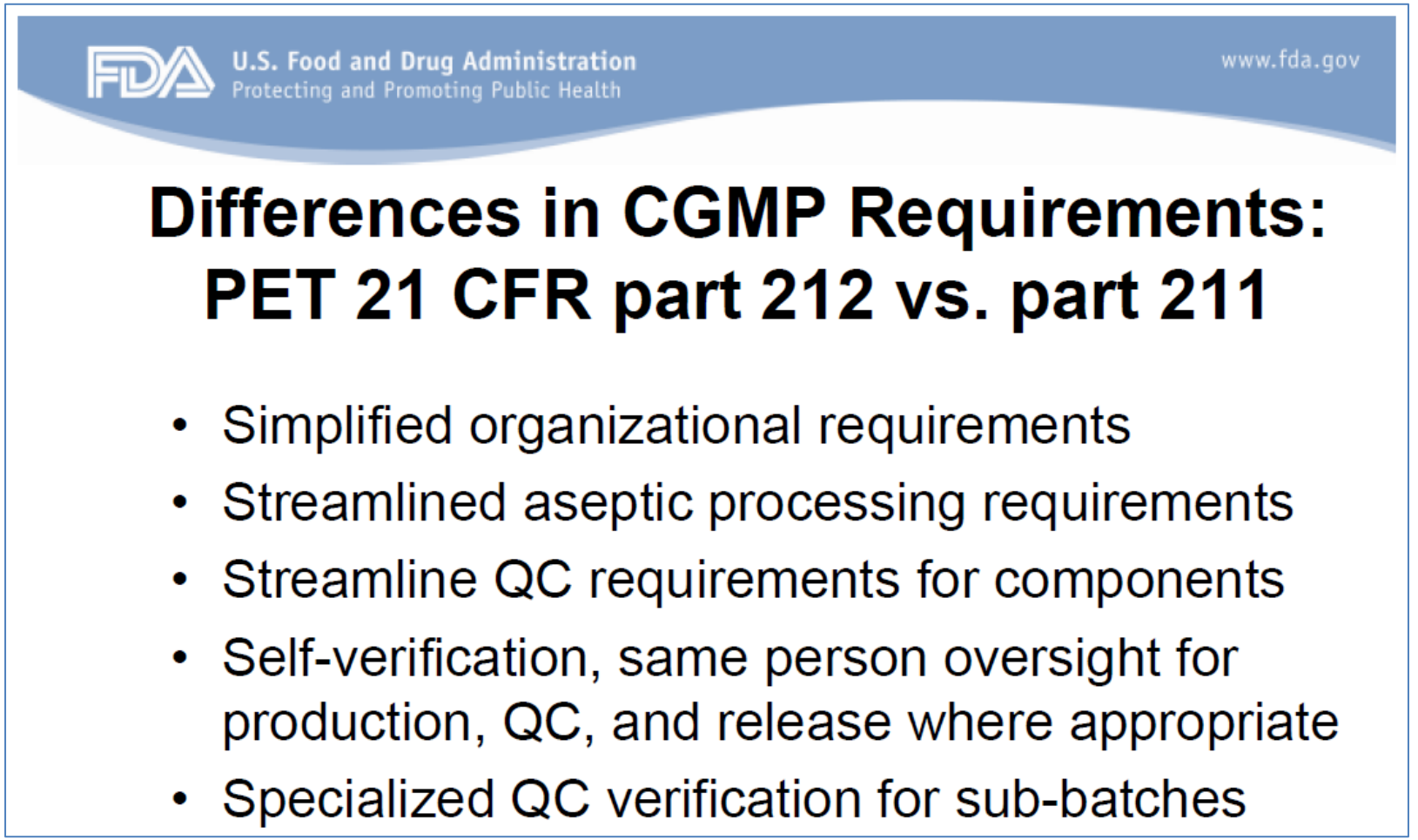
  (longer half lives, kit-based manufacturing approaches, generator produced PET radionuclides, larger molecules including biologics, and radionuclides with multiple emissions and the potential for therapeutic uses)

- Conclusions

Unique Characteristics of PET Drugs

- ***Short shelf life*** precludes proliferation of microorganisms
- ***Shielding*** defines workflow and allows safe handling by operators / healthcare providers
- ***Active ingredient*** does not cause a pharmacologic effect
- ***Limited doses/batch*** requires tens of 1000s of batches for national supply
- ***100% sample size*** for QC testing overcomes sterility test limitations (all vials tested)
- ***Closed system*** precludes exposure to unclassified air during manufacturing
- ***Diagnostic agents*** only used a limited number of times in a patient

What did FDA say?



Simplified Organizational requirements

- **Fewer required personnel with fewer organizational restrictions consistent with the scope and complexity of operations**
- Staffing levels
  - Correspond to the size and complexity of the operation
  - Enable the facility to complete all intended tasks in a timely manner before administration of a finished PET drug product to humans.
- We recommend that the responsibilities and assigned duties of all staff be clearly identified in written policies.

Streamlined aseptic processing requirements

- Each batch must be tested, and sterility testing must be started within 30 hours after completion of production (more than 30 acceptable if validated).
- Microbiological monitoring should be performed during sterility testing and aseptic manipulation.
- Media fills are used to simulate aseptic manipulations with operators requalified annually.

Streamlined QC requirements for components

- **Organizations with more than one PET drug production facility could store and perform QC testing and approval of components at a centralized facility**.
- Acceptance testing: COA with scientific rationale and supporting data as to why ID testing is not necessary for components that yield API.
- **When the identity of the F 18 radionuclide is established as part of the finished-product testing, it is appropriate to use the COA without performing identity testing.**
- **For the production of a PET drug where the finished-product testing does not ensure that the correct components have been used, identity testing must be performed**. When specific identity tests exist, we recommend that they be used.
- The inactive ingredients in PET drugs usually consist of a diluent, a stabilizer, and/or a preservative. **If a product that is marketed as a finished drug product intended for intravenous administration is used as an inactive ingredient, it is not necessary to perform a specific identity test for that ingredient**.

Self-verification, same person oversight for production, QC, and release where appropriate

- Under current CGMP regulations for conventional drug products in part 211, FDA normally requires second-person checks at various stages of production as well as test verification. **In a PET drug production facility with only one person assigned to perform production and quality assurance tasks, it is recommended that that person recheck his or her own work.**

Specialized QC verification for sub-batches

- **PET drugs that have a very short half-life (e.g., ammonia N 13) can be produced in multiple sub-batches on the same day.** Finished-product testing of the initial sub-batch can be conducted, provided a sufficient number of sub-batches (beginning, middle, and end) have been demonstrated to produce a product meeting the predetermined acceptance criteria. For routine production in this circumstance, the release of subsequent sub-batches can be qualified if the initial sub-batch meets all acceptance criteria. In certain cases, testing each sub-batch for certain attributes prior to release may be appropriate.

Other differences needing clarification

- Stability testing – long standing FDA policy has been that site specific stability is not required as long as the manufacturing process is the same and uses the same synthesizer.
  - Recently some reviewer and/or inspectors have been requesting site specific stability annually for each product
- Annual Product Reviews – not explicitly required in 212.
- Does FDA recognize the use of Risk Management for PET Drugs?
  - Embedded philosophy for 211
- Aseptic Processing Guidance not designed for PET Drugs.
- Other guidance documents (e.g., CMO QA Agreements, etc.) don't reference applicability to PET Drugs.

Evolving Landscape of PET Radiotracers

FDAMA

- Non-kit based radiotracers (e.g., FDG, NaF, Ammonia)
- Pure positron-emitting radionuclides (i.e., diagnostic "nostic" only)
- Short half life (many small-scale manufacturing facilities needed)

Today

- Chelator-based radiotracers (i.e., kit-based)
- Non-pure positron emitters (i.e., therapy "thera" possibilities)
- Biologics
- Longer half life (potential for large-scale manufacturing)
- Kit-based "nostic" only radiotracers with generators (e.g., ^{68}Ga)

Do we need to think beyond radioactive emissions to determine the appropriate GMPs?

Potential Regulatory Landscape

"Nostic" Short $T_{1/2}$	Kit-based	"Thera" Long $T_{1/2}$	Applicable GMP Regulations
Yes	**No**	**No**	**212**
Yes	No	Yes	212 FDP* 211 "thera"
Yes	Yes	No	212 FDP* 211 kit
Yes	Yes	Yes	212 FDP* 211 kit and "thera"

Open Questions

- Stability requirements for various combinations
- Facility qualification requirements
- Should half life be used to determine appropriate regulatory pathway?
- Is it more appropriate to regulate all finished PET drugs/biologics under 212? Too confusing for the industry to comply with separate regulatory pathways.

Unique Characteristics of Investigational PET Drugs

- ^{89}Zr ImmunoPET
  - Mass of the injected compound plays a role
  - Regulatory guidance on the quality of the antibody precursor material may be needed
  - Production and characterization of conjugated material key intermediate is required
  - Longer final drug product shelf-life

Zeglis, *et al. Dalton Transactions* 2011, 40: 6168-6195.

Typical Academic PET Drug Producing Facility

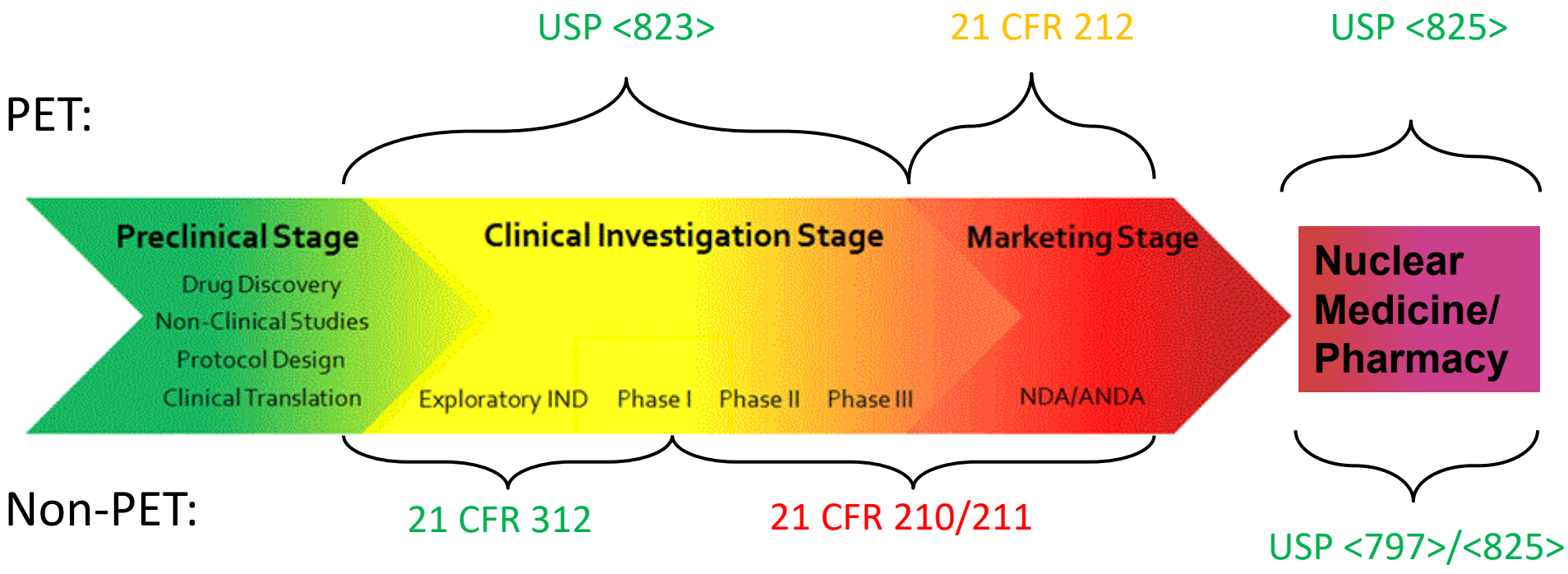
Types of Operations Commonly Conducted

- Manufacture of one or several ANDA/NDA PET tracers.
- Reconstitution of cold ^{68}Ga kits
- Manufacture of investigational PET tracers for Phase I and II.
- Manufacture of investigational radiotherapeutics for Phase I.

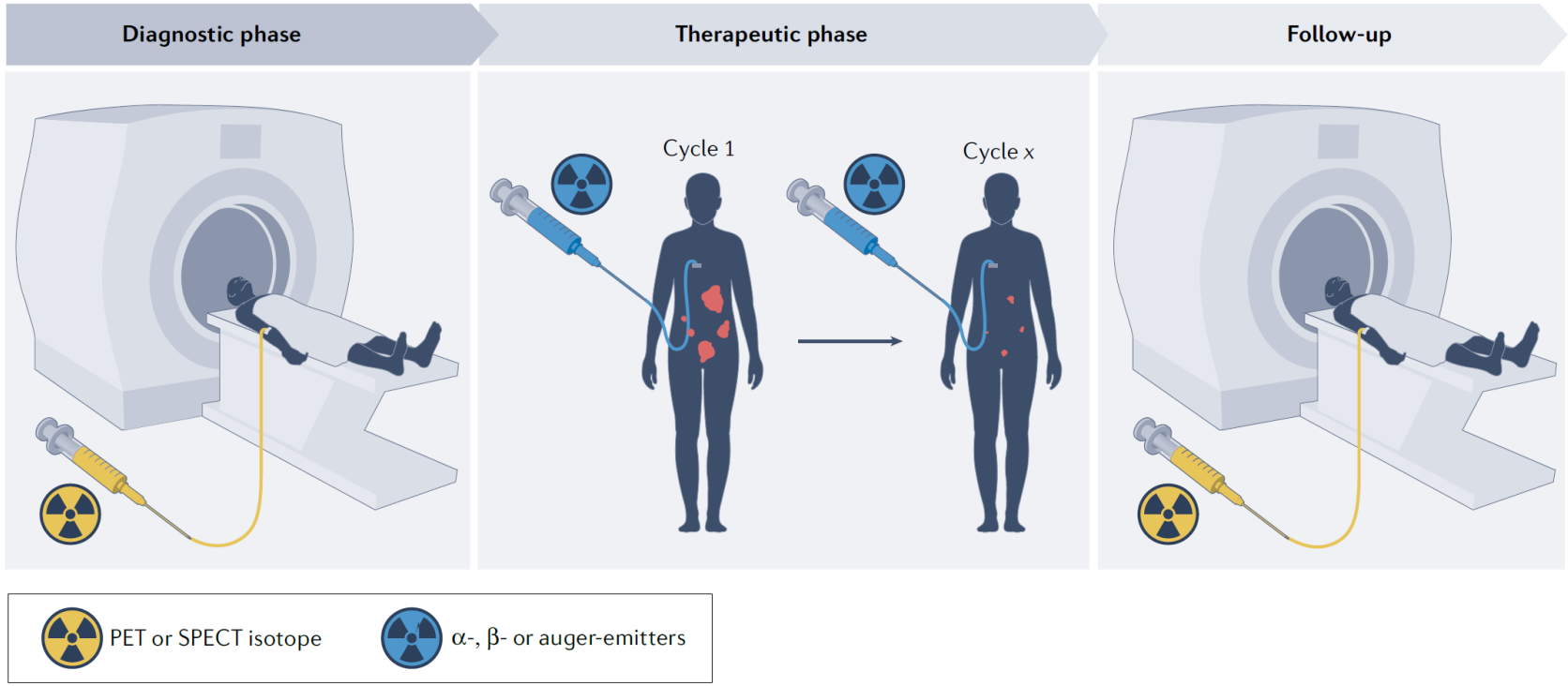
Commonly Shared Characteristics

- Regulatory compliance related experiences are shared freely
- Resources are limited, compared to industry
- Staff perform multiple functions
- Degree of operator scientific knowledge and training is generally higher, compared to industry
- The physical manufacturing process is the same for PET and non-PET, and will require changes should clinical development progress beyond Phase I.
- Investigational product production is sporadic and the number of batches is limited

Which Regulations/Standards may Academic PET Producers Rely On?



Increased Commercial Interest In PET Companion Diagnostics from Pharma



Nat Rev Clin Oncol 19:589-608, 2022

Impactful Points of Discussion During Pharma QA Audits

- Analytical method validation requirements in Phase I
- Complete separation of worker roles
- Collection of retention samples
- Dedicated QMS and training system
- Materials acceptance process
  - COA review versus in-house testing
  - Use of non-compendial grade materials
- Media Fill Testing Study Design
- Equipment Vendor Validation Reports Verification

Conclusions

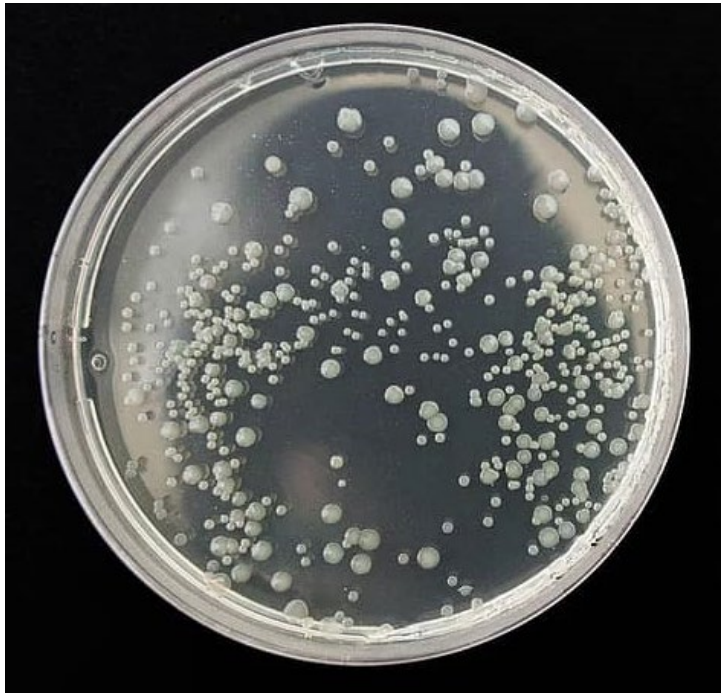
- The unique difference of PET continues to necessitate separate GMP regulations for PET Drug Manufacturing
- The existing regulatory framework supports new products
- FDA and PET community need to work together to determine applicability (212 vs 211)
- Consider using half life to determine appropriate regulatory pathway
- Path forward needs to be science and risk based (objective vs. subjective)

Compliance Update – Microbiological Quality Deviations and Failures – Robust CAPAs and Real-Life Success Stories

Timothy J. Pohlhaus, Ph.D.
CDER/Office of Compliance/Office of Manufacturing Quality

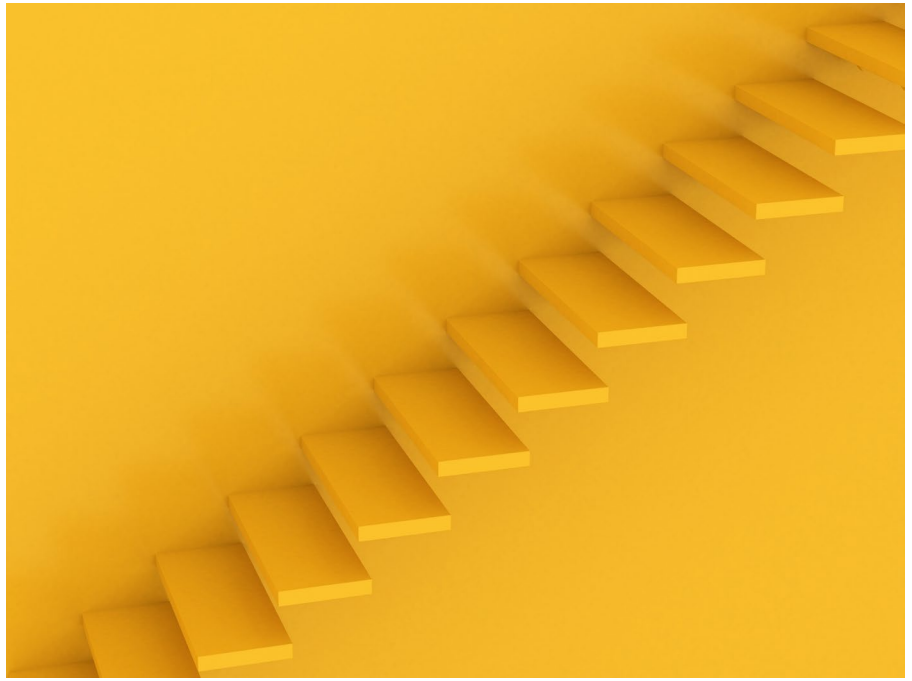
Background / Perspective

- PET Drug CGMP Regulations – *Relatively* New
- PET Drug Manufacturer OAI Rate vs. Overall Drug Manufacturer OAI Rate
- Compliance Cases – Common Thread – Microbiological Concerns



Case Studies

- Two CGMP compliance cases from 2019
- Both cases clearly demonstrate significant steps forward in quality maturity



Case #1

- Manufacturer inspected mid-2019
- 5-item Form FDA 483 (FDA 483) issued

Inspection Findings (Microbiological)

- *Staphylococcus aureus* recovered in hot cell - not investigated (21 CFR 212.20(d))
- Smoke (airflow visualization) studies not conducted for initial qualification of laminar airflow hood (21 CFR 212.30(b))
- Lack of documentation to support a major change - installation of new biological safety cabinet (21 CFR 212.20(c))
- Growth promotion testing had not been conducted on microbiological media in approximately 5 years (21 CFR 212.60(b))

FDA 483 Responses

- Contracted with 3rd party to conduct airflow visualization studies
- Revised relevant SOP to include investigation into recovery of atypical organisms
- Committed to conducting growth promotion testing on all new lots of growth media received

Remaining Concerns

- Lack of supporting documentation for FDA 483 responses
- Environmental monitoring SOP revised to include investigation of atypical organisms, but the *S. aureus* recovery was not addressed
- No retrospective review of equipment qualification (BSC and other pieces of equipment)

Regulatory Meeting (Early 2020)

- Producer updated FDA 483 responses and provided documentation
- FDA recommended smoke studies under most challenging conditions
- Producer conceded that they do not have appropriate microbiological oversight, but committed to ensuring appropriate technical competencies
- Producer provided retrospective review of environmental monitoring data
- FDA and producer had a productive discussion on the handling of OOS results

2021 Follow-Up Inspection

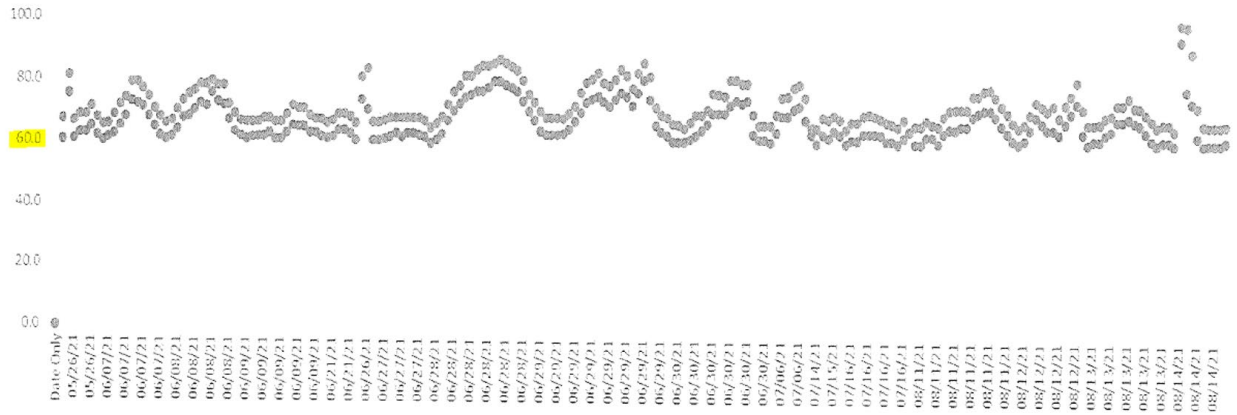
- Not there yet - some progress, but new issues
- Although SOPs are important, more than SOPs are needed for a quality system to function properly
- Producer's overall approach to assure quality - still insufficient
- FDA 483 responses lacking

Follow-Up Inspection Findings

- Eighteen ISO 5 environmental excursions identified as “objectionable” by the producer within a 6-month timeframe
  - One investigation, which was still open
  - Producer’s SOP says all atypical organisms are action level and must have corrective actions, with evidence of effectiveness
- Six water intrusions events within the facility
  - Fungi recovered (*Cladosporium spp.*, *Aspergillus spp.*, *Trichophyton spp.*, *Rhodotorula bacarium*, and *Rhodotorula mucilaginosa*)
  - Piecemeal approach to facility remediation
  - Leaking water observed during inspection
  - Evidence of water leak into materials storage room

Follow-Up Inspection Findings

- Producer had a 60% relative humidity limit for the facility; however, they exceeded that limit multiple times in a ~four-month timeframe.
- Producer's SOP stated that "Engineers should be contacted whenever the relative humidity exceeds 60%."



Follow-Up Inspection Findings

- Producer used a contact time of 10 minutes for a sporicidal agent, in contrast to the product manufacturer's recommended contact time of 60-120 minutes for bacillus spores. Producer had frequently recovered sporeforming microorganisms in ISO 5 areas over the last two years.

FDA 483 Responses

- Producer responded to each FDA 483 item, but responses generally lacked full remediation plans and/or supporting documentation
- Producer updated SOP to include a CAPA close-out check, but did not address the retrospective review of past CAPAs to ensure that they had been appropriately closed and were effective
- Persistent facility issues and lack of investigations are major unresolved deficiencies

Warning Letter Issued

1. **Your facilities are not adequate to ensure the prevention of contamination of equipment or product by substances, personnel, or environmental conditions that could reasonably be expected to have an adverse effect on product quality. Procedures to ensure that all equipment is clean, suitable for its intended purposes, properly installed, maintained, and capable of repeatedly producing valid results, are not adequately followed. (21 CFR 212.30(a) and (b)).**
2. **Your firm failed to conduct adequate investigations and take appropriate corrective action when a failure of a production batch or any component of the batch failed to meet any of its specifications. (21 CFR 212.20(d)).**

WL Follow-Up Inspection – 2023

- NAI inspection classification (No Action Indicated)
- Significant improvement in the quality of corrective and preventative actions

Findings – Good CAPAs

- Conducted engineering review
- Significant work done to address water intrusion issues and humidity control, as well as air exchange rates and differential pressure issues that the producer had identified
- Change management documented
- Qualification completed for new equipment
- Smoke studies complete

Findings – Good CAPAs

- Updated cleaning and disinfection practices
- Producer had temporarily ceased distribution of some products while remediation was ongoing

Case #2

- Inspection Mid-2019
- 6-item FDA 483

Inspection Findings

- Matter appeared in sterility test samples during incubation, sterility test samples went missing. Neither were appropriately investigated. Personnel were not adequately trained to read sterility test results.
- Water repeatedly leaking into cleanroom (ISO 7) where ISO 5 cabinets are located. Cleanroom did not appear to be clean and was cluttered. Airflow was inadequate for cleanroom design.
- Humidity uncontrolled in the area where aseptic processing occurs. High humidity measurement during inspection.

Inspection Findings (cont.)

- Not all cleaning agents used for the cleaning of ISO 5 classified equipment are sterile or sterile filtered prior to use
- Non-sterile wipes and gloves used for cleaning ISO 5 areas
- ISO 5 smoke studies poorly captured and did not include relevant transfer operations
- Producer had repeated recoveries of microorganisms in ISO 5 areas, including Bacillus, spp.; others were not evaluated to determine whether they were atypical/pathogenic

FDA 483 Responses

- Producer submitted FDA 483 responses, but many initial responses were inadequate

Concerns Remaining

- Investigations – scope and timeframes
- Facility design – assessment of risk
- Environmental monitoring program – responses to recoveries

Regulatory Meeting Held / Additional Responses Submitted Several Weeks Later

- Very productive discussions during regulatory meeting
- Producer committed to immediate QA responses to deviations warranting immediate action
- Producer committed to short-term, medium-term, and long-term facility renovations (a new facility)
- Producer committed to better understanding EM recoveries in their ISO 5 areas, including trending ISO 5 recoveries and speciating them

Reinspection - 2022

- Not there yet
- Findings indicate room for higher quality maturity
- However, FDA 483 responses indicated producer was headed in the right direction

Specific Findings

- Humidity remains an issue and producer is seeing fungal recoveries in cleanroom areas
- Frequent ISO 5 settle plate recoveries, but no investigation into this adverse trend
- Several month trend of an increase in microbial recoveries on glove and surface samples, just below action level, but no investigation into the adverse trend
- Contact times for sporicidal agents less than what product labeling indicated

FDA 483 Response

Findings themselves could have led to a final violative inspection classification

However,

- Overall, producer's response was acceptable and far superior to their FDA 483 responses to 2019 inspection
- Specific dates provided for each CAPA to be completed
- Firm response noted that their goal was "exceeding the agency's expectations in ensuring sustained cGMP compliance"
- In addition, the producer "recognizes the 483 identifies opportunities to further enhance the site's facilities, operations, and quality systems"
- Firm engaged subject matter experts for each observation
- Ongoing comprehensive risk assessment of operations

Specific Corrective Actions

- Engaged a third party to identify weaknesses in current process for identifying and handling deviations
- Updated SOPs now require any mold recovery to be investigated and ISO 5 action limit reduced to anything greater than 0 cfu
- More routine recordings of humidity levels. >70%RH requires action to reduce humidity; engaging contractor to get further control over humidity.
- Had a 4 cfu ISO 5 excursion. Investigated, speciated, determined it came from personnel, retrained personnel on proper gowning, hygiene, and cleaning
- Committed to using disinfection contact times supported by scientific studies

Summary

- Quality maturity is the key to sustainable compliance.
- The 212 regulations do not prescribe everything needed to meet CGMP.
- Avoid “tunnel vision” when addressing deviations or findings of non-compliance.
- Engage appropriate experts (e.g., microbiological, engineering) when needed.
- You got this!

Thank You!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U.S. FOOD & DRUG
ADMINISTRATION


COALITION OF PET DRUG MANUFACTURERS


MITA


SNMMI
Value Initiative


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U.S. FOOD & DRUG
ADMINISTRATION

PET Product Availability: Drug Shortage Mitigation and Prevention Efforts

November 14, 2023

Captain Leo Zadecky, RPh, MS

Senior Reviewer, Drug Shortage Staff

Center for Drug Evaluation and Research

Food and Drug Administration

Drug Shortage Mission

- Our mission is to prevent, mitigate and alleviate drug shortages
- Patient and practitioner access to life-saving medication is our #1 priority
- Drug Shortage Staff works with professional organizations, patient groups, clinicians and other stakeholders (E.g. DOE, NNSA, ACR)

Brief History

- Part of FDA's Center for Drug Evaluation & Research (CDER)
- Drug Shortage Program began in 1999
- 2011- President Obama signed *Executive Order 13588-Reducing Prescription Drug Shortages*
- 2012-Requirements to Industry For Early Notifications Under Section 506C of the FD&C Act
- CDER Drug Shortage Program (DSP) changed to Drug Shortage Staff (DSS) in 2012
- Moved under the CDER Office of the Center Director in 2014
- Additional drug shortage staff in other Centers (e.g. CBER, CDRH)
- Coronavirus Aid, Relief, and Economic Security Act (CARES Act) 2020

FDA Drug Shortage Staff (DSS)

Drug Shortage Staff: The program office that is designated by FDA to oversee and facilitate the resolution of all drug shortage situations

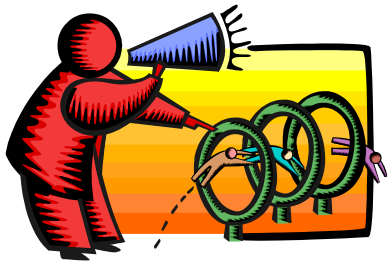
DSS serves to support FDA's mission of ensuring that safe and effective drugs are available to patients

- Facilitate temporary and long-term strategies to address shortages
- Coordinate for timely and comprehensive risk/benefit decisions
- Distribute information (web posting, professional organizations, e.g. ASHP)

Often working across suppliers, facilities, and issues - multiple moving parts, urgency

→ Maintain availability while minimizing risk to patients

FDA Drug Shortage Staff - Key Communications



Important Definitions

Drug Shortage or Shortage: A period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug (21 CFR 314.81). DSS determines if a shortage concern exists, and what FDA action if any is needed. DSS is designated to oversee and facilitate the resolution of all drug shortage situations.

In general, the Agency focuses on shortages of products that have a significant effect on public health:

- **Life Supporting or Life Sustaining**

  A drug product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life (21 CFR 314.81).

- **Debilitating Disease or Condition**

  A drug product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning (21 CFR 314.81). Equivalent to serious disease or condition (80 FR 38915).

- Including any such drug used in **emergency medical care** or during **surgery** or any such drug that is critical to the public health during a **public health emergency** declared by the Secretary under section 319 of the Public Health Service Act.

Notification Requirements Under Section 506C of the FD&C Act and FDA Regulations

Notify DSS no later than 5 days after a manufacturing interruption (21 CFR 314.81), ahead of any supply disruption at **drugshortages@fda.hhs.gov** (80 FR 38915)

Manufacturers are required to notify the FDA of a permanent discontinuance in the manufacture of a covered drug or an interruption of the manufacture of a covered drug that is likely to lead to a meaningful disruption in the supply of the drug in the United States

- "At least 6 months in advance of the date of the permanent discontinuance or interruption in manufacturing; or, if 6 months' advance notice is not possible no later than 5 business days after the…permanent discontinuance or interruption in manufacturing occurs"
- Not limited to medically necessary products
- Regardless of market share, or number of companies marketing, or wholesaler volumes
- **Notification is not required for radiopharmaceutical drug products.**

Manufacturers Report on Potential Impact to Supply

At the time of any change in manufacturing that may lead to a reduction in supply of a product*, e.g.:

- Plans for upgrade or remediation
- Manufacturing issues
  - Environmental concerns
  - Equipment failures
- Container closure issues
  - Changing stopper or vial suppliers

*Note, product refers to a specific strength, dosage form, and route of administration

The Agency's Approach to Prevention and Mitigation

Early notification is key!!

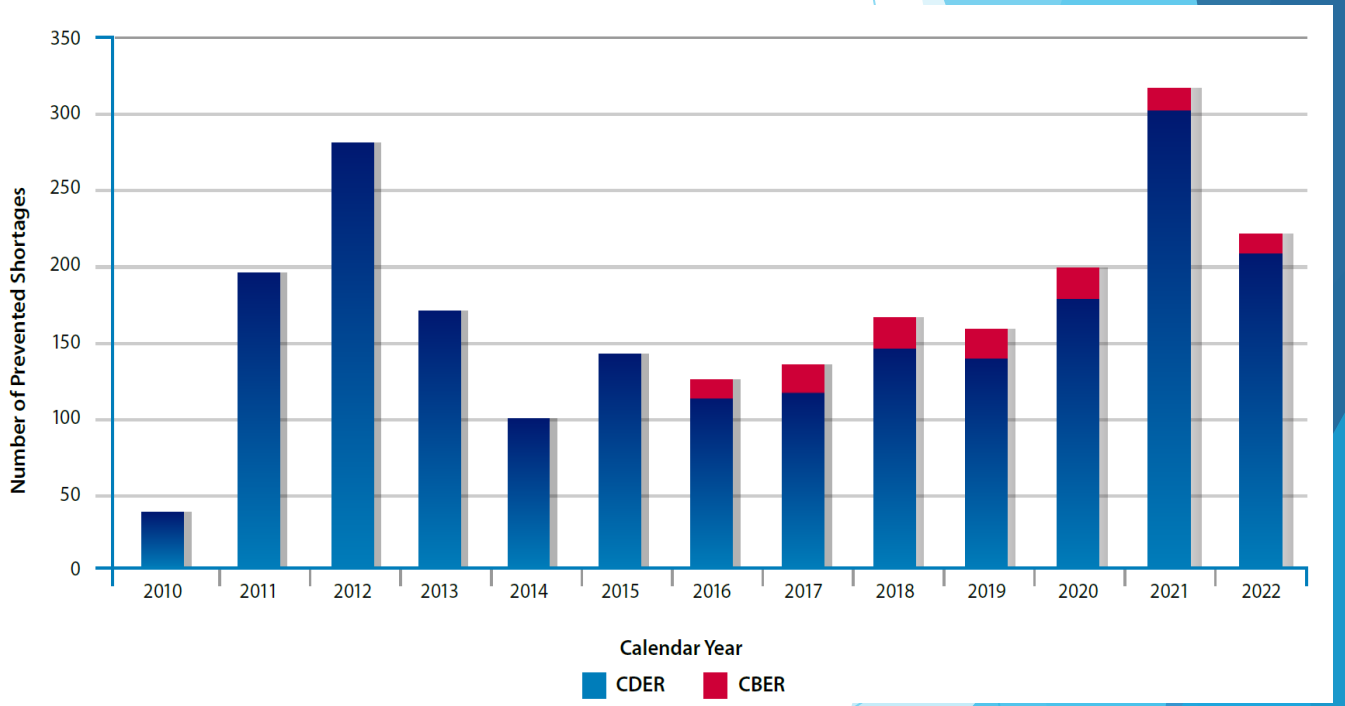
- Prioritize products that are medically necessary
- Risk/Benefit of the drug in question
- Maintain availability while minimizing risk to patients
- Work with firms to address problems
  - We can advise, assist, and expedite inspections and reviews,
  - The manufacturer must fix the problem
- Drug shortages cannot always be prevented
  - Unanticipated events occur
    - Manufacturing breakdown or
    - Natural disaster(Hurricanes & Floods)
  - If systemic issues are present, the facility may have to close to repair

FDA Toolbox

- Proactive outreach through CDER NextGen Drug Shortage Emergency Event Portal
- Communicate possible shortage concerns on a product or material issue
- Regulatory Discretion:
  - Manufacture of medically necessary products during remediation
  - Use of additional safety controls
    - Special instructions for safe use
    - Filters with injectable products to remove particulate concerns
    - Extra testing at production facility
    - 3rd party oversight of production
- Expedited review of company proposals
  - New manufacturing sites,
  - New material source(s),
  - Changes in specifications, etc.

Impact of Early Notifications to the FDA

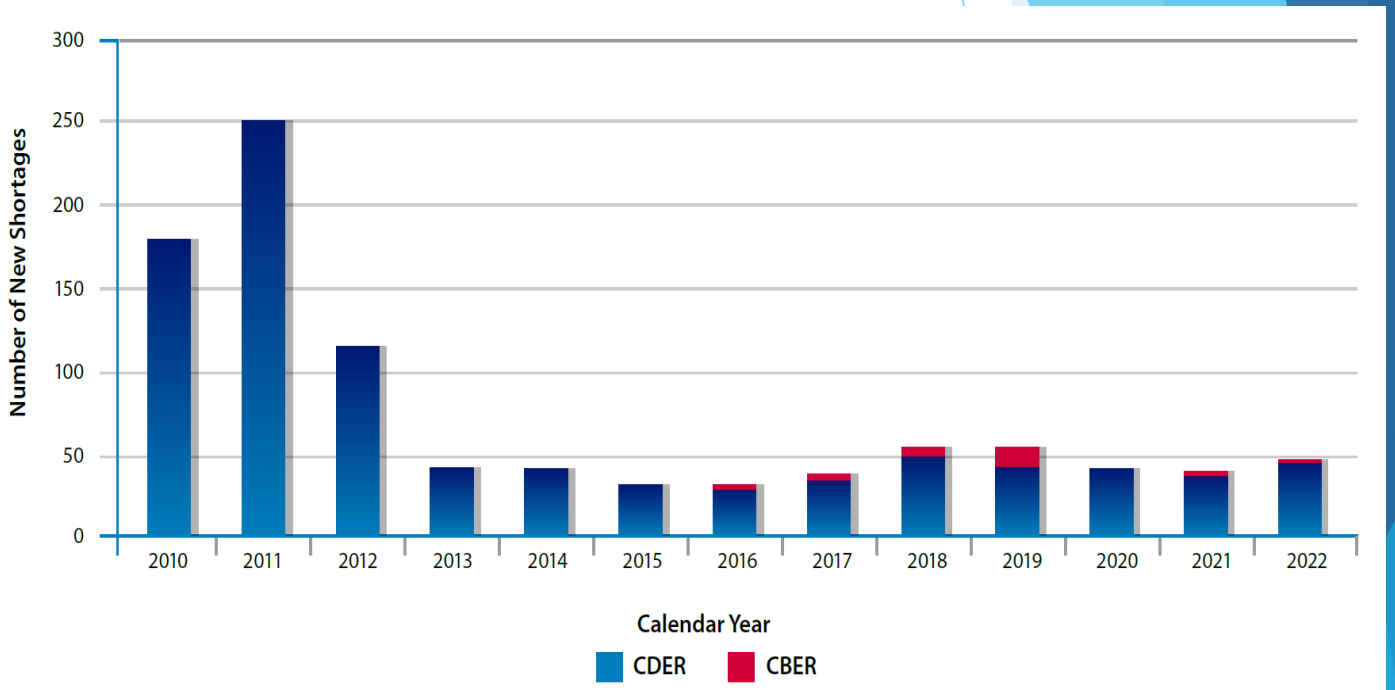
- Ongoing dialogue/work with industry – high numbers of prevented shortages continue
- Depending on the precipitating events, some drug shortages can endure for months to years. (Ex: Plant remediations and agency approvals)



Total Prevented US Drug Shortages Per Year

Current Challenges: New Shortages and Persistent Shortages

- Shortages peaked in 2011 at 251 and continued to decline through 2016. Shortages rose again in 2017 and 2018 due in part to the 2017 hurricane impact as well as ongoing problems with manufacturers. With last year's tripledemic, we ended 2022 with 48 new shortages.
- Depending on the precipitating events, some drug shortages can endure for months to years. (Ex: Plant remediations)



Total New US Drug Shortages Per Year

Role of Industry to Help Prevent and Mitigate Drug Shortages

- Understand the frailties in their supply chain
- Communicate early about potential shortages
- Provide short term and long-term plans for preventing and addressing shortages while maintaining and improving quality
- Work with FDA to minimize shutdowns or slowdowns that will lead to shortages
- Provide shortage information for posting on FDA website when a shortage is unavoidable

Enduring Solutions: What's Still Needed?

- Companies need to have **Risk Management Plans** in place – build better inventories of essential materials and components, have a backup plan for when things fail or demand increases
- **Redundancy in manufacturing** and suppliers –encouraging industry to have alternative sources, components and supplies at the ready for critical drugs
- Communication is key
    - Guidance to Industry issued April 2023 requesting notifications on increased demand in addition to supply disruptions
    - Ongoing Collaboration – Industry, Outside Stakeholders

Contacts:

Current shortage information updated daily at: https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

To contact DSS:

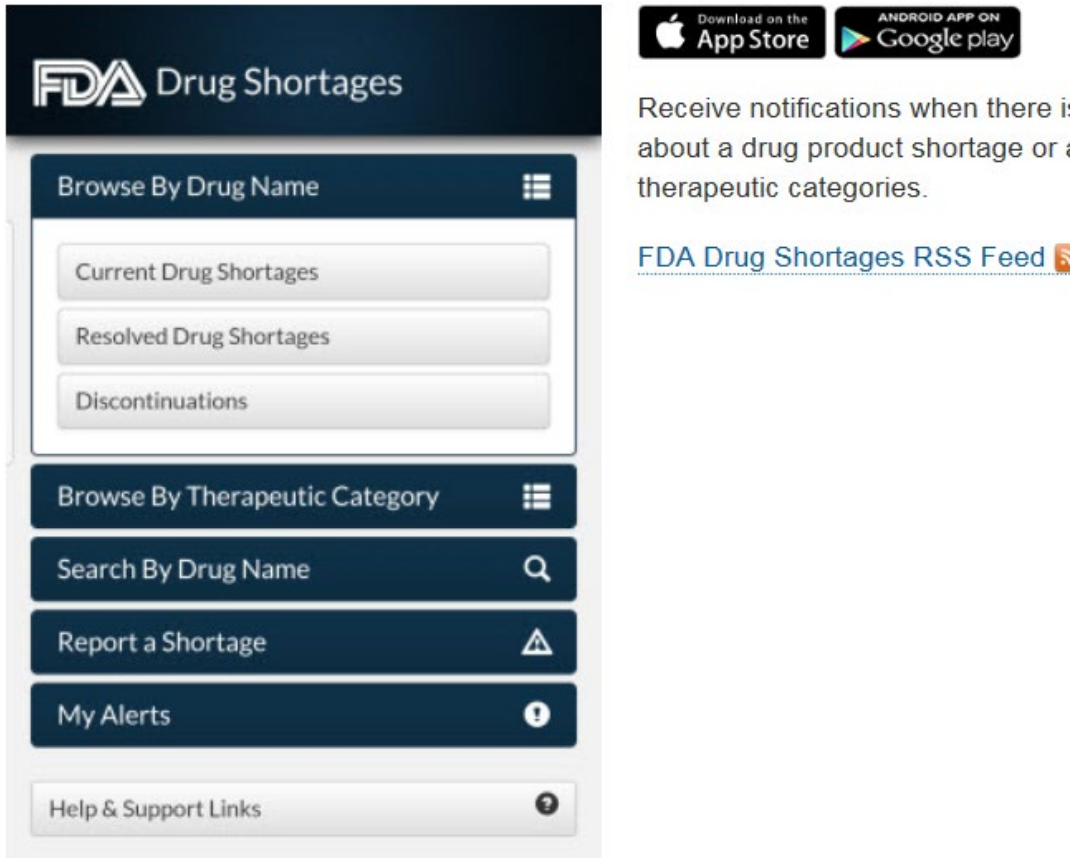
Email: drugshortages@fda.hhs.gov

FDA Drug Shortages Homepage:

https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm

Drug Shortage Mobile APP

FDA Drug Shortages Mobile App



Thank You

Questions ?

U.S. FOOD & DRUG ADMINISTRATION

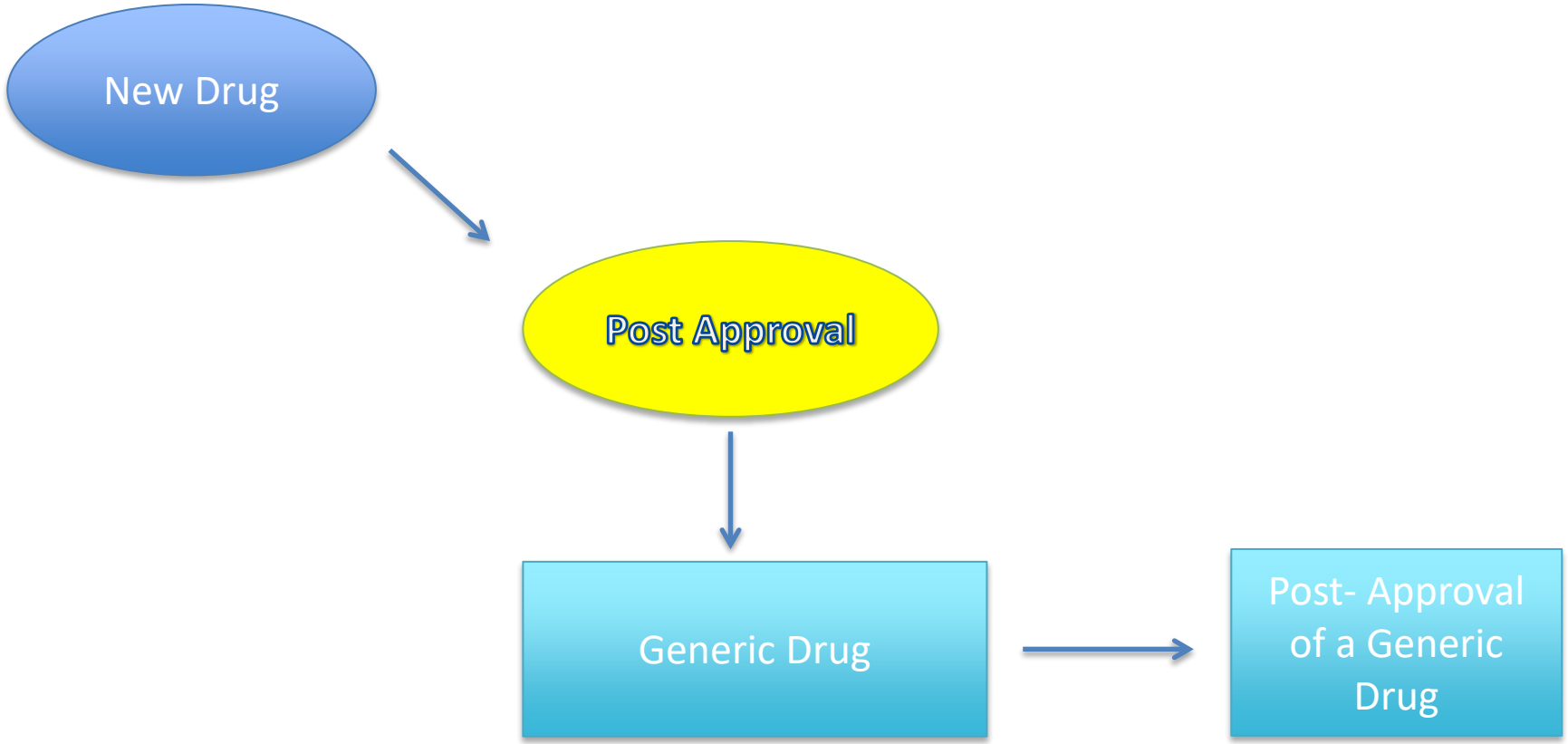
Positron Emission Tomography Drugs Workshop

PET: Product Lifecycle

Presented by:
Ramesh Raghavachari, PhD, Chief, Branch I/DPMA I/
Office of Lifecycle Drug Products/OPQ/CDER

FDA White Oak Campus
November 13, 2023

The Lifecycle



Why Post-Approval CMC Changes?

- Continuous improvement
  - Product Optimization
  - Incorporating new technologies
  - Process improvement (based on historical knowledge)
- Regulatory Requirements/Commitments
- Product quality issues
- Business Reasons
  - Supply & Demand

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Types of Supplements

- Efficacy supplements
  - New Indication
  - Changes in the dosing regimen
  - Safety Changes (precautionary statements/Blackbox warning/new contraindications)
  - Addition of dosing information for special population
- Labeling supplements
  - Changes in the approved labeling, including prescribing information, immediate container and carton labels, medication guide, etc.
- CMC Supplements
  - Changes in the drug substance and/or drug product manufacturing, analytical changes, site changes etc..

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Typical Post-Approval CMC Changes

- Drug Substance- Changes to:
  - New manufacturing site (including for the kits)
  - New supplier for regulatory starting materials
  - Route/Method of synthesis
  - Manufacturing process
  - In-process controls and/or drug substance specifications
  - Shelf life or retest period....

Typical Post-Approval CMC Changes

- Drug Product - Changes to:
  - New manufacturing site
  - Manufacturing process and/or equipment
  - Formulation
  - Container closure system
  - Specifications
  - Shelf-life (extension or reduction)
  - Introduction of new strengths

Regulatory Basis for Post-Approval Changes

- 21 CFR 314.70

  § 314.70 Supplements and other changes to an approved application.

  – The applicant must notify FDA about each change in each condition established in an approved application

Regulatory Basis- FDA Guidances

- Changes to an approved NDA or ANDA
- Scale-up and post-approval changes (SUPAC)
- SUPAC: Manufacturing equipment addendum
- CMC post-approval manufacturing changes to be documented in annual report
- Comparability protocol – Chemistry, Manufacturing, and Controls information
- PAC-ATLS: post-approval changes – analytical testing laboratories sites

Classification of CMC Changes

- Major changes (Prior Approval Supplements)
  - High impact to the product quality
  - Cannot be implemented until approved
  - Four months review clock
- Moderate changes (Changes Being Effected in 30 Days or Changes Being Effected in 0 Days Supplements)
  - Moderate impact to the product quality
  - Can be implemented 30 days after submission at the applicants own risk
  - Six months review clock
- Minor changes (Annual Reportable)
  - Minimal risk to product quality
  - Can be implemented immediately after submission
  - Six months review clock for supplements

Response to Some Questions?

Question:

- **For CMC, if the equipment changes, but the testing and specifications do not change, can this be submitted as part of the product's Annual Report?**

Response:

It depends upon the exact change- PAS or CBE-30 certainly not AR!

Response to Some Questions?

Question:

- **What is FDA's current response/approval timelines for PAS submissions?**

Response:

Prior Approval Supplements have a PDUFA clock of Four months from the date of receipt.

Thank you!

PANEL DISCUSSION/AUDIENCE Q&A

Certain types of sterility test deviations can occur (e.g., accidentally dropping a sterility test tube during transport, inadvertently inoculating the wrong sterility test media type). What is the FDA's expectation on submission of Field Alert Reports (FARs) in these circumstances?

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CLOSING REMARKS AND NEXT STEPS

THANK YOU FOR YOUR ATTENDANCE!

HOUSEKEEPING SLIDES

In-Person Attendees

- Please submit your lunch order before 9:30 AM at the kiosk (located in the main hall) and pick-up during lunch break.
  - Lunch can be eaten within the room, or any tables in the main hallway.
  - Coffees and assorted beverages can be purchased at the kiosk throughout the day.
- Bathrooms are located behind the kiosk in the main hall.
- Any phone calls should be taken in the main hall, outside of the presentation room. Please ensure they are silenced throughout the presentations.
- There will be an opportunity to ask questions:
  - Please hold comments for the Open Discussion sections of the meeting.
  - Microphones will be available for use located in the room.

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COALITION OF PET DRUG MANUFACTURERS

SNMMI Value Initiative

FDA U.S. FOOD & DRUG ADMINISTRATION

POSITRON EMISSION TOMOGRAPHY DRUGS: PRODUCT QUALITY, REGULATORY SUBMISSIONS, FACILITY INSPECTIONS, AND BENEFIT-RISK CONSIDERATIONS (TUESDAY, NOVEMBER 14, 2023)

Q&A RELATED TO CONSIDERATIONS AND TRANDS IN FACILITY INSPECTIONS AND COMPLIANCE

There continues to be inconsistency between the FDA Districts/Divisions with respect to inspections and inspector expectations. Can FDA comment on inspector training for PET Drug GMP regulations? Are inspectors receiving training about PET Drugs and the relevant differences between 21 CFR Part 211 and Part 212? Is it the intent of the FDA to ensure the consistency of inspections? PET drug manufacturers are concerned that inconsistent inspections will lead to an inconsistent drug supply in the US.

Stability Testing: How are inspectors trained to assess adequacy of stability programs? For PET multi-sites/networks, submitting stability data per product from one representative site is considered compliant. Can FDA provide specific examples where single site stability annual submission was considered inadequate?

As discussed during the 2020 PET drug Workshop, FDA was testing new inspectional tools in support of standardization, such as tablets and checklists. Can FDA Provide an update on these and any other tools in development?

What is FDA's policy on taking photos during inspections and providing documentation to inspectors in an electronic format?

Inspectors have expressed concerns about long standing processes for which firms have substantial in-house performance and safety records. Can FDA discuss the need for additional controls that increase regulatory burden and cost in light of historical documented evidence for substantial safety and compliance? What can PET manufacturers do to help the FDA recognize such evidence as part of a Sponsor risk management program?

To facilitate alignment regarding data integrity requirements, can FDA comment on expectations regarding review of audit trail information in support of product release (frequency, timing etc), areas of applicability (QC laboratory, manufacturing), and provide current areas of inspectional deficiency?

As PET drug manufacturing firms move into electronic systems, what are the expectations for data integrity?

Is data integrity still a major compliance issue in FDA PET drug inspections?

What are the guidelines and recommendations for performing environmental monitoring for manufacturing rooms for a PET drug production facility? USP <823> is very vague.

USP <797> now states that PET falls under USP <825>. Does FDA find it acceptable for PET facilities to only follow USP <825>?

What is FDA’s expectation for audit trail reviews of batch data using electronic systems?

PET Drug Workshop: Q&A Related to Session I: Trends in Facility Inspection & Compliance

Q&A RELATED TO PRODUCT QUALITY AND REGULATORY SUBMISSIONS

What are FDA's expectations around Disinfectant Efficacy Studies (DES) and cleaning validation studies for PET manufacturers?

Upon considering the decentralized manufacturing of PET drugs, will the FDA allow the NDA/ANDA holder of a given PET drug to sublicense the release of the drug product to the site of manufacturing (i.e., hospital or site of use)? And if yes, would the site of manufacturing have to be included on the Prescribing Information in Section 17 (i.e., would the PI have to be updated for each additional hospital site added)?

Can FDA highlight a compliant manner for a sponsor to delegate drug product batch release activity to a 3rd party (e.g., CMO)? Are there any implications for product labeling information (such as section 17)?

Can the FDA provide guidance on when a QC test can move from per batch to a PQIT, how a company should evaluate and justify, and also is there any guidance on this transition process?

According to the package inserts of the three reagent kits (NETSPOT kit for the preparation of gallium Ga 68 dotatate injection, LOCAMETZ kit for the preparation of gallium Ga 68 gozetotide injection, ILLUCCIX kit for preparation of gallium Ga 68 gozetotide injection), appearance, pH, and radiochemical purity (labeling efficiency) are the three quality control attributes to be evaluated prior to the injection be dispensed. Is this a correct understanding?

What is FDA's expectation regarding vendor qualification for PET manufacturers? Are onsite audits required for critical vendors or can they be qualified by alternative means?

Would FDA regulate under 21.CFR.212 a drug product containing an isotope commonly used for an imaging indication (e.g. Cu64), when used instead as a therapeutic drug based on its other emissions (beta and Auger electron)?

Would FDA please discuss QC testing expectations for PET drugs prepared by pharmacists from cold kits? Can FDA confirm that the PI listed tests (e.g. pH, appearance and RCP) are sufficient for patient dose release?

Will the FDA be updating and/or issuing new media fill guidance for PET drug manufacturers?

BREAK

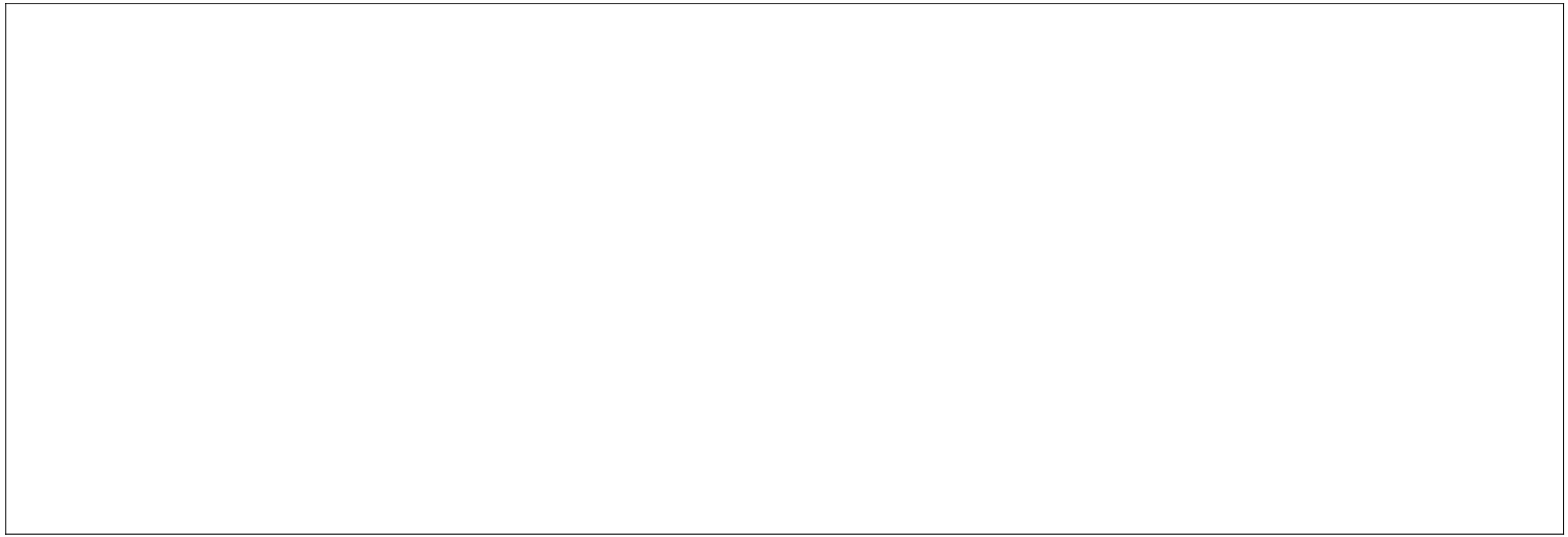
Q&A RELATED TO SAFETY AND RISK ASSESSMENT

We have seen 483 issued by inspectors related to perceived risk levels of manufacturing processes for which the applicant had generated internal data within a risk assessment approach that supported low to negligible risk. How can the manufacturer receive recognition for the objective evidence (data) generated rather than the inspector fact-free concern?

When an OOS for sterility is detected; at what point should a FAR be raised? Is it immediate upon detection? After assessments on test validity? After investigating the potential causes? After receiving the microbial identification and completing the investigation?

The agency has confirmed the notion that the FAR system can be updated to enhance the value of quality event reporting within the context of a product already administered to a patient. Can the Agenda provide current thoughts and considerations regarding the filing of FARs within the process of initial discovery, investigation and root cause determination?

What are the provisions for a sterility retest; and how is the data interpreted? What level of validation is required to perform a retest? If the second result passes, what is the overall disposition of the batch? What level of validation is required to perform a retest? If the second result passes, what is the overall disposition of the batch?



Q&A RELATED TO MANAGEMENT OF PET RUG LIFECRCLE

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Q&A RELATED TO "OTHER" QUESTIONS (ONES WHICH DON'T NEATLY FIT IN THE COUTHER FOUR A

Can FDA confirm that FDA-approved kits for the preparation of Ga-68 PET radiopharmaceuticals will be regulated by FDA in a manner similar to FDA-approved kits for the preparation of Tc-99m products, i.e., as a pharmacy-based activity?

Response: *Approved Kit for the Preparation of Ga-68 PET radiopharmaceutical is an FDA approved product and can be used as described in the PI under practice of Medicine and Practice of Pharmacy. So it can be prepared as described in PI by a nuclear pharmacy.*

Would two orthogonal HPLC methods be accepted for precursor ID?

If HPLC is not an ideal for precursor testing, as it is not considered a characterization technique, what level of precursor characterization is required?

Do intermediates and precursors require GMP manufacturing for an IND (FIH & clinical trials)

If an organization will be manufacturing the same product at multiple facilities, using an outsourced model (contracted manufacturers), for initial application, is it requred to submit initial validation package (3 full batches) from each facility? If yes, if some of the contracted facilities are a network of facilities, only one set of stability validation is required initially. Correct?

Are all radiopharmaceutical drug products, including SPECT drugs and Therapy drugs considered PET Drugs, in regards to compliance requirements?

Why the extensive requirements of identity and purity for precursors and not for other “chemical pieces” which end up in the radiopharmaceutical? Plus, impurities may come from solvents, salts, acids, bases, kryptofix, etc which are almost never of pharmaceutical grade

Are the 3 batches requires need to be at the highest dose, or do they span the high and low of a process?

For large molecules, such as peptides, antibodies, and nanoparticles, what are the requirements for intermediates and precursors in terms of purity (chemical & radiochemical), GMP/GLP, etc.?

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Does the hot-DP manufacturer also needs to perform extensive incoming controls if the Precusor is provided as a cold Kit for Radiolabeling (cold Drug Product)?

Since several commercial cassettes / kits are provided with solution precursor vials, does the FDA have a recommended ID test?

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My question is regarding Precursor identification test. Its not clear what kind of test (if HPLC or TLC is not enough) to do the complete identification test for the precursor? If we need to do the complete test like done in C of A, it's need to have several equipment in the facility which may not have in every facility. In this instance how do we proceed this test? Sending the sample another lab to do and get the appropriate paper works? How do we judge then this second lab's authetication of the testing?

Is a Letter of Authorization to DMF of precursor also needed for Phase II studies?

Microbiology: Could the Agency please expand during which circumstances validation of sterilising filter will be required?

Can you please define "QC on sub batches for O15 (LAL)" ? Thank you

Sterility testing - what does "initiate the test within 30h mean"? Timepoint of Inoculation of the media, or timepoint of starting incubation of the inoculted media?

Would you consider monitoring of loading of VHP connected to hot cell as part of media fill requirements

Using erasable labels for outer containers can be ok, right ?

Are cells radiolabeled with radiometals included in biological radiolabeled samples ?

What are the requirements for TFA content in the radiopharmaceutical drug product release, is there any guidance?

At what point in the PET drug regulatory phase (IND vs NDA), is there an expectation to treat precursor as an API (per ICH Q7 guidelines)? If such an expectation exists at all.

To Henry VanBrocklin: do you know how many of the AE were directly related to lack of sterility of the dose as opposed to an unrelated cause (i.e., anaphylactic reaction, stroke or seizure that happen during the scan but was unrelated to the dose)

I missed the part on growth promotion testing. If we are provided a CofA with growth promotion testing results, do we need to repeat the tests with each batch of media ?

For Samantha Cotter: I’m assuming the spike in A.E.’s in 2018 was due to the overuse issues of the Rb-82 generator. Do you have any insight as to what has caused the spike of A.E.’s in 2022, i.e., do you have the A.E.’s categorized by drug?

Does the AE information compiled and presented by FDA include the specific incidents like the described Sr-82 issue? Harm clearly occurred, but in that case it seems due to adulteration and gross malpractice, and really does not reflect the safety of the actual drug product.

If the cold ligand content is very low e.g., 1 or lower microgram, there may not even be an analytical method that can detect or quantify a 1% impurity. Is it accepted then to justify a higher limit based on the analytical method capability?

A previous presentation said that sterility testing is not required for PET drugs to be used within 24h, can we stop doing sterility testing?

Can a new additional manufacturing site (operationally identical) with no inspection history request a pre-approval inspection so a CBE-30 to add the site would be acceptable?

THANK YOU FOR ATTENDING