

# **PET Drug Inspections and Compliance Update**

**Society of Nuclear Medicine and Molecular  
Imaging Annual Meeting**

**Philadelphia , PA**

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# Agenda

- PET drug inspection updates- 2016-2018 May
- Inspection classifications and trends
- PAI risk framework and PAI withholds
- New Requirements: Annual registration and listing of drug products
- PET drug listing and registration issues
- Responses to some data integrity questions
- Inspectional issues- Recommended Resolution pathway and ORA contacts

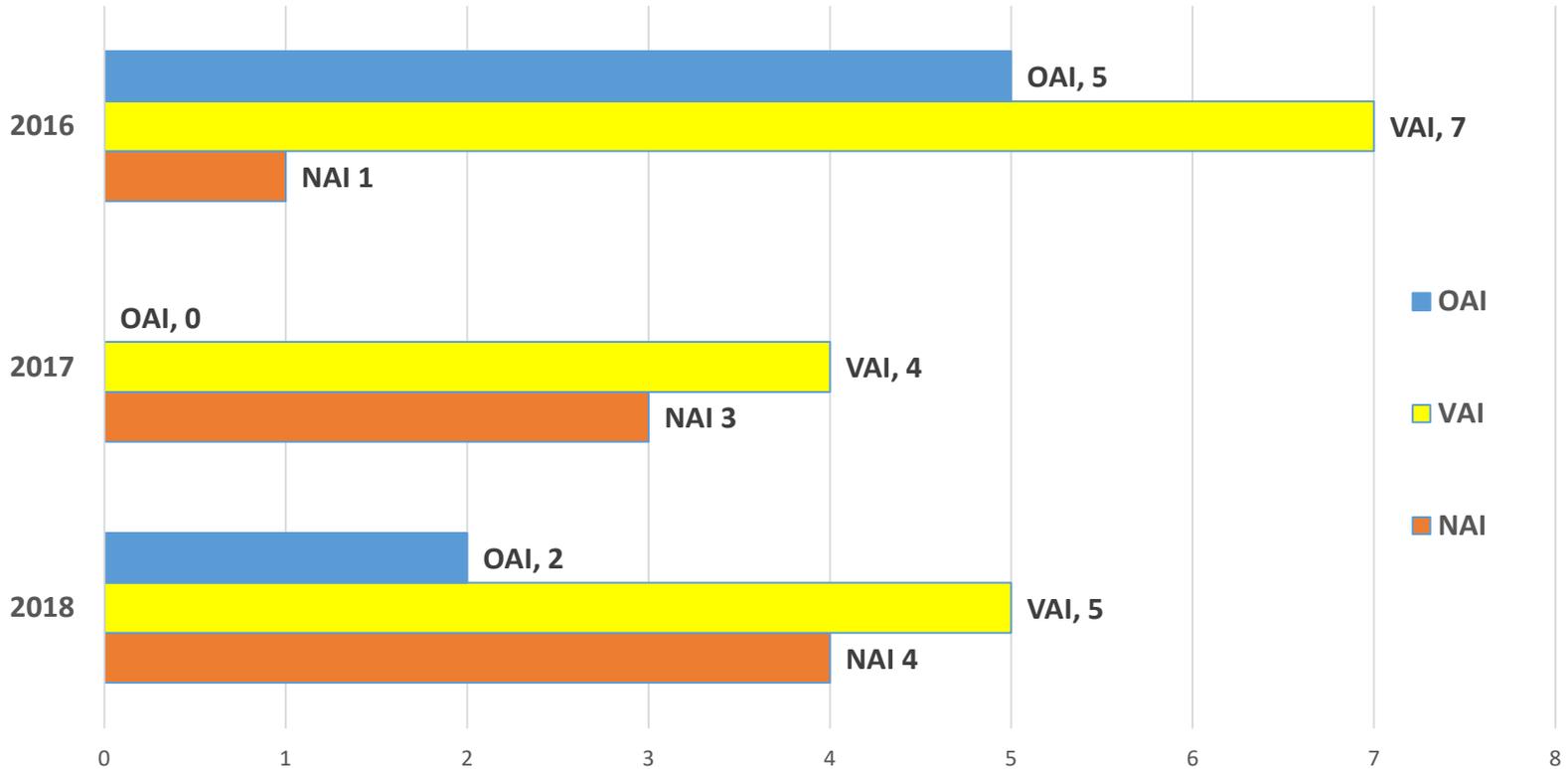
# PET Drug Inspections 2016-2018 May



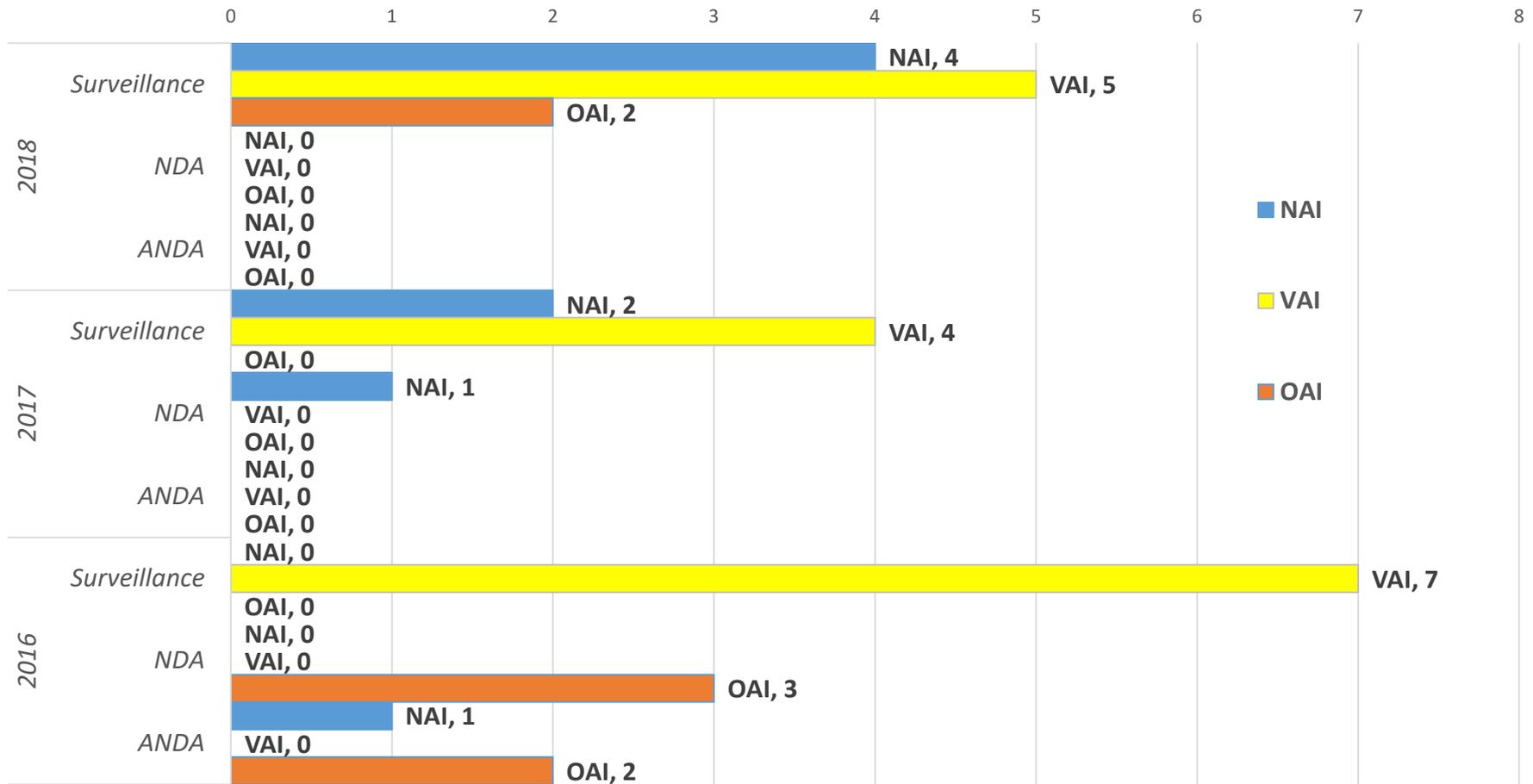
Inspections	<u>2016</u>	<u>2017*</u>	<u>May 2018*</u>
PAI / NDA	3	1	0
PAI / ANDA	3	0	0
Surveillance	7	6	11
Totals	13	7	11

*\*Note: Inspections under review and not finally classified may not be reflected*

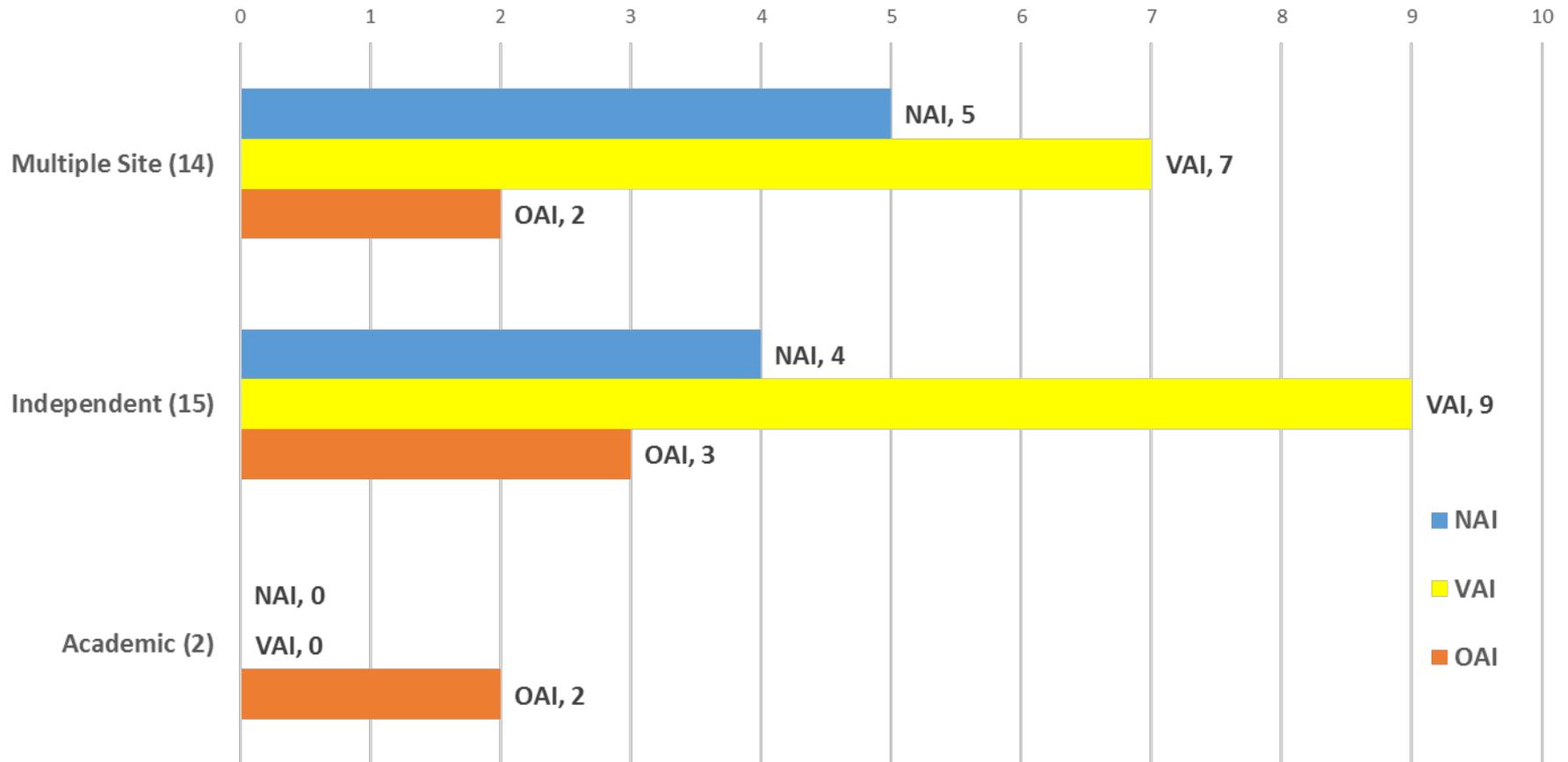
# 2016 - 2018 Inspection Trends



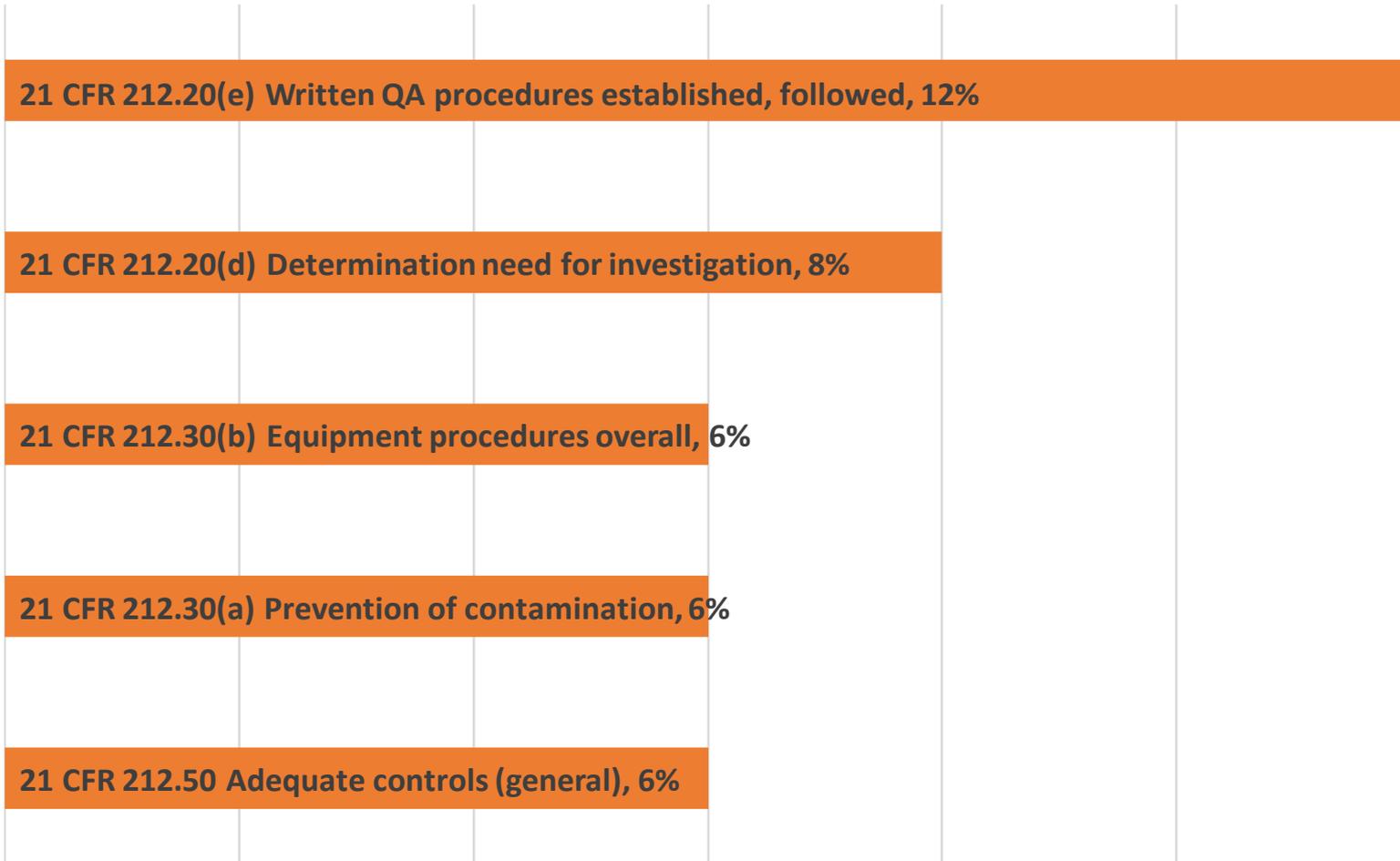
# 2016-2018 Outcomes by Inspection Type



# 2016-2018 Inspection Outcomes By Firm Types



# Top Five 483 Observations 2016- 2018



# Risk Framework for PAI Inspections



## FDA uses a risk-based facility assessment :

### Facility Risks

- Compliance history and current status
- Recalls and field alerts
- Observational Trends

**Process Risk** – Are there risks associated with the manufacturing process design and control strategy?

- Inherent process complexities
- Unique process characteristics
- 

**Product specific Risk Factors-** Are there risks associated with the finished product characteristics?

- Light and temp sensitive products
- Combination Products
- Radiopharmaceuticals/ PET Drugs
- Low dose API products

# 21 CFR Part 207

## Listing and Registration of Drugs



- New Rule proposed in 2006
- Final Rule published: August 31, 2016
- Effective date: November 29, 2016



# PET Drug Definition



Under section 121(a) of the FDA Modernization Act, a “compounded positron emission tomography drug” is a drug that “exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon emission tomographic diagnostic images” (codified as section 201(ii)(1)(A) of the act). 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.**

## Listing and Certifications of PET Drugs

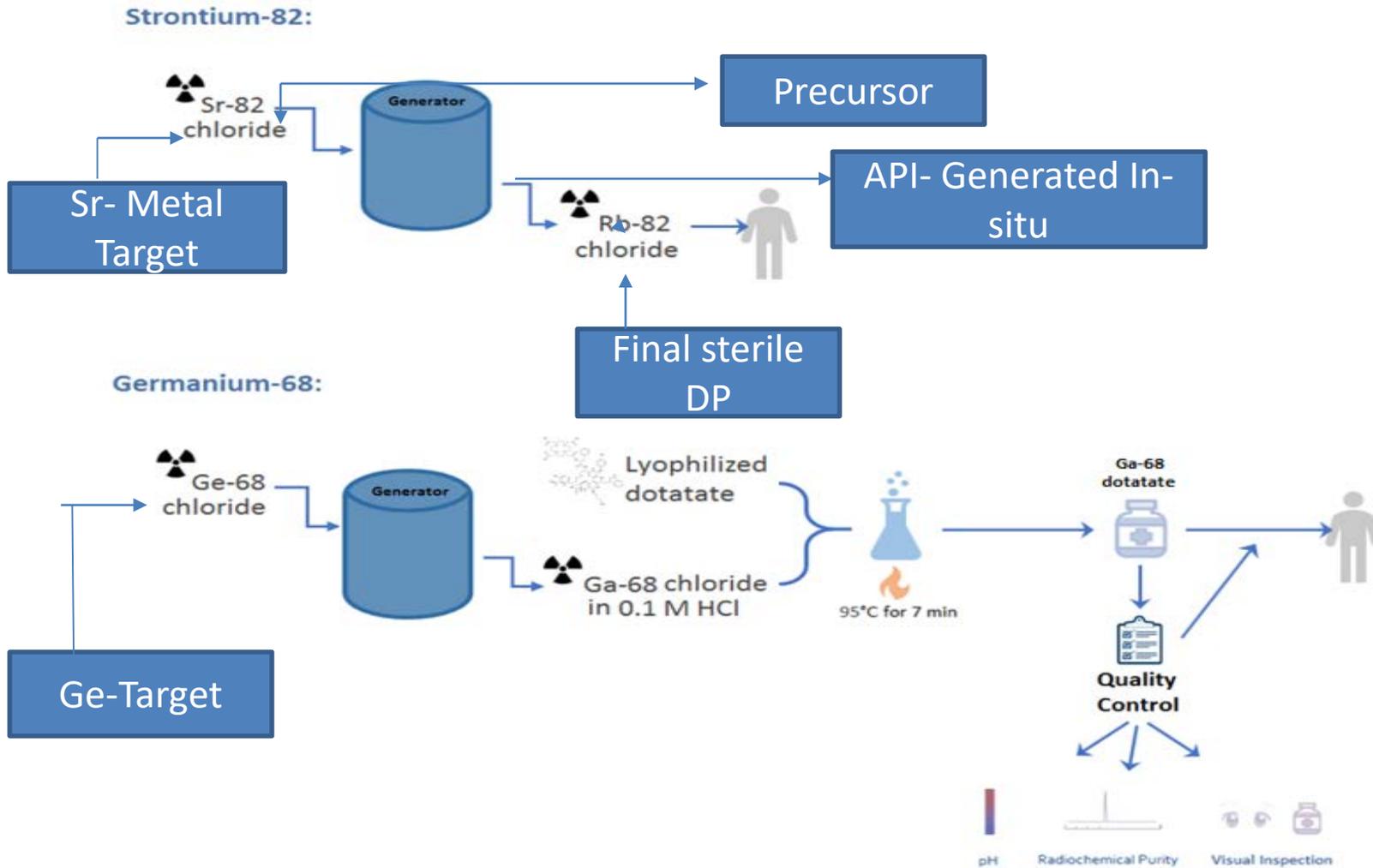
- Radioactive reagents and bulk non sterile radioactive starting materials
- Nonradioactive reagents and other chemical starting materials
- Reagents and Reagent kits
- Nuclide generators and Chemical Synthesizer manufacturers
- Final Sterile Drug Product



# PET Drugs – Listing and Registration Issues Observed

- Not all PET drugs are listed and registered
- All PET drug categories should be clearly identified as PET drugs to ensure they are regulated under 21 CFR Part 212
- Sterile vs non sterile drug components not clearly identified
- Precursors should be registered as bulk non-sterile radioactive starting materials
- Reagents and Reagent kits
- Equipment and Generator manufacturers should clearly identify and describe the listed products

# Radioactive Sr- 82 Vs Ge-68



# Establishment Registration

- Registration and listing information must be submitted to FDA electronically (FDAAA)
- Adds the registration update window (October-December) consistent with FDASIA
- Adds requirement of Unique Facility Identifier (UFI) for establishment registration (FDASIA)

# Drug Listing

- **Adds no change certification for drug listing! (§207.29(b)(3))**
  - Must be submitted October 1 - December 31
- Requires the inclusion of inactive ingredients for drug listing
- **Labeler code contact information must be update within 30 calendar days (§207.33(c)(2))**
  - Different from Establishment Registration SPL contact information
  - NDC Labeler Code Request SPL

# Drug Listing Certification

## What and When



- **All human drug document types now require annual update or no change certification**
  - A new listing or an update to an existing listing within the calendar year certifies listing for the next calendar year
  - It applies to drug listings not submitted or updated in the year
  - Blanket No Changes Certification SPL is submitted during the renewal period (October – December) each calendar year
    - Allows for certification of multiple products under one labeler code

# Listing Certification – Who

- Registered establishments have the ultimate responsibility for listing; they also have certification responsibility
- PLDs and CMOs should work together to ensure all NDCs involved in their business relationships are properly certified
- U.S. agents, importers, consultants or anyone acting as an authorized agent for a registrant may submit a product listing certification

# Listing Certification

## What Cannot be Certified?

- **Product listings with active compliance cases**
  - A full product listing SPL correcting the deficiency must be submitted
  - A compliance officer will review the updated SPL before the compliance case is closed and certification date is extended
- **Discontinued/delisted or expired listing cannot be certified**
  - A full product listing SPL must be submitted

## What Happens to Expired Listings?

- All non-certified/non-updated listings are considered expired
  - Companies are required to notify FDA of products which are no longer in commercial distribution.
- All expired listings are currently identified in the NDC Directory
- Regular review and certification of listing data is critical to FDA operations and downstream stakeholders of listing data.

# **Responses to some Data Integrity Questions from PET drug manufacturers**

# Does each workflow on our computer system need to be validated?



- Yes, a workflow, such as creation of an electronic batch record, is an intended use of a computer system to be checked through validation.
- If you validate the computer system, but you do not validate it for its intended use, you cannot know if your workflow runs correctly.

# How should access to CGMP computer systems be restricted?



- Recommend system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content.
- Recommend maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use.
- Recommend restricting the ability to alter:
  - Specifications
  - Process parameters
  - Manufacturing or testing methods

# Who should review audit trails?

## (21 CFR PART 212.20)

- Audit trails are considered part of the associated records.
- Personnel responsible for record review under CGMP should review the audit trails that capture changes to critical data...as they review the rest of the record.



# Why is FDA concerned with the use of shared login accounts for computer systems?

**A firm must: (21 CFR Part 212.50 (c) 10)**

- Exercise appropriate controls to assure that only authorized personnel make changes to computerized records
- Ensure actions are attributable to a specific individual.

# Case study: Shared logins

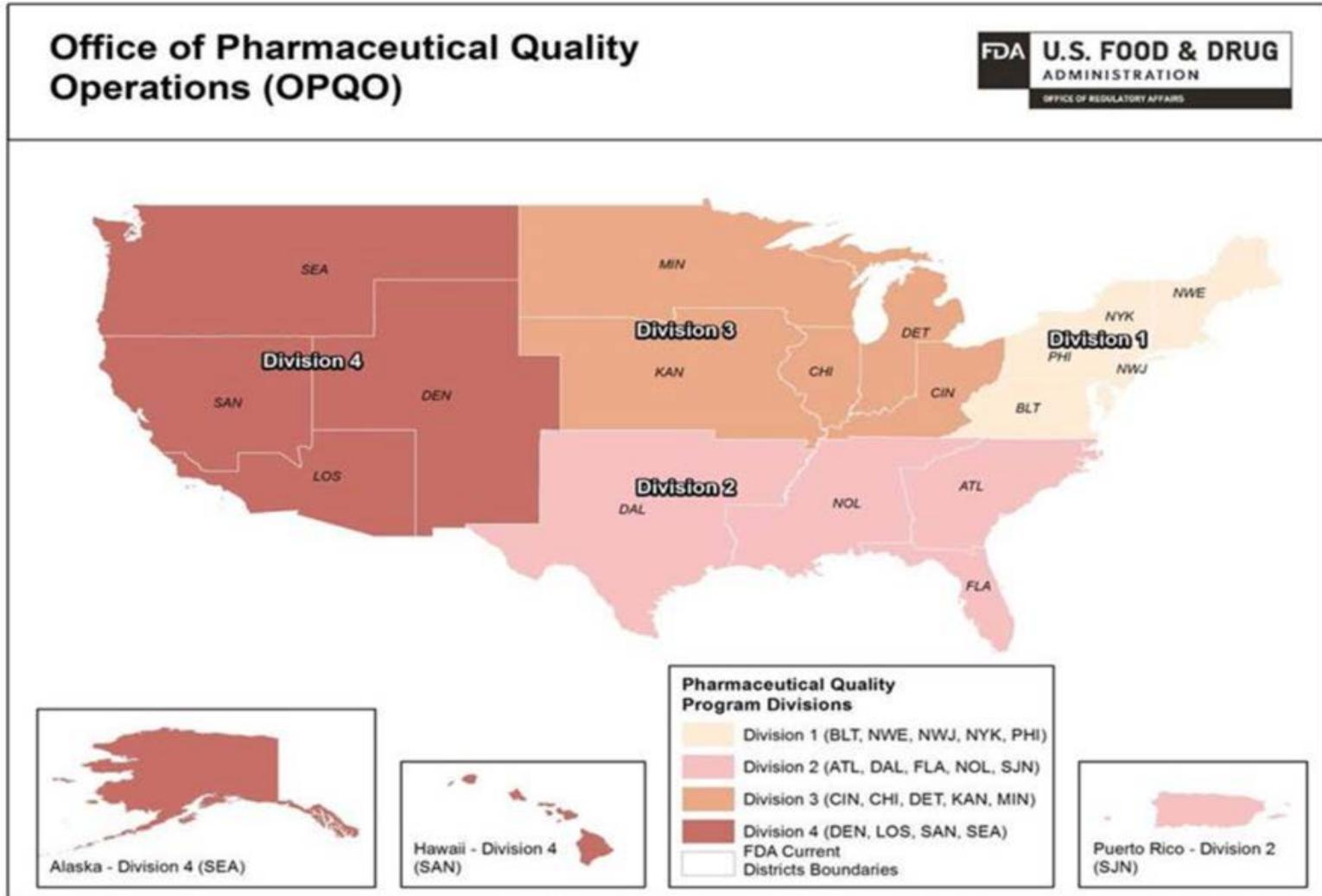
## 21 CFR Part 212.50 (c)



- No passwords were required to login.
- Anyone who accessed the system had full software administrator privileges.
- An analyst stated that **someone else had used their login** to delete and modify data.

***Recommendations:*** Provide specific details of the steps you have taken to prevent unauthorized access to your electronic data systems and to ensure that data systems retain complete, accurate, reliable, and traceable results of analyses performed.

# Office Of Regulatory Affairs(ORA) Program Divisions



Source: ORA

Prepared by Office of Regulatory Affairs (ORA) Division of Planning, Evaluation & Management (DPEM), Program Evaluation Branch, 2017

# Resolution of PET Drug Inspectional Observations



**Contact Director of Investigation Branch immediately to resolve incorrect  
FDA 483 citations with a CC: CDER PET SME  
Email format: First.lastname@fda.hhs.gov**

Office of Pharmaceutical Quality Operations	Boundaries	District Director or Program Division Director	Director of Investigations Branch	Director of Compliance Branch
Division 1	NWJ/NWE/NYK/PHI/BLT	District Director: <a href="#">Diana Amador Toro</a>	<a href="#">Nerizza Guerin</a> & <a href="#">Karyn Campbell</a>	<a href="#">Stephanie Durso</a>
Division 2	DAL/ATL/FLA/NOL/SJN	Program Division Director: <a href="#">Monica Maxwell</a>	<a href="#">Tamala Magee</a>	<a href="#">John Diehl</a>
Division 3	DET/CHI/CIN/KAN/MIN	District Director: <a href="#">Art Czabaniuk</a>	<a href="#">Jeffrey Meng</a>	<a href="#">Nicholas Lyons</a>
Division 4	LOS/DEN/SAN/SEA	District Director: <a href="#">Steven Porter</a>	<a href="#">Katherine Jacobitz</a>	<a href="#">Thomas Berry</a>

# Questions?

**For More CGMP Information...**

**Data integrity guidance document 2016 (Draft)**

**<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf>**

**PET drug web page**

**<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm>**

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