Workshop Agenda

PET Drugs: A Workshop on Inspections Management and Regulatory Considerations

Friday, February 21, 2020
08:00 am EST to 05:00 pm EST

FDA White Oak Conference Center
Bldg 31 Conference Center, The Great Room (Rm 1503)
10903 New Hampshire Ave
Silver Spring, MD 20993

8:00	**Welcoming Remarks** **Sally Schwarz, R.Ph., Henry VanBrocklin, Ph.D., Sue Bunning, M.A., Louis Marzella, M.D., Ph.D.**
Session I:	**Considerations and Trends in Inspections and Compliance** **Moderators: Steve Zigler, Ph.D., Krishna Ghosh, Ph.D.**
8:15-8:50	**Manufacturing Process Assessment and Pre-approval Inspections** **Speaker: Krishna Ghosh, Ph.D., FDA**
8:50-9:10	**Recent Experience with PET Surveillance cGMP Inspections of PET Manufacturers** **Speakers: Rick Friedman, M.S., FDA**
9:10-9:50	**Current Trends and Observations on Inspections** **Speakers: Sally Schwarz, R.Ph., BCNP, and Peter Webner**
9:50-10:05	**BREAK**
10:05-10:45	**PET Surveillance Inspections: FDA Pilot Program for Tablet-Based Inspections for PET Drugs**

Speakers: CDR Binh Nguyen, Pharm.D., MS Reg Sci, BCSCP and CAPT Ileana Barreto-Pettit, R.N., M.P.H., FDA

10:45-11:15 Panel Discussion and Questions: Current Trends and Observations

Moderators: Steve Zigler and Krishna Ghosh

Panelists: Ravi Kasliwal. Sally Schwarz, Ileana Pettit, Peter Webner, Tim Pohlhaus, Rick Friedman and Michael Nazerias

Session II: Lifecycle Management of PET Drug Applications

Moderators: Peter Scott, Ph.D., and Ramesh Raghavachari, Ph.D.

11:15-11:35 Management of PET Drug Applications (NDA or ANDA)

Speakers: Ramesh Raghavachari, Ph.D. and LCDR Yen Anh Bui, Pharm.D.

11:35-11:55 Management of PET Drug Applications – PET Community Perspective

Speakers: Peter Scott, Ph.D. and Sarah DeMare, Ph.D.

11:55 -12:20 Panel Discussion and Questions: Lifecycle Management of PET Drug Applications

Moderators: Peter Scott and Ramesh Raghvachari

Panelists: Peter Scott, Sarah DeMare, Kyong "Kaye" Kang, Pharm.D., Ravi Kasliwal, LCDR Yen Anh Bui, Pharm. D., Bankim Patel, RPh, Alyssa Carter, M.A., RAC and Ron Niles, Ph.D.

12:20-1:20 LUNCH

Session III: Chemistry and Product Quality Assurance

Moderators: Steve Mattmuller, R.Ph., BCNP, and Ravi Kasliwal, Ph.D.

1:20-1:40 Product Quality Assurance: Microbiological Regulatory Perspective

Speaker: Laura Wasil, Ph.D.

1:40-2:00 Product Quality and Sterility Assurance

Speakers: Henry VanBrocklin, Ph.D. and David Hussong, Ph.D.

2:00-2:20 Chemistry and Product Quality Assurance

Speaker: Christopher Ignace, Pharm.D., Ph.D.

2:20-2:50 Panel Discussion and Questions: Product Quality Assurance

Moderators: Steve Mattmuller and Ravi Kasliwal, Ph.D.

Panelists: Laura Wasil, Henry VanBrocklin, Christopher Ignace. David Hussong, Rick Friedman, Krishna Ghosh, and David Jaworski

2:50-3:10 BREAK

Session IV: Changing Landscape of PET Drugs, Labeling Requirements, and Electronic Filing Requirements

Moderators: Michael Nazerias, M.S., and Louis Marzella, M.D., Ph.D.

3:10-3:30 Changing Landscape of PET Drugs

Speaker: Ravi Kasliwal, Ph.D., FDA

3:30-3:50 Labeling Requirements for NDAs

Speaker: Michelle Fedowitz, M.D., FDA

3:50-4:10 Requirements for Electronic Filing of Regulatory Applications

Speaker: Mathilda Fienkeng, Pharm.D., FDA

4:10-4:45 Panel Discussion and Questions: Changing Landscape, Labeling Requirements, and Electronic Filing

Moderators: Michael Nazerias and Louis Marzella

Panelists: Ravi Kasliwal, Michele Fedowitz, Mathilda Fienkeng

4:45 Closing Remarks, Next Steps

Steve Zigler, Ph.D. and Louis Marzella, M.D., Ph.D.

5:00 Close

Introduction – Additional Details

The co-authors on this paper are all members of the workshop organizing committee.

The presentations and a recording of the workshop are currently available on the FDA's website at www.fda.gov/drugs/pet-drugs-workshop-inspections-management-and-regulatory-considerations-02212020-02212020 (accessed July 2021).

The workshop evolved out of a series of continuing education sessions organized by the Coalition of PET Drug Manufacturers (the Coalition) at SNMMI meetings from 2014 to 2019. Planning for the workshop began in earnest after the SNMMI Annual meeting in 2019 when the organizing committee held a series of discussions to define the scope, purpose, and target audience for the workshop. Early in these discussions, the organizers opted to exclude efficacy, dosimetry, indications, and reimbursement from the scope of topics for the workshop. Ultimately, the organizers defined the purpose of the workshop as "a forum for the exchange of information and perspectives on the regulatory and compliance framework for PET drug manufacturing."

Each session consisted of presentations from FDA staff members and members of the PET community with the goal of sharing experiences and recommendations. Panel discussions were included at the end of each session.

Further Detail from the "Opening Remarks"

The short shelf life and very low injected mass (microdose) of the active radiopharmaceutical ingredient are the primary characteristics that define the risk profile of PET drugs. Secondary characteristics include the use of microbiologically hostile and often lethal synthesis steps, pre-sterilized components, aseptic component assemblies and manipulations, and the use of closed containers during the automated synthesis process for a typical PET drug. These secondary characteristics result in an extremely low – typically zero – bioburden process stream before sterile membrane filtration in the final production step. Together, the primary and secondary characteristics greatly reduce the probability of microbiological contamination in PET drugs. Consistent with this outcome, PET manufacturers experience low rates of sterility test failures in the routine supply of approximately 100,000 batches of PET drugs annually required for a nationwide supply (1). The practical ramifications of these characteristics have resulted in negligible rates of patient adverse events following the administration of PET drugs (2,3,4,5,6). The clinical and commercial history of this product class have demonstrated that PET drugs are safe and low risk. The PET GMP regulations have been effective in maintaining a safe supply of PET drugs. Through a comprehensive workflow from manufacturing through pharmacy dispensing under State regulations, PET drugs have firmly proven their medical value to patient care.

The Coalition has helped bridge the gap between the FDA and the PET community to enable the development of scientifically sound and rational practices associated with the manufacture of PET drugs. The impetus to establish the Coalition was originally provided by the FDA to create a

single conduit for communication of regulatory issues between the FDA and the PET community. To this end, the Coalition has represented the interests of academic, government and commercial PET drug manufacturers since 2010.

At the time of the workshop, there were approximately 50 holders of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) supporting a dozen PET drugs. The most widely used PET drug, Fludeoxyglucose F 18 Injection (FDG), accounted for more than 35 NDAs and/or ANDAs. There were approximately 150 PET manufacturing facilities in the US in 2012, representing a growing pharmaceutical segment as a result of the approvals of newer therapeutic radiopharmaceuticals that require patient specific diagnostic modalities. According to market research data, slightly more than 2 million PET scans were performed in the US in 2018 (7). Thus, the size of the US market for PET drugs is quite small compared to the pharmaceutical industry. Considering these factors, the public health risk of PET drugs is miniscule compared to that of traditionally manufactured pharmaceutical products. In addition, the large number of PET manufacturing facilities required to supply a relatively small number of patients creates a unique business model under the umbrella of FDA regulation.

Session I – Considerations and Trends in Inspections and Compliance

Further Detail from "Manufacturing Process Assessment and Pre-approval Inspections" Presentation

Product quality is a scientific discipline that is applied throughout the product lifecycle. The Agency encourages the documentation and implementation of quality by design concepts in the early stages of development, including about the understanding the manufacturing process for approved products. After approval, the quality management system should make decisions based on science and risk management principles. Risk management, which plays an important role in each phase of the product lifecycle, may be product based depending on the complexity of a particular product. Going forward, the FDA will continue to evolve its regulatory approach to PET drugs, including: (a) leveraging past knowledge to encourage a preventive action culture, (b) improving quality concepts by enhanced monitoring and review (including deviations, root cause analysis, investigations, environmental monitoring and controls, data evaluation, and change control measures) and (c) adoption of new tools, technologies, manufacturing control strategies, and quality concepts for complex PET drugs. Ghosh did not discuss the criteria FDA uses to determine the risk level or complexity of PET drugs[1] but noted that the FDA and the community of PET manufacturers should work together to achieve these outcomes.

Various offices play important roles in the review and approval of an NDA or ANDA for a PET drug. Within CDER, the clinical review divisions and the OPQ play the most significant roles. The OPQ is a "super" office consisting of nine offices with different responsibilities. Outside of CDER, the ORA plays a major role in the inspection process since this office is responsible for routine surveillance inspections. Of the nine offices within the OPQ, the most pertinent in terms of this workshop are:

[1] Complex PET drugs were discussed in a later FDA presentation, but this topic remains a subjective concept.

- *Office of Quality Surveillance* is responsible for Field Alert Reports and surveillance inspection plans
- *Office of New Drugs* conducts reviews of new drug and investigational new drug applications (NDAs and INDs)
- *Office of Pharmaceutical Manufacturing Assessment (OPMA)* oversees the scientific assessment and quality evaluation of pharmaceutical manufacturing processes and facilities, including microbiology, pre-approval inspections, and post-approval inspections
- *Office of Life Cycle Drug Products* reviews abbreviated new drug applications (ANDAs) and supplements to all approved applications
- *Office of Program and Regulatory Operations* manages the application review process and serves as the contact point between all offices and application sponsors

The FDA conducts four different types of inspections. The goals and FDA offices involved in each inspection are:

- *Pre-approval inspections (PAI)* are conducted for both NDAs and ANDAs. The purpose of a PAI is to make sure the facility is capable of manufacturing the product according to the conditions described in the application and according to the PET GMP regulations. These inspections are managed by the OPMA and the ORA.
- *Post-approval inspections* are relatively new. These inspections are performed to audit for changes in production and control practices after product approval. These inspections are also managed by the OPMA and the ORA.
- *Routine surveillance inspections* are routine periodic inspections of manufacturing facilities. These inspections are managed by the ORA, the Office of Surveillance (OS), and the Office of Compliance (OC).
- *For-cause inspections* result from potential indication or evidence of non-compliance by the manufacturer. These inspections are managed by the OC and the ORA.

The review process for the chemistry, manufacturing and controls (CMC) section of an application involves an integrated quality assessment performed by as many as eight different teams that focus on the drug substance, drug product, and manufacturing (process, facilities, and microbiology). This team-based approach is embodied in the FDA's "One Quality Voice" initiative that forms the core of the OPQ's science- and risk-based review of drug applications (8).

The definition of a PET drug was first included in Section 121 of FDAMA and was also subsequently included in the PET GMP regulations. In addition to the active radiopharmaceutical ingredient, the definition broadly includes "the precursor, any non-radioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program used in the preparation of the PET drug" (**Error! Bookmark not defined.**). The FDA considers these elements part of the

approved product but takes a risk-based approach to determine when to conduct inspections of the individual elements.

The FDA expectations for a complete marketing application for a new PET drug include:

- A list of all the manufacturing facilities on FDA Form 356h, including manufacturers of precursors, synthesizers, reagent kits, generators, non-radioactive components, cassettes, etc.
- A detailed description of the roles and responsibilities for each manufacturing facility
- FDA Establishment Identification (FEI) number for all manufacturing facilities
- Assurance that all manufacturing facilities are registered in the FDA's Electronic Drug Registration and Listing System (eDRLS)
- A list of all external sterility and microbiological testing labs, including specific tests performed by each lab
- Confirmation that all manufacturing facilities are ready for inspection prior to submission of the application to the FDA

Common deficiencies occur in the description of the manufacturing process in PET drug applications. Such deficiencies often result in information requests from the FDA to the sponsor and delays in the review of the application. Examples of common deficiencies include:

- Incomplete manufacturing flow charts and unit process descriptions
- Lack of supportive studies for proposed process control parameters (reaction times, temperature ranges, pressures etc.)
- Inadequate extractable and leachable studies (e.g., tubing, connectors, fittings)
- Incomplete description of in-process controls for the manufacturing process (environmental, microbiology and chemistry controls)
- Batch records that lack critical process checks and minimum radioactive yields
- Inadequate controls for critical steps in automated synthesis sequences
- Inadequate information and conditioning for purification columns
- Inadequate or missing final quality assurance checks and sign off for batch release

The FDA considers at least three specific risk factors during the pre-approval inspection (PAI) process, including (a) facility risks, (b) process risks, and (c) product risks. In the evaluation of facility risks, the FDA considers the compliance history of the facility, including whether or not the facility has been previously inspected for the unit operation described in the drug application under review. A unit operation is "from start to finish," but specific examples of the criteria that define unit operations were not included in this presentation. Process risks include process characteristics and complexities, including the microbiological aspects of the PET drug. Product risk factors are based on the unique characteristics of PET drugs, referred to as critical quality attributes (CQA)

There are three primary objectives for the PAI process that differ from the objectives of a typical surveillance inspection:

- Determine if the establishment has a quality system designed to achieve sufficient control over the facility and commercial manufacturing operations
- Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the application
- Audit the raw data in analytical and manufacturing equipment (hardcopy or electronic) to authenticate the integrity of the data submitted in the application

Practically speaking, the core issue for the PAI is to determine if the manufacturing process can reliably ensure that critical quality attributes are achievable and met. Deficiencies found during the PAI process include media fill simulations and various elements of the analytical laboratory information in the application. In addressing deficiencies, it is important for the applicant to adequately respond to Form 483 observations. Effective 483 responses rely on scientific and technical rationale, as well as supportive evidence. This may require upgrade, or commitment to upgrade, the QMS itself. Further, a successful response addresses corrective actions with sufficient breadth and includes assurances that corrective actions will be successfully implemented. The final stages of the approval process depend on the suitability of the applicant's responses. In the worst-case scenario, the facility may require a re-inspection or other FDA actions.

Going forward, the Agency plans to focus on improving the quality of 483 responses provided by the PET community to the FDA. In addition, the development of new PET drugs may result in additional complexities that were not considered when the PET GMP regulations and the accompanying guidance documents were originally developed.

Further Detail from "Recent Experience with CGMP Surveillance Inspections of Commercial PET Manufacturers" Presentation

Upon completion of a surveillance inspection, the ORA classifies the inspection outcome into one of three categories: No Action Indicated (NAI), Voluntary Action Indicated (VAI), and Official Action Indicated (OAI). Inspections with minor findings are classified as NAI or VAI, whereas inspections with the most problematic findings may be classified as OAI. OAI inspections are referred to CDER and reviewed by multiple offices and staff within the ORA and CDER.

Between June 2018 and January 2020, the ORA finalized the classification of 45 PET facility inspections. The breakdown of the classifications were: NAI (n = 17, 38%), VAI (n = 24, 53%) and OAI (n = 4, 9%). Based on a review of inspection reports, the FDA found that not all sterility test failures were reported in a FAR, even though the FDA requires PET manufacturers to immediately file a FAR in the event of a sterility test positive. This requirement holds even if the positive test result is later determined to be due to a laboratory error (9).

Examples of objectional facilities and equipment found during FDA inspections of PET manufacturers include damaged floors, leaking pipes, spots and stains on floors and ceilings, porous materials and uncovered holes in hot cells, and holes/gaps in laminar airflow workstations. The Agency reported occasional spore formation in ISO 5 locations. Since the hot cells used in PET manufacturing are typically non-sterile, the occasional occurrence of low levels of environmental microbial contamination is not unexpected. On the other hand, excessive levels of microbial contamination may result from situations where environmental controls are ineffective. Therefore, discriminating between acceptable and excessive levels of environmental contaminants is important, as this supports the need for corrective actions, including facility remodeling or redesign if needed. Friedman did not offer criteria to determine when low levels of environmental microbial contamination are acceptable or objectional.

Based on a retrospective analysis of recent inspections and data from FARs, Friedman offered several observations related to product sterility, including:

- The importance of an effective environmental monitoring (EM) program and analysis of adverse trends in the EM data
- A notation that some PET manufacturing facilities have reported recurring sterility test failures while other facilities have a history of few or no sterility test failures
- The investigation of sterility test failures can be improved
  - Some investigations assume that the test results were “false positives” without clearly establishing that laboratory error was the root cause
  - A probable root cause is only identified in approximately 30% of sterility test failure investigations
  - Spore forming microbes (e.g., bacillus) were isolated in 53% of sterility test failures
  - Operator error or poor aseptic technique are identified as the most common root cause in sterility test failure investigations
- Even though the most significant risk for product sterility is the relatively simple assembly of vial components, connections, and puncture of a septum, microbial contamination is still possible

The general principles of sterile drug manufacturing dictate that all injectable drug products are expected to be sterile at the time of administration. Non-sterile products represent an intolerable risk to patients. The risk of a non-sterile PET drug product is reduced by commonly used production techniques and further mitigated by the short half-life (see other discussions throughout this paper), but the short timeline before patient administration does not eliminate the risk of a non-sterile administration. This is the basis of the GMP requirement to immediately notify the receiving facility in the event of a sterility test failure (10).

In closing, Friedman noted sterility is a critical attribute for PET drugs. It is important to promptly address facility and environmental conditions that may pose a significant hazard to product sterility. The implementation of the FDA’s GMP regulations for PET drugs over the last decade has provided substantial insights into process hazards and good practices. The PET community and the FDA have made major strides in understanding and implementing the PET

GMPs. In the future, continued dialog and information-sharing between the FDA and the PET community are necessary to maintain the safe supply of PET drugs.

Further Detail from "Current Trends and Observations on Inspections – the PET Community Perspective" Presentation

The Academic Perspective

Several examples were provided to illustrate the inconsistent enforcement that academic PET manufacturers sometimes experience between FDA inspections and FDA regulations (**Error! Bookmark not defined.**), guidance documents (11), and policy guides (12).

Most of the inconsistencies reflect the fact that FDA investigators translate common practices, experiences, and expectations from traditional pharmaceutical manufacturing into the PET manufacturing setting. Of course, pharmaceutical manufacturing is regulated under traditional GMP regulations found at 21 CFR 211 (13) whereas PET manufacturing is regulated under the PET GMP regulations found at 21 CFR 212 (**Error! Bookmark not defined.**). The enforcement inconsistencies with PET inspections result from several factors, including untrained FDA investigators, undocumented changes to FDA guidance and policies, and, on rare occasions, the personal agenda of the individual investigator. Regardless of the cause, the net effect of these enforcement inconsistencies is confusion within the PET community and the slow ratcheting of PET manufacturing practices toward traditional manufacturing practices without a discussed, let alone communicated, scientific rationale for the added regulatory burden. This ultimately erodes the PET GMP regulations, which were originally promulgated based on the unique characteristics of PET drugs (**Error! Bookmark not defined.**).

Some of the inconsistent enforcement policies encountered during FDA inspections of academic PET manufacturing facilities include:

1. *The lack of a written agreement with vendors and a vendor qualification program.* The GMP guidance document for PET drugs (11) recommends that only qualified vendors be used and that there is evidence to demonstrate materials and components meet all quality specifications. However, the guidance document does not state how vendors should be qualified or that PET manufacturing facilities are specifically required to maintain vendor agreements or vendor qualification programs.
2. *The lack of controls for final product labeling.* Labels used for the PET drug product are printed without a product batch number, which is recorded on the label during production. In addition, labels are not reconciled to capture the number of labels used, damaged, or returned for a specific batch of a PET drug. In addition, the PET GMPs and the guidance document note that labeling must be controlled to prevent mix-ups, but neither document contains specific instructions for when the label is applied to the final product container, what information is on label, and reconciliation of unused labels. Common practices in PET manufacturing require a "just in time" approach to completing and applying labels to the final product container. Radiation safety considerations also play an important role in defining the workflow for labeling PET drugs.

3. *Action limits and identification requirements for microbes detected during environmental monitoring*. Aseptic areas used in the preparation of PET drugs are routinely sampled for the presence of objectional levels of microbes. USP general chapters <823> and <797> recommend alert/action limits at 3 colony forming units for aseptic areas. The inspectional observation in this case noted that all samples with more than one colony forming unit are objectional and all detected microbes should be identified. However, the PET GMP regulations and the FDA guidance document lack recommendations for alert/action limits and requirements for identification of detected microbes. The enforcement of alert/action limits at a single colony forming unit and the identification of all detected microbes was only announced during an FDA inspection.
4. *Regulation of the practice of pharmacy*. The most common workflow for the delivery of PET drugs involves the manufacturing of a vial under FDA regulation followed by the dispensing of unit doses under the practice of pharmacy. At least one FDA inspector requested to review procedures for dispensing and diluting PET drugs under the practice of pharmacy. This contradicts the FDA policy guide, which states, "PET drug production includes all operations to the point of final release of a finished dosage form" and "dispensing of patient unit doses under the practice of pharmacy is not covered under Part 212" (12).
5. *Lack of a program for in-house testing of components.* The PET GMP regulations state that only a certificate of analysis (COA) from the supplier must be checked for incoming components and the COA must be evaluated against written specifications. The regulations do not require in-house testing.
6. *Lack of a control system for implementing changes in facilities, equipment, materials, etc*. While changes must be appropriately managed, PET GMPs do not specifically require a program for change control. Based on the structure of most academic PET manufacturers, facility management and routine manufacturing operations are separate organizational entities. It would be difficult to incorporate facility management and manufacturing under one control system.
7. *Failure to implement a minimum of three system suitability runs for chromatography equipment*. This contradicts the PET GMP guidance, which notes that at least one analysis of a known standard should be performed before conducting tests on the finished product.

The Commercial Perspective

Inconsistent enforcement actions during FDA inspections also challenge commercial PET manufacturers. This is especially problematic for small innovator companies that have one or more investigational products under development.

Several questions solicited before the workshop from commercial PET manufacturers revealed examples of these challenges, including:

1. *FDA policy changes related to radiosynthesizers.* Additional requirements for radiosynthesizers used in the preparation of PET drugs have included failure mode analysis and automated features for aborting failed batches before the end of synthesis.

Reliance on quality control to detect synthesis failures was deemed inappropriate. These capabilities are beyond the design expertise of the companies that produce the current generation of commercially available radiosynthesizers.

2. *Changes to protocols used in the approval of new manufacturing facilities.* Comparability protocols described in the approved drug application have been changed without the knowledge of the sponsor before the pre-approval inspection. Existing guidance and information state that changing the radiosynthesizer would be acceptable with a 30-day notification to the FDA (CBE 30) provided the product strength, concentration, and excipient profile were identical. Recent reviews indicate that the FDA now require a pre-approval supplement for such changes. This is especially problematic for start-up firms planning for the contract manufacturing of their product across a nationwide network of manufacturing facilities.
3. *Changes in requirements for the testing of incoming components and materials.* After qualifying the supplier of a critical material (e.g., precursor and standard), the PET GMP regulations provide for acceptance of incoming lots of the materials based on COAs. However, an investigator on a recent PAI required that each lot undergo in-house testing before use. As in the previous example, this is problematic for start-up firms planning for the contract manufacturing.
4. *Enforcement of traditional GMP regulations (21 CFR 211) instead of the PET GMP regulations.* It is not clear to commercial PET manufactures how best to work with the FDA to address situations when FDA investigators opt to apply traditional GMP regulations instead of the PET GMPs.
5. *Action limits and identification requirements for microbes detected during environmental monitoring*. Changes to these limits were discussed in the previous section. However, a further complication for start-up firms is that the FDA recently suggested that a new manufacturing facility cannot be added if the facility has encountered greater than one colony forming unit in the aseptic manufacturing area within the last year. This could significantly hinder innovation for the development of new PET drugs.

Numerous academic facilities, commercial facilities, and small innovation-driven companies create a complex network of PET manufacturers that requires an organized and well-communicated system for changes to regulatory guidance and policies. “Regulation by inspection” may provide an effective framework for the evolution of regulatory requirements in the traditional pharmaceutical manufacturing setting. However, this approach creates chaos across 150 academic and commercial manufacturing facilities dedicated to manufacturing a small number of PET drugs. In order to drive compliance across all PET manufacturing facilities, changes to regulatory enforcement standards must be implemented in a controlled and methodical fashion.

Further Details from the "Office of Regulatory Affairs (ORA) PET Surveillance Inspections" Presentation

The FDA uses a risk-based site selection model to identify manufacturing facilities for surveillance inspections (14). The Agency ranks drug manufacturing facilities for surveillance inspections based on risks to drug quality. Risk-based inspectional frequency considers the compliance history of the facility, the history and nature of recalls linked to the facility, the inherent risk of the drug product, and other criteria deemed necessary and appropriate by the FDA for purposes of allocating inspection resources. From these considerations, the FDA generates a numerical risk score for the facility. Currently, the risk score is derived from 6 categories, namely the type of facility, the time since the last inspection, inspection history, patient exposure (volume of products produced by the facility), hazard signals (e.g., field alert reports, recalls, complaints, adverse drug experiences), and inherent product risk. The traditional biennial inspection frequency has been replaced with a "risk-based" schedule that considers a facility's "known safety risks." This assures that FDA resources address the most significant public health risks with inspectional coverage. The FDA did not discuss the criteria for assigning a risk score for type of facility, patient exposure, or the inherent product risk.

FDA surveillance inspections differ from pre-approval inspections (PAIs) described by previous speakers. A surveillance inspection is designed to monitor a facility's conformance to GMP requirements at a system level and is not necessarily an assessment of a specific product. An inspection may focus on two or more of six possible systems. The purpose of a surveillance inspection is to identify quality problems and adverse trends at facilities so the FDA can develop strategies to mitigate them. The process flow for surveillance inspections begins with site selection by CDER's Office of Surveillance (OS). Once a facility is selected, the ORA schedules the inspection using a facility dossier prepared by the OS. The dossier includes suggested areas for the inspection to cover. The ORA investigators then conduct the investigation, sometimes accompanied by subject matter experts from CDER. At the end of the inspection, a classification is assigned for the inspection based on the findings. The classification system was described by previous FDA speakers. For VAI and OAI classifications, the investigator may issue a list of observations on FDA form 483. The manufacturer's responses play an important role in the FDA's classification and follow-up to an inspection, which can include various options such as regulatory meetings, warning letters, and judicial actions. Once a facility has been classified as OAI, this status remains until the facility is inspected again.

Objectional inspection findings are communicated to the manufacturer at the end of the inspection on FDA form 483. In the event of disagreements between the investigator and the manufacturer, it is important to address these in real-time with the investigator during the inspection. The manufacturer may refer to the GMP regulations, guidance documents, and other information from the FDA during these discussions. This may prevent a misunderstanding from becoming a 483 observation. If a disagreement cannot be resolved and a 483 is issued, the manufacturer is strongly encouraged to submit a written response to the FDA within 15 business days. The manufacturer's response should include information discussed during the inspection, as well as any further information ascertained after the inspection.

FDA investigators have undergone training on the PET GMP regulations. The Agency acknowledged that some gaps exist in the training for the PET GMPs. In addition, some misunderstandings exist on the part of some investigators on the applicability of the PET GMPs to PET manufacturers. The FDA is working to close these deficiencies. The training program is under revision to address known gaps and to provide refresher training with a scheduled rollout in March 2020. In addition, the FDA is developing an electronic tablet-based approach for PET inspections and the Agency has initiated a New Inspection Protocols Project (NIPP) with the goal of modernizing inspections through the collection of structured data. The expected outcomes of this project include:

- The ability to quantitate the state of pharmaceutical quality
- Accelerated pace of making informed, data-driven decisions for pre-approval and surveillance inspections
- More efficient and consistent inspections
- Identification of policy and outreach opportunities across the industry
- Evidence for additional or modification of regulations

Further Detail from the "FDA Pilot Program for Tablet-Based Inspections for PET Drugs" Presentation

Historically, the execution of PET inspections and the associated reporting is a time-consuming process for the FDA. A typical abbreviated PET inspection that covers two of the six quality systems requires 3 to 5 days for the actual inspection and an additional 5 to 7 days to write the Establishment Investigation Report (EIR). A comprehensive PET inspection that covers four or more quality systems typically requires 3 to 7 days for the actual inspection and an additional 5 to 10 days to write the EIR. In addition to the time required for paper-based inspections, the historical inspection process results in inconsistency of inspections and EIRs as well as a lack of real-time awareness due to the delayed availability of the EIR. The new inspection protocol and the associated electronic tool (eNSpect) are designed to expedite the inspection process and preparation of EIRs. The protocol will also deliver more consistent results across numerous PET manufacturing facilities. The eNSpect tool has been piloted for surveillance inspections of PET manufacturers but has not been adapted for PET pre-approval inspections.

The electronic platform also offers the potential for the FDA to enhance the inputs for inspectional information beyond the tradition sources such as the PET GMP regulations, compliance policy guides, guidance documents, and USP standards. Additional sources of information may be available during the inspection, including frequently asked questions, work aids, specific technical questions and notes, pre-approval and data integrity questions, and application specific information.

The development of a tablet-based approach for PET inspections began in March 2007 before the FDA finalized the PET GMP regulations. The project was then shelved awaiting the new PET GMPs and restarted in May 2017. The inspection protocol and internal mock inspections were

completed in August 2018 and the PET protocols were released into eNSpect. At the end of 2018, the FDA conducted three field surveillance inspections and finalized the PET protocols in August 2019. At the time of the PET workshop in February 2020, the implementation for inspections across all PET facilities was pending training of FDA investigators.

Various features and sections of the eNSpect platform were reviewed. The platform has a field client and on-line capability, including the ability to upload pictures, the use of a stylus, and voice recognition. The system prevents citations that fall outside the scope of the PET GMPs and ensures an audit trail of all entries. As the time of the workshop more than 50% of EIRs were closed by the end of the inspection, significantly accelerating the process. The Agency recognizes the increased need for technical resources to support and maintain the deployment of the eNSpect platform in PET. Some of the positive aspects identified for the system by FDA investigators and inspected firms include more consistent inspections, more rapid availability of EIRs, availability of references, less paper, more appropriate citations, and user friendliness. Concerns and areas for improvement include the use of the camera, pen sensitivity, and the potential of voice recognition software to record routine discussions. Based on the impact of COVID-19, the status of the new PET inspection protocols and the eNSpect implementation is currently unknown.

Session I – Panel Discussion – Further Details

During the panel discussion for the first session, discussion points from the PET community were considered by the speakers and the audience. The first discussion point concerned action limits and identification requirements for microbes detected during environmental monitoring of aseptic areas. Based on different enforcement approaches by different investigators, the FDA's expectations in this area are not clear to the PET community. Members of the audience noted that the limits in USP general chapters currently serve as the standard, which differ from levels recently enforced during some FDA inspections. The audience questioned if these potential changes add a margin of safety that is worth the additional financial burden associated with the identification of each colony forming unit. Since a typical PET manufacturing facility generates numerous batches per day and does not have in-house microbiology lab capabilities, the cost of identifying each unique microbe would be prohibitive. Further discussion addressed the challenges associated with speciation of microbial findings during environmental monitoring, including the inherent difficulties in determining the source of contamination in a small facility in the event of a positive sterility test result. FDA acknowledged the emergence of low-cost testing commercial tools that could support EM trend without resorting to systematic/extensive and costly speciation, although some speciation information supports root cause analysis, and along with trending, is part of overall control. FDA acknowledged this being in scope of upcoming CFR (212) and Guidance background work to be released in the near future.

A second point in the panel discussion concerned how manufacturers should handle situations when an FDA investigator deems that a method or procedure described in an approved NDA or ANDA is inadequate or when an investigator opts to enforce a standard beyond the PET GMP

regulations or USP standards. The audience recommended that the FDA update the PET GMP regulations and/or the PET guidance document and only enforce standards defined therein. In addition, the audience recommended that such revisions be open to the public comment process. The FDA confirmed the importance of a single authoritative standard and noted that the Agency plans to revise the PET guidance document and the PET GMP regulations by the end of 2020. The effect of delays that have occurred in light of the COVID-19 pandemic is not known at this time. In the meantime, when disagreements exist between the manufacturer and the investigator, the investigator's management may be contacted, although the FDA noted that the supervisor is generally not expected to overturn or amend the investigator's findings and conclusions. In the end, the only option available to the manufacturer may be a well-developed 483 response as the "best shot" to articulate fully a sponsor's position.

Session II – Lifecycle Management of PET Drug Applications

Further Detail from the "Lifecycle Management of PET Drugs – the FDA Perspective" Presentation

The typical lifecycle of a drug begins with the discovery and development phases and continues with clinical development (investigational new drug or IND) and ultimately with FDA marketing approval (new drug application or NDA) and finally with generic drug approval (abbreviated new drug approval or ANDA). After NDA approval, the lifecycle of a drug may be affected by:

- Indications and changes to the indication(s)
- Efficacy and safety in patients
- Large scale manufacturing
- Quality and continuous improvement

Changes to approved applications and the lifecycle of a drug can be achieved by a variety of mechanisms based on the risk of the change. The FDA has four defined risk categories:

- 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

Changes that the FDA has encountered with PET drug applications include the following:

- Addition of new manufacturing facilities
- New source of raw materials
- Specific activity
- Extension of shelf-life
- Generator modifications
- Sterility issues
- Analytical method changes

- New equipment (cyclotron, radiosynthesizer, purification system)

Details about the appropriate risk category for these changes (PAS, CBE-30, CBE-0) were not provided. FDA mentioned the submission by sponsors of comparability protocols within a PAS in order to "*provide predictability for applicants who anticipate the need to implement future changes to an approved product, including its manufacturing process*." The FDA defines a comparability protocol as "*a comprehensive, prospectively written plan for assessing the effect of a proposed CMC post-approval change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product (i.e., product), as these factors may relate to the safety or effectiveness of the product (i.e., product quality)*" (15). The drivers for such anticipated changes might include business needs, growing markets, and process improvements. By describing the specific approach an applicant intends to use to evaluate future CMC changes, as well as the rationale for that approach, the applicant can gain the Agency's approval of the plan well in advance of the need to implement any changes. This subject was a common topic throughout the workshop, but many questions remain open at this time.

The Office of Generic Drugs (OGD) is responsible for the review of generic drug applications and is a separate office within FDA from the Office of New Drug Products. The Office of New Drug Products is responsible for the review and approval of new drug applications. This means that different FDA staff members review applications for NDAs and ANDAs, even though the content may be the same in certain sections of the application. This can lead to variations in the review of PET drug applications.

Upon receipt of an ANDA, the OGD conducts an initial review of the application to ensure it is complete. Major deficiencies in the application may lead to a refusal to file. Examples of such deficiencies that the FDA has encountered in PET ANDAs include:

- Lack of evidence of sterilization techniques for sterile PET products
- Lack of method validation and/or verification reports
- Failure to provide blank manufacturing records
- Failure to provide examples of executed batch records
- Content and format of the ANDA is inadequate

Minor deficiencies do not trigger a refusal to file determination unless the application contains more than ten minor deficiencies. Minor deficiencies are addressed by the OGD during the review of the application. Examples of minor deficiencies in PET ANDAs include:

- Inadequate patent certifications provided within the application
- Labeling deficiencies, including absence of side-by-side labeling, proposed package insert for the generic product, or the package insert of the reference listed drug
- Lack of a bioequivalence waiver
- Lack of diagrams for the container closure system

- Orientation of vials not provided in the stability datasheets
- Certificates of analysis not provided for all components

The timeline for the review of an ANDA depends on if the submission is a standard application (10 months) or if a priority review (8 months) has been explicitly requested. The FDA may also prioritize review if it a submission for a product with not more than three approved drug products, or if the product is subject to supply shortages. A regulatory project manager oversees the review of all ANDAs across the FDA review disciplines. The regulatory project manager also manages communications with the applicant at specific milestones during the application review.

Further Detail from the "Management of PET Drug Applications – the PET Community Perspective" Presentation

Since the drug substance (also known as the active radiopharmaceutical ingredient) is usually produced *in situ* during the manufacturing process, the description, composition, manufacturing, controls, reference standards, container closure, and stability should be included in the drug product section. After the approval of an application for a PET drug, common changes include the addition of new manufacturing facilities, new precursor suppliers, and alternative synthesis methods. Providing information on material control can reduce the overall need for an FDA inspection. As noted in other presentations, the inclusion of a Comparability Protocol (15) in the application can be an effective strategy to define the criteria for these modifications at the time of application review.

Several cases studies were collected from academic PET manufacturers prior to the workshop and presented for discussion with attendees. The case studies included:

- *Challenges with FDA electronic signature requirements found in 21 CFR Part 11 (16).* PET manufacturers rely on specialized equipment that in many instances does not have electronic signature or audit trail capabilities. In addition, some of this equipment is manufactured outside of the US by small companies for small markets. Thus, their investment to develop this capability is not justified. Further, these companies are often unfamiliar with FDA regulations. Staffing levels of typical PET facilities do not support the audit trail review required under the electronic signature regulations.
- *Challenges with specific excipient requirements.* The reference listed drug for common PET drugs often contain specific requirements for excipients, additives, and stabilizers. Exceptions to traditional ANDA labeling requirements would benefit PET manufacturers and would not cause issues with uptake of the drug.
- *Conflation of PET GMP regulations with traditional GMP regulations.* This topic was discussed extensively elsewhere during the workshop and in this paper. It is included again here to reflect the presentation and the consensus within the PET community.
- *More stringent identification of microbes in aseptic areas.* This topic was also discussed extensively elsewhere during the workshop and in this paper. It is included again here to reflect the presentation and the consensus within the PET community.

- *Challenges with electronic submissions.* The cost and burden of electronically submitted reports in the eCTD format[2] is prohibitive for some academic manufacturers. This issue can be addressed with the eCTD waiver option introduced by the FDA later in the workshop (*see below*).

The increased regulatory burden due to more stringent inspections is concerning to PET manufacturers because the PET community does not set the payment levels for PET drugs. Instead, payment is dictated by Medicare and other payers. As such, PET manufacturers have no mechanism to increase pricing to cover additional costs associated with electronic submissions, new microbiology requirements, or further expansion of compliance activities. If current trends continue, there is a risk that increased costs with no change in reimbursement will lead to an unsustainable business for some PET manufacturers thereby causing patient access issues.

Session II – Panel Discussion – Further Details

The first discussion point in the panel session concerned regulations associated with electronic data integrity, audit trails, and electronic signatures. A specific concern within the PET community is that specialized legacy equipment does not have the software capability to comply with these regulations. In response, two FDA participants acknowledged that legacy equipment may lack this capability and noted that PET manufacturers should make this clear to the investigator during the inspection or as part of communication with the Agency. The FDA also stressed that compliance with electronic records regulations is more than software and encouraged PET manufacturers to develop other control strategies that may address the concept of data integrity and thereby comply with regulatory requirements.

Questions from the audience focused on the regulatory requirements for modifications to an approved application. A specific concern within the PET community is that burdensome regulatory requirements hinder innovation and the adoption of new manufacturing and testing technologies. Several scenarios were discussed, including:

- The use of a second equipment line to produce an existing product
- The addition of a new product at a facility that has previously been inspected by the FDA
- The addition of a new product to a facility that has never been inspected by the FDA

The FDA noted that a second equipment line should be qualified and reported in a supplement but did not state if the supplement would require pre-approval. Several FDA participants discussed the scenarios related to new products and new facilities. The addition of a new product to a facility that has never been inspected requires a pre-approval supplement. The addition of a new product to a facility that has previously been inspected may or may not require a pre-approval supplement depending on the characteristics of the new product and the track record of the facility regarding FDA inspections.

[2] Electronic common technical document format

Additional discussion points were raised by the PET community but were not addressed by the panel in the interest of time. These points included the type of information that should be included in a supplement, how to respond to requests for information that have already been provided in the application or supplement, and how a PET manufacturer would begin manufacturing an approved product that has been delisted (not for reasons of safety or efficacy) by the FDA.

Session III – Chemistry and Product Quality Assurance

Further Detail from the "Product Quality Assurance: Microbiological Regulatory Perspective" Presentation

The FDA microbiology review division is separate from the chemistry review division, but both divisions are in CDER's Office of Pharmaceutical Quality. Although there may be some overlap in terms of the review of NDAs and ANDAs for PET drugs, the two divisions perform separate reviews of the applications, which explains the different questions and information requests that may occur before approval of the application.

Since PET drugs are administered to patients before the results of sterility test are known, aseptic operations and procedures are critical to adequately ensure the sterility of PET drug products. The critical operations that must be aseptically executed are the following:

- The assembly of the components used in the final product vial assembly
- The transfer of the assembled product vial to the hot cell or otherwise shielded area
- All manufacturing steps that occur downstream of the membrane sterilizing filter (e.g., transfer of the filtered solution into the product vial, optional product dilution, withdrawal of QC samples)
- Sterility testing
- Gowning/gloving procedures for personnel working in aseptic areas
- Environmental monitoring and cleaning/disinfection of aseptic/critical areas

ISO Class 5 workstations and other critical areas should be cleaned and disinfected before use. A routine environmental monitoring program should be established for these areas and should be described in the NDA or ANDA for the PET drug. The description should include the type of monitoring (airborne, surface, and personnel), locations, frequency, alert and action levels, and actions when levels are exceeded.

Pre-sealed, sterile, and pyrogen-free container closures consisting of a glass vial, rubber stopper and crimp seal should be purchased from a commercial supplier. The NDA or ANDA should include both a certificate of analysis and a drug master file number (with letter of authorization) for the container closure.

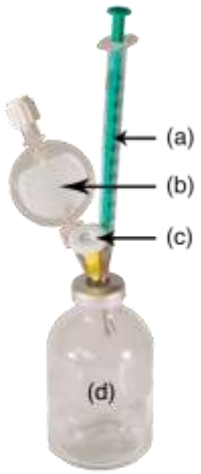

Figure 1. Assembled final product vial commonly used in PET manufacturing. (a) QC syringe, (b) membrane sterilizing filter, (c) filter vent, (d) product vial.

The final step on the production of a PET drug typically involves the passage of the product through a sterile 0.22 µm sterilizing filter. While the synthesis may take place in an open or closed environment, it is critical that the filtration occur in a closed system (i.e., into a septum closed vial without exposure of the filtered solution to the hot cell environment). The NDA or ANDA should include either a certificate of analysis or a drug master file number (with letter of authorization) for the filter(s) and all other sterile components. Any reusable components in the final product vial assembly and associated tubing should be highlighted in the NDA or ANDA along with a description of the cleaning and disinfection for these items.

Training is required for all operators involved in aseptic manipulations and operations that occur during production, including the assembly of sterile components, filtration, QC sampling, product dilutions or transfers that comprise manufacturing steps. Required gowning for aseptic manipulations can include clean lab coats, forearm sleeves, hair and beard covers, and sterile/sanitized gloves that cover wrist. Personnel must perform media simulations to demonstrate competency in the execution of these operations.

Media simulations use microbial growth media in place of the product solution to assess the quality of aseptic operations. In the PET manufacturing setting, media simulations may be used to:

- Evaluate the aseptic assembly and operation of critical, sterile equipment
- Qualify operators and assess operator technique
- Demonstrate adequate environmental controls
- Evaluate the transfer of the product vial assembly to the hot cell or shielded location
- Evaluate aseptic manipulations downstream of the product filter to the point of product release and packaging into finished product containers

Media simulations should represent worst-case conditions for aseptic operations using the same locations and equipment used in routine production. Media simulations should include a positive control to ensure the media is responding appropriately. Each new operator must successfully complete three simulations for qualification in routine production. Simulations must be repeated annually for each operator or when procedures and/or equipment change significantly. After the simulation, the media filled vial(s) should be incubated for 14 days and assessed for microbial growth every two to three days. The absence of visual evidence for growth indicates a successful simulation. Failed media simulations require re-training for the operator and repeat simulations. The FDA has prepared a guidance document for media simulations in PET drug manufacturing (17).

Microbiological tests for PET drugs include filter integrity, bacterial endotoxins, and sterility. For purposes of defining PET drug stability within an NDA or ANDA, microbiological testing is typically not required, but microbiological testing may be necessary to demonstrate the stability of products that are not administered on the same day of production. For all PET drugs, the filter integrity must be evaluated after completion of membrane filtration but before release for administration. The most common integrity test is the bubble point test. The test method, wetting agent, and acceptance criteria should be included in the release specification described in the NDA or ANDA. The test results should be included on the batch record. The test for bacterial endotoxins should be performed in accordance with USP general chapter <85>. The test should be initiated promptly after production and before release. For adult patients, the specification is 175 endotoxin units per injected volume and should be adjusted for intrathecal administration and for pediatric patients. For PET drugs with radionuclides that have very short half-lives, the bacterial endotoxin test may be performed on sub-batches dedicated for quality control testing. The test method and acceptance criteria should be included in the release specification described in the NDA or ANDA and test results should be included on the batch record.

Sterility testing cannot be completed before the release and administration of PET drugs. The sterility test should be performed in accordance with USP general chapter <71>, including the test media, incubation time and incubation temperature.[3] The sterility test should be initiated within 30 hours of the completion of manufacture and should be performed in an ISO Class 5 environment to reduce the risk of false positives. The test method and acceptance criteria should be included in the release specification described in the NDA or ANDA and test results should be included on the batch record.

Method suitability studies and results for proposed bacterial endotoxins and sterility test methods should be described in the NDA or ANDA for the PET drug. In addition, actions to be taken in the event of test failures should be described in the application.

The FDA concluded this portion of the program with a review of three case studies related to microbiology portion of an NDA or ANDA for a PET drug. The first case study involved a

[3] The inoculated volume of the product may differ from the criteria described in USP <71>

personnel environmental monitoring program that indicated fingertip monitoring is not performed after six months of passing results. This is inadequate since fingertip monitoring should be routinely performed for all operators performing aseptic manipulations. In the second case study, the manufacturing process involved the addition of sterile saline for tonicity adjustment, but the addition of the sterile saline was not part of the media simulation to validate the process. This is inadequate since all aseptic operations downstream of the sterile filtration step must be included in the media simulation. In the third case study, the method suitability testing (inhibition/enhancement) for the bacterial endotoxins test method that did not use the subject product solution. This is inadequate since all method suitability testing must be performed with the subject drug product to ensure that the results are reliable.

Further Detail from the "Microbiological Considerations for PET Drugs – the PET Community Perspective" Presentation

The FDA involvement in the regulation of PET drugs began in earnest in the early 1990s with public workshops, the development of proposed rules and guidance documents, and contributions to the development of USP standards for PET drugs. Many of these initial efforts by the FDA were overturned with the passage of the FDA Modernization Act of 1997 (**Error! Bookmark not defined.**). Also in the early 1990s, the FDA conducted site visits to PET manufacturing facilities and collaborated with the PET community on the development of key processing steps that addressed restrictions based on the short-life and the safe handling of PET drugs. This included the development of the final product vial assembly by FDA personnel (see **Error! Reference source not found.**), strategies for environmental monitoring, sterility testing, media simulations, and other techniques that remain important in the PET community today.

Microorganisms are ubiquitous in the environment. The primary human defense mechanism against pathological microorganisms is the skin, but immune defenses effectively deal with small numbers of harmful microorganisms that enter through the skin during injections and even during ordinary dental cleanings. Infection results when defenses are overwhelmed by invasive or large numbers of microorganisms. Sterility is an absolute condition defined as the complete absence of viable microorganisms. Sterility is notoriously difficult to prove and cannot be measured, even for non-PET drugs, due to statistical and microbiological limitations in test methods (18,19,20). Sampling for sterility testing of pharmaceuticals can only detect contaminated units when 10% or more of the batch is contaminated (21). Therefore, a passing sterility test does not indicate sterility of the product. Instead, a passing sterility test only indicates the absence of evidence for contamination of the batch. Thus, "sterility" is a condition that cannot be proven for any pharmaceutical product. Consequently, process controls are a better indicator of product sterility than the results of the sterility test.

As noted in other presentations at the workshop, the process controls used in PET manufacturing include the use of pre-sterilized commercial components that are assembled using aseptic techniques in classified environments. PET drugs are then synthesized in closed systems and transferred to the final product vial where the membrane filtration occurs to produce the sterile product. Since all components used for the final product vial are dry,

microbial growth is not possible during storage due to the absence of moisture. Vegetative contaminants will die in this situation. In addition, microbially lethal steps such as heated acid or base hydrolysis reactions are often employed in the synthesis before the membrane filtration. This drastically reduces the bioburden of the production solution before filtration. Although the results of the sterility test are not known prior to administration, most PET processes employ 100% testing of the manufactured vials and subject a large fraction of the product solution to sterility testing. The filter integrity test, which occurs as part of release testing to ensure the effectiveness of the filtration step, is a critical control step for PET drugs.

Controls for classified aseptic environments are defined in ISO standards (22). This standard maintains that the action and alert limits for microbial levels in aseptic environments are set by the user, and should be based on the risk of contamination, which is the probability of occurrence and the severity of harm that may result from the occurrence.

Environmental microbial monitoring of air, surfaces, and personnel were addressed by the FDA in 1995 when the Agency determined that quantitative methods used in traditional manufacturing settings were too intrusive for PET facilities and created opportunities for process failures in small spaces. As a result, passive settle plates were found to be adequate for detecting contamination without process interference and an increase in the risk of contamination during the act of measurement. In addition, periodic requalification of classified areas was deemed sufficient for environmental control and environmental monitoring for air, surfaces, and personnel could be used as process control indicators.

According to a survey of 13 academic and 5 commercial PET manufacturers conducted in February 2020, more than 370,000 batches of PET drugs were manufactured from 2013 to 2019. No adverse events were reported for these batches. The frequency of out-of-specification (OOS) sterility test results was 18 batches, or 0.013%. Nearly all OOS test results were attributed to laboratory error. These results represent an estimated 50% of the batches produced during this timeframe and indicate that aseptic process controls are effective in maintaining sterile product conditions across the entire community of PET manufacturers. Further evidence for the aseptic quality of PET drugs lies in surveys of adverse event reports (AERs) (2,3,4,5,6). In one study of a million radiopharmaceutical procedures between 2007 and 2011, the incidence of AERs for was 2.1 ± 0.6 per 100,000 studies (3). PET procedures accounted for about 25% of the procedures in this study. These results indicate there is no evidence of public health risks due to sterility failures in PET drug manufacturing.

Moving forward, CDER's "Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach" (23) provides guiding principles that may be applied to PET drugs, including a risk-based orientation, science-based policies and standards, and integrated quality systems that result in strong public health protection. Standards should be established for all PET drug manufacturers to ensure the uniformity of compliance among all PET facilities.

Due to the short half-live of PET drugs, manufacturers must produce an extraordinary number of batches to meet clinical demand. Therefore, PET facilities generate a vast amount of

manufacturing data, which creates a unique challenge for trending, review, and analysis of data-driven metrics typically associated with GMP requirements. However, the PET GMP regulations provide little information regarding data analysis and management reviews. ICH Q10 Pharmaceutical Quality System (24) provides guidance on the review of process performance and product quality, but the applicability to PET manufacturers is unclear. The guidance notes that, "Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management…" This opens the door to a discussion of the review of batch data that is appropriate for individual PET facility and networks of PET facilities, including the possibility of alternative data review formats.

The FDA often presents new expectations and standards at symposia and conferences. Such "podium policies" become new *de facto* regulatory requirements without a general awareness and vetting across the PET community. Two-thirds of PET manufacturers have received 483 observations based on new interpretations of existing regulations. An effective "change control" process for the interpretation and implementation of regulations, including input from the PET community and a reasonable implementation time would result in improved and more uniform compliance of PET manufacturers.

FDA inspections typically include daily debriefing sessions for discussion of potential issues with the sponsor. Experience has shown that some investigators will only communicate with local manufacturing staff or are unwilling to describe findings and rationale for potential non-compliance prior to issuing a 483. Considerations should be made by investigators to include personnel responsible for quality assurance at the corporate level if the company has such a structure. In addition, guidance on how to maintain effective lines of communication, including involvement from the FDA Office of Compliance (in addition to the Office of Regulatory Affairs, see above for discussions by previous speakers) prior to the issuance of a 483 would improve the process of identifying and correcting legitimate areas of non-compliance.

Recent experience has shown that some FDA investigators accept staff training on microbiology topics only if the training was delivered by a degreed microbiologist. Training performed by a non-degreed microbiologist was unacceptable. By this logic, other areas of training in PET manufacturing would require degreed chemists, pharmacists, and physicists. Guidance and discussions are necessary to define compliant training programs and expectations for training by degreed subject matter experts versus trainers qualified by on-the-job programs.

As noted numerous times by other speakers in the workshop, commercial PET manufacturers need clarification on several requirements associated with environmental microbial monitoring. Key areas include:

- Appropriate action and alert limits
- Environmental monitoring requirements during process qualification
- Incubation temperatures (including dual temperatures) required for environmental monitoring samples
- Potential applicability of USP chapter <825> on radiopharmaceutical compounding

As discussed by other speakers in the workshop, a failed sterility test requires the manufacturer to file a field alert report (FAR). Clarification is needed regarding the requirement for a FAR if the 14-day incubation is not completed because of a dropped sample or other unexpected deviation. It is an open question if a FAR is required in these situations.

The scope of pre-approval and surveillance inspections should be well defined. The pre-approval inspection (PAI) is typically the time when science-related issues in the drug application are discussed and reviewed. On the other hand, a surveillance inspection is typically limited to a review of the facility's quality system and compliance with the PET GMP regulations. However, during PET surveillance inspections, FDA investigators often delve into topics typically covered in a PAI. This effectively results in a re-negotiation of the original approval commitments and the appearance that an investigator is enforcing their personal area of expertise. This requires training on the part of FDA investigators to ensure the appropriate application of the PET GMP regulations and guidance documents.

Session III – Panel Discussion – Further Details

The first discussion point in the panel session concerned endotoxin limits for PET drugs administered to pediatric patients. The FDA noted that pediatric growth charts available from the Center for Disease Control should be used to set endotoxin limits for PET drugs by age, gender, and weight. The next discussion point centered on the requirement that chemical precursors for PET drugs are required to be manufactured under GMP conditions. The primary basis for this requirement is that the active radiopharmaceutical ingredient is not isolated and characterized before formulation into the final drug product.

The next discussion point concerned quality control tests in an NDA or ANDA that conform to USP monograph standards. If the USP monograph changes, the question arises, is the applicant forced to implement the revised USP method? The FDA noted that the applicant may continue to use the method originally included in the approved NDA or ANDA.

Confusion exists within the PET community regarding the sterility assurance information that should be submitted in NDAs and ANDAs. This may be attributable to the fact that IND applications are much shorter but require sterility assurance information as a marketing application. Information that is commonly omitted from NDAs and ANDAs for PET drugs includes the following:

- Facility or equipment descriptions
- Description of the environmental microbial monitoring program
- Certificates of analysis for all sterile filtration and final product vial components
- Filter integrity testing as a release specification for the product
- Justification for sterility inoculations performed beyond the 30-hour period contained in the PET GMP regulations

Validation of the filtration process may be included in the certificate of analysis for the filter. Data on extractable and leachable substances must be included in NDAs for new products not previously reviewed by FDA.

Session IV – Changing Landscape of PET Drugs, Labeling Requirements, and Electronic Filing Requirements

Further Detail from the "Changing Landscape of PET Drugs" Presentation

FDA regulations and USP standards for PET drugs were originally developed in the 1990s and early 2000s based on four cyclotron-produced PET radionuclides and three PET drugs. Since 2009, the list of approved PET drugs has grown significantly and now includes generator-produced PET radionuclides in association with a sterile non-radioactive kit for the preparation of the injectable PET drug. There are critical differences between these two classes of products. In the first case, exemplified by Fludeoxyglucose F 18 Injection, the marketed product is manufactured as a multiple dose vial in a ready-to-use solution. The product is 100% tested and dispensed into unit doses under the practice of pharmacy. The second case is exemplified by Gallium Ga 68 Dotatate Injection, which employs gallium Ga 68 chloride produced in a ^{68}Ge/^{68}Ga generator and a kit (the marketed product) consisting of two vials, one with the dotatate chelate and another with a buffered water solution for the injection. A single specific formulation for the generator eluate was originally approved by the FDA for the dotatate kit. The radiolabeling of the kit with the generator eluate is performed under the practice of pharmacy according to instructions provided in the package insert. Quality control testing on the prepared kit includes visual inspection, pH, and radiochemical purity.

This latter class of PET drug is similar to technetium-based radiopharmaceuticals used in traditional nuclear medicine. Kits for the radiolabeling of generator-produced PET radionuclides may take the form of small molecules, peptides, modified peptides, monoclonal antibodies, protein conjugates, and other modifications. The manufacturing of these kits may be considerably more complex than traditional PET drugs like Fludeoxyglucose F 18 Injection. New classes of PET drugs involve antibody manufacture, antibody/peptide conjugate manufacture, and kit lyophilization with terminal sterilization. Consequently, the regulatory framework for new kit-based PET drugs may be a complex combination of drug master files, new drug applications, traditional GMP regulations (21 CFR Part 211), and the practice of pharmacy.

In addition, new PET radionuclide generators may have unique requirements due to the long shelf-life as compared to other currently marketed radionuclide generators. For example, microbiology considerations, stability, and leachable substances must be addressed for new generators with long shelf-lives. Other issues associated with newer PET radionuclides include longer-lived radionuclidic impurities, multiple production methods, multiple suppliers, and the equivalency of isotopic preparation techniques (e.g., generator versus cyclotron produced ^{68}Ga). As new radionuclides and their inherent radionuclidic impurities are developed, the FDA encourages sponsors to coordinate with the Nuclear Regulatory Commission regarding issues specific to the NRC.

The characterization of complex PET drugs may require the sponsor to prepare and characterize non-radioactive drug substance reference standards that are not commercially available. If isomeric structures are possible for the radioactive drug substance, it may be necessary to remove the isomeric impurity. This may require advanced analytical methods for purification and quality control testing. Safety and efficacy concerns should be addressed for isomeric impurities.

The regulatory framework is different for drugs and biologics and this difference may affect the review division within the FDA for certain PET drugs. Any polymer composed of 40 or fewer amino acids is considered a peptide, which is regulated by the FDA as a drug that requires an NDA or ANDA. Proteins are composed of more than 40 amino acids and are regulated by the FDA as a biologic that requires either a Biologics License Application (BLA) or designation as a biosimilar. The review of biologic products may occur in the Center for Drug Evaluation (CDER) or the Center for Biologics Evaluation (CBER) depending on the nature of the final product.

Drug Master Files (DMFs) provide a mechanism to share information with the FDA that is not included in an NDA or ANDA. The NDA or ANDA must include a letter of authorization from the DMF holder to reference the information for the PET drug application. The most common DMF for PET drug applications is a Type II DMF, which is used to describe radionuclides, radionuclide generators, precursors, synthesizer cassettes, final product vials, etc.

Going forward, the evolution of PET drugs is expected to continue. The FDA organizational structure and multidisciplinary review of PET drug applications must be responsive to the development of new products and manufacturing technologies that require more complex information in the application.

Further Detail from the "NDA Drug Labeling" Presentation

In FDA terminology, the "label" and "labeling" are two different things. The "label" is written, printed, or graphic matter on the immediate syringe, vial, or package. The "labeling" includes the "label" and all other written, printed, or graphic matter accompanying the product. Thus, "labeling" includes carton and container labels, prescribing information (PI) or "package insert," patient instructions and information, and user manuals. Patient instructions are not common for radiopharmaceuticals since the patient does not use the drug directly. User manuals are becoming more common for radiopharmaceuticals, especially for generator/kit products and direct patient infusion systems.

The prescribing information or package insert (PI) is written in technical terms for the prescriber (not the patient) and contains a summary of the essential scientific information needed for the safe and effective use of the drug. The data to support the PI starts during the first stages of the entire drug development process. The Physician Labeling Rule of 2006 (25) changed the format of information in the PI to improve the availability of clinical data and is required for all drugs and biologics.

Section 2 of the PI for radiopharmaceuticals includes information on dosage, administration, imaging instructions, preparation, dosimetry, and special instructions. The dosage section should include the recommended optimal dose, the dose range, and the maximum dose. The administration section should include the duration of the injection (bolus or infusion) and any requirements for medication withdrawal (due to drug interactions), and instructions for patient fasting, exercise abstinence, etc. required for optimal uptake. The imaging instructions section includes image acquisition guidelines that describe the timing of imaging after administration, the duration of the scan, anatomical location of the scan, patient instructions (voiding), device parameters (e.g., 2D or 3D PET, software reconstruction), image display factors and orientation, coloring display schemes, and important image interpretation factors that define a "positive" or "negative" result. The preparation section may be minimal for ready-to-use radiopharmaceuticals but may be quite extensive for kit-based radiopharmaceuticals that use generator-produced radionuclides. This section may describe reconstitution of the kit, generator elution, quality control tests with acceptance criteria for release, the shelf-life of the final product, storage conditions, and disposal of residual radioactive product. The dosimetry section describes the estimated radiation absorbed dose to the patient by organ and total effective dose. The special instructions section includes information to reduce the radiation exposure to patients (e.g., voiding and hydration), reduction of radiation exposure for workers (e.g., shielding, handling), and proper disposal of unused product.

Section 8 of the PI for radiopharmaceuticals includes information for special populations. In June 2015, the Pregnancy and Lactation Labeling Rule (PLLR) revised the format and content of this section to reflect an integrated assessment of known risks relevant to pregnancy, lactation, and infertility based on available information and data (25). The revised labeling requirements are retroactive to all labeling approved after June 30, 2001. Most diagnostic radiopharmaceuticals are not contraindicated in pregnant women since situations exist where the benefit to the mother outweighs the risk to the fetus. This section also contains information about the potential excretion of the radiopharmaceutical in breast milk and possible ingestion by the baby, including the duration of breastfeeding interruption to limit exposure to the baby.

Section 11 of the PI contains important chemical and physical information about the radiopharmaceutical, including the strength, chemical formula, dosage form, pH, and radioactive decay scheme with types of emitted radiation and the half-life of the radionuclide.

Section 16 of the PI contains storage and handling information, typically for the pharmacist or the technologist receiving the radioactive shipment. This section contains the NDC code for the product and the requirement that the radiopharmaceutical is safe and effective when used according to a radioactive materials license.

Section 17 of the PI contains patient counseling information that should be provided by the healthcare provider to the patient after administration of a radiopharmaceutical. This includes measures to reduce radiation exposure to the patient, precautions for household contact, and

potential breastfeeding interruption. This section does not include contraindications or patient instructions for use.

ANDA holders are required to update ANDA labeling to comply with the labeling in the NDA for the reference listed drug. The timeframe to update the ANDA labeling is not listed in the regulations, but an acceptable implementation would be achieved with an immediate change being effective through the CBE-0 mechanism described in other presentations. The section of the FDA website devoted to prescription drug labeling resources contains a labeling template that may be incorporated into an NDA or ANDA.

Further Detail from the "Electronic Filing of Regulatory Applications" Presentation

The FDA is authorized to require electronic submissions for NDAs, ANDAs, INDs, and other applications. The Agency is also authorized to establish exemptions from the electronic submission requirements. Beginning in the late 2010s, the FDA mandated that these submissions must be electronic, and that the Agency would no longer accept paper-based submissions. The organization and content of electronic submissions, which are formatted according to the common technical document (eCTD) format, are described in a guidance document that became effective in May 2020 (26). The guidance document describes how sponsors and applicants must organize the content of electronic submissions to the Agency. Section III.D. of the guidance document grants a long-term waiver to certain PET drug applications and Type II Drug Master Files (DMFs). In effect, this means that applications and DMFs that meet the criteria for a waiver may continue to prepare paper-based submissions.

The criteria that a PET drug application must meet to qualify for the waiver are:

- The applicant produces PET drugs at a single manufacturing facility
- PET drugs are the only FDA-regulated products (other than non-commercial drug or biologic products) manufactured or produced by the applicant
- The applicant explains that, because it meets the criteria above, it cannot achieve compliance with eCTD requirements

To meet the criteria for an eCTD waiver, a Type II DMF must:

- Be submitted in support of an application (i.e., IND, NDA, ANDA, or BLA) for a PET drug and
- Contain information regarding radiolabeled drug products or production of PET radionuclides, and
- The Type II DMF holder is an academic institution, government (state or federal) entity, or a non-profit research organization

A waiver request must be sent to FDA before submitting the document(s) for which the corresponding waiver is being requested. The request must include an explanation why eCTD compliance cannot be achieved and a description of the proposed alternative submission

format to be used during the waiver period (e.g., PDF files following CTD structure). The waiver request should reference all products that are to be covered by the waiver and the request should be clearly titled “LONG-TERM WAIVER REQUEST — eCTD REQUIREMENTS” in bold capital letters at the top of the first page of the submission.

The FDA will consider waiver requests on a case-by-case basis. Generally, the FDA will respond in writing noting whether the waiver is granted or denied, and whether the proposed alternative submission format is acceptable. After the initial waiver request is granted, subsequent requests should include a statement in the cover letter of each submission indicating that an eCTD submission waiver has been granted previously by FDA, including the date for the waiver.

PET waiver requests are valid for five (5) years from the date the waiver is granted and only apply to the requestor. Waivers are not transferrable to another sponsor or applicant. A sponsor or applicant may reapply to recertify their eligibility for a waiver up to 6 months before the waiver expiration date using the same process. If the criteria are no longer valid at the time of recertification, the waiver will not be granted.

Short-term waivers for the eCTD requirements are rare and only apply special situations where a PET facility’s computer infrastructure is temporarily compromised (e.g., a nature disaster, computer malware attack).

If a sponsor or applicant does not qualify for an eCTD waiver, applications must be submitted electronically. In this case, the sponsor must submit electronic submissions using the eCTD version currently supported by FDA. Before making the first electronic submission to an application, a pre-assigned application number must be obtained by contacting the FDA. The submission structure and document granularity must be consistent with ICH guidance (26, 27). Files within an eCTD submission must adhere to the formats and versions specified in the associated FDA technical specification.

If a submitted document replaces one previously submitted with an eCTD backbone file within the same application, the applicant must use the eCTD “replace operation” to indicate this. The location of clinical efficacy and safety summaries within the eCTD must adhere to FDA guidance (28). Datasets and study information must only be provided in Modules 3, 4, or 5 of the eCTD.

For submissions that are 10 GB or smaller, the submitter must use the FDA electronic submission gateway. Electronic submissions must include only FDA-fillable forms (e.g., Form FDA 1571 or Form FDA 356h) and electronic signatures. The receipt date for an electronic submission will be determined only after the submission has passed a technical validation check to ensure that it can be opened, processed, and archived. The submitter is responsible for monitoring their receipt pathway to determine whether a submission has been rejected. Paper copies of the submission, including review copies and desk copies in paper, must not be submitted. The only exception is the submission of paper copies of meeting briefing materials,

when requested, as described in the FDA guidance documents on formal meetings between the FDA and sponsors or applicants.

Session IV – Panel Discussion – Further Details

The first discussion point in the panel session concerned stability data submitted in support of an application. In the past FDA has indicated that stability data for three batches at the upper range of the proposed radioactive concentration (strength) should be provided to support the expiration dating period. In addition, release data from three batches should be provided from each manufacturing facility to qualify the facility for the manufacture of the drug product. The FDA has also noted that site-specific stability data is not required as long as the manufacturing process, procedures, synthesizer, source of raw materials are the same. In this case, stability data from a central facility could apply to all manufacturing facilities and stability data from each manufacturing facility is not necessary. The FDA noted that this approach is acceptable for the initial application and facility qualification, but also noted that each facility must complete one stability for each product on an annual basis.

The next discussion point concerned the length of time the FDA will take to respond to a request for a long-term waiver for the eCTD requirements. The Agency will respond as soon as possible based on the assumption that the request meets the criteria outlined previously. Further, the FDA may verify that a facility meets the eCTD waiver criteria during an inspection or through a records request. Regarding the format for non-electronic PET submissions, the FDA is working on a guidance document to address this topic but recommends using a PDF format in the meantime.

Another question from the PET community related to whether an approved PET ANDA holder could perform additional clinical studies to allow for labeling changes for the ANDA product. The FDA responded that this is not a typical situation since the Office of Generic Drugs does not review safety and efficacy data, but a definitive answer was not provided.

The next question was about the validation or verification of USP compendial methods at multiple facilities. The FDA's expectation for compendial methods is that compendial methods are not required to be validated facility-by-facility, but verification should be performed to ensure proper implementation of the method. In a related question, the FDA's expectations regarding method transfer for newly developed products to multiple manufacturing locations was discussed. The first requirement is that the method is validated for accuracy, precision, etc. Next, the method should be written from the perspective that it will be transferred to multiple facilities. USP general chapter <1224> describes principles for method transfer. Effective method transfer should include identical procedures, methods, standards, equipment, materials, etc. Personnel should be trained on the identical processes and procedures.

The next portion of the panel discussion focused on how the PET community can be kept up to date with changes in FDA expectations. Historically, the FDA created a webpage to

communicate PET-specific changes but has been challenged with maintaining it. Further policy discussions are required to define effective ways to accomplish this.

The discussion turned to the equivalence of ^{68}Ga produced in a cyclotron versus that from a generator. Differences in chemical profile, quality control, radionuclidic impurities, and process chemistry must be considered in the application. In addition, process controls may impact GMP requirements for different sources of the radionuclide. If an ANDA were to be filed for a kit-based product and the applicant sought approval for cyclotron-produced ^{68}Ga, the application would need to address these concerns.

As noted in the labeling presentation for this session, the Pregnancy and Lactation Labeling Rule (PLLR) requires ANDA holders to update their labeling to comply with the labeling in the NDA for the reference listed drug. In the event that the NDA has been withdrawn (not for reasons of safety or efficacy), it is not clear who is responsible for the labeling updates. This is the case for Sodium Fluoride F 18 Injection, which was sponsored by the National Cancer Institute and then later withdrawn. At the time of the workshop, it was unknown if the NDA or ANDA holders are responsible for implementing the labeling changes first.

Guidance was requested from the FDA on the appropriate approval mechanism for major PET facility renovations, including new air handling systems, new laboratory space, etc. Such changes would require a pre-approval supplement before the renovated space can be used in production. FDA recommendations include discussing the renovation plan with the appropriate FDA division office before the renovations begin. In addition, the pre-approval supplement may be submitted in advance of the projected start-up date to minimize the wait time between completing the renovations and undergoing the pre-approval inspection.

Further Details on Workshop Closing and Summary of Key Points

Four predominant themes emerged throughout the workshop:

1. The uniformity of FDA inspections of PET manufacturing facilities
2. A science-based risk profile for PET drugs
3. Improvements to training for FDA investigators and the regulated community
4. Continued dialog between the FDA and the PET community

As noted previously, the organizing committee defined the workshop as “a forum for the exchange of information and perspectives on the regulatory and compliance framework for PET drug manufacturing and thereby improve global understanding of issues and challenges facing PET manufacturers.” In that spirit, the remainder of this paper discusses each of these four themes along with recommendations for consideration by the FDA.

1. The uniformity of FDA inspections at PET manufacturing facilities

A core principle of the PET GMP regulations is uniformity of the radiopharmaceutical supply. Under GMP, it should not matter where a drug is made, or who made it, or when it was made. A drug should always have the quality characteristics described in the application and applicable monograph. Product uniformity is also embodied in the "one quality voice" campaign, which is a core mission of CDER's Office of Pharmaceutical Quality (OPQ). "One quality voice" is designed to create uniform drug quality standards across all manufacturing sites (29).

Consequently, it seems self-evident that FDA inspections of PET drug manufacturing facilities should be uniform. All PET manufacturers should be held to consistent and transparent risk-based standards described in the PET GMP regulations and applicable guidance. As described numerous times by speakers at the workshop, experience among various PET manufacturing facilities has shown this is not the case. For example, some FDA investigators have employed traditional GMP regulations (21 CFR 211) in the inspection of PET facilities. In other cases, PET facilities have been held to different inspectional standards for operator qualification, sterility testing, environment microbial monitoring, etc. Moreover, speakers at the workshop noted that the incidence of non-uniform inspections seems to have increased in recent times.

The non-uniformity in FDA inspections potentially results from various factors, including inadequate organizational controls within the Agency, inadequate training of FDA investigators, inconsistent adherence to FDA applicable Manual of Policies and Procedures (MAPPs), *ad hoc* considerations of conditions for approval, and efforts by individual FDA investigators through "regulation-by-inspection." Various speakers noted that manufacturing processes evolve, science evolves, and PET manufacturers find new efficiencies. In turn, regulatory standards must evolve commensurately to maintain product quality standards. Along these lines, the "regulation-by-inspection" approach is often employed by individual FDA investigators to spur continuous improvement in a regulated community and this approach can lead to specific improvements at a specific manufacturing facility. One the other hand, PET manufacturers know that piecemeal implementation is not an effective strategy in a distributed manufacturing environment such as PET. Changes and improvements must be systematically implemented across all 150 PET drug facilities. In fact, a poor change implementation process can do more harm than the intended benefit of the change in the first place. Such is the case with *ad hoc* changes that inevitably result from non-uniform FDA inspections. Therefore, efforts to spur continuous improvement in PET drug manufacturing facilities should avoid "regulation-by-inspection" strategies and instead focus on revisions to regulations, guidance documents, and inspection manuals. The PET community has worked diligently to achieve a uniform supply of PET drugs through the adoption of the PET GMP regulations and the implementation of best practices (30). In order to continue to realize this goal, it is critical that the FDA inspection process is uniformly implemented across all PET manufacturers.

Therefore, the PET community calls on the FDA to improve the uniformity of FDA inspections at PET manufacturing facilities. One FDA speaker at the workshop conceded that "the variability of FDA inspections is inevitable." However, the FDA can minimize, if not eliminate, variability in PET inspections by implementing the following recommendations:

i. The FDA should organize a designated team of investigators to perform inspections of PET manufacturing facilities. The team may be organized at the national level or according to regional divisions. The investigators must be trained through a comprehensive program that includes topics such as the intrinsic properties of PET drugs, the characteristics of the PET manufacturing supply chain, etc. More importantly, the training program must include how these factors define the risk profile of PET drugs and the resulting manufacturing environment. Additional recommendations for training appear below.
ii. FDA investigators should employ a prescribed checklist during inspections of PET manufacturers. This is imperative since deviations in inspectional approaches inevitably lead to non-uniform inspections. To this end, FDA speakers at the workshop described a tablet-based approach to manage inspectional checklists during PET inspections. The FDA should accelerate their efforts on this project and seek guidance on the program from the PET community. Although FDA stated that sponsors may not be allowed to view screen shots of the tablet screen, the inspectional checklist should be publicly available to the PET community outside of the inspection process. This transparency will significantly inform the PET community's efforts toward compliance and ensure a level playing field in the regulated community.
iii. During the development of the PET GMP regulations, the FDA found that product quality depends on the scope and complexity of PET manufacturing facilities. Historically, this finding has provided FDA the latitude to adapt inspectional strategies and regulatory actions based on whether a facility is an academic self-producer or a single-site or network commercial distributor. According to today's understanding of PET manufacturing facilities, "the scope and complexity of operations" do not vary systematically from one facility to another. Some facilities produce larger quantities of a few PET drugs and other facilities produce a greater variety in smaller quantities. Further, there are no objective metrics to differentiate the complexity of PET manufacturing facilities. In the absence of such metrics, it is reasonable to conclude that all PET facilities are similar in the day-to-day complexity of operations regardless of whether they are associated with an academic medical center or a commercial distributor. Therefore, the FDA should discontinue the practice of defining inspectional strategies and regulatory actions based on whether a facility is academic or commercial.
iv. In the event of a disagreement between an FDA investigator and the personnel at a PET facility during an inspection, there are few options available to the PET facility for mediation of the disagreement. At the workshop, a panel discussion on this topic concluded that oftentimes the only practical option in this situation is the issuance of a 483 observation. The use of the Tablet guided inspections, by accelerating the

inspection process and issuance of FDA reports (including EIR), the ability to address disagreements in real time becomes more acute. The upfront and systematic issuance of a 483 observation is an inappropriate means to resolve such disagreements and undermines the spirit of cooperation. In fact, this approach is tantamount to the presumption of guilt until being proven innocent. In order to provide relief in the event of such disagreements, the FDA should implement a formal process for the elevation and mediation of disputes during an inspection. A possible solution would be the implementation of a mediator and resolution process/policy to evaluate disputes during inspections. The mediator should be organizationally outside the chain of command of the Office of Regulatory Affairs, which manages inspections. In this way, the mediator would provide the equivalent of QA oversight for inspections, much like the second person operational checks that ensure quality and prevent the inherent bias that occurs when an operator performs QC on their own work.

2. A science-based risk profile for PET drugs

In 2002 the FDA introduced an initiative to modernize the Agency's approach to the quality of pharmaceutical products (23). Known as "Pharmaceutical CGMP Initiative for the 21st Century – a Risk Based Approach," the initiative encouraged the implementation of risk-based approaches that focus industry and the Agency on critical areas, policies based on state-of-the-art science, and the integration quality systems into the Agency's business processes, regulatory reviews, and inspection activities. This initiative was later renamed as "Pharmaceutical Quality for the 21st Century – A Risked Based Approach" to expand the focus beyond GMP regulations (23).

As with all medical procedures, inherent risk factors are associated with the use of PET drugs. Several FDA speakers during the workshop described the importance of risk-based approaches for both the review of applications for PET drugs and in the execution of inspections of PET manufacturers. This approach is consistent with the pharmaceutical quality initiative described above. However, the PET community is not aware of a science-based risk profile that is based on the intrinsic properties of PET drugs and the manufacturing processes used in their preparation. Further, the little information that exists in this area is not uniformly understood within the FDA or across the PET community. Thus, the application of the risk-based approach to PET drugs can only be characterized as a subjective exercise in perceived risk by individual reviewers and investigators.

To correct this deficiency*, the PET community calls on the FDA to work with PET manufacturers to develop a science-based risk profile for PET drugs*. The evaluation of risk factors, rates of occurrence, and mitigating strategies should be evaluated based on the characteristics of PET drugs. The risk analysis should consider the intrinsic safety factors of PET drug products, such as the mass of the active radiopharmaceutical ingredient, the likelihood of a pharmacological response, radioactivity levels, potential for repeat uses, etc. These factors are already considered in regulatory assessments such as the exploratory IND pathway (31). The risk analysis should also include mitigation strategies employed in PET manufacturing as described

throughout this workshop, including the use of closed systems, pre-sterilized components, aseptic environments, microbiologically lethal processing steps, etc. The analysis should be published in the peer-reviewed literature (or a white paper) and openly available to the regulated community. By working together with PET manufacturers, the results of this exercise will provide transparency to the regulated community and will better inform FDA review practices and inspectional policies according to the PET GMP regulations and Guidance.

During the workshop, FDA speakers described that the agency has undertaken the revision of the PET GMP regulations and associated guidance documents. Similarly, speakers from the PET community described the continued track record of safety associated with PET drugs. This questions the immediate need for the revision of the PET GMP regulations, which have only been in use for ten years since being finalized. If the FDA continues to pursue these revisions, the rulemaking efforts should be tethered to the development of a risk profile for PET drugs, and therefore may be delayed until this has been completed as described in the previous paragraph. This will allow for revisions to the regulations that more accurately reflect actual risk versus perceived risk.

3. Improvements to training for FDA investigators and the regulated community

Over time, FDA personnel change and new people become involved in the review of PET drug applications and in the inspection of PET drug manufacturing facilities. Consequently, there is a continual need for educational resources for new entrants in this field.

During the workshop, the FDA noted the need to improve training programs for investigators. After the workshop, the FDA reached out to SNMMI to share training materials included in the SNMMI's Quality System Personnel Training Program (QSPTP). Historically, few educational programs exist to address the technology of PET drug manufacturing and the SNMMI's QSPTP is unique in this regard. The FDA should continue to work with the PET community to adopt and revise existing training programs such as the SNMMI QSPTP and other educational resources from the PET community. Like all continuing education materials, the FDA's training program for investigators should be regularly reviewed, updated, and administered.

4. Continued dialog between the FDA and PET manufacturing community

The workshop provided an invaluable forum for the FDA and PET drug stakeholders to exchange ideas, issues, and challenges associated with the regulation of PET drugs. The workshop was only a start: the PET GMP regulations are less than 10 years old and the experiences with the Agency and the PET community will continue to evolve. The long-term sustainable implementation of new regulations requires time and a routine dialog. It is critical for the FDA and the PET community to share information outside formal channels associated with the review of an application or an inspection. To that end, the FDA and the PET community should commit to holding this workshop in alternating years for the foreseeable future. Interim informational meetings should continue to take place between the FDA and PET stakeholders during the SNMMI annual meeting to address new and ongoing issues associated with the approval and regulation of PET drugs.

Conclusion

PET drugs have opened the door for molecular imaging and offer the potential realization of personalized medicine in the clinical environment. A regulatory framework that maintains the existing PET supply chain, guards against shortages, and ensures continued investment in the expanding pipeline of PET drugs is critical for the long-term health of this important imaging modality. To that end, the established safety profile of radiopharmaceutical imaging modalities must be an important consideration in future upgrades, as manufacturers continue a strong track record of public health and safety to meet regulatory requirements and guidance. The compliance programs which are enforced, and the risk mitigation strategies that underline them, must also support a realistic economic climate around PET drugs. The adoption of the recommendations described in this publication, will provide a sustainable supply of safe and effective PET drugs in the clinical environment, thus ensuring widespread patient access to life saving diagnoses available only through PET imaging.

References

1. SNMMI/MITA Survey of PET drug manufacturers, February 4-10, 2020 (in PET Drugs Presentations Part I). U.S. Food and Drug Administration website. https://www.fda.gov/media/136480/download. Dec 21, 2021.
2. Silberstein, EB. Prevalence of adverse events to radiopharmaceuticals from 2007 to 2011. *J Nucl Med*. 2014;55:1308-1310.
3. Silberstein, EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. *J Nucl Med*. 1998;39:2190-2192.
4. Laroche, MI, Quelven, I, Mazere, J, Merle, L. Adverse reactions to radiopharmaceuticals in France: analysis of the national pharmacovigilance database. *Ann Pharmacother*. 2015;49:39-47.
5. Kennedy-Dixon, T-G, Gossell-Williams, M, Cooper, M, Trabelsi, M, Vinjamuri, S. Evaluation of radiopharmaceutical adverse reaction reports to the British nuclear medicine society from 2007 to 2016. *J Nucl Med.* 2017;58:2010-2012.
6. Schreuder, N, Koopman, D, Jager, PL, Kosterink, JGW, van Puijenbroek, E. Adverse events of diagnostic radiopharmaceuticals: a systematic review. *Semin Nucl Med.* 2019;49:382-410.
7. Global imaging market outlook report, IMV Medical Information Division, Arlington VA, 2019.
8. FDA Pharmaceutical Quality Oversight – One Quality Voice, FDA Office of Pharmaceutical Quality. U.S. Food and Drug Administration website. www.fda.gov/media/91721/download. Accessed Dec 21, 2021.
9. Applications for FDA approval to market a new drug, Title 21 CFR Part 314.81(b)(1)(ii). U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.81. Accessed Dec 21, 2021.
10. Current Good Manufacturing Practice for Positron Emission Tomography Drugs, Title 21 CFR Part 212.70(e). U.S. Food and Drug Administration website.

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=212. Accessed Dec 21, 2021.
11. US FDA. Guidance: PET drugs - current good manufacturing practice (cGMP), December 2009. U.S. Food and Drug Administration website. https://www.fda.gov/media/71013/download. Accessed Dec 21, 2021.
12. US FDA. Compliance program guidance manual: positron emission tomography (PET) cGMP drug process and pre-approval inspections/investigations. 7356.002P, September 11, 2015. U.S. Food and Drug Administration website. https://www.fda.gov/media/82370/download. Accessed Dec 21, 2021.
13. Current Good Manufacturing Practice for Finished Pharmaceuticals. Code of Federal Regulations Title 21 Part 211. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211. Accessed Dec 21, 2021.
14. Understanding CDER's risk-based site selection model, FDA Office of Pharmaceutical Quality, MAPP 5014.1. U.S. Food and Drug Administration website. www.fda.gov/media/116004/download. Accessed Dec 21, 2021.
15. US FDA. Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information, April 2016. U.S. Food and Drug Administration website. https://www.fda.gov/media/97148/download. Accessed Dec 21, 2021.
16. Electronic Records; Electronic Signatures. Code of Federal Regulations Title 21 Part 11. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11. Accessed Dec 21, 2021.
17. US FDA. Guidance: Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs, April 2012. U.S. Food and Drug Administration website. https://www.fda.gov/media/81974/download. Accessed Dec 21, 2021.
18. Halvorson, HO, Ziegler, NR. Application of statistics to problems in bacteriology. *J Bacteri*ol. 1933;26:559-567.
19. Bowman, FW. The sterility testing of pharmaceuticals. *J Pharm Sci.* 1969;58:1301-1308.
20. Bryce, DM. Tests for the sterility of pharmaceutical preparations; the design and interpretation of sterility tests. *J Pharm Pharmacol*. 1956;8:561–572.
21. Sutton, S. The sterility tests. In: rapid sterility testing, Moldenhauer, J. ed., PDA, Bethesda, 2011.
22. ISO Technical Standard 14698-1, Cleanrooms and associated controlled environments—Biocontamination control, Part 1: General principles and methods. *Geneva: ISO*, 2003: 32.
23. Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach, Final Report, Department of Health and Human Services, U.S. Food and Drug Administration, September 2004. U.S. Food and Drug Administration website. https://www.fda.gov/media/77391/download. Accessed Dec 21, 2021.
24. US FDA. Guidance for Industry: Q10 Pharmaceutical Quality System, April 2009. U.S. Food and Drug Administration website. https://www.fda.gov/media/71553/download. Accessed Dec 21, 2021.

25. Labeling, Title 21 CFR Part 201. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=201&showFR=1. Accessed Dec 21, 2021.
26. US FDA. Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, February 2020. U.S. Food and Drug Administration website. https://www.fda.gov/media/135373/download. Accessed Dec 21, 2021.
27. US FDA. Guidance for Industry: ICH M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use, October 2017. U.S. Food and Drug Administration website. https://www.fda.gov/media/71551/download. Accessed Dec 21, 2021.
28. US FDA. Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, April 2009. U.S. Food and Drug Administration website. https://www.fda.gov/media/75783/download. Accessed Dec 21, 2021.
29. CDER Office of Pharmaceutical Quality. Report on the state of Pharmaceutical quality: Fiscal year 2019, February 2020. U.S. Food and Drug Administration website. https://www.fda.gov/media/135046/download?utm_campaign=SBIA%3A%20OPQ%20Issues%20Annual%20Report%20for%202019&utm_medium=email&utm_source=Eloqua. Accessed Dec 21, 2021.
30. Best chemistry practices to support the development of PET Drugs, Categorical Session, SNMMI Annual Meeting, June 10, 2017, Denver, CO. Coalition for PET Drugs website. https://coalitionforpetdrugs.org/2017/07/11/coalition-for-pet-drugs-sponsors-three-sessions-at-snmmi-annual-meeting/. Accessed December 21, 2021.
31. US FDA. Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies, January 2006. U.S. Food and Drug Administration website. https://www.fda.gov/media/72325/download. Accessed December 21, 2021.