



Introduction to PET Drugs

Society of Nuclear Medicine and Molecular Imaging
(SNMMI)

**PET Drugs: A Workshop on Inspections Management and
Regulatory Considerations**

FDA White Oak Conference Center
Silver Spring, MD USA

February 21, 2020

What are the Unique Characteristics of PET Drugs?

- Short half-life means the typical shelf life is minutes to hours
- High energy radiation (511 keV) necessitates heavy shielding
- Active ingredient is present in nanogram to microgram quantities
- Each batch provides only a handful of patient doses
- Sample size for QC testing is 100% of vials in each batch
- Closed system - pre-sterilized components assembled in ISO5 environment
- Diagnostic agents used as adjuncts to therapy planning and evaluation

Practical Ramifications – PET Drugs are Safe and Low Risk

- *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 atmosphere during manufacturing
- *Diagnostic agents* only used a limited number of times in a patient

Occurrence rate of adverse reactions is negligible
Part 212 has been effective in maintaining a safe supply of PET drugs

PET Drug Workflow

Manufacturing
Regulated by FDA



**Radionuclide
Production**



**Radiochemical
Synthesis**



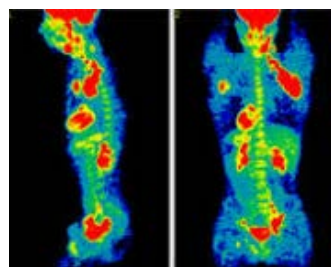
**Membrane
Filtration**



QC



Drug Product



**Injection /
PET Scan**



**Handling /
Transport**



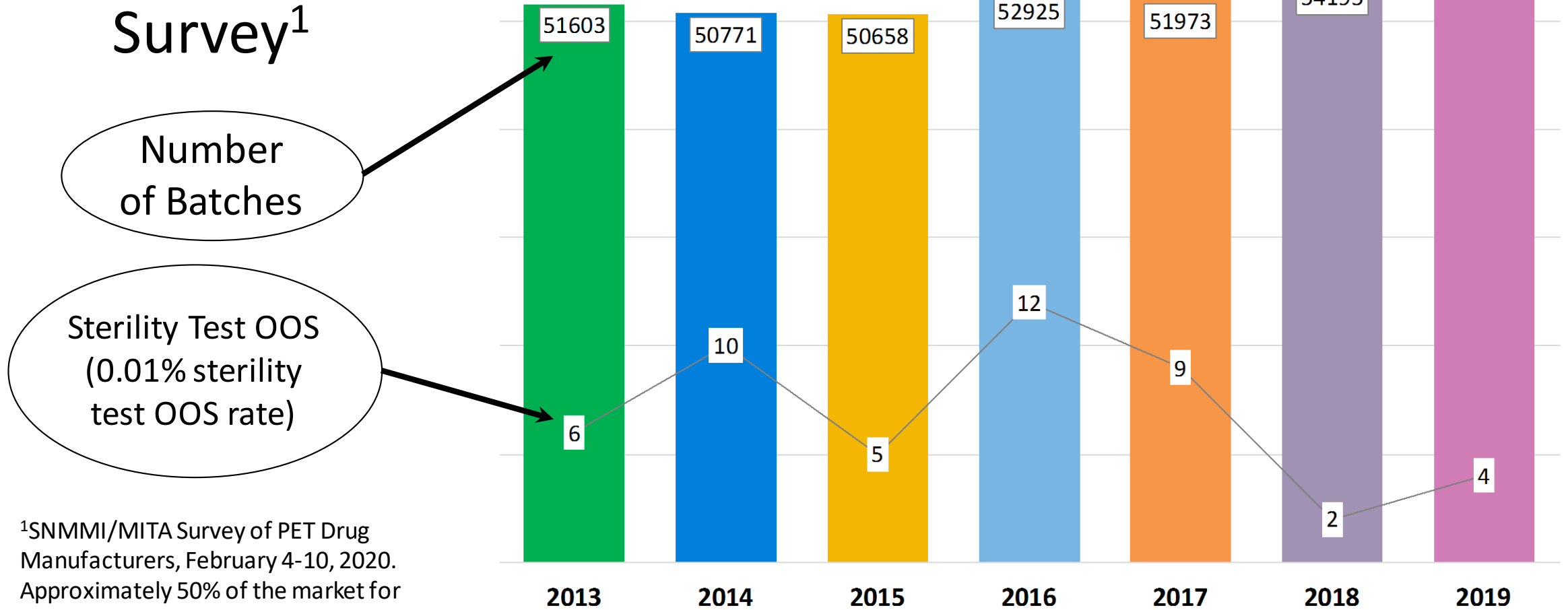
**Dose
Dispensing**



Pharmacy/medicine
Regulated by states

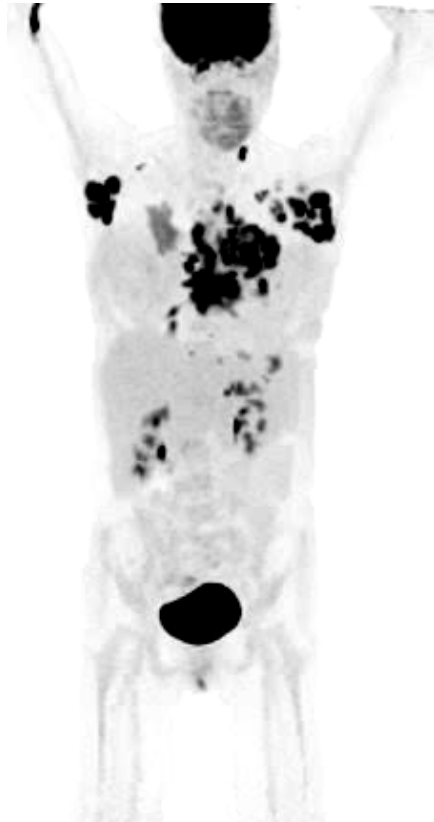
PET Drug Manufacturers Survey¹

Number of Batches and Sterility Test OOS Results



¹SNMMI/MITA Survey of PET Drug Manufacturers, February 4-10, 2020. Approximately 50% of the market for PET drugs is represented in this data.

PET Drugs Monitor Therapy



Before Therapy

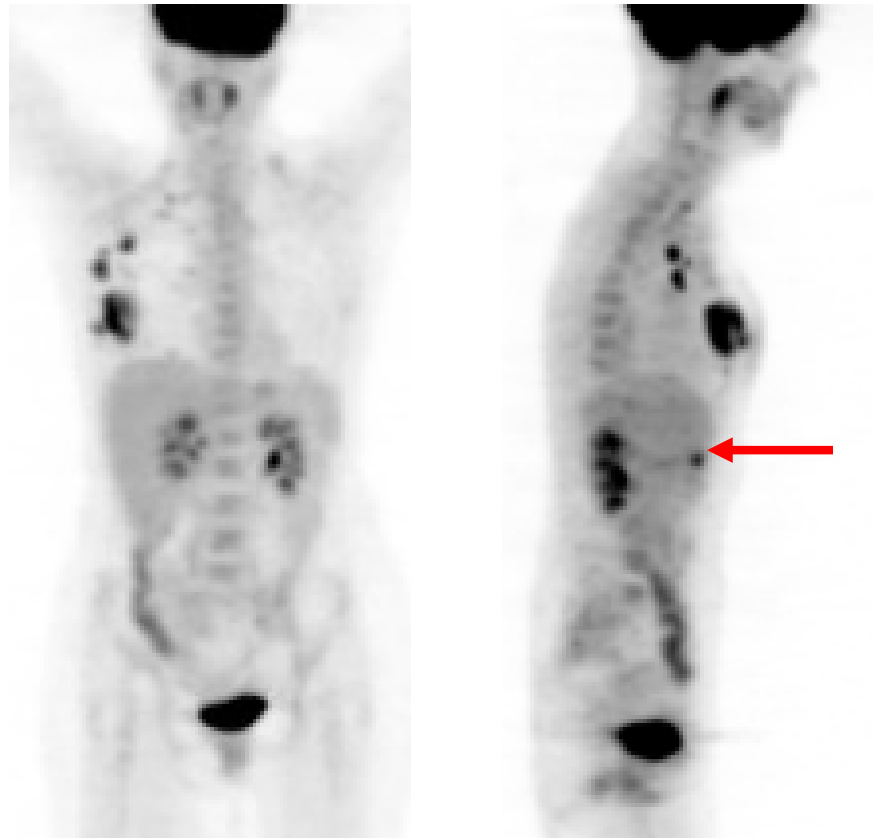


After Chemotherapy

FDG PET shows complete response in a Hodgkin's Lymphoma patient after therapy

PET Drugs Save Lives

45-year-old woman with new diagnosis of right breast cancer



FDG PET scan
detected previously
unknown metastatic
disease in liver



The Value of PET Drugs

Medical Imaging & Technology Alliance (MITA)

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- **The Society of Nuclear Medicine and Molecular Imaging (SNMMI)**, is a nonprofit scientific and professional organization that promotes the science, technology and practical application of nuclear medicine and molecular imaging. SNMMI strives to be a leader in unifying, advancing and optimizing molecular imaging, with an ultimate goal of improving human health. With 15,000 members worldwide, SNMMI represents nuclear and molecular imaging professionals, all of whom are committed to the advancement of the field.
- **The Medical Imaging & Technology Alliance (MITA)**, a division of the National Electrical Manufacturers Association (NEMA), is the leading organization and collective voice of medical imaging equipment, radiopharmaceutical manufacturers, innovators and product developers. It represents companies whose sales make up more than 90 percent of the global market for advanced imaging technologies. MITA is the Secretariat of Digital Imaging and Communications in Medicine (DICOM).
- **The World Molecular Imaging Society (WMIS)** is an international scientific educational organization dedicated to the understanding of biology and medicine through multimodal *in vivo* imaging of cellular and molecular events involved in normal and pathologic processes and utilization of quantitative molecular imaging in patient care. It was established in 2011 by integrating the Academy of Molecular Imaging and the Society for Molecular Imaging into a single streamlined society focused on advancing the field of molecular imaging (MI).



Demographics of PET Drugs

According to the FDA Orange Book as of January 8, 2020 –

- There are 12 PET drugs currently approved by the FDA in the US
- There are approximately 50 NDA/ANDA holders for PET drugs in the US
- There are more than 35 NDA/ANDA holders for FDG

According to the 2019 IMV PET and PETCT Report (referencing 2018 data) –

- There was an estimated 2,372 PET and PETCT programs in the US
- 1,316 hospital programs and 1056 non-hospital based programs of which 950 are serviced by a mobile vendor
- There were 2,086,000 PET and PETCT procedures performed of which 91% were oncology, 3% neurology, 6% cardiac

Other Demographic Data –

- There were approximately 150 PET drug manufacturing facilities in the US in 2012¹
- The 100th top selling drug in the US in 2013 was an anti-viral medication called Complera. It had revenues of about \$700 million in 2013²
- Thus, the market for all FDG from all NDA/ANDA holders at all manufacturing facilities is less than half of the 100th ranked pharmaceutical.

Bottom line: PET drug manufacturing is a cottage industry compared to pharma.

¹Ikotun, O, Clarke, B, Sunderland, J. J Nucl Med. 2012:53, May Supplement, 1085.

²Wikipedia

The New Era of PET Radiopharmaceuticals

- Advancements in Cancer
 - Neuroendocrine diagnostics - now a treatment
 - Recurrent prostate cancer agents - assists the clinician in restaging and informing treatment planning
- Advancements in Alzheimer's
 - Diagnostics for Alzheimer's – we may now see the first disease modifying treatment
- Advancements in Parkinson's
- Many additional diagnostic imaging drugs in Phase 2 and Phase 3 studies for breast cancer, cardiac conditions, etc.

Challenges/Opportunities for PET Development

- Stabilize the cost of PET manufacturing
 - **PET community collaboration with the FDA to create a regulatory framework that guards against shortages and ensures investment in a vibrant product pipeline**
 - Continues strong track record of public health and safety
 - Meets regulatory requirements and guidance
 - Can be executed in the PET economic climate
- Stabilize the reimbursements for diagnostic radiopharmaceuticals
 - **PET community collaboration with CMS on coverage, coding and payment challenges**
 - Infrastructure costs and complex supply chain
 - Labor, transportation and just-in-time delivery



The Future of PET Drugs

World Molecular Imaging Society

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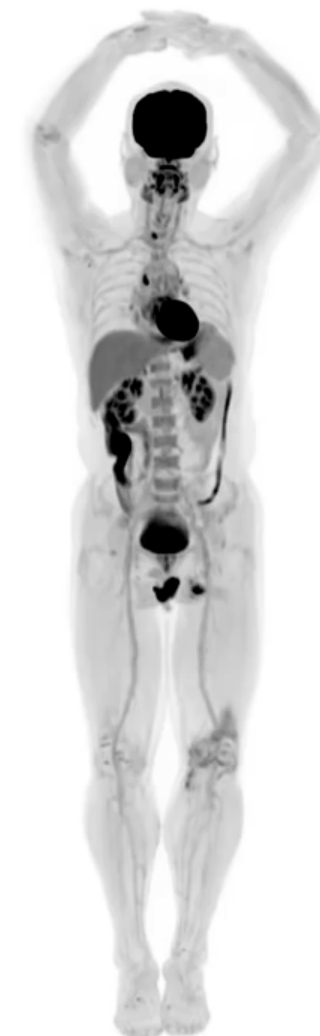
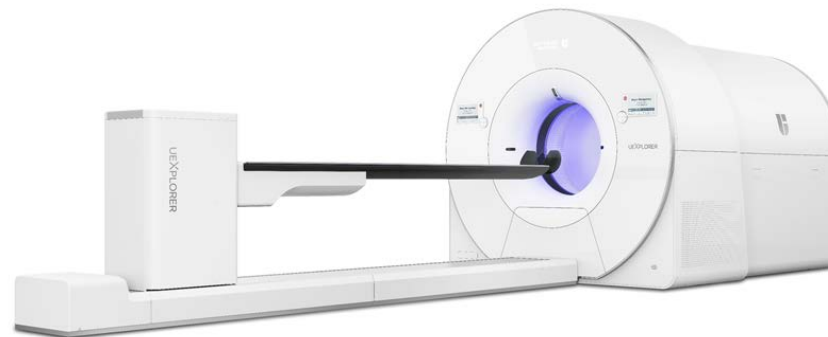
February 21, 2020

Scanner Innovations

Digital PET/CT

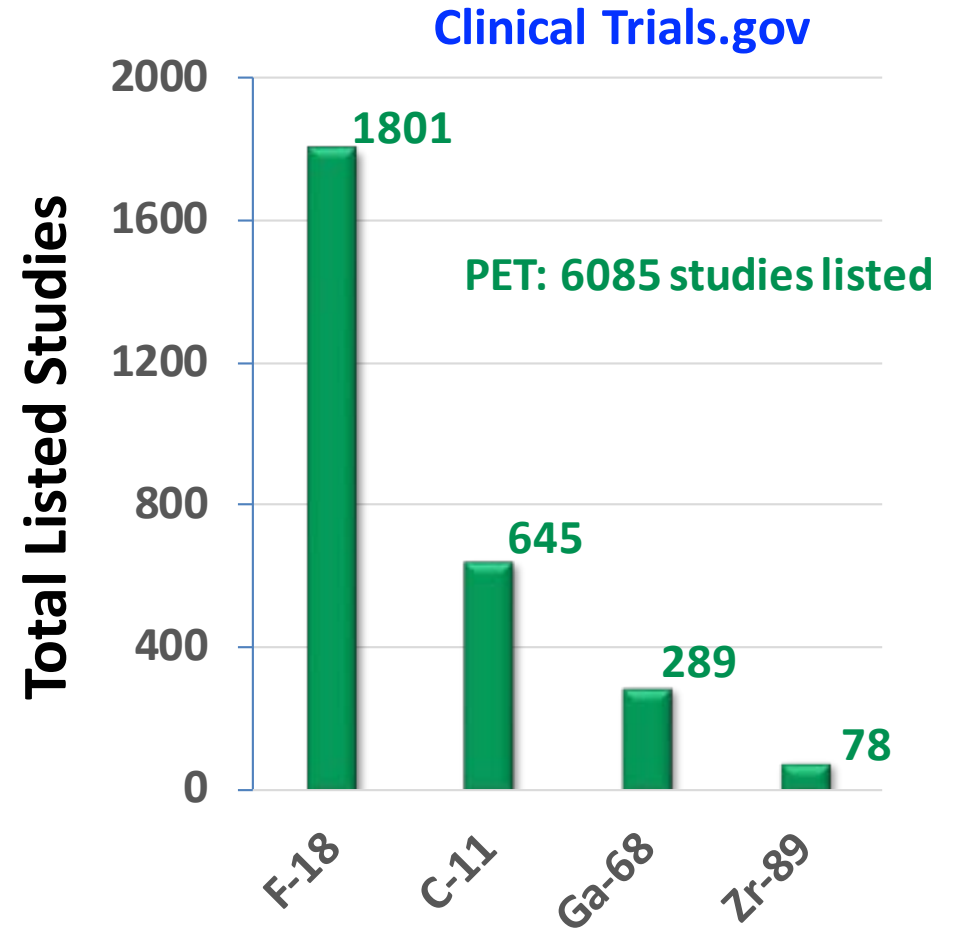
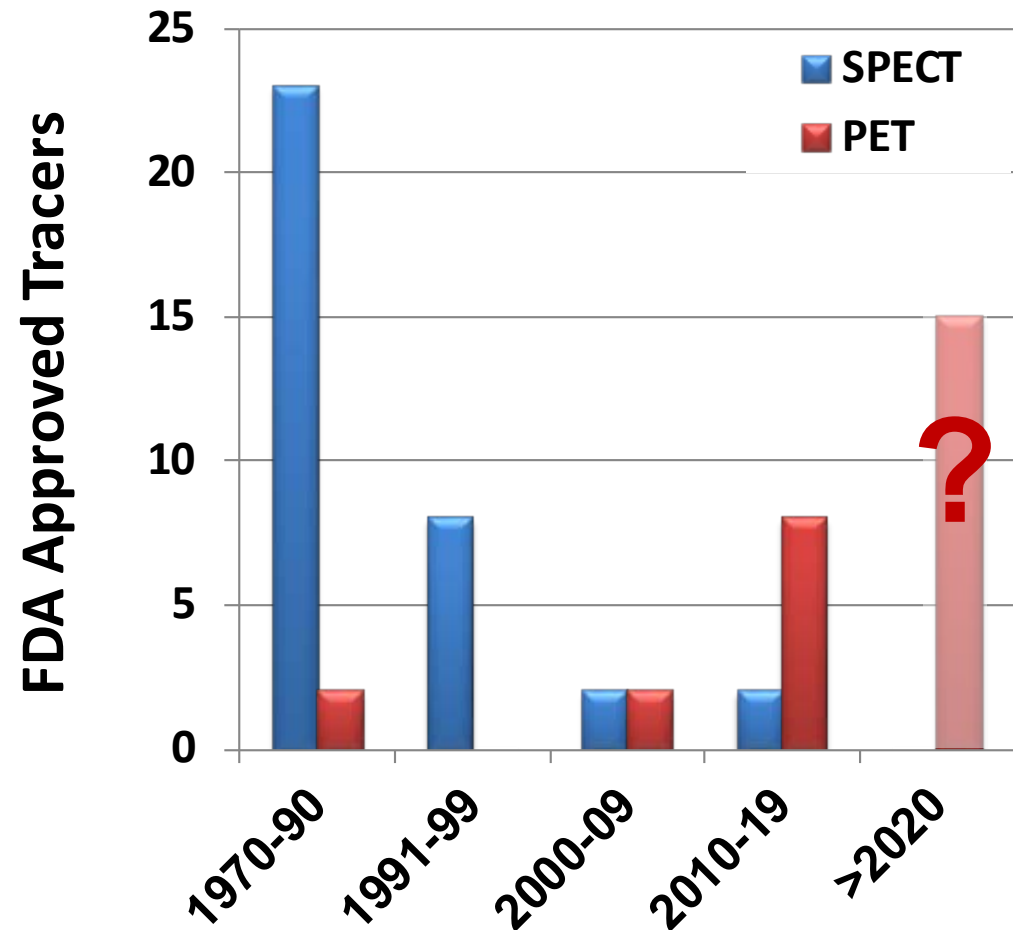


Total Body PET



Without PET drugs none of this would be possible

Approved Tracers and Future Pipeline



The future is contingent on the supply of PET drugs and adequate reimbursement

Purpose and Goals of this Workshop

Purpose: The purpose of this workshop is to provide a forum for the exchange of information and perspectives on the regulatory and compliance framework for Positron Emission Tomography (PET) drug manufacturing.

Goals:

- To discuss regulatory compliance expectations for the development and manufacturing of PET drugs and to identify pathways for drug approval, application maintenance, and inspections based on Part 212
- To share perspectives from industry, academia, investigators and regulators relative to inspectional findings and trends.
- To provide useful information on how to manage Part 212 inspections and maintain PET NDAs and ANDAs.

Manufacturing Process assessment and Pre approval Inspection

Krishna Ghosh, Ph.D.
Senior Policy Advisor
CDER/OPQ/OPMA



Disclaimer

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

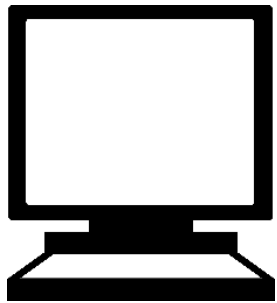
Presentation Outline

- PET Drug Regulations –A historical journey
- Quality initiatives for a better tomorrow
- NDA/ANDA applications – Integrated Team Reviews
- Manufacturing Process Assessment and Facility –
 - 356 h review and Facility assessments for PET ANDA/NDA
 - Listing and registration issues
 - Manufacturing Process –IR requests
 - PAI Inspection, objectives and Withholds- Deficiencies
 - FDA 483 Responses and deficiencies from PAI inspections
 - EIR Review and RAI Letter
 - Post CR Facility action letter
 - FMD 145 Letter and Redacted EIR
- Review some case Studies

Pharmaceutical Quality



A quality product of any kind consistently meets the expectations of the user.



Drugs are no different.



Patients expect safe and effective medicine with every dose they take.

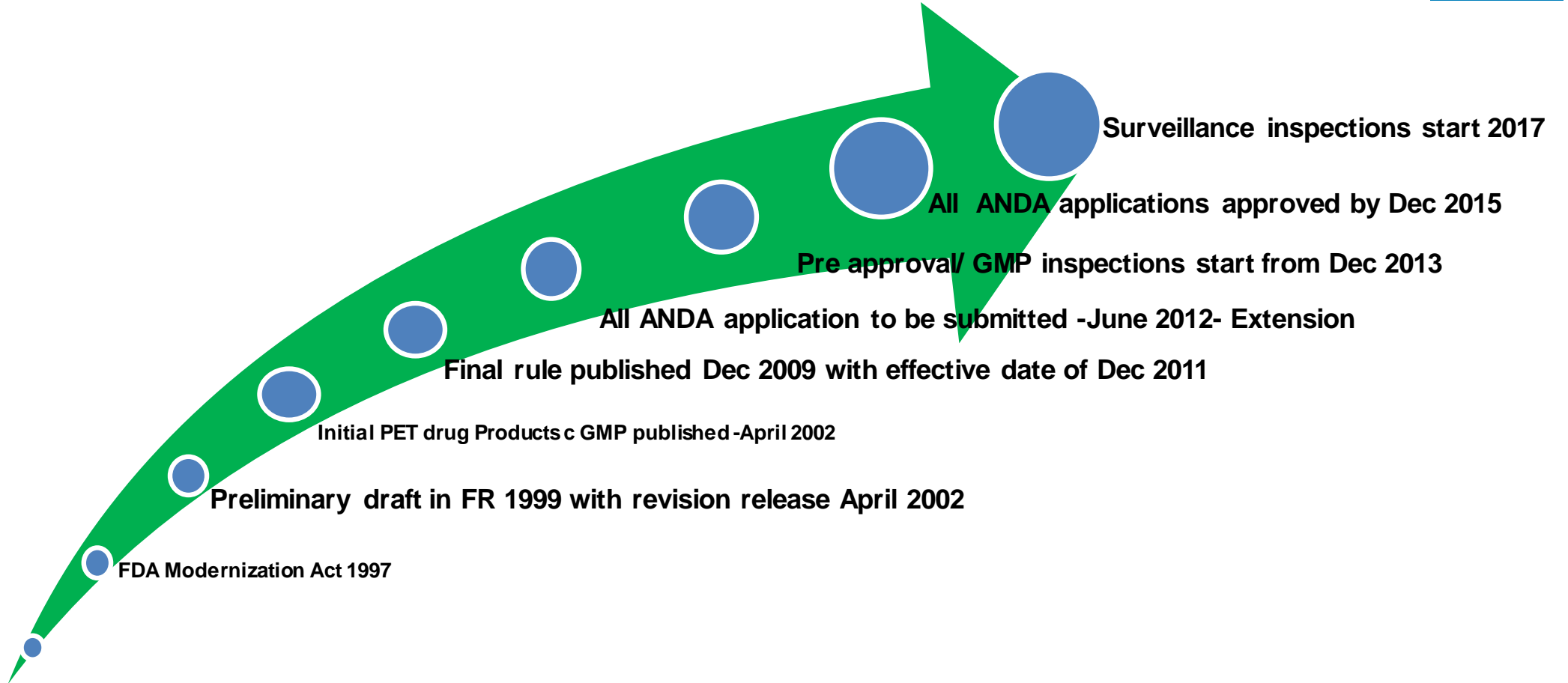


Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

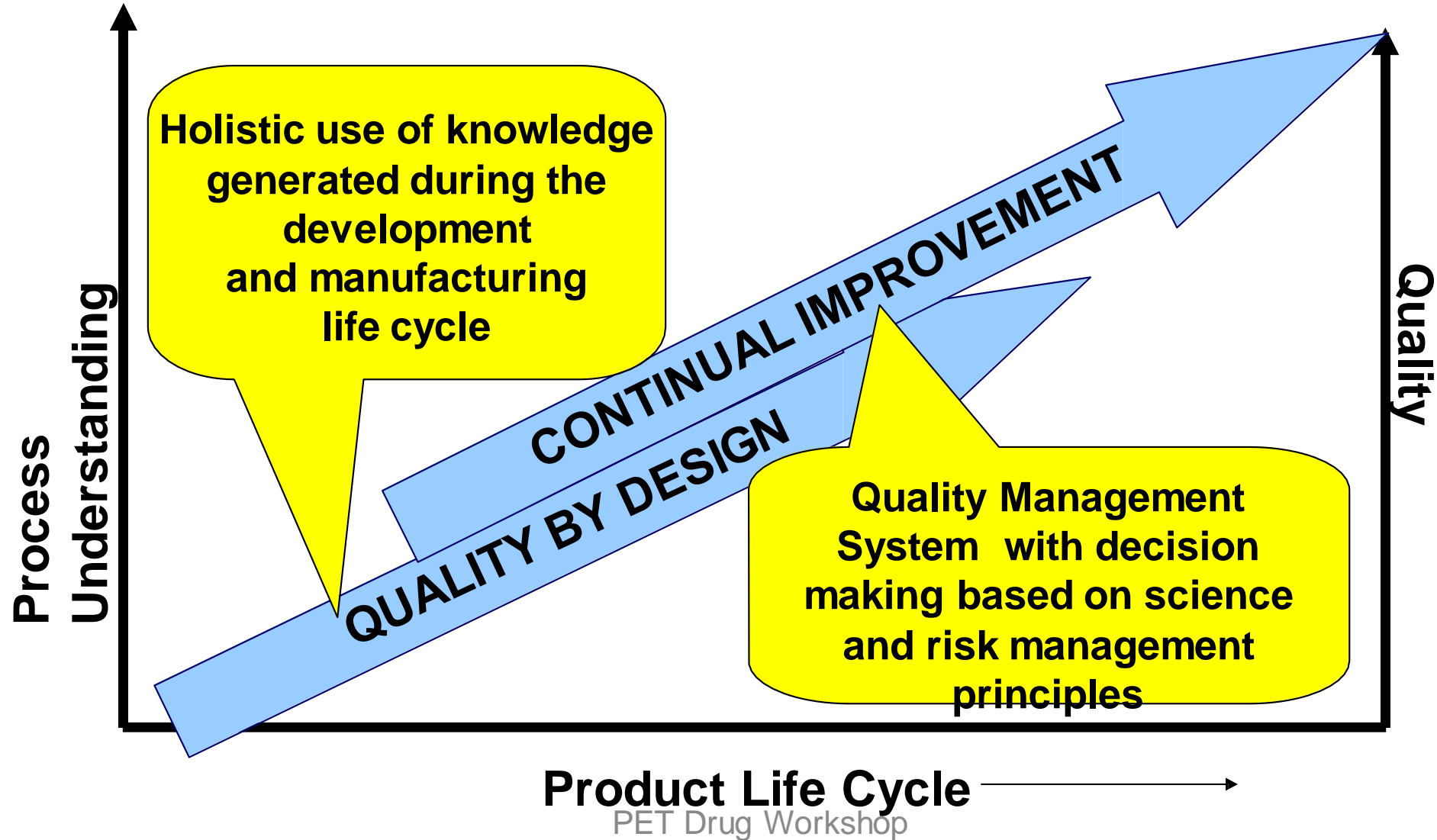
A close-up photograph showing a hand holding an orange pill bottle, pouring several white, oval-shaped pills into the palm of another hand. The background is softly blurred, focusing attention on the action of dispensing medication.

**It is what gives patients confidence
in their *next* dose of medicine.**

Genesis of 21 CFR Part 212 PET Regulations – Historical Journey



Quality is driven by science throughout the product life cycle



Product Life Cycle
PET Drug Workshop

Looking Forward..



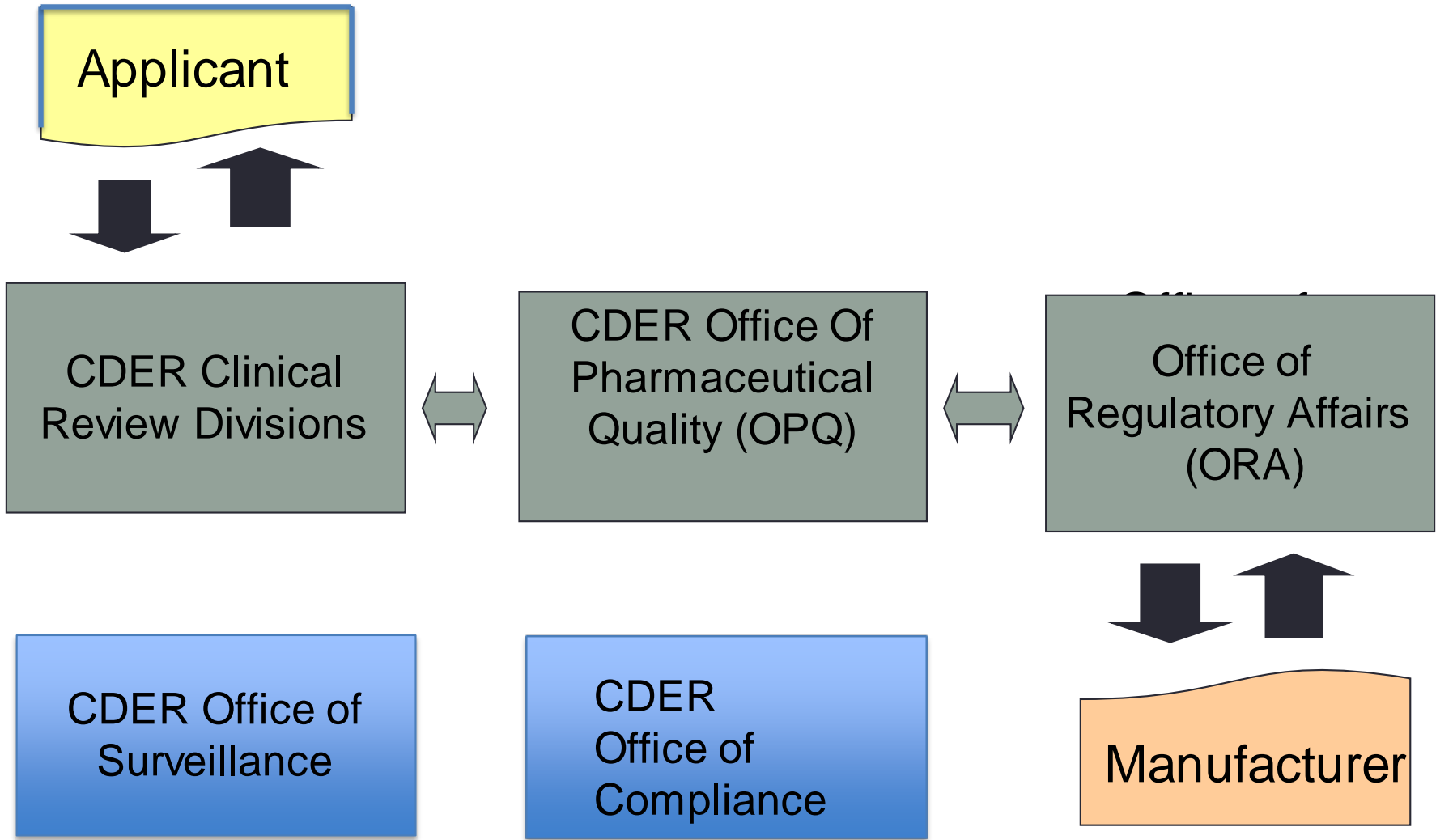
- Leverage past knowledge and encourage a **preventive action culture**
- Improve quality concepts by enhanced monitoring and review (e.g. **deviations, root cause analysis, robust investigations, environmental monitoring and controls, data evaluation, enhanced change control measures**) and
- Adoption of new tools, technologies, manufacturing control strategies and Quality concepts with complex PET drugs**

We need to improve and transform by being flexibleto help to implement a flexible regulatory framework



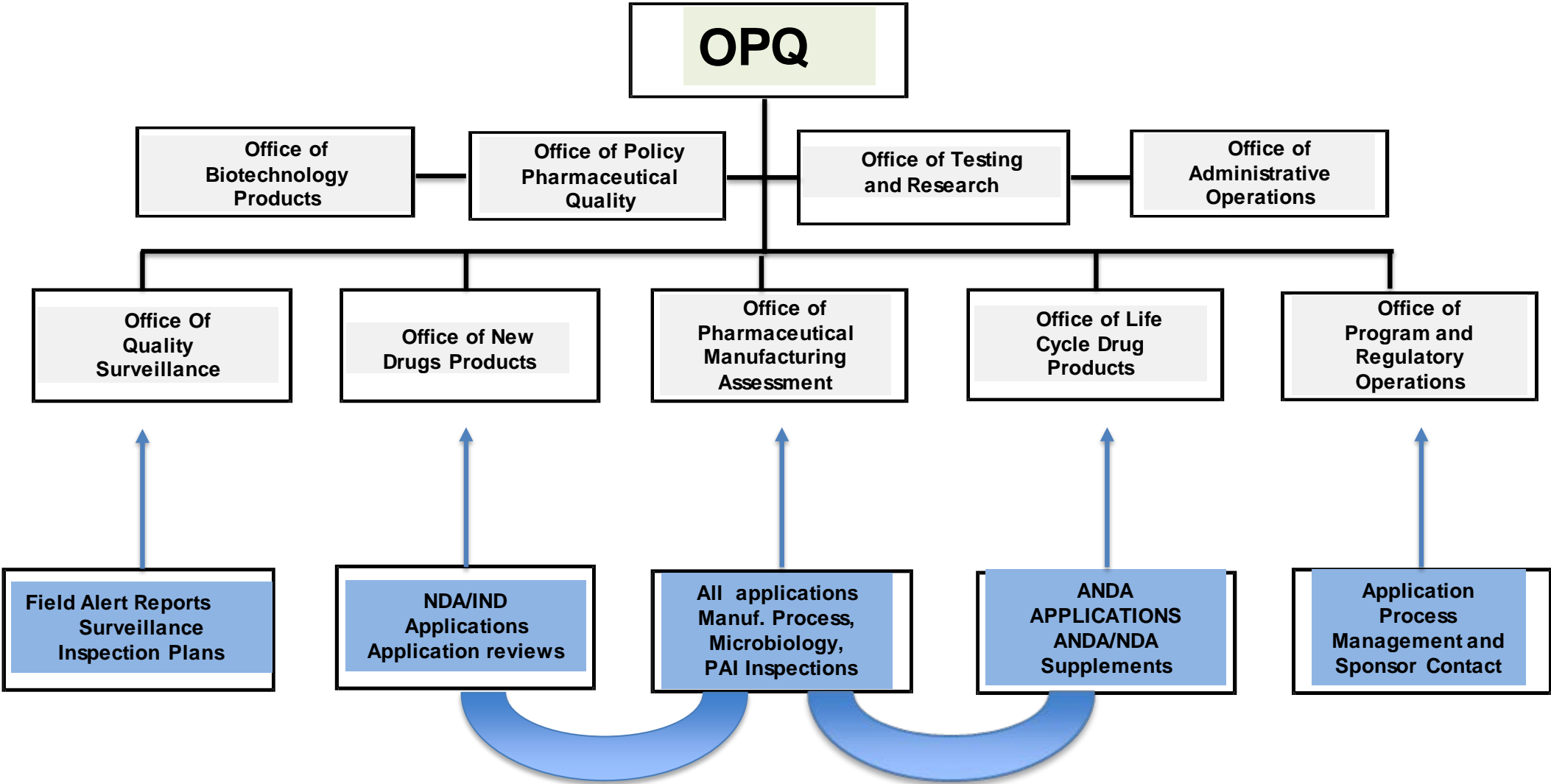


Application Approval Process





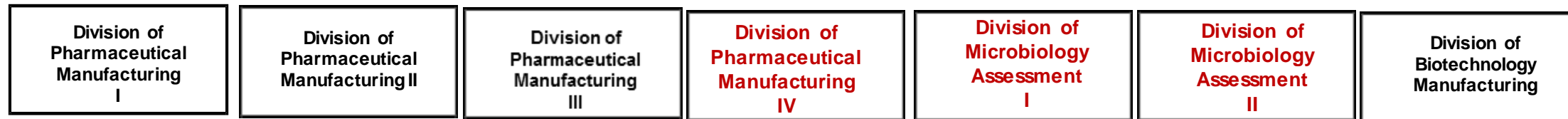
Office of Pharmaceutical Quality



Office of Pharmaceutical Manufacturing Assessment



OPMA



- ***Oversees the scientific assessment and quality evaluation of pharmaceutical manufacturing including process and facilities***
- ***Advises Center for Drug Evaluation and Research (CDER) and other Centers on scientific and regulatory issues associated with manufacturing assessment, and inspectional and facilities activities related to pre-approval and post-approval inspections.***

Management and Type of Drug Inspections



Pre-Approval (PAI) - OPMA and ORA

- New products (NDA and ANDA)
- Changes to a manufacturing process and facility- Supplements

Post-Approval - OPMA and ORA

Audit for changes in production and control practices after drug approval

- Ensuring approved products are meeting their quality objectives
- Address residual risks identified during application review

Routine/Surveillance

Periodic evaluation of a regulated facility- **ORA, OS, OC**

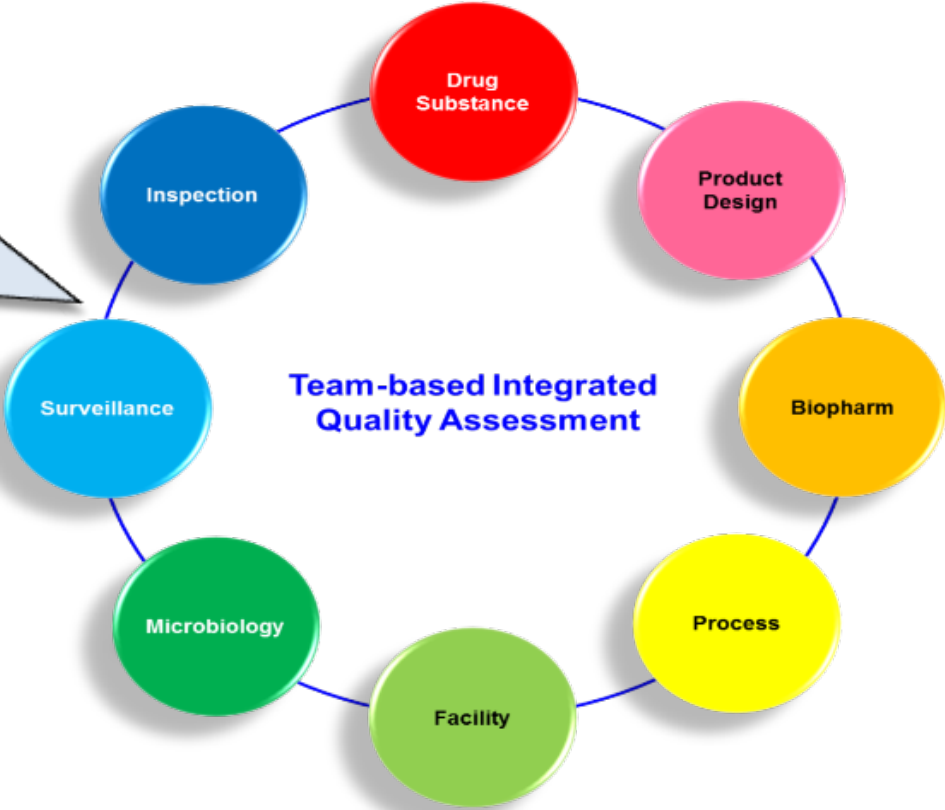
For Cause- Evidence of non-compliance- **OC, ORA**



Team-based Integrated Quality Assessment executed by OPQ (CMC Review) One Quality Voice



- Inclusive of drug substance, drug product, and manufacturing (process, facilities, microbiology), and maximizes each team member's expertise



Science- and Risk-Based approach that is patient-focused

PET Drug Definition

According to 21 CFR Part 212 *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 product is included under “PET Drug”***

Facility Assessment

356h Form Expectations



- List all the sites in the 356h form –(e.g.-Precursors, synthesizers, Reagent Kits, generators, non radioactive components, cassettes)
- Describe in details the roles and responsibilities of each site
- Ensure FEI numbers are included for all sites
- Ensure all facilities are registered with FDA in eDRLS
- List all external sterility and microbiological testing labs by specifying sterility test or Microbiological tests
- Confirm readiness for inspection for the facilities prior to submission of applications

PET Drugs – Listing and Registration Issues

- Not all PET drug manufacturing sites (precursors, kits, generator, synthesizers...) are listed and sites registered
- All categories of PET drugs not clearly identified during registration 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 starting materials
- Reagents and Reagent kits for DP synthesis
- Synthesizer and Generator manufacturers should clearly identify and describe the listed products

Manufacturing Process Deficiencies (Common Information Requests)



- Manufacturing flow charts- Missing Unit process
- Lack of supportive studies for proposed process control parameters (duration, temperature ranges, pressures etc.)
- Detailed unit process descriptions
- Extractable and leachable studies (e.g. -transfer tubes, connectors, equipment fittings used during manufacturing etc.)
- In-depth description of in-process controls for manufacturing (environmental, microbiology and chemistry)
- Batch records – Lacking critical process control checks, minimum radioactive yields, operational controls
- Automated synthesis sequences controls for critical steps
- Column conditioning and use of various types of columns with details
- Final QA checks and batch release sign off

Pre- Approval Inspections



Risk-based facility assessment

Facility Risks

- Compliance history and current status
- Competency of the firm to manufacture the product under evaluation
- FDA 483 Observational Trends

Process Risk- Are there risks associated with the execution of manufacturing process design and control strategy?

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

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

Radiopharmaceuticals/ PET Drugs

Integrated Manufacturing Process Assessment and PAI Inspection

Can the manufacturing process yield material with the target CQAs?

Process Design and
Control

Process Implementation
and Control

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

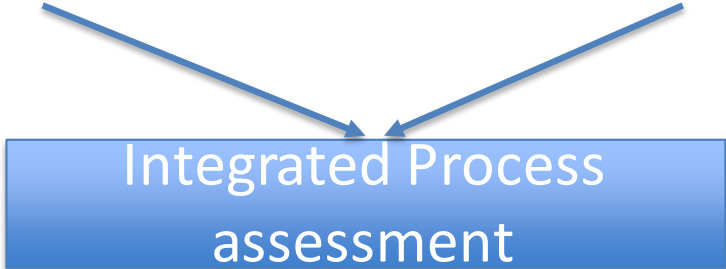
Assessment: Application vs. PAI

	Application Assessment	PAI EIR Assessment
What assessment standards do we apply?	Scientific principles and industry standards, so as to meet 314.125(b)(1) and 127(a)(1)	Objectives laid out in the PET Drug PAI Compliance Program Guidance Manual, applicable standards and PET CGMP regulations

A Pre-Approval inspection has formal goals to ensure that all critical “on-site information” is evaluated.

Assessment: Application vs. PAI

	Manufacturing Process Application Assessment	PAI EIR Assessment
What do we assess?	Submission documents and IR responses	Information that is not part of the Submission: <ul style="list-style-type: none"> • Inspection narrative (EIR) and exhibits including test results, equipment, procedures, and personnel • Firm’s response to any 483 Observations and RAI responses



A target icon with three arrows hitting the bullseye, symbolizing focus or goals.

CDER and ORA collaboration

PET PAI Inspections

- A knowledge transfer memo is provided to ORA investigator from reviewers based on application review if SME not participating during PAI inspection
- Reviewer concerns are discussed with ORA investigators in advance of the inspection
- OPMA/SME is in touch with ORA through out the inspection process if not participating
- Investigators try to cover items based on priority but also have the flexibility to follow an major observation what they find



Common PAI Media Fill Deficiencies

- Media fills did not simulate production
 - Bulk product vial hold: not the worst case
 - Product dilution step
 - Manufacturing process flow
 - Withdrawal of QC samples not simulated
 - Missing positive control or negative control
 - Growth media not qualified
- Media does not come into contact with all interior surface
- Not all production personnel participate in media fills

Common deficiencies in Analytical Lab



1. System suitability
 - GC and HPLC: Inadequate and non supportable acceptance criteria
 - Lack of documentation on daily system suitability
2. Lack of Analytical Method Validations for non USP methods
3. Analytical Method verifications lacking for USP methods executed on individual equipment
4. Control of reagents and reference standards
 - No expiration dates for reference standards, reagents and formulated solution,
5. Manual Integrations of chromatograms/ Lack of controls
6. Access controls of analytical and manufacturing equipment
7. Dose calibrator not calibrated for the linearity range being used

Expectations- FDA 483 Responses



- Have you addressed the deficiency adequately?
 - Provided sufficient technical analysis, scientific justifications
 - Identify the root cause and execute corrective actions
 - Provide any investigation reports on technical issues to address the gap
 - Provide data to confirm that corrective action was completed
- Have you addressed any underlying quality issues?
 - Procedural and oversight gaps; adequate scope
- Do you have all the supportive evidence document and information needed?
 - Submit any study report, root cause investigation report , raw data from studies or new SOP to confirm the issue is resolved
 - Have you submitted all the evidence documents in your response?



Resolving Inspectional Deficiencies

- Sometimes the firm's response is not adequate
 - Didn't understand or address the underlying deficiency or issue
 - Didn't provide all the details or supportive documents
- A "Request for Additional Information" (RAI) is issued to the site to resolve the deficiencies.
 - Can be issued for any inspections with initial NAI, VAI OR OAI PAI inspections

PAI Facility Withhold

- Significant inspectional findings not meeting the requirements of Objective 1, 2 or 3- OAI classification and a product specific PAI Withhold
- Reinspection may be required for verification of corrective actions in the next review cycle



OPMA Post Application Action Letter



- This letter is issued by OPMA after the CR letter is issued to the applicant
- The purpose of a Post- Action Letter is to communicate to the firm the ***reason for the facility withhold recommendation*** – since this is not communicated in the CRL to the applicant
- **Official closure of Inspection**
 - Issuance of FMD 145 Letter and Redacted EIR to the inspected firm



OPMA POST- APPLICATION ACTION LETTER

- OPMA USE ONLY:
- Check here if 483 issued
 - Check here if RAI Letter issued
 - Check here if Expedited

DATE:

FROM: [Enter Assessor Name]

SUBJECT: Review of Pre-Approval Inspectional Findings at [NAME OF FACILITY] in support of [APPLICATION(S), PRODUCT(S)]STRENGTH(S)]

THROUGH: [BRANCH CHIEF NAME or DESIGNEE]

TO: [FACILITY POC INFO FROM EIR]
[FEI #]

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has completed their assessment of the Establishment Inspection Report for the subject facility. Pre-Approval Inspection coverage for the subject pending application(s) was provided during the inspection.

Following review of the inspection and your written responses, OPMA does not consider your facility ready to support commercial operations of the subject drug application(s). The remaining deficiencies outlined on the following page(s) should be addressed. Corrective actions, quality system improvements, and supportive studies completed to address the deficiency(ies) will be evaluated during the next review cycle and may be verified during a future on-site evaluation of the facility.

Provide your written response to the deficiency(ies) to the email address below. If you have questions regarding this Memorandum, please contact: CDERPAIProgram@fda.hhs.gov.

Sincerely,



Regulatory Business Process Manager
CDER/OPQ/OPRO



PAI Review Case Study 1

Application indicated that commercial production of the subject PET drug product is performed in room A. Media fill simulations were performed in B and C. The firm has multiple hot cells and LAF enclosures and plans to use them all for commercial manufacturing. PAI demonstration batch was performed in room A and C observed during PAI inspection

What did we observe?

- The site map, room and area classification did not match with application submission
- Aseptic LFH and hot cell cleaning practices were not the same for all the rooms
- EM action levels were not adequately investigated for each unit
- An operator with no aseptic training records performed media fill

Conclusion:

- Media fill needs to be conducted for the exact commercial process flow with trained operators and all equipment used for commercial product must be qualified for media fill
- Quality procedures require revisions
- Inadequate investigations require further evaluations and adequate corrective actions



PAI Review Case Study 2



The sponsor manufactured a precursor for an NME in small scales and performed development studies for the PET drug. PET drugs were manufactured for development batches and IND batches by a commercial PET facility. A contract manufacturer was engaged by the sponsor for commercial manufacturing of the precursor but only one batch was manufactured by the vendor (not the same chemical process) which was used for the 3 exhibit batches.

What did we observe during PAI inspection?

- Precursor was accepted on Certificate of Analysis only
- Reference standard accepted and used with no incoming testing and characterization
- No risk assessment performed on the critical vendor/ no mitigation plans available
- No material qualification records for the precursor as records of vendor qualification

Conclusion:

Incoming acceptance testing and vendor qualification for the precursor/Reference standard inadequate

Recent Experience with CGMP Surveillance Inspections of Commercial PET Manufacturers

Rick Friedman

Deputy Director, Office of Manufacturing Quality

CDER Office of Compliance

Overview

- Recent CGMP Surveillance Inspection Outcomes
- Recent FAR/Defect Trends
- Significant Inspection Findings
 - Examples
- General Principles for Injections
- Summary

DISCLAIMER

The views and opinions expressed in this presentation are those of the author and do not necessarily represent the official policy or position of the Food and Drug Administration

Review of CGMP Surveillance Inspections

- Issuance of FDA Form 483 (listing of potential PET CGMP violations) by ORA investigator
 - *ORA makes initial classification of the inspection (NAI, VAI, OAI)*
 - *Inspectional findings are reviewed by supervisor and, if applicable, by ORA Division Compliance Branch*
- OAI inspection recommendations reviewed by CDER Office of Compliance
 - *Review includes input from compliance staff knowledgeable in PET drug manufacture and familiar with past PET compliance cases*
 - *Review often includes input and consultation with CDER microbiologists and chemists*

PET Drug CGMP Surveillance Inspection Outcomes

January 2019 – January 2020 (1 year)

Total CGMP Inspections with Final Classification	26	
No Action Indicated (NAI) Classification	10	39%
Voluntary Action Indicated (VAI) Classification	12	46%
Official Action Indicated (OAI) Classification	4	15%

June 2018 – January 2020 (18 months)

Total CGMP Inspections with Final Classification	45	
No Action Indicated (NAI) Classification	17	37%
Voluntary Action Indicated (VAI) Classification	24	53%
Official Action Indicated (OAI) Classification	4	9%

OAI Actions

January 2018 – January 2020

Regulatory Meetings	3
Warning Letters (WL)	3
Total Number of Actions	6

Of note:

- All three **Warning Letters** were issued to non-academic, non-hospital producers. (One WL also included a follow-up F2F meeting.)
- Two of the **Regulatory Meetings** were held with producers in hospitals / medical centers.
- The other regulatory meeting involved very significant sterility assurance issues, but the firm had not yet distributed product.

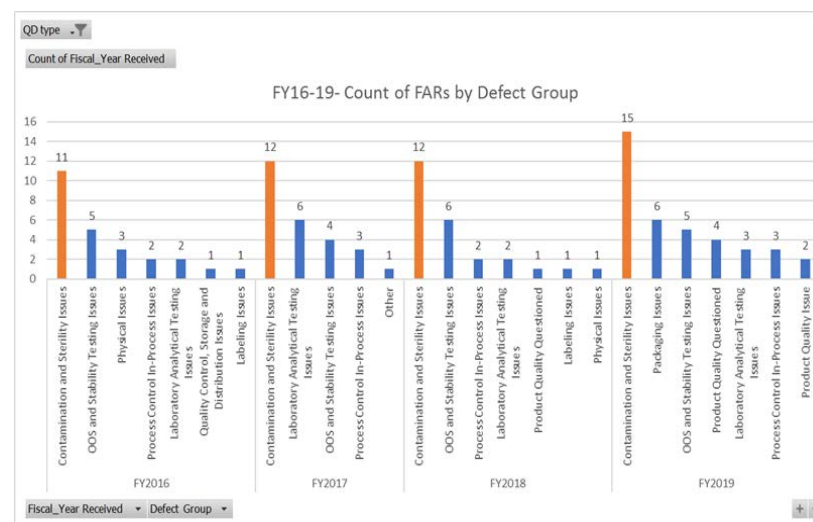
OAI Actions

January 2018 – January 2020

- Each of the OAI cases involved a failure to maintain a suitable environment for aseptic processing operations.
- 21 CFR 212.30 (a):
PET drug manufacturers “must provide adequate facilities to ensure the orderly handling of materials and equipment, the prevention of mix-ups, and 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.”

Recent FAR Trends

- 4 years of Field Alert Reports (FARs).
- 27% of current commercial PET producers (n=141) submitted reports for contamination/potential contamination in this 4 year period.
- “Contamination and Sterility Issues” is by far the most common defect reporting category. (50/118 reports)
 - *Inspections have revealed a substantial number of additional sterility failures that were not reported as FARs.*



OAI Inspection Findings

Sterility Failures & ISO Class 5 Recoveries

- Sterility Test Failures:
 - 4/6 firms had sterility test failures within the past 4 years
 - 3/4 with sterility failures had multiple failures within the past 4 years
 - 1 firm without a reported sterility test failure had significant deviations that compromised the reliability of sterility test results
- ISO Class 5 Recoveries:
 - 4/6 firms had a significant adverse trend of mold and spore-forming bacteria recoveries in their ISO Class 5 areas
 - 5/6 firms failed to take appropriate actions in a timely manner to prevent the persistence of the ISO 5 environmental control issues
 - Inspection package did not contain EM data for the 6th firm.

Examples of Facility and Equipment Conditions

Facility Conditions

- cracked, damaged floors
- pipes leaking into the ISO Class 7 cleanroom area in which aseptic processing occurs
- spots on ceiling in room adjacent to cleanroom, contamination is consistent with visible mold growth
- black stains on floor under entry door to ISO Class 7 room and stains (unknown source) on floor beneath ISO Class 5 aseptic workstation

Equipment Conditions

- hot cell contained wooden boards and bench paper
- hole in roof of negatively pressurized hot cell; dust and residue on top of hot cell
- rust inside aseptic processing area of hot cell
- 1" diameter holes on each side of laminar airflow workstation; brown residue observed in several places (including contact surfaces)
- large gap of 24 square inches in ceiling of workstation with mechanical parts visible; unshielded fluorescent bulb
- Inadequate environmental conditions in hood. *Multiple sterility failures* attributed to insufficient disinfection of materials and hood with solely isopropyl alcohol. (Firm changed to use of sporicidal on daily basis to disinfect ISO 5 areas and materials.)

Example: Commercial PET Facility

- **Sterility failure:** Brevibacillus, *sp.*
- Unable to identify root cause. Not easily discerned as firm did not have IDs for several ISO 5 EM recoveries (personnel and ISO 5 surfaces) occurring within weeks of the sterility failure.
 - *Microbial identification data can be critical in determining the route of contamination (i.e., root cause) and taking appropriate corrective actions to prevent further non-sterility.*
- Firm had persistent issue of excessive findings of sporeformers. Adverse trends were identified in environmental and personnel monitoring samples taken from the ISO 5 areas.
 - *Isolates from the samples frequently included gram positive sporeforming bacteria (e.g., Bacillus, *spp.*)*
 - *Also, during the semi-annual certifications conducted by a third party, sporeforming fungi were repeatedly identified in the ISO 8 area of the hot cell immediately adjacent to the ISO 5 area.*

What We've Learned

Sterility Failures



- It is important to be vigilant to environmental monitoring data and adverse trends.
- Some facilities are experiencing recurring sterility failures, while some have a history of little or no sterility failures.
- Some sterility test failure investigations have assumed that the results were “false positives” without clearly establishing that laboratory error was the root cause.
 - USP <71> *Sterility Tests* not consistently followed
- Inspectional findings and FARS data indicate that non-sterility investigations are an area that can improve in the industry.
- Contamination can occur in these aseptic operations, although the most significant hazard to the product container is typically only:
 - a. pre-assembly of vial components, and
 - b. connections/puncture of a septum
- FAR sterility test failure investigation trends include:
 - A probable root cause is only identified in approximately 30% of the cases.
 - Bacillus, spp. (sporeforming microbes) were isolated in 53% of the failures.
 - In vast majority of cases, operator error or poor aseptic technique named as possible root cause

Getting to Root Cause...

“ Unless the routes and sources of contamination are determined, the direction in which efforts should be made to contain it will be unknown. ”



Whyte, 1982

General Principles for Injections

- All injectable drug products are expected to be sterile at the time of release.
 - *The sterility requirement is derived from the knowledge that product non-sterility represents an intolerable risk to patients.*
 - *Numerous journal papers cite **incidental contamination** of injections with virulent microbes (e.g., due to poor hygiene; contaminated connectors) to be the cause of severe infections.*
 - *While the risk posed to patients by a non-sterile units may be lessened by short half-lives and expiry periods of some PET products, the timelines before administration do not eliminate risk.*
- The importance of injectable sterility is the public health basis for the PET Regulation 212.70(3)(e) requirement to “immediately notify” all facilities that received a product that failed the sterility test.

Summary

- PET manufacturers play a critical role in providing powerful diagnostic agents to the healthcare system, and use of robust manufacturing practices to produce these drugs is integral to that role.
- Implementation of PET CGMPs over the last decade has provided substantial insights into process hazards and good practices.
- As with all injectable drug products, sterility is a critical attribute. It is important to promptly address facility and environmental conditions that may pose a significant hazard to product sterility.
- The industry has made major strides in implementing 21 CFR 212, and we look forward to continued information-sharing and progress to optimize robustness throughout the industry.



Inspections

Sally W. Schwarz, RPh, MS
Professor of Radiology
Washington University School of Medicine in St. Louis

**PET Drugs: A Workshop on Inspections Management and
Regulatory Considerations**

FDA White Oak Conference Center
Silver Spring, MD USA
February 21, 2020

Overview

- Historical regulatory overview
- 21 CFR Part 212 CGMP for PET
- Investigational PET Drugs, IND and RDRC
- Inspection Findings (Observations) vs Regulatory Requirements
- Need for inspections to be performed against Part 212 and the PET Guidance documents

US Food & Drug Administration Modernization Act (FDAMA) 1997



US Food & Drug Modernization Act (FDAMA) required establishment of PET Radiopharmaceutical (RP) Good Manufacturing Practice (GMP) separate from traditional drugs

FDAMA required a new approval path and separate Current Good Manufacturing Practices (cGMP) for PET from those cGMP for drugs

Prior to adoption of final CGMP for PET rule, which would become effective 2 years after FDA published a cGMP for PET rule, FDAMA required PET RP production to follow: USP General Chapter <823> for Production of PET RP

FDA Published Final Rule
21 CFR Part 212; Current Good Manufacturing (cGMP) for Positron Emission Tomography (PET) Drugs
December 10, 2009



Regulation became effective June 12, 2012

Required facilities to register as Drug Manufacturers

Regulation applies solely to PET drugs for routine clinical use

The rule §212.5(b) also provides that **investigational and research** PET drugs, cGMP may be met by producing PET drugs in accordance with Part 212, **or** in accordance with USP General Chapter <823> *“POSITRON EMISSION TOMOGRAPHY DRUGS FOR COMPOUNDING INVESTIGATIONAL, AND RESEARCH USES”*

- Includes:
 - PET Drugs produced under Investigational New Drug (**IND**) Application in accordance with Part 312 of this chapter or
 - PET Drugs approved through a Radioactive Drug Research Committee (**RDRC**) in accordance with Part 361 of this chapter

Inspection Finding

Your firm failed to maintain agreements with your materials vendors concerning modifications of materials utilized during the production of ANDA Ammonia (NH₃) N 13 Injection, USP, and ANDA Fludeoxyglucose (FDG) F 18 Injection, USP.

Per your firm management you do not have vendor agreements to specify that any changes in the materials, construction or processing of component be communicated to allow for determination of impact on quality characteristics of components and/or finished products.

Per firm management, you do not have a vendor qualification program.

FDA Guidance: PET Drugs – Current Good Manufacturing Practice (CGMP) August 2011

We recommend that only qualified vendors be used. A vendor is qualified when there is evidence to support its ability to supply a material that consistently meet all quality specifications. We also recommend that PET drug production facilities ask the vendor to report any major change in the manufacture of an item. It is preferable to have more than one qualified vendor for a component. A vendor should be replaced if there is an indication that it is supplying unsatisfactory materials.

Comment: There is no requirement for vendor agreements

Inspection Finding

Label and packaging operations are not adequately controlled to prevent labeling mix-ups. Specifically, Citation: 212. 80(d)

- Your firm's quality assurance department failed to issue labels utilized for the labeling of your PET drug product, ANDA Ammonia (NH3) N 13 Injection, USP. The labels utilized by the chief radiochemist during production did not specify a batch number for the product being produced; this information was completed by the chief radiochemist. Your chief radiochemist entered the batch number, NH3-11082018-01, during production.*
- Your firm's label controls do not allow for label reconciliation to capture number of labels used, damaged or returned for a specific lot of PET drug product.*

21 CFR Part 212. 80(d) Labeling and packaging operations must be controlled to prevent labeling and product mix-ups.

Comment: The time of label placement on the vial is not specified in rule or Guidance. FDA Guidance: PET Drugs –Current Good Manufacturing Practice (CGMP) August 2011
There is no requirement or recommendation for label reconciliation in either document.

Inspection Issues

- The inspector was a sterile compounding pharmacist (PHS) and normally conducts 503A and sterile drug manufacturer inspections. He had only performed a few PET inspections.
- One of the potential observations was that we should have an action limit of 1 CFU in ISO 5 and ID all growths on ISO 5 settling, hand and contact plates. The inspector's justification given was that all potential organisms need an ID by a microbiologist to determine if appropriate sanitization is being used.
- When questioned why we weren't given pre-warning of this regulatory change, he replied this is a new enforcement area for the FDA.

Comment: Changes in regulation/guidance cannot be enforced until the document is finalized after comment and published. USP Chapters <823> and <797> recommended Action Level for Microbial Contamination is > 3 CFU, and this limit has allowed for safe and low risk PET drugs. The cost to speciate each CFU will significantly increase cost of operations, and not improve the quality of PET drugs.

Inspection Issues

- Another item of note is the inspector made it clear, that while the “**nuclear pharmacy**” activities of repacking the FDG and diluting is under practice of pharmacy, they were under his purview and asked for the SOPs and procedures of how it was being done.
- This has changed from our last inspection 5 years ago when they left the clean room after we drew the sterility and QC samples from the FDG multi-dose vial.
- The inspector stated they have the ability now to follow the drug from manufacturing release through hand off to the medical staff to determine if there is any public health concerns.

Inspection Guidance Program 7356.002P

Part II, Page 2/5: PET drug production includes all operations to the point of final release of a finished dosage form.

Part II – Page 5/19: Dispensing of patient unit doses under the practice of pharmacy is not covered under Part 212 CGMP.

Inspection Observation

You have failed to validate the use of detergents with respect to contact times for cleaning ISO 5 laminar flow hoods and ISO 7 area.

The FDA Microbiology requested validation of the contact times.

21 CFR Part 212 requires the use of qualified vendors, and information provided by these qualified vendors can be accepted without further in-house testing,

Comment: We have obtained bactericidal and fungicidal contact time information from our qualified vendors and have included this information in our SOPs.

Development of a nation wide approved Vendor system could assist smaller PET facilities.

Inspection Finding

“Control of components used to produce PET drugs and the containers and closures used to package them are deficient in that they do not assure the reliability of suppliers. Specifically,

Citation: 212.40(c)

Certificate of Analysis (COA) from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier’s analyses through appropriate qualification of the supplier’s test results at appropriate intervals. Per firm management vendor qualification and/or validation of supplier’s test results are not performed. The following is a list of components with acceptance of testing per vendor COA.

1. **Product Code: SB026, Needle, 20G x 1 1/2"**, Vendor: Becton – Dickinson & Co, Purity Test
2. **Product Code: SB025A, Needle, 18G x 1 1/2"**, Vendor: Becton – Dickinson & Co. Purity Test
3. **Product Code: SB036, Syringe, 20 ml**, Purity IsoSolutions Marketing & Management Inc. (Nukem), 125A-1030 Denman St., Suite 329, V6G2M6 Vancouver, BC, Canada
4. **Product Code: SB001**, [18O] Water, Purity Test, Identity
GE Healthcare, Amersham Place Little Chalfont, Buckinghamshire HP& 9NA, United Kingdom
5. **Product Code: SB013B, FDG Synthesizer, FASTlab Citrate Cassette**, Purity
EMD Millipore. 290 concord Road, Billerica, MA, 01821
6. **Product Code: SB012, Alcohol, Ethyl** – Ethanol for [13N]NH3 Target Solution, Purity
Honeywell, 115 Tabor Road, Morris Plains, NJ 07950
7. **Product Code: SB009A**, Water, TraceSELECT, Purity

21 CFR Part 212.40 (c) (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.

Inspection Observation

You do not have a control system for implementing changes in facilities or equipment, materials handling, packaging and labeling, laboratory, or production system operations. In addition, you have made the following significant changes without control:

- Your firm has made major changes to the facility by adding a walk in refrigerator and an ISO-7 area without documented change management.*

Facility Response: The renovation of existing lab that housed a walk-in cooler refrigerator purchased in 5/23/2011 with installation beginning in 07/1/2011, was completed prior to the Cyclotron Facility being given this space from the Radiology Department in 2019.

The actual plan for the renovation of the lab was to install an ISO 7 room for use in preparation of reagents. There were no plans to use the refrigerator, but it was left intact since it was a working refrigerator.

The Engineer Co-Director had worked with the Facilities Group to design and renovate the lab, but at the time of renovation, a Facility wide change control plan or process validation program were not in place. After completion of the room, the Cyclotron Facility had an outside Certification Company determine that the room met ISO 7 standards.

Comment: There is no mention of an overall Change Control Management program in Part 212 or the Guidance. An overall Change Control Management Program is an expensive, time consuming requirement that does not make PET drugs more safe, and adds to the overall cost of the PET drugs. Additionally at most academic institutions the Facilities Group is not under control of the PET Facility.

Inspection Observation

You have failed to implement a minimum of three system suitability runs for your HPLC and GC analysis systems with defined acceptance criteria (e.g. RSD, tailing factor etc.) for chromatographic specification to assure the suitability of the integrated analysis system.

Guidance: PET Drugs –Current Good Manufacturing Practice (CGMP) August 2011 Page 13

B. Control of Components, containers, and Closures

2. Quality Control Equipment:

- (a) Gas Chromatograph Prior to each day of its use,at least one injection of the standard preparation....should be done before the injection of test samples.
- (b) High performance liquid chromatograph (HPLC)....Prior to each day of its at least one injection of the standard preparation....should be done before the injection of test samples.

Inspection Observation

You have failed to validate your procedure SOP 739 Environmental Monitoring of a Laminar Airflow Hot Cell Equipped with Manipulator Arms, to ensure the accurate CFU counts can be obtained for the contact plates at 120 hours.

Response: performed the validation to compare the CFU counts on APs and CPs at times 120, 144, 168 and 192 hours post sampling and have generated a Process Validation/Verification Testing Protocol, Validation of the Colony Forming Unit (CF) counts on Air-settling Plates (APs) and Contact Plates (CPs) for extended time.

Comment: Once bacterial growth is present on a contact plate, it is highly unlikely that the CFU will disappear after additional time in an incubator. Due to holidays, some plates are placed in the incubator and read after 120 hours. This type of testing, uses resources and personnel time, to “validate” an obvious result.

Inspection Observation

Your personnel lack the necessary training and experience to perform their assigned functions.

Your procedures for qualification of operators for aseptic processing of PET drug products does not include media fills performed in all areas and include all processes involved in the manufacture of the PET drug.

Comment: Media fill testing is a procedure that evaluates an operator's ability to perform an aseptic procedure without bacterial contamination. It is impossible for us to train all of our operators in each ISO5 area where final product vial setup will occur, and where final QC and sterility samples are drawn. This type of training should be able to be translated to other ISO5 LAFW and Laminar Flow Hot Cell without additional training. It is very costly and time consuming to require multiple media fills be performed for each drug, and each type of ISO 5 area used.

Inspection Observation

In addition, your firm does not maintain control over the humidity of classified areas, including the ISO Class 7 Cleanroom . In May of 2019 at approximately 6:00 am, the humidity within the ISO Class 7 Cleanroom was observed at 75.4%.

Comment: The regulations don't mention controlling the humidity. Often PET facilities are located in the basement. In academic institutions, humidity is often controlled by Facilities Management. Humidity can be recorded, and environmental monitoring can be used to assess the impact of humidity.

Additionally PET production employs closed systems for the production of PET drugs, essentially reducing the impact of humidity. Final product testing, including sterility testing for all PET drugs, has defined the products administered to humans are acceptable.

FDA Regulatory Pre-Meeting Questions

Provide implementation of requirement of sterile gloves during aseptic manufacturing operations

FDA Guidance: PET Drugs –Current Good Manufacturing Practice (CGMP) August 2011 Page 10.

Have operators wear clean lab coats and sanitized gloves when conducting aseptic manipulation within the aseptic workstation. Frequently sanitize gloved hands or frequently change gloves when working in the aseptic workstation.

Summary

- Significant time was spent developing 21 CFR Part 212 for the production of PET drugs
- Inspections need to focus on Part 212 and the PET Guidance documents, not Part 211
- If new Guidance is being developed the PET community needs to know the basis for this Guidance and be able to comment on it
- PET Community needs to work with the agency to improve inspections. Inspectors need training in Part 212 prior to inspecting the facility, not while conducting inspections
- Manufacturing inspections should end after withdrawal of the QC sample--dispensing is under pharmacy practice.
- Investigational PET Drugs, under FDA approved IND or RDRC, should not be inspected as part of an ANDA/NDA manufacturing inspection
- Part 212 is still appropriate today, as evidenced by our track record, for the production of safe and low risk diagnostic PET radiopharmaceuticals
- Non-uniform inspections across the US create confusion in the PET Community concerning which regulations to follow or what guidance is applicable. This in turn jeopardizes the uniformity of the PET drug supply in the US.



Current Trends and Observations on Inspection

Peter Webner RT(N),CNMT

**PET Drugs: A Workshop on Inspections Management and
Regulatory Considerations**

FDA White Oak Conference Center
Silver Spring, MD USA

February 21, 2020

Regulations and small companies

- Building the 212 regulatory guidance framework has helped to spur innovation
 - We have seen several new precision PET diagnostics recently approved
 - More have been submitted for review
- Small companies rely heavily on regulatory guidance documents
 - This helps us build adequate controls on our manufacturing and Quality systems
 - Allows us to be proactive and build our submissions to meet the agency's expectations
 - Guidance helps us establish timelines for regulatory processes and potential product launch
 - Allows to budget both our talent and capital

Regulations and small companies

- Many of these companies are pre-revenue
- A consistent regulatory environment has helped to spur investment into these precision diagnostic drugs, however:
 - Timelines are critical
 - Resources and budgets are extremely tight
- Finding out that the FDA's "thinking on some existing guidance" has evolved during an inspection can be a tremendous hurdle for a small company, especially in the middle of the review of an NDA
 - The ability for a small company to continue to support a product diminishes with every extension of review cycle

1. Questions from the PET Community

Is the FDA taking a new approach to the use of radiosynthesizers?

Comment

- On a recent inspection it was recommended that the radiosynthesis process on a commercial radiosynthesizer be subject to full DFMEA
- The process be auto-aborted if any critical process parameters go out of range
- Failing synthesis at EOS was deemed not adequate, nor was reliance on QC to catch synthesis failures

1. Question from the PET Community

Response

- Most systems are not designed to auto-abort
- Process validation is designed to define product characteristics as well as manufacturing and release parameters
- These tools are critical for us to be able to manufacture our products in compliance with both GMP and radiation safety in mind
- Some additional discussion the use of these devices for new compounds will be helpful

2. Question from the PET Community

- Existing guidance and Q&A state that changing the radiosynthesizer for a PET radiopharmaceutical would be accepted as a CBE 30 provided the product strength, concentration, and excipient profile were identical
- A recent review of a comparability protocol indicated that the agency will require a post approval supplement for the above case

Response

- Comparability protocols and flexibility on manufacturing platforms are an important part of scalability in the PET world
- Unlike traditional Pharma products, we need to be able to qualify dozens of sites to make our products available nationally

3. Question from the PET Community

- Under 212, once a critical material supplier had multiple lots of material tested and validated by a manufacturer (i.e., precursor and standards), the manufacturer can accept incoming material based on certificate of analysis and material specifications
- During recent pre-approval inspections, and application reviews, inspectors/reviewers have mandated manufacturers to test samples of each shipment of incoming materials

Response

- This type of expectation introduced during a drug application review, or during pre-approval inspection is challenging
- This type of change can require procedure and method development, validation, transfer, and verification during a very time sensitive process

4. Question from the PET Community

- What is the FDA's recommended course of action when an inspector opts to inspect against 211 instead of 212?

Response

- We recognize that the vast majority of the inspections the FDA performs are for part 211 or other drug types
- Inspectors have a well-practiced approach to assess these facilities
- How do we best work with the FDA to address observations or violations that arise from a Part 211 expectation for a Part 212 product?

5. Question from the PET Community

- At a recent inspection, an inspector indicated that the agency was taking a different approach for new products based on the individual drug profile (this product is an F-18 PET drug, small molecule, microgram level drug mass, microgram level impurity limit).
- Is the FDA going to switch to a risk-based assessment based on the PET drug's profile?

Response

- Understanding the regulatory approach prior to constructing a NDA is KEY
- Expecting to be treated under part 212 when submitting an NDA and finding out that not all aspects of 212 are applicable during the review process causes significant challenges for both the sponsor and the reviewers during the review process
- Understanding how risk assessment is performed and communicating the expectations during a pre-NDA or other early meetings would be ideal

6. Question from the PET Community

- USP chapter <797> arises during some inspections
- USP <825> will soon become official for radiopharmaceuticals
- Companies that work both in the EU and US often use ICH as a reference for procedures

Response

- Absent specific FDA guidance on specific topics we use these types of guidance to help us draft procedures or use best practices
- Change in these guidance documents will ultimately have downstream effects on existing A/NDA's and manufacturing facilities
- It would be great for there to be a shared timeline for complying with new guidelines to allow for change control and implementation

7. Question from the PET Community

- Several recent inspections have indicated that the FDA is changing its requirements around trigger limits in environmental monitoring
 - This expectation has only recently been communicated at a few inspections
- Sterility assurance and environmental monitoring are important elements

Response

- Time to transition and implement new action limits is essential
- Issuing new expectations at inspections makes it challenging for the community's network of 150+ manufacturing sites to become compliant
- It also makes it difficult for new drug sponsors to be able to build these expectations into submissions

8. Question from the PET Community

- During the review of a recent comparability protocol the agency suggested that they would only allow a site to be added if:
 - Environmental monitoring program with no microbiological excursions exceeding 1 CFU in the past 1 year for the ISO 5 laminar flow hoods have been observed

Response

- Time to transition and implement new action limits is essential
- Expecting a limit not consistent with current practices for adding a new product would significantly delay the ability to provide adequate manufacturing sites and hinder patient access
 - We would hope to be able to add sites compliant with their current EM programs, and would implement new trigger limits as guidance is provided

9. Question from the PET Community

- On recent inspections, FDA has requested second person verification of some activities
- Regarding these second person observations:

Response

- Do the individuals observing/verifying the activities need to be qualified for the activity being observed/verified?
- This new requirement brings new complexity to procedures and wasn't framed with any additional guidance on the personnel requirements
- It seems that there may be some additional concern specific to data integrity during either the manufacturing or release processes

Summary

- The hard part of cGMP compliance is the little “c”
- Processes change, science evolves, industry finds new efficiencies
- Regulation evolves to protect both the public and manufacturers
- The challenge manufacturing our products is the short half and shelf-life which requires the use of distributed manufacturing networks
- The fact that there are many manufacturing facilities, both commercial and academic, PLUS many small companies are creating new PET drugs and trying to interface into existing manufacturing networks makes change control and communication of changes to regulations essential

Thank You!

***OFFICE OF REGULATORY AFFAIRS
(ORA)
PET SURVEILLANCE INSPECTIONS***

CAPT Ileana Barreto-Pettit, R.N., M.P.H.

Drug National Expert

Pharmaceutical Quality Programs Branch
Division of Pharmaceutical Quality Programs
Office of Pharmaceutical Quality Operations
Office of Regulatory Affairs

PET Drugs: A Workshop on Inspections Management and Regulatory Considerations

February 21, 2020

Outline



ORA Organizational Charts



Site Selection Model



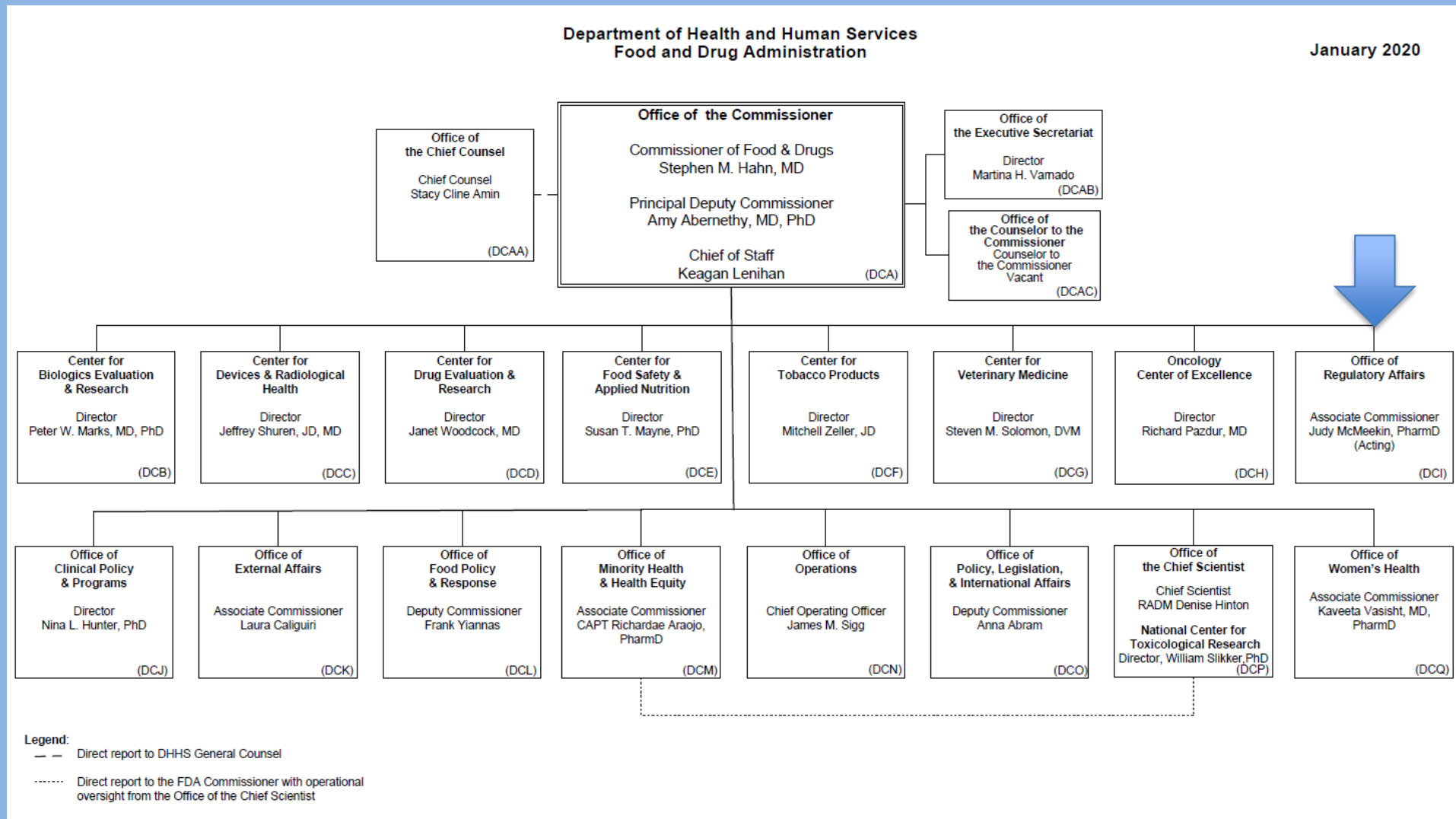
Concept of Operations (ConOps)

Surveillance Inspections



New Inspection Protocols

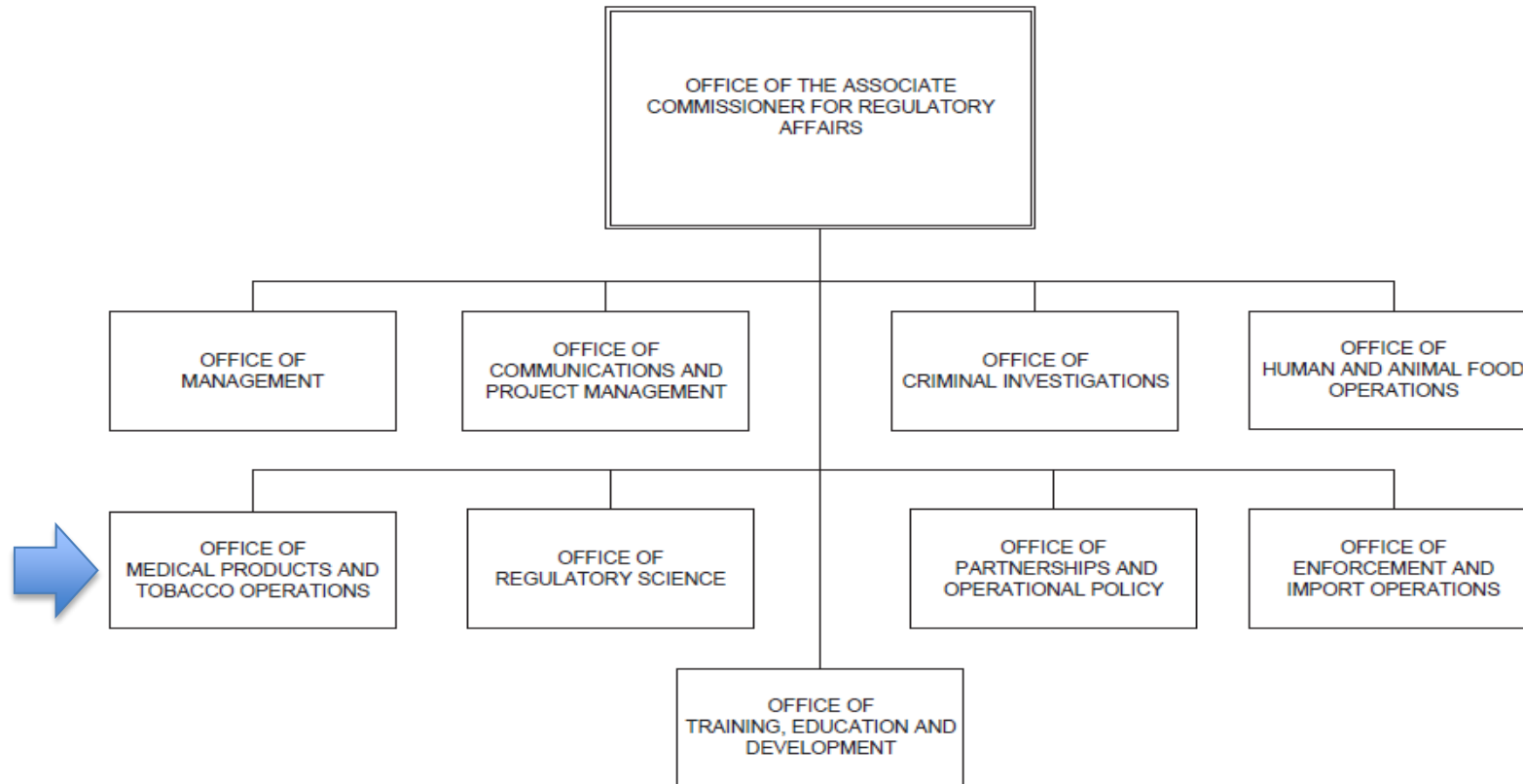
Office of Regulatory Affairs (ORA)



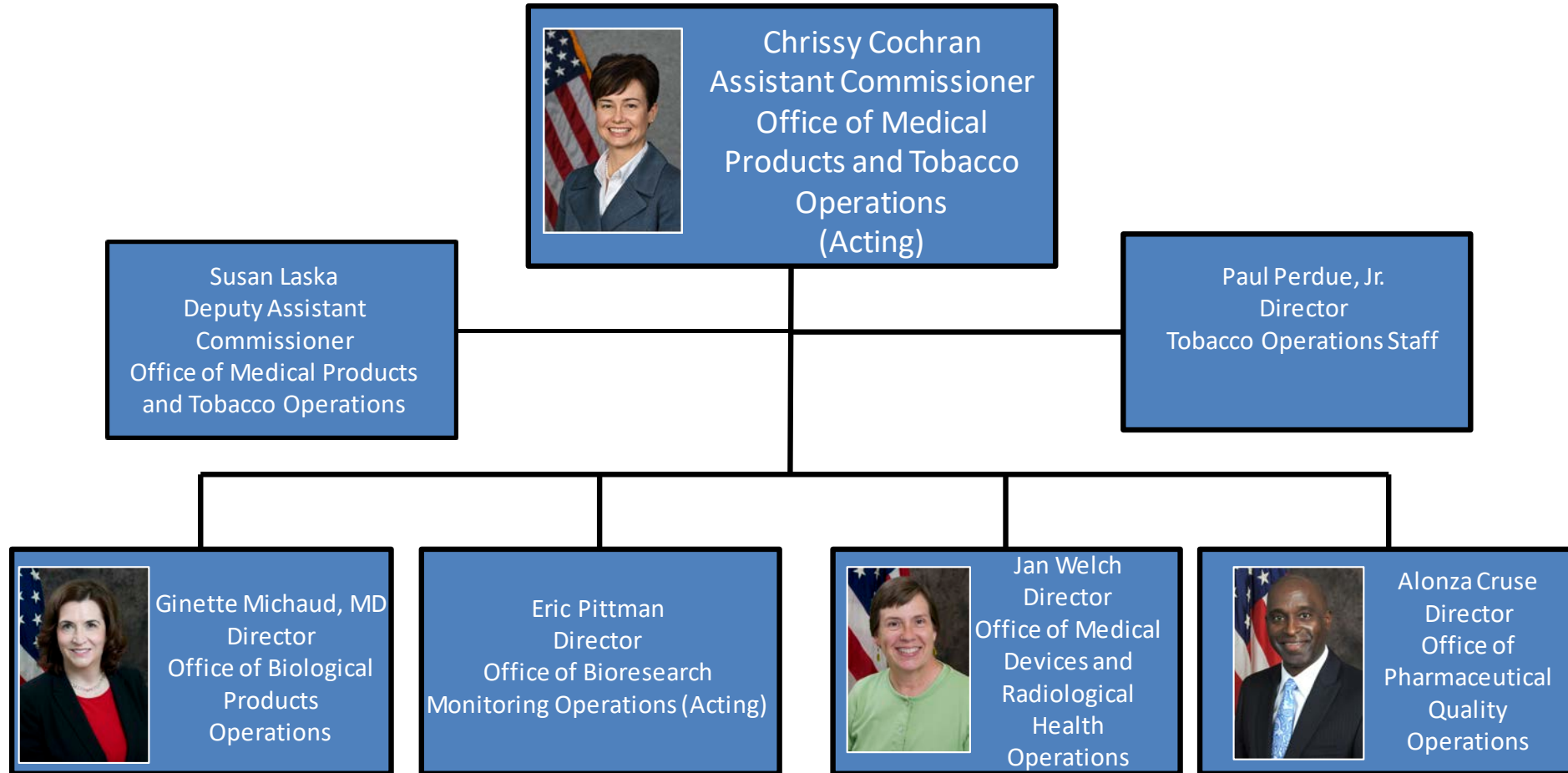
Office of Medical Products and Tobacco Operations (OMPTO)



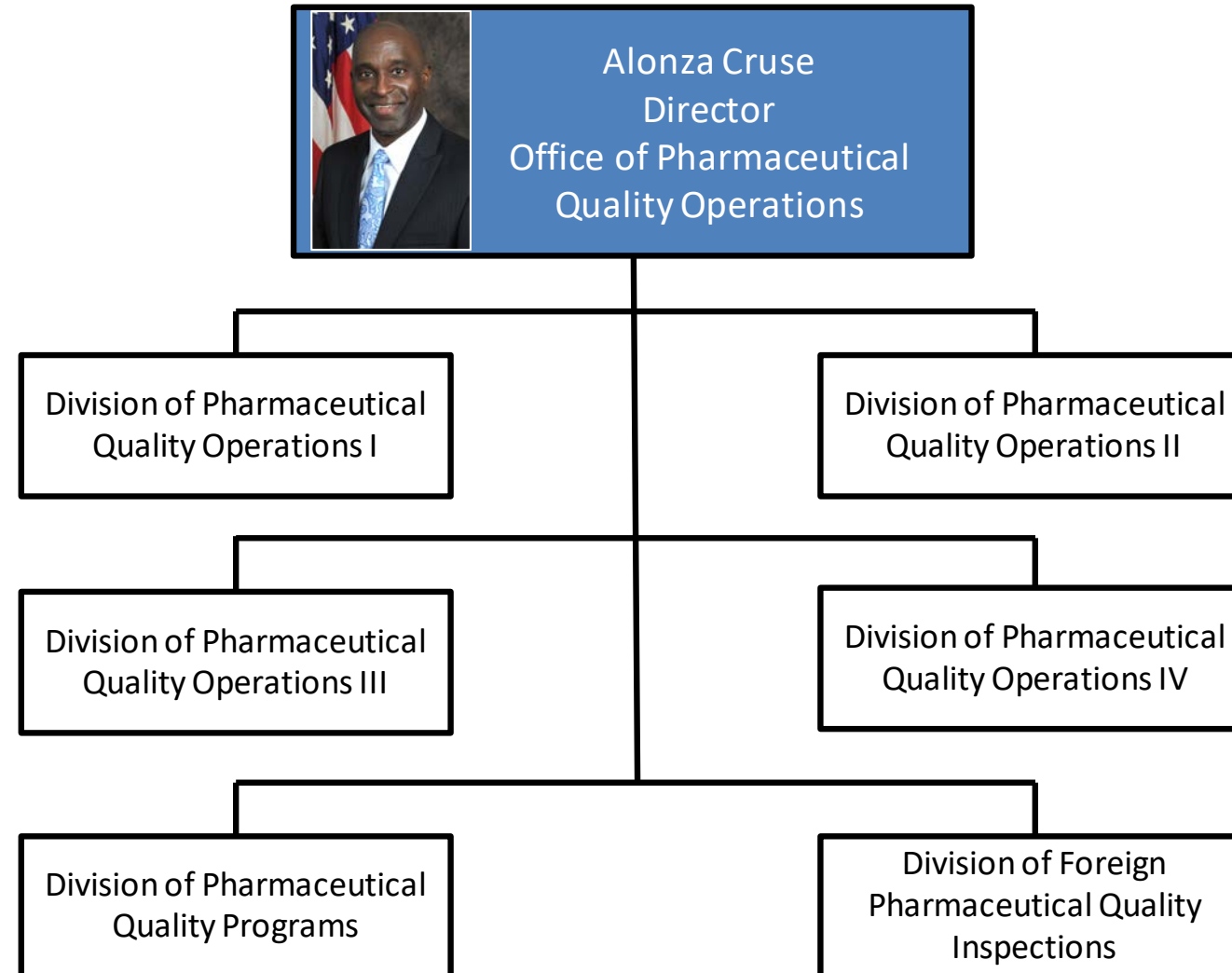
FOOD AND DRUG ADMINISTRATION
OFFICE OF GLOBAL REGULATORY OPERATIONS AND POLICY
OFFICE OF REGULATORY AFFAIRS



Office of Medical Products and Tobacco Operations (OMPTO)



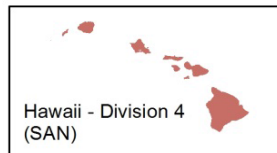
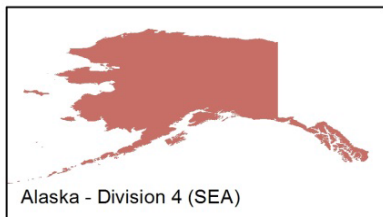
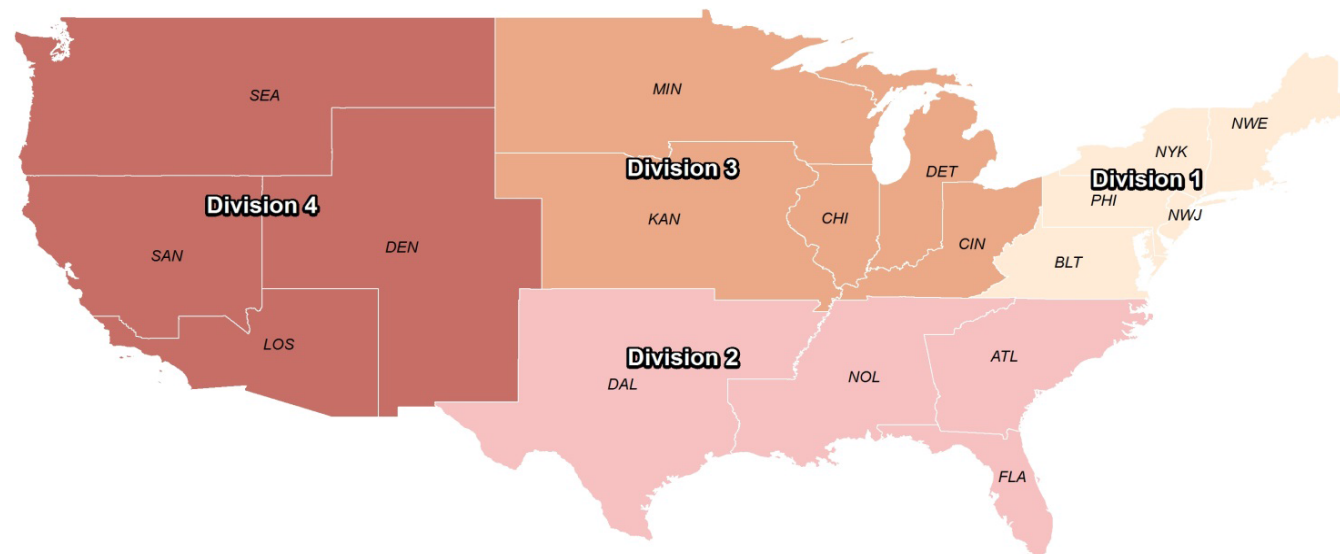
Office of Pharmaceutical Quality Operations (OPQO)



ORA Pharmaceutical Program Divisions

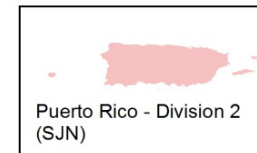


Office of Pharmaceutical Quality Operations (OPQO)



Pharmaceutical Quality Program Divisions

- Division 1 (BLT, NWE, NWJ, NYK, PHI)
- Division 2 (ATL, DAL, FLA, NOL, SJA)
- Division 3 (CIN, CHI, DET, KAN, MIN)
- Division 4 (DEN, LOS, SAN, SEA)
- FDA Current Districts Boundaries



OPQO Staff Contacts

Program Director: [Alonza Cruse](#)
 Deputy Program Director: [Nancy Rolli](#)

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: Diana Amador Toro	Nerizza Guerin	Stephanie Durso
Division 2	DAL/ATL/FLA/NOL/SJN	Program Division Director: Monica Maxwell	Tamala Bogan	John Diehl
Division 3	DET/CHI/CIN/KAN/MIN	District Director: Art Czabaniuk	Jeffrey Meng	Nicholas Lyons
Division 4	LOS/DEN/SAN/SEA	District Director: Steven Porter	Katherine Jacobitz	Thomas Berry

Site Selection Model (SSM)

- Routine surveillance inspections are prioritized using a site selection model (SSM)
- Manual of Policies & Procedures (MAPP) 5014.1: *Understanding CDER's Risk-based Site Selection Model*
 - Published 9/5/18 (Effective 9/26/18)
 - <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM619302.pdf>

CDER-ORA Site Selection Model (SSM)



PURPOSE

- *Risk management tool developed to support* the prioritization of both domestic and foreign manufacturing surveillance inspections.
- *Implement a consistent, science-based approach* to identify and allocate resources to sites that can potentially impact public health.

OBJECTIVE

- *Rank* drug manufacturing sites for CGMP surveillance inspections *based on risks to drug quality*.

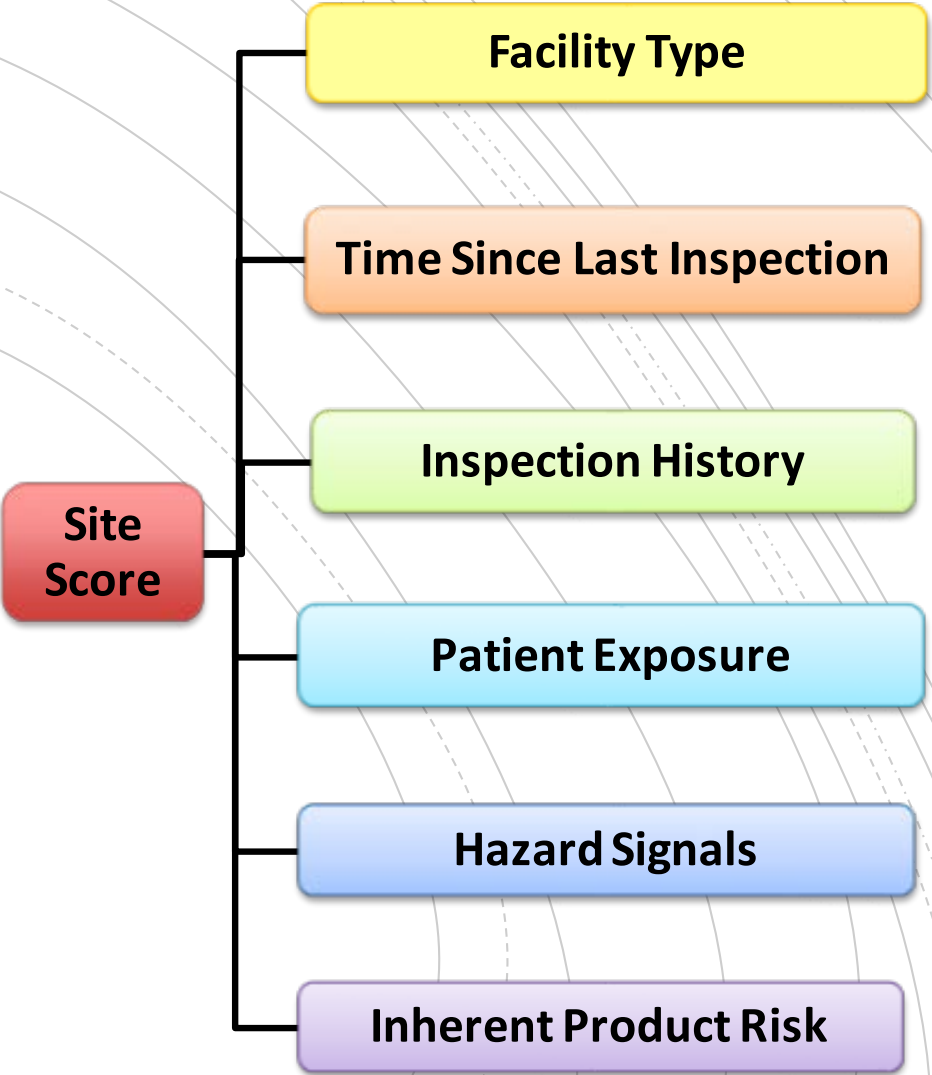
SSM Compliance with the FD&C Act



Risk-based inspection frequency considers:

- ✓ The **compliance history** of the establishment.
- ✓ The record, history, and nature of **recalls** linked to the establishment.
- ✓ The **inherent risk of the drug** manufactured, prepared, propagated, compounded, or processed at the establishment.
- ✓ The **inspection frequency and history** of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years.
- ✓ Whether the establishment has been **inspected by a foreign government** or an agency of a foreign government recognized under section 809 (EU Mutual Recognition Agreement).
- ✓ Any **other criteria deemed necessary** and appropriate by the Secretary for purposes of allocating inspection resources.

Current SSM Factors





Hazard Signals

Field Alert Reports

Biological Product Deviation Reports (BPDRs)

Recalls

Complaints, MedWatch

Adverse Drug Experiences

Time Since Last Inspection



- ❖ State of quality in a facility is a function of time between inspections
- ❖ Risk of a facility being non-compliant with cGMP and priority for re-inspection increase with increased time since last inspection



510(h) of the FD&C Act was amended in 2012

Biennial inspection frequency replaced with a “*risk-based schedule*” that considers establishments’ “*known safety risks.*”



Promotes parity in inspectional coverage



Assures FDA resources address the most significant public health risks.

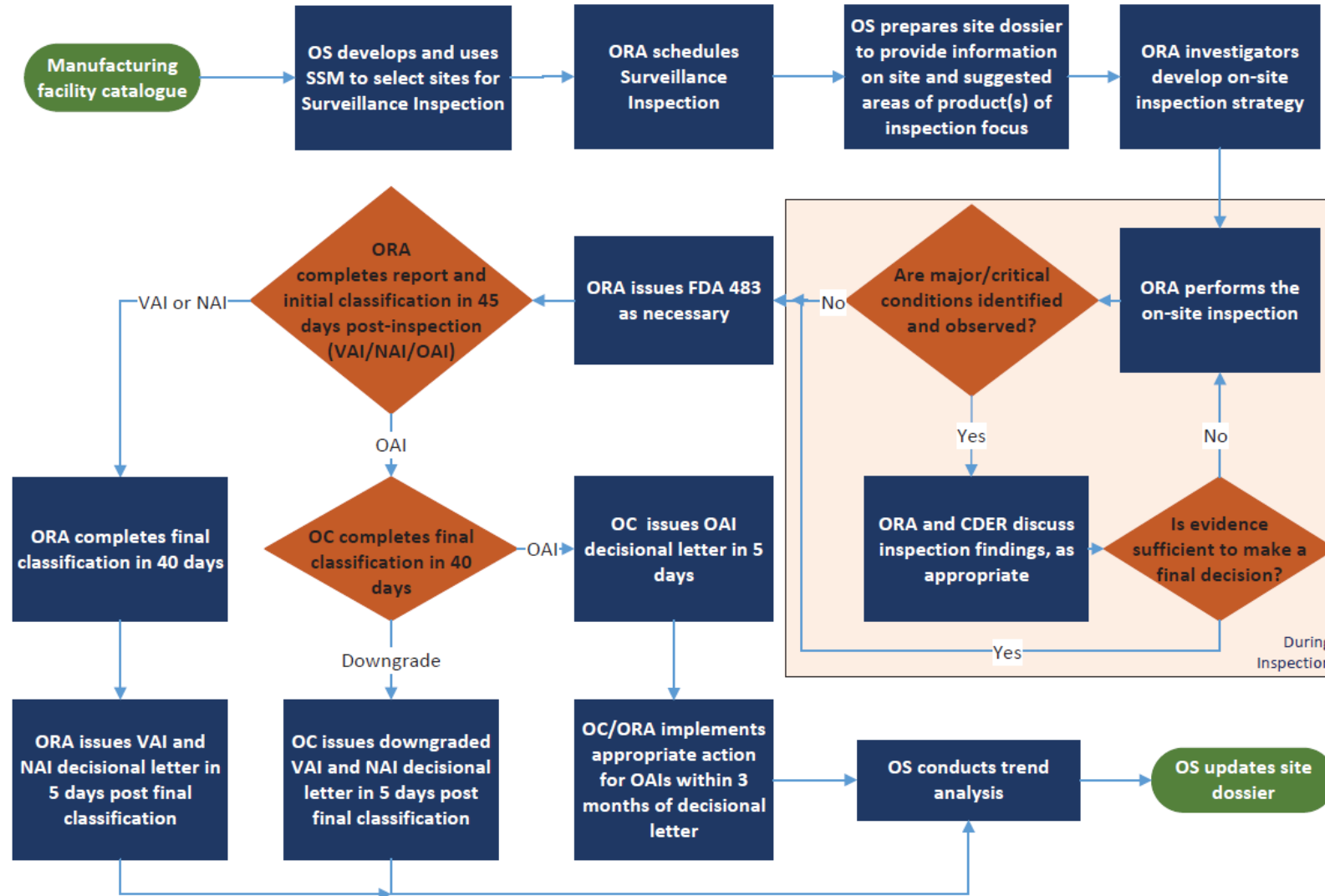
Benefits

Surveillance Inspections

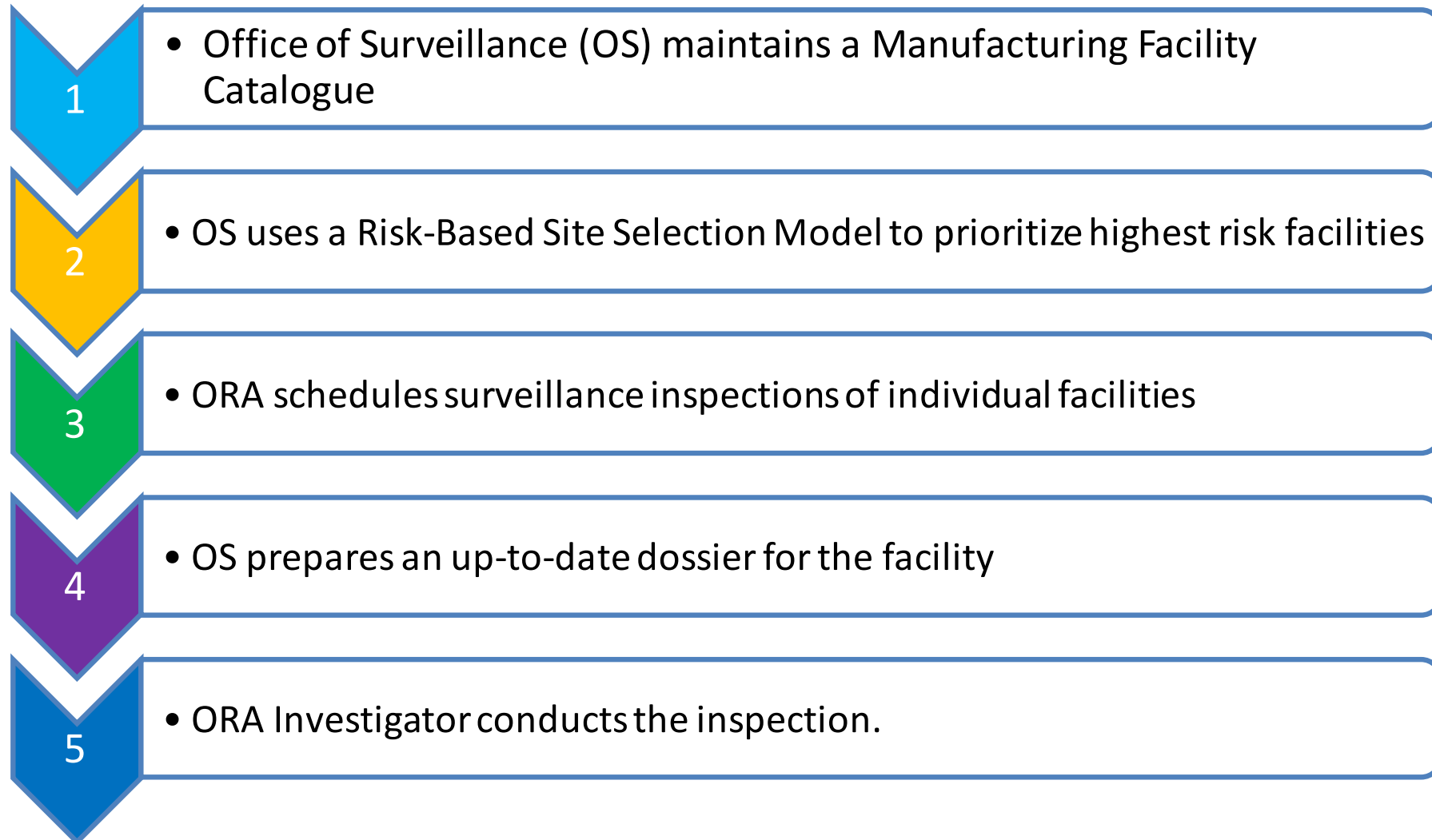
This type of inspection is meant to monitor the conformance to CGMP requirements and is not necessarily an assessment of a specific product. Rather, it is a system-based inspection.

The purpose of this type of inspection is to identify quality problems and adverse trends at facilities so that the FDA can develop strategies to mitigate them.

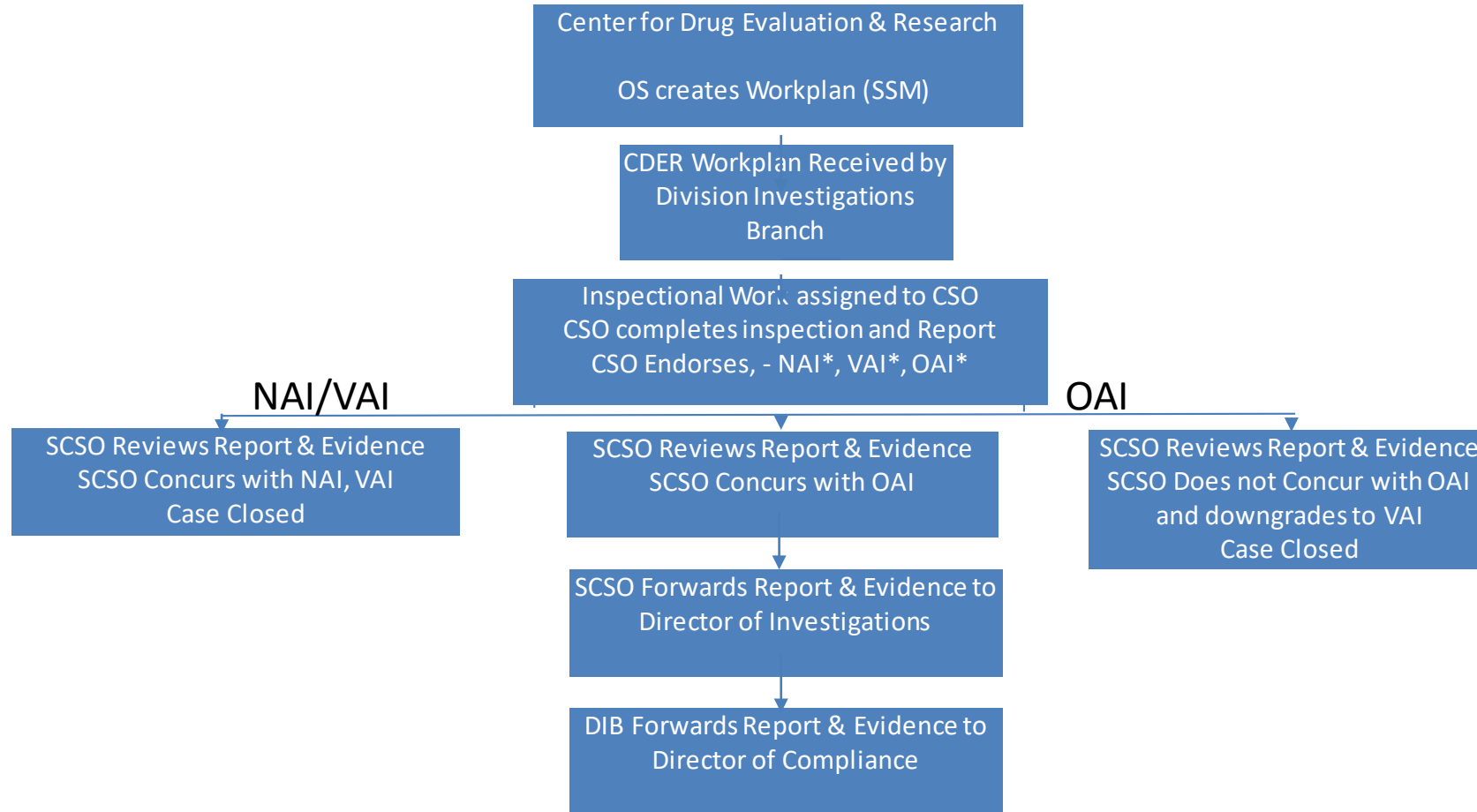
CDER/ORA Process Flow for Surveillance Inspections



Surveillance Inspection

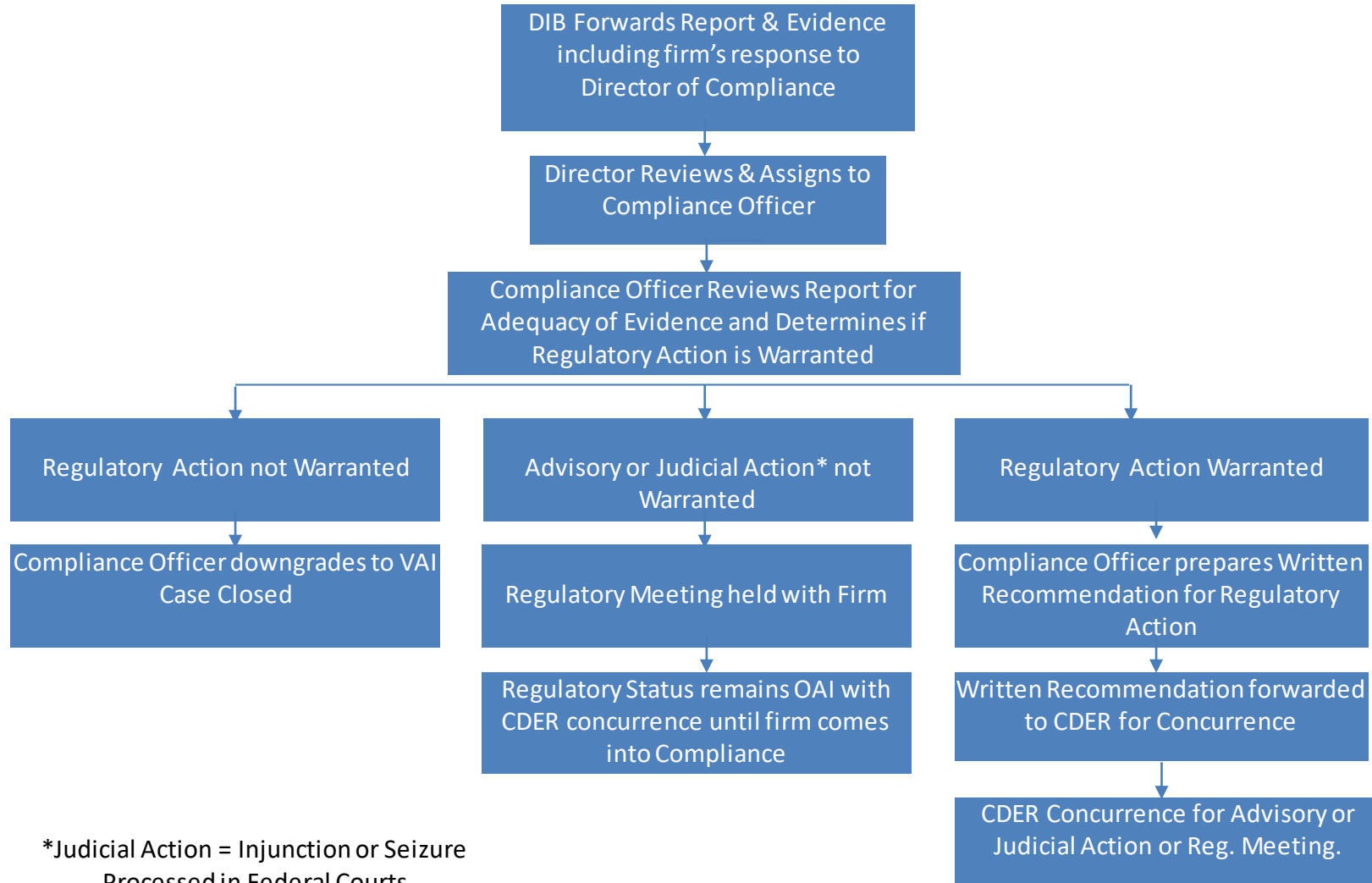


Division's Investigations Branch Process Flow



- *NAI= No Action Indicated (No 483)
- *VAI= Voluntary Action Indicated (Form 483)
- *OAI= Official Action Indicated (Form 483)

Division's Compliance Branch Process Flow



*Judicial Action = Injunction or Seizure
Processed in Federal Courts

Communicating Inspectional Findings

An FDA-483, Inspectional Observations, is issued to the firm at the close of the inspection if significant deviations from the regulations are found.

The firm should submit a written response to the FDA-483 within 15 business days to the Agency's address on the top left of the FDA-483 form.

FDA sends an electronic FMD-145/decisional letter via email no later than 90 days following inspection closing.

Updates to FDA's Public Inspection Classification Database

The database includes...

- an update **every 30 days** that covers all drug surveillance inspection **final classifications** (i.e., compliance status). The final classification is generally completed within 90 days of the end of a surveillance inspection, which means the entry for the site will be within 120 days of the close of an inspection.
- a link from the introductory page to **definitions of final inspection classifications**—NAI, VAI, OAI—and to a new FAQs page

<https://www.accessdata.fda.gov/scripts/inspsearch/>

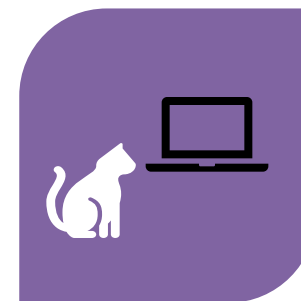
Drug Investigator Training



FDA INVESTIGATORS
HAVE BEEN TRAINED ON
21 CFR 212 IN THE PAST.



CURRENTLY THE DRUG
TRAINING PROGRAM IS
BEING REVAMPED TO
ADDRESS GAPS IN
INVESTIGATOR
TRAINING. THE FIRST
PILOT CLASS IS
SCHEDULED FOR
MARCH 2020.



TRAINING WILL BE
PROVIDED TO
INVESTIGATORS ON THE
USE OF THE ELECTRONIC
PET-INSPECTION
PROTOCOL (PET-IP).



New Inspection Protocols Project (NIPP)

Modernize inspections through collecting structured data that can be analyzed over time:

- Quantitate the state of pharmaceutical quality
- Accelerate the pace of making informed, data-driven decisions
 - Pre-approval: application decisions
 - Surveillance: resource allocation
- Lead to more efficient and consistent inspections
- Identify policy and outreach opportunities across the industry
- Provide evidence for addition or modification of regulations



Acknowledgments

- Ann Marie Montemurro, ORA
- Kevin Gonzalez, ORA
- Krishna Ghosh, PhD, CDER
- Jennifer Maguire, PhD, CDER
- Art O. Czabaniuk, ORA
- Obinna Ugwu-Oju, CDER

Thank You!



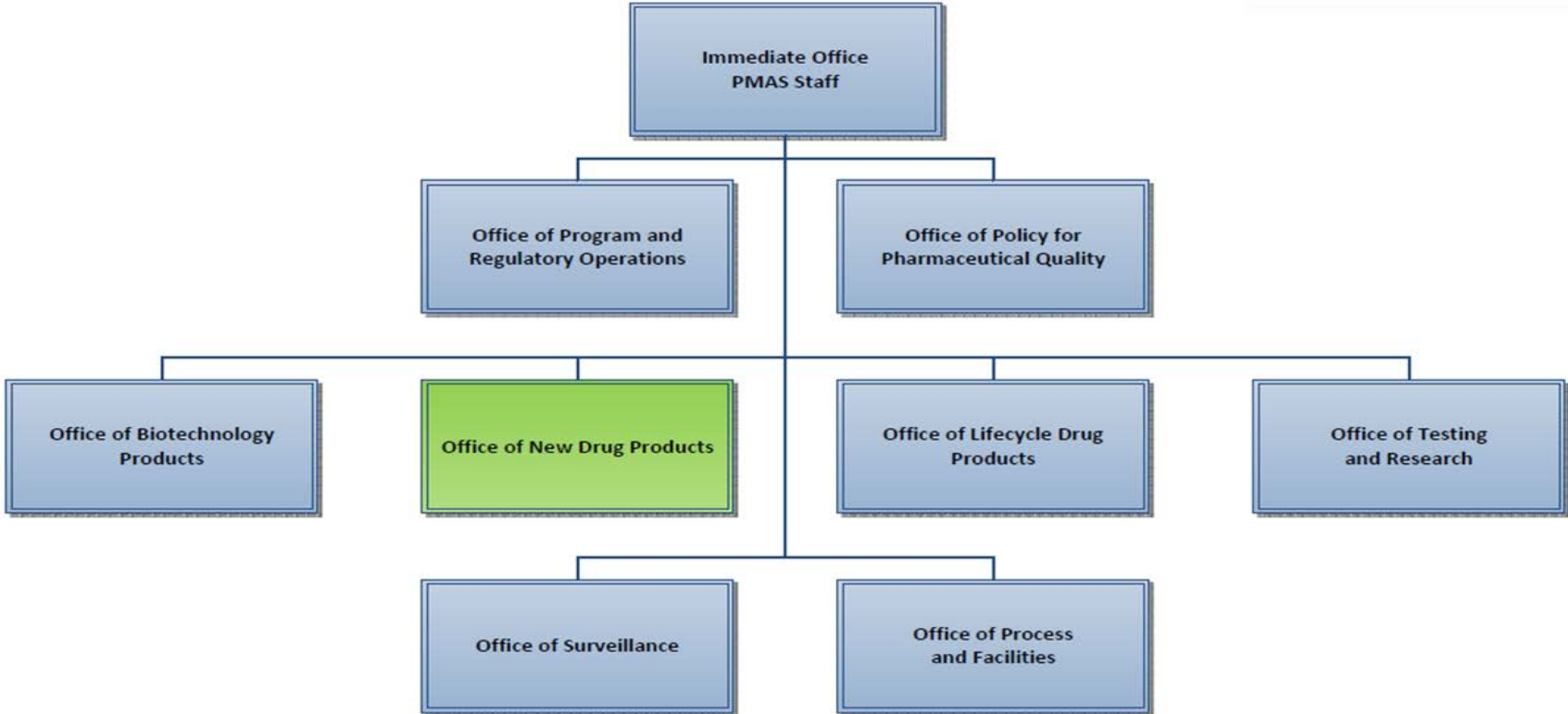
CAPT Ileana Barreto-Pettit, R.N., M.P.H.
Drug National Expert
1800 Eller Drive, Suite 200
Fort Lauderdale, FL 33316
786-459-2492

Lifecycle Management of PET Drugs

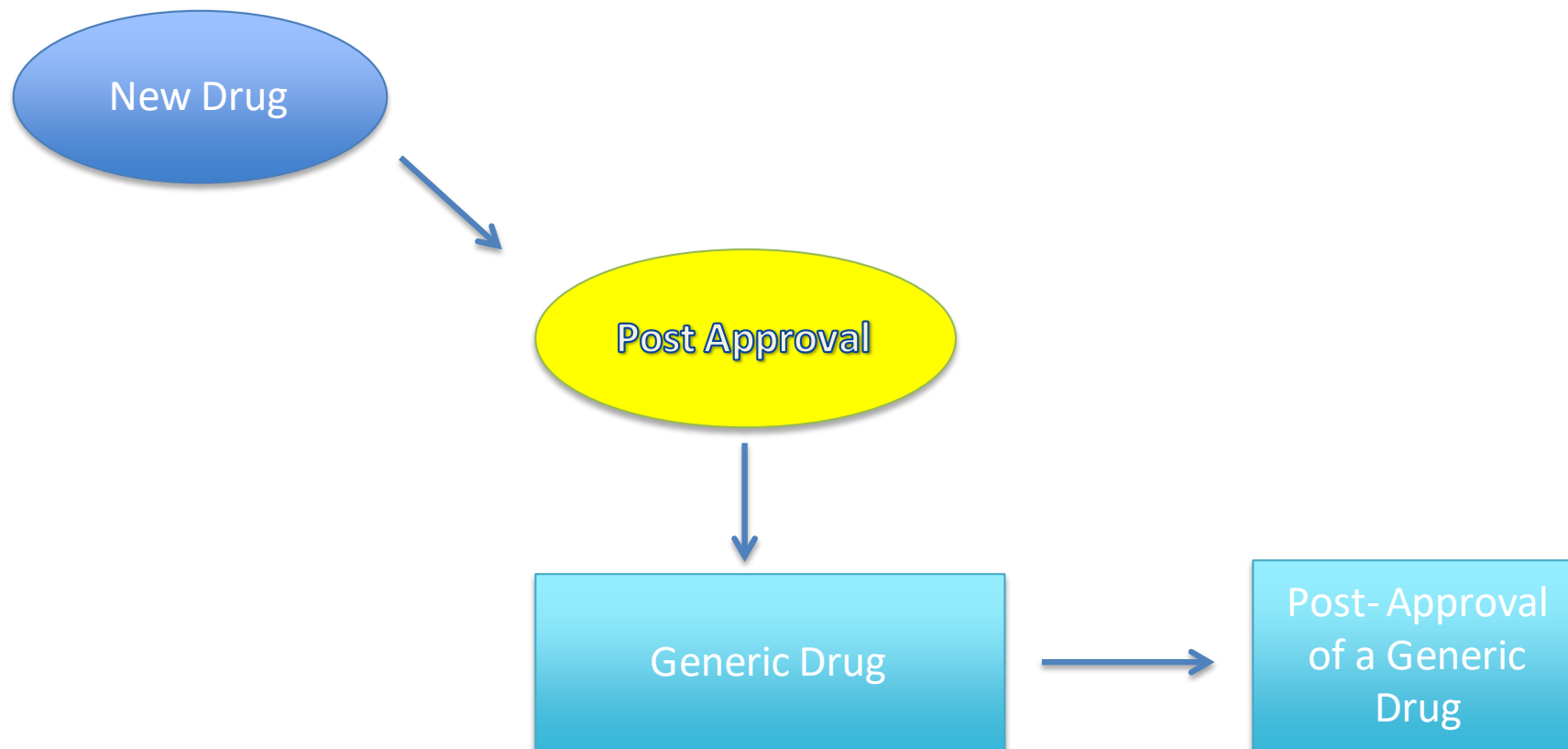
PET Drug Workshop

**Ramesh Raghavachari
Chief, Branch I/DPMA I
OLDP/OPQ/CDER**

THE OFFICE OF PHARMACEUTICAL QUALITY



Defining the Lifecycle



Drug Approval Process-Overview

- Discovery
- Development-
Chemistry/Biology/Feasibility
- Non-Clinical
- Pre- IND
- IND- Phase I

Drug Approval Process-Overview (cont.)

- IND- Phase II
- IND-Phase III
- NDA Submission to FDA for Approval
- Phase IV-Post Marketing Surveillance

What Determines the Lifecycle

Opportunities after the approval of a new drug:

- Indication
- Efficacy in Patients
- Safety in Patients
- Large Scale Manufacturability/Streamlining
- Quality
- Continuous Improvement

What Happens in a Lifecycle?

- Reality for a drug starts only after an approval
 - Real efficacy in patients
 - Long term safety data
 - Stability issues related to the formulation
 - Challenges in maintaining high standards of Quality

During the Lifecycle....

- May prove to be more effective for another indication

Examples:

- Minoxidil for hair growth originally developed for hypertension
- Lumigan for glaucoma also sold as Latisse for thicker eyelashes

Examples of Drug Lifecycle

- Understanding the past
- Evaluating the present situation
- Planning for a better future with all the lessons learnt
- Making Changes for product improvement
- Avoiding pitfalls
- Better risk management

Evaluating the present situation

- After approval changes are inevitable
 - Optimization of process
 - Production scale
 - Fine tuning the controls
- Changes are global
- Quality changes tied to economics of the product/company
- Multiple changes at multiple levels
- § 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

Typical Lifecycle Changes

- Prior Approval Changes (PAS) – High Risk
- Changes Being Effected in 30 days (CBE-30) - Moderate Risk
- Changes Being Effected in 0 days (CBE-0) – Low Risk
- Annual Reportable Changes- Low Risk

PAS Changes (Examples)

- New Formulation (including changes to excipients)
- Labeling Changes
- Additional strengths
- Primary Container Closure System changes
- Comparability Protocols
- Change to a New Manufacturing /Testing Facility
- Stability Protocol

CBE-30 Changes (Examples)

- Manufacturing process changes
- Analytical method changes

CBE-0 Changes (Examples)

- Additional Specification to controls
- Method modifications
- Editorial changes
- Corrections
- Missing data
- Changes that do not impact Quality/Safety/Efficacy in any way

Some Changes Pertaining to PET products

- Addition of New manufacturing site(s)
- New Source of Raw Materials
- Specific Activity
- Extension of Shelf-Life
- Modifications to the Generator
- Sterility Issues
- Analytical Method Changes
- Addition of a New Equipment
 - Cyclotron
 - Synthesizer
 - Purification System

Conclusion

- Agency encourages innovation and new PET products
- For an approved NDA, every change is product specific and the regulatory requirements are evaluated on a case by case basis
 - Scientific Data requirements, regulatory requirements, process etc.
 - When you are not sure, request a meeting with the Agency with questions, we are here to help.
- High quality, safe and efficacious product is the ultimate public health mission.

References

- § 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
- Changes to an approved NDA or ANDA
- Scale-up and post-approval change (SUPAC)
- SUPAC-IR, SUPAC-MR, SUPAC-SS
- 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
- All ICH quality guidances

THANK YOU!

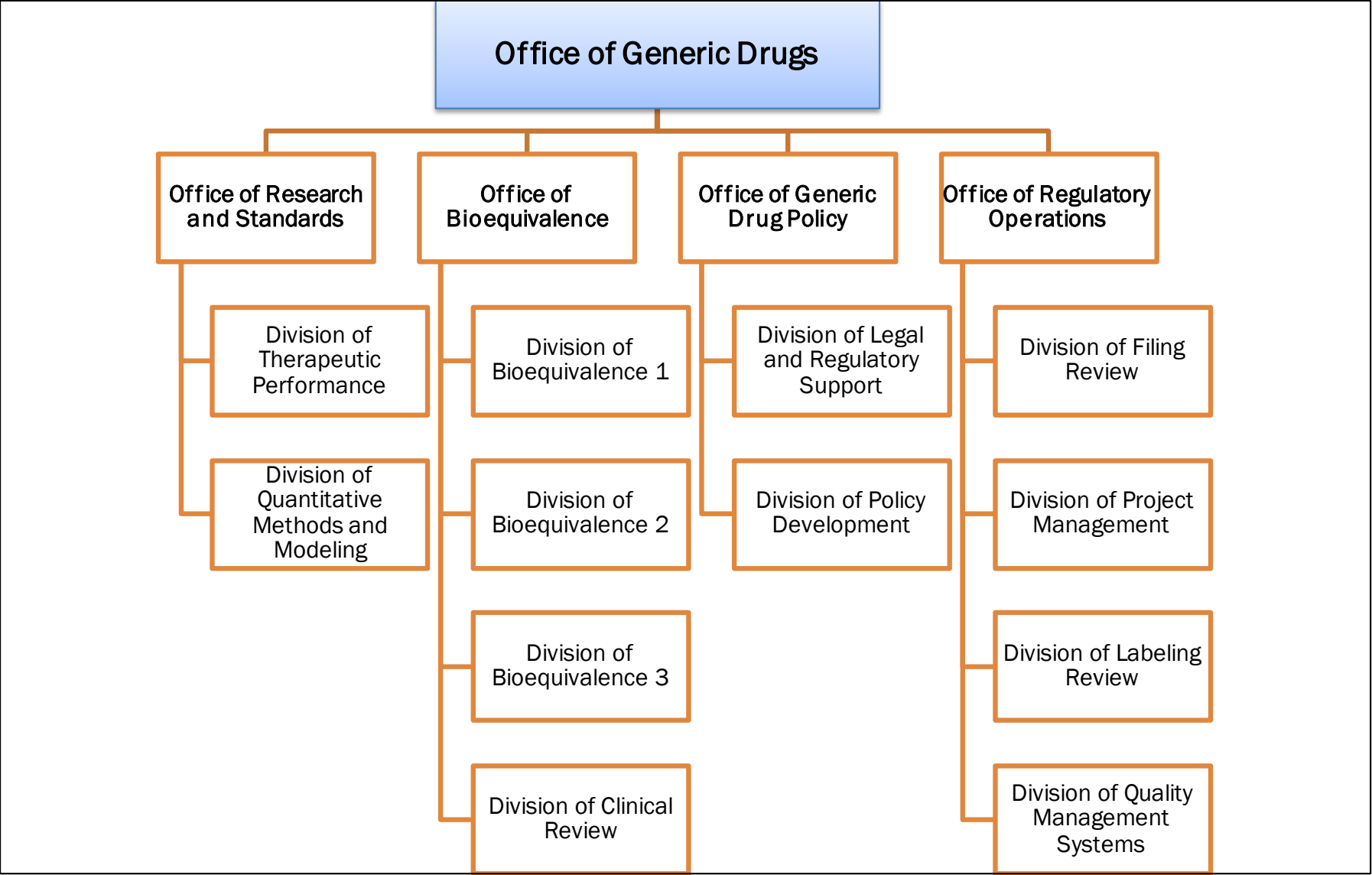


Management of ANDAs for PET Drugs

LCDR Yen Anh Bui, Pharm.D.

**Regulatory Project Manager Team Lead
Division of Project Management
Office of Generic Drugs**

February 21, 2020





FILING PROCESS



REVIEW PROCESS
AND TIMELINE

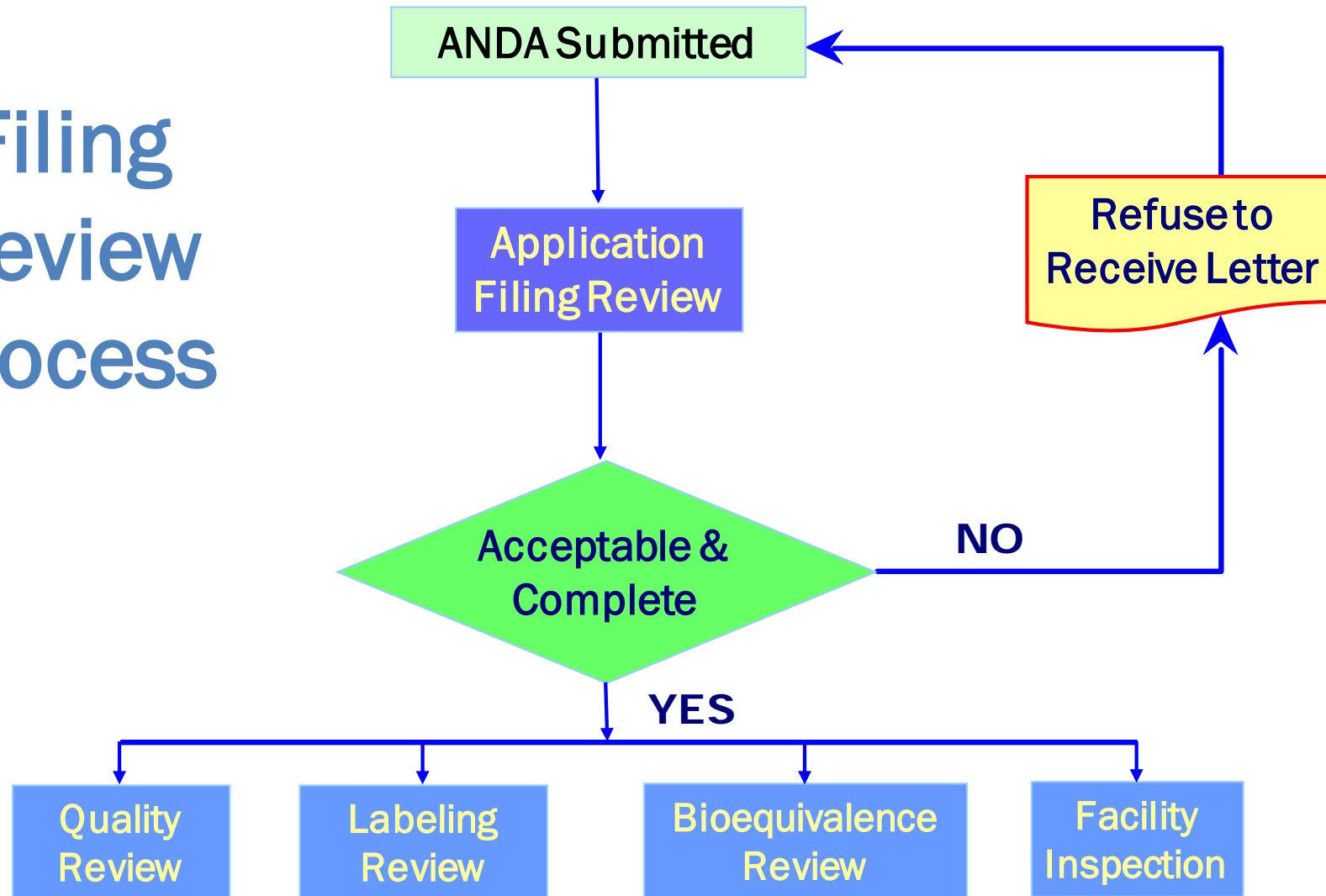


COMMUNICATIONS



RESOURCES

Filing Review Process



Common PET ANDA Filing Deficiencies

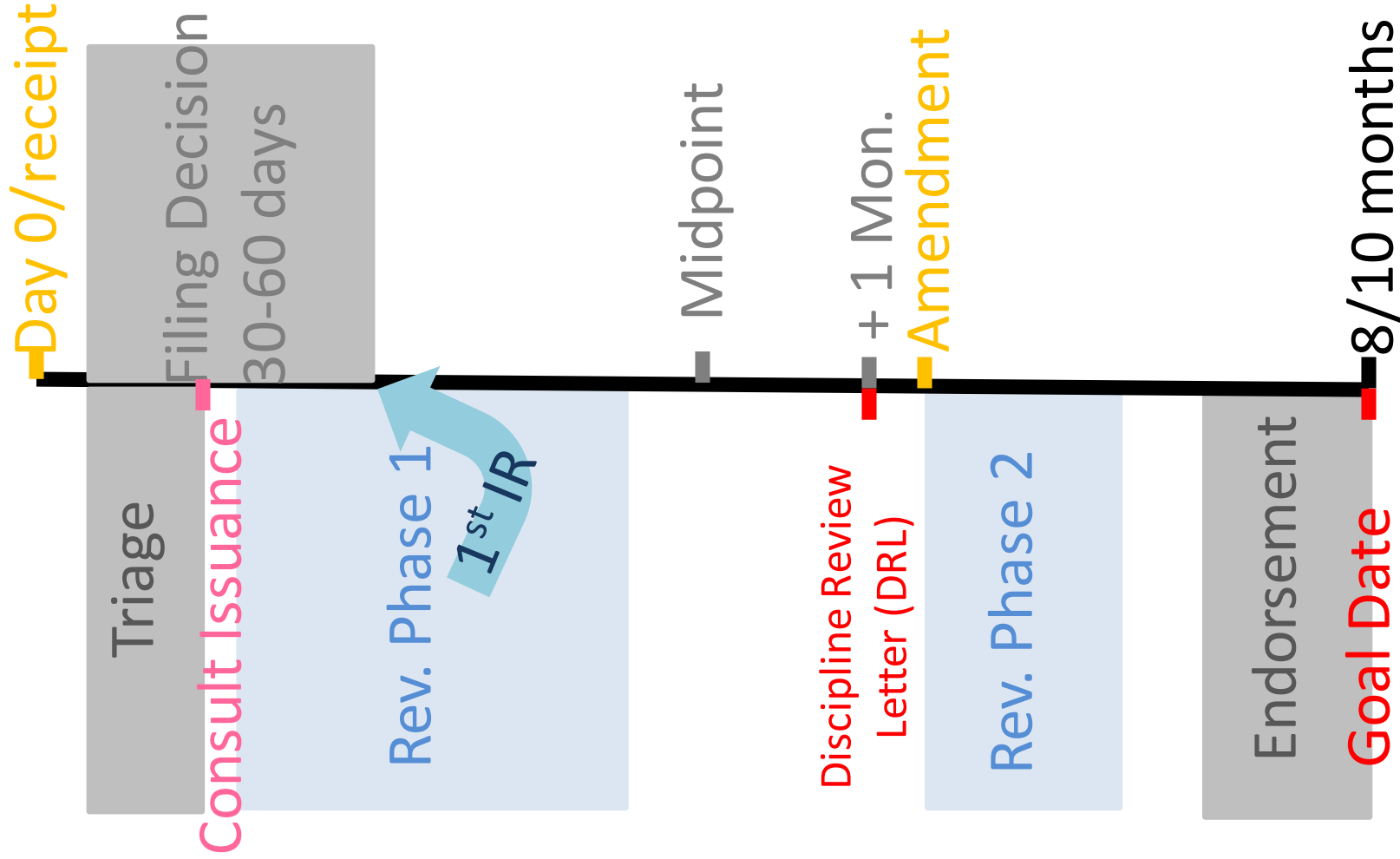
- **Major**

- Lack of evidence of aseptic fill/terminal sterilization procedures and techniques for a sterile drug product
- Lack of drug product method validation/verification reports
- Failure to provide blank manufacturing records
- Failure to provide exhibit (executed) batch manufacturing and packaging records
- Content and format of the ANDA is inadequate
 - *Guidance for Industry: ANDA Submission – Content and Format of Abbreviated New Drug Applications*

Common PET ANDA Filing Deficiencies (Cont.)

- **Minor**

- Inadequate patent certifications provided within ANDA submission
- Labeling deficiencies
 - Side-by-side labeling not provided
 - Proposed package insert (test product) not provided
 - Package insert (Reference Listed Drug) not provided
- Lack of bioequivalence waiver
- Lack of diagrams of container closure systems
- Orientation of vials not provided on the stability data sheets
- Certificate of analysis for all components are not provided



Review Process and Timeline

ORIGINAL	Prior Approval Supplement for ANDAs
----------	-------------------------------------

- **Standard:** 10 months from submission date
 - **Priority:** 8 months with PFC* from submission date
 - **Amendments:**
 - **Standard Major:** 8 months (no inspection) or 10 months (with inspection) from submission date
 - **Priority Major:** 6 months (no inspection), 8 months (w/ inspection & PFC unchanged), and 10 months (w/inspection & no PFC or changed) from submission date
 - **Standard/Priority Minor:** 3 months from submission date
- **Standard:** 6 months (with no inspection) or 10 months (with inspection) from submission date
 - **Priority:** 4 months with PFC* from submission date
 - **Amendments:**
 - **Standard Major:** 6 months (no inspection) or 10 months (with inspection) from submission date
 - **Priority Major:** 4 months (no inspection), 8 months (w/inspection & PFC unchanged), and 10 months (w/inspection & no PFC or changed) from submission date
 - **Standard/Priority Minor:** 3 months from submission date

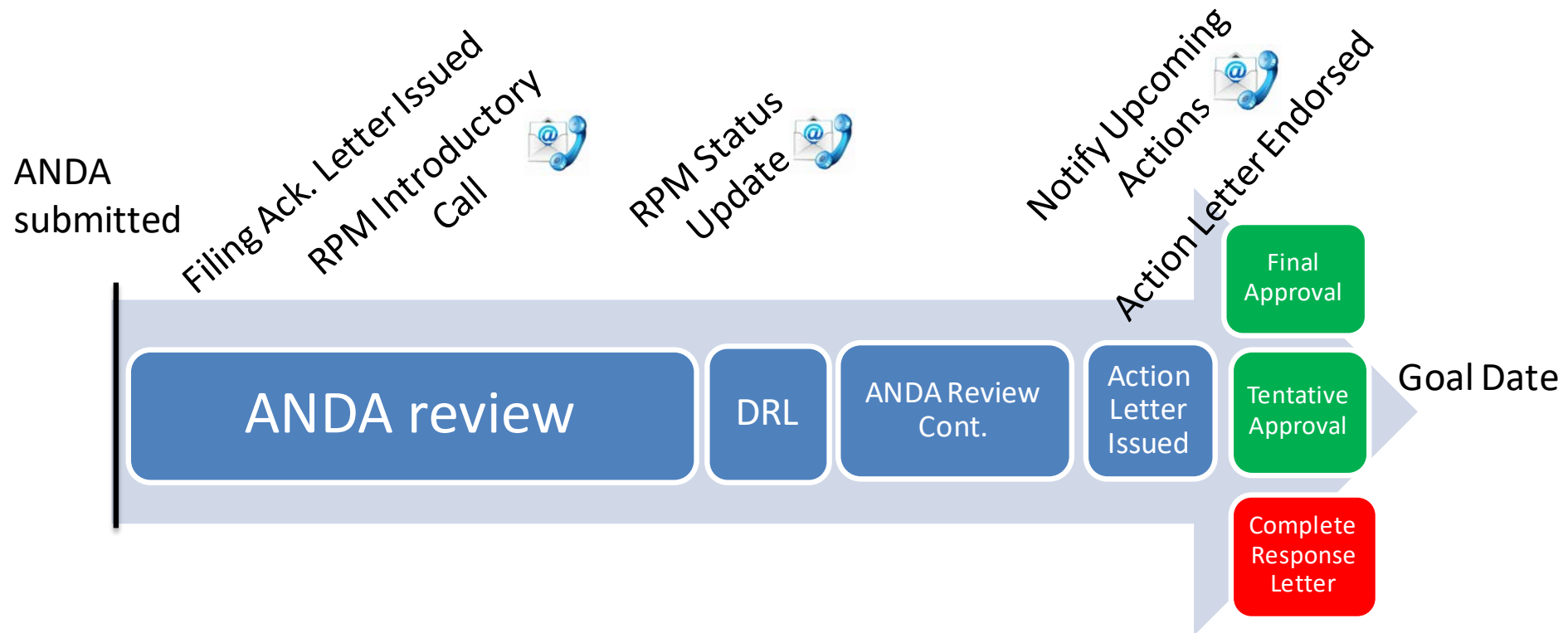
*PFC: Pre-Submission Facility Correspondence

See Guidance for Industry: <https://www.fda.gov/media/105794/download>

Regulatory Project Manager

- **Oversee the review of ANDAs**
 - Provide oversight across all review disciplines
 - Work to ensure all reviews are complete
 - Work to ensure OGD meets goal dates
- **Triage all amendments from receipt of ANDA to approval**
 - Assessing Standard/Priority with each submission. See MAPP 5240.3 rev.4 <https://www.fda.gov/media/89061/download>
 - Assign received amendments to the applicable disciplines
- **Communicate key events in the approval process**
 - MAPP 5200.12
- **Serve as point of contact**
 - All communications will go through RPM
 - Exception: responding directly, as requested by a discipline (i.e., Discipline Review Letter)

Communications



Post Approval Changes

- Guidance for Industry: Changes to an Approved NDA or ANDA
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-nda-or-anda>
- Controlled correspondence (CC) seeking information on post-approval submission requirements:
 - not be covered by existing CDER post-approval changes guidance, **AND**
 - not be related to a specific ANDA
 - Examples:
 - questions related to a product site transfer that would impact more than one approved ANDA
 - questions relating to modernizing a manufacturing facility that is approved for more than one ANDA
- CC mailbox: GenericDrugs@fda.hhs.gov

Resources

- Office of Generic Drugs
<https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm119100.htm>
- Link to FDA guidance
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents>
- Contact RPM for ANDA specific questions
 - If RPM is unknown or unavailable, contact: Yenanh.Bui@fda.hhs.gov



THANK YOU!





Management of PET Drug Applications-PET Community Perspective

Sarah DeMare, M.S.
Facet Life Sciences

**PET Drugs: A Workshop on Inspections Management and
Regulatory Considerations**

FDA White Oak Conference Center
Silver Spring, MD USA
February 21, 2020

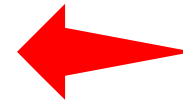
Management of PET Drug Applications-PET Community Perspective

- **DISCLAIMER**—I am not a member of the PET community, however I work with many members of the PET community to advise them on the content and format of their applications. The views expressed herein are my own.

Organization of the Application

During review, information requests have been received asking for information that is already included. Are there recommendations or suggestions for how the applicant can guide the reviewer to make the process more efficient for both sides?

1-Reviewer cannot find the information



2-Misunderstanding on the part of the applicant, as to what information FDA is requesting

Organization of the Application

Precursor

- S1-General Information
- S2-Manufacture
- S3-Characterization
- S4-Control of Precursor
- S5-Reference Standards
- S6-Container Closure System
- S7-Stability

Drug Substance

- S1-General Information

Drug Product

- P1-Description and Composition
- P2-Pharmaceutical Development
- P3-Manufacture
- P4-Control of Excipients
- P5-Control of Drug Product
- P6-Reference Standards
- P7-Container Closure System
- P8-Stability

Organization of the Application

Table 1: Equipment and Ancillary Materials

Equipment	Step Used
Sterile Vial - CoA	Step 2
Filter – CoA	Step 7
Sterile Syringe - CoA	Step 7

← Example Table in P.3.3

Table 1: Validation Reports

Method	Validation Report
HPLC	Report 123
iTLC	Report 456
Sterility	Report 789

← Example Table in P.5.3

Organization of the Application

- **REVIEWER'S GUIDE** (for original application)
 - Placed in 1.2 Cover Letter. Can help orient the reviewer to the set up of the application, and alert the reviewer to anything special about how the application is organized.
- **1.6.3 Correspondence Regarding Meetings** (for original application)
 - A table of all FDA interactions, and requests for information to be included in the application. Usually derived from official meeting minutes.
- **1.11.1 Quality Information Amendment** (supplements and information requests)
 - Orients the reviewer as to what data are being provided and includes hyperlinks. Try to avoid placing data here that should be elsewhere in Module 3.

Information Requests

During review, information requests have been received asking for information that does not appear to be directly relevant to the change and that we would consider to be more appropriate for review at a GMP inspection. For example, a certificate of conformance for a laminar flow hood.

What is appropriate to include in a supplement and what is reasonable for a reviewer to request?

Information Requests

CONSIDER the possibility....

1-FDA reviewers see many more applications than individual sponsors.

2-What if providing the requested information reduced the chance of inspection?

Post Approval Changes

Would the FDA consider conditional approval for a new manufacturing facility under a PET ANDA if the facility has not been previously inspected for the product, but the manufacturer has other facilities with a satisfactory inspection history for the product? Or allow, at least a CBE-30 submission instead of requiring a pre-approval inspection when adding a new site?

Post-Approval Changes

- Addition of a Manufacturing Site
- New Manufacturer of Precursor
- Alternate method of synthesis of the Drug Product

Comparability Protocols

Draft Guidance for Industry *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing and Controls Information* (April 2016)

“A CP is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC postapproval change on the identity, strength, quality, purity and potency of a drug product....Submission of a CP in a original application or PAS allows the agency to review a description of one or more proposed CMC postapproval changes, supporting information including an any analysis and risk assessment activities, a plan to implement the change, and if appropriate, a reduced reporting category for the change.”

Final Thoughts

- More novel PET products are being developed
- Desire to streamline the review process
- Opportunity for more consistency in the content/format of applications and supplements
- FDA/Industry Working Group to identify and publish best practices for the PET community



Management of PET Drug Applications: PET Community Perspective

Prof. Peter J. H. Scott, PhD

University of Michigan PET Center

**PET Drugs: A Workshop on Inspections Management and
Regulatory Considerations**

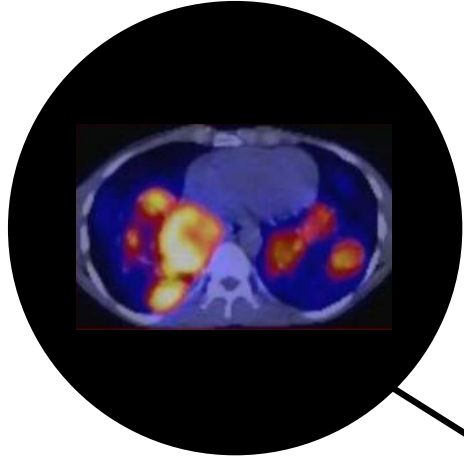
FDA White Oak Conference Center
Silver Spring, MD USA

February 21, 2020

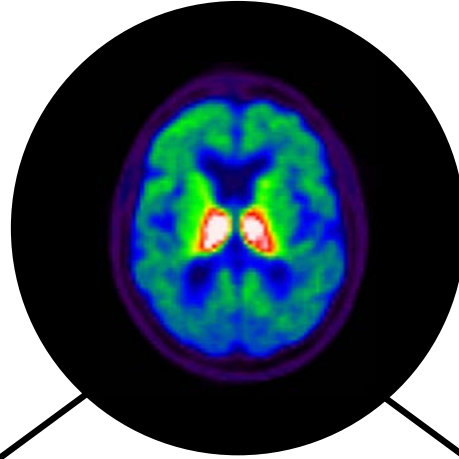


Scott Lab Overview

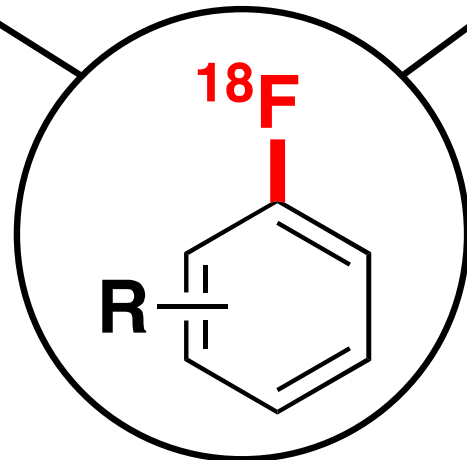
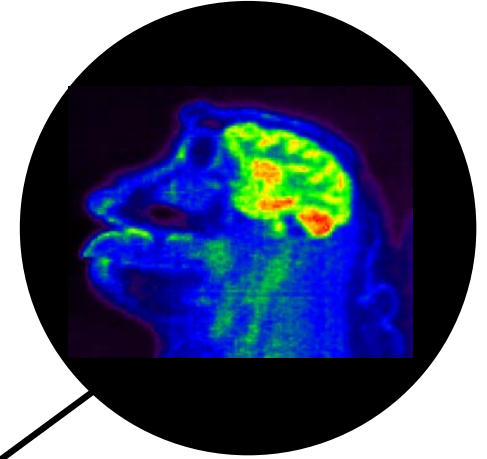
Clinical Production



Clinical Research



Novel Tracer Discovery



New Radiochemistry



New Tech Development

Radiotracers Synthesized for Clinical Use @ UM

CARBON-11

- [¹¹C]Acetate (TCA Cycle – Cardiac, Oncology) -- RDRC
- [¹¹C]Butanol (Blood flow) -- RDRC
- [¹¹C]Carfentanil (Opioid) -- RDRC
- [¹¹C]Choline (Oncology) -- RDRC
- [¹¹C]DASB (SERT) -- RDRC
- [¹¹C]DTBZ (VMAT2) – IND / -- RDRC
- [¹¹C]FMZ (BZD) – IND / -- RDRC
- [¹¹C]HED (Adrenergic) -- RDRC
- [¹¹C]Methionine (Oncology) -- RDRC
- [¹¹C]Palmitate (Cardiac) -- RDRC
- [¹¹C]PBR28 (Neuro, Cardiac and Oncology) -- RDRC
- [¹¹C]PE2I (Dopamine transport) -- RDRC
- [¹¹C]PiB (Amyloid) -- RDRC
- [¹¹C]PMP (Acetylcholinesterase) -- RDRC
- [¹¹C]Raclopride (Dopamine) -- RDRC
- [¹¹C]Sarcosine (Prostate cancer) -- IND

GALLIUM-68

- [⁶⁸Ga]NETSPOT (Neuroendocrine tumors) – Parent NDA
- [⁶⁸Ga]PSMA-11 (prostate cancer) – Cost-recovery IND

FLUORINE-18

- [¹⁸F]FDG (Glucose metabolism) -- ANDA
- [¹⁸F]NaF (Bone) -- RDRC
- [¹⁸F]FLT (Cell proliferation) -- RDRC
- [¹⁸F]FAZA (Hypoxia) -- RDRC
- [¹⁸F]Flubatine (NAChRs) -- RDRC
- [¹⁸F]Fluorocholine (Prostate cancer) -- RDRC
- [¹⁸F]FEOBV (VAcHT) -- RDRC
- [¹⁸F]MPPF (5HT-1A) -- RDRC
- [¹⁸F]ASEM (alpha 7) -- RDRC
- [¹⁸F]MHPG / [¹⁸F]PHPG (Cardiac NET) -- IND
- [¹⁸F]N-Methyl Lansoprazole (Tau) -- RDRC
- [¹⁸F]AV1451 (Tau) – RDRC

NITROGEN-13

- [¹³N]NH₃ (cardiac) – IND

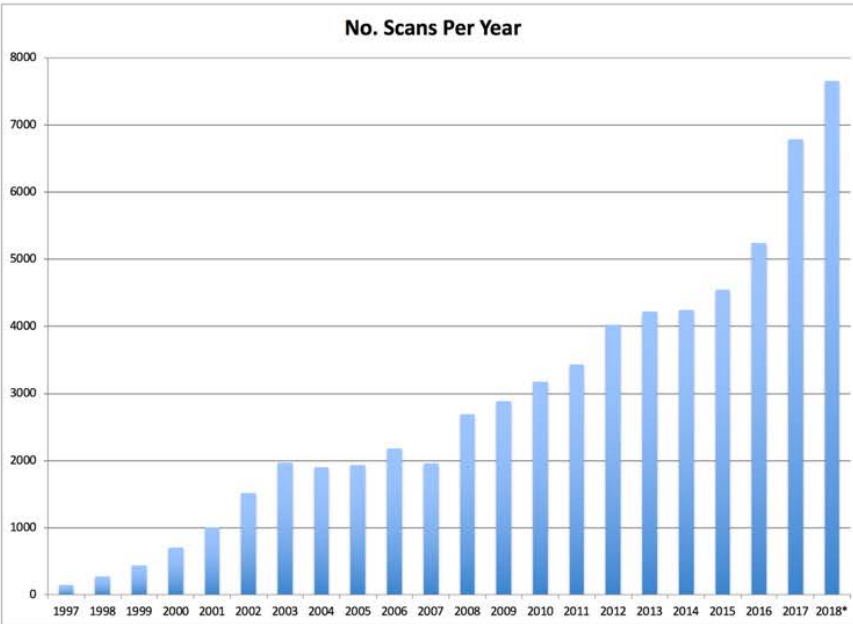
RUBIDIUM-82

- RbCl₂ (Cardiac Rest/stress) – Parent NDA

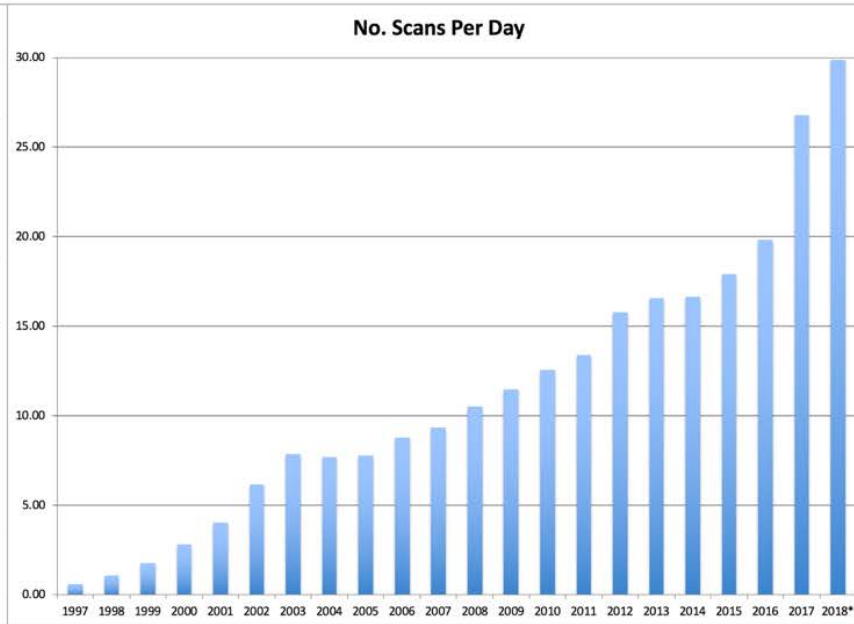


PET Utilization for Clinical Care @ UM

No. Scans Per Year



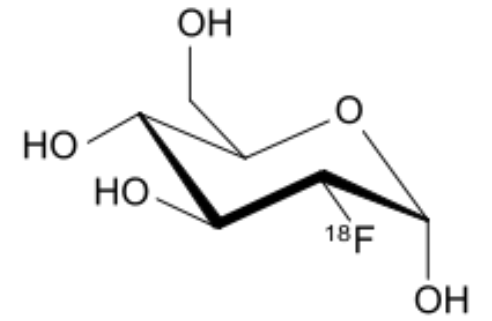
No. Scans Per Day



- Clinical PET utilization at Michigan Medicine doubled between 2014 and 2018. Driven by migration from cardiac SPECT to cardiac PET, introduction of NETSPOT and ^{68}Ga -PSMA, and growth in FDG utilization;
- Current scanner capacity is 2 x PET-CTs for clinical care and 1 PET-CT for clinical research. Two new clinical PET-CT scanners are being obtained to expand clinical bandwidth.

[¹⁸F]FDG @ UM

- Synthesized using the FASTLab 2;
- 2 x 750 mCi batches prepared per day (M – F);
- ~6000-8000 patients receive FDG PET at UM per year;
- ANDA filed June 2012 and approved July 2015;
- FDA Inspections Feb 2014 (pre-approval), March 2019 (routine).



PET Drugs Are Safe and Low Risk!

- PET drugs are sub-pharmacological microdoses (typically $\ll \mu\text{g}/\text{kg}$ administered mass) and end-product testing occurs on every batch;
- During 15 years operating out of new UM PET Center (~8000-10,000 PET scans per year), there have been no sterility failures and no adverse events;
- From our recent PET manufacturers survey, in 2019 >58,000 radiopharmaceutical batches were prepared. 6 sterility failures (including false positives) and 0 adverse events were reported;
- Across the greater PET community, a median frequency for adverse events in diagnostical radiopharmaceuticals of 1.63 (interquartile range: 1.09-2.29) per 100,000 has been reported (Schreuder et al., 2019).

Discussion Items – 21CFR11

2009

(Comment 43) We received one comment on electronic audit trail capabilities. The comment stated that, as we estimated, there is very little if any software of this nature in use by PET drug producers. The comment stated that many items of production equipment are incapable of the necessary software upgrades due to age and existing operating systems. The comment maintained that requiring the use of electronic audit trail software would be unduly burdensome for the PET community, and it recommended that we not require an electronic audit trail as part of PET CGMP provisions.

(Response) We agree that the additional level of quality assurance that might be provided through the use of electronic audit trail capability does not warrant the additional costs that would be imposed to implement this capability. Therefore, the CGMP requirements for PET drugs do not include electronic audit trail requirements.

<https://www.federalregister.gov/documents/2009/12/10/E9-29285/current-good-manufacturing-practice-for-positron-emission-tomography-drugs>

Discussion Items – 21CFR11

1. Following the December 2018 Guidance Document, there has been a push during inspections about electronic data integrity and compliance with 21CFR11. Is full Part 11 compliance expected for PET drugs and, if so, what does this look like and what is the timeline? It does present challenges to the PET community, including:

- PET drug manufacture uses very specialized equipment, much of which is not currently available with 21CFR11 capabilities;
- Many equipment manufacturers are based outside the US and not familiar with the US regulatory environment. The market is also small, meaning they are hesitant to invest in new product development without a clear understanding of regulatory expectations;
- Academic PET Centers are operating within the confines of campus-wide IT systems, adding an additional layer of complexity;
- PET Centers have small numbers of staff and 21CFR11 requirements can be prohibitively burdensome. For example, reviewing audit trails on up to 10 pieces of equipment before release of every batch of PET drug could delay release of a short-lived product by ≥ 0.5 h. This impacts staff work schedules and our overall capacity to produce PET drugs.

Discussion Items – Exception Excipients

2. Can the PET community get clarification regarding application of the Exception Excipient rule to PET drug formulations. Specifically, its application to the RLD for the [F-18]FDOPA NDA. It is our understanding of the rule that any material which is not a preservative, buffer, or antioxidant cannot *qualitatively or quantitatively* be different from the RLD formulation. This causes a problem for any group applying for an ANDA for [F-18]FDOPA because sodium chloride (108 mg) and acetic acid (12.72 mg) are present in the final RLD formulation but are not a preservatives, buffers, or antioxidants. Is there any wiggle room here, particularly given that most patients will only receive one PET scan in their lives.

Discussion Items – 21CFR211 Creep

3. There seems to be a push at the FDA to conflate 211 standards to the 212 production of PET radiopharmaceuticals. For example, numerous colleagues have had controversial inspections involving 211 specific issues, and have received 483 observations citing 211 regulations. We think this is inappropriate for sites that are producing relatively small number of doses per day, and the fact that the CFR states that PET drugs are regulated according to 21CFR212 and are exempt from 21CFR211.

Sec. 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs) for administration to humans or animals.

Why are these inspections still happening? The common excuse that some inspectors are more familiar with 21CFR211 is unacceptable.

Discussion Items – Quarterly Safety Reports

4. Is FDA expecting if we have a new ANDA approved (FDOPA, NaF, etc) that we would still be expected to file quarterly safety summary reports for the first 3 years post approval? We have heard that FDA is no longer holding strong on this with transition to eCTD, as the data is all captured in the annual report. There is a lot of cost, particularly to small sites and academic labs, for quarterly eCTD filings for a one page no adverse event report.

Discussion Items – Increasing Micro Costs

5. The PET community has had some significant increases in costs related to microbiology testing and validation. In fact, in the last 2 years the costs for just microbiology related testing at one site were about 10x what they were previously. The amount of growth promotion testing, bioburden testing, microbial identification tests and disinfection validation studies being requested have really affected that sites bottom line. Most of this was instituted in order to address the FDA inspectors observations during the last audit of this site, which relies on a third-party service provider for these studies because of the small and limited size of the operation.

Costs may increase substantially again in light of recent talk about house Flora testing and speciation requirements. Is this required in light of a very low AE rate (1.63/100,000) and sterility failures (2019: 6/58,225)?

Closing Thoughts

- **PET drugs are safe and low risk (very low sterility positives and AEs)!**
- The community has made significant strides in cGMP compliance since the introduction of 21CFR212 in 2009;
- Field and inspection discussions that our approved manufacturing facilities/processes and/or stipulations of 21CFR212 are no longer adequate, and of increasing regulatory burden to address this, are concerning to PET drug manufacturers operating small facilities for a number of reasons:
 - The PET community does not set the price of PET drugs -- this is dictated by CMS;
 - As such, we have no mechanism to increase pricing to cover new costs associated with eCTD, 21CFR11, and new microbiology requirements, or any additional costs associated with further expansion of compliance activities;
 - There is a real risk that increased costs with no change in reimbursement will lead some PET drug manufacturers to exit the market, causing patient access issues.

