

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

Sue Bunning,¹ Christopher Ignace,² Steve Mattmuller,³ Sally W. Schwarz,⁴ Peter J. H. Scott,^{5*} Henry F. VanBrocklin,⁶ Steven S. Zigler⁷ on behalf of the Coalition of PET Drug Manufacturers.

1. Medical Imaging and Technology Alliance, Arlington, VA
2. Cardinal Health, Dublin, OH
3. Kettering Medical Center, Kettering, OH
4. Department of Radiology, Washington University School of Medicine, St. Louis, MO
5. Department of Radiology, University of Michigan, Ann Arbor, MI
6. University of California San Francisco, San Francisco, CA
7. Siemens PETNET Solutions, Knoxville, TN

* Correspondence to Peter J. H. Scott, pjhscott@umich.edu (ORCID: 0000-0002-6505-0450)

ABSTRACT

Recent advances in the development of new molecular imaging agents for positron emission tomography (PET) have led to the approval of several new molecular entities for PET imaging by the U.S. Food and Drug Administration (FDA) within the last ten years. However, the continued use of PET drugs for diagnostic imaging procedures is reliant upon a sustainable network of PET manufacturing facilities operating in accordance with the current good manufacturing practice (cGMP) regulations for PET drugs (21 CFR Part 212). With this goal in mind, a public workshop entitled “PET Drugs: A Workshop on Inspections Management and Regulatory Considerations” was held on the FDA campus in Silver Spring, MD, on February 21, 2020. The workshop was co-sponsored by the FDA’s Center for Drug Evaluation and Research, the Society of Nuclear Medicine and Molecular Imaging, the Medical Imaging Technology Alliance, and the World Molecular Imaging Society, in collaboration with the Coalition of PET Drug Manufacturers. The organizing committee for the workshop consisted of members of academic and commercial PET manufacturers as well as representatives from the FDA. The co-authors on this paper are all members of the workshop organizing committee.

INTRODUCTION

Over the last two decades, significant advances have been made in the development of new molecular imaging agents for positron emission tomography (PET). These developments have led to the recent approval of several new molecular entities for PET by the U.S. Food and Drug Administration (FDA). As of July 2021, the number of FDA-approved PET drugs stands at 17 (1). Most of these approvals have occurred within the last decade. Notwithstanding this success, the continued use of PET drugs for diagnostic imaging applications must be assured by a sustainable supply chain of PET manufacturing facilities operating in accordance with FDA current good manufacturing practice (cGMP) regulations for PET drugs (21 CFR Part 212). With this goal in mind, a public workshop was held on the FDA campus in Silver Spring, MD, on February 21, 2020. Entitled “PET Drugs: A Workshop on Inspections Management and

Regulatory Considerations,” the workshop was jointly sponsored by the FDA’s Center for Drug Evaluation and Research (CDER), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the Medical Imaging Technology Alliance (MITA), and the World Molecular Imaging Society (WMIS) in collaboration with the Coalition of PET Drug Manufacturers. The organizing committee for the workshop consisted of members of academic and commercial PET manufacturers as well as representatives from the FDA.

The workshop was attended by radiopharmaceutical scientists, nuclear pharmacists, regulatory affairs professionals, and compliance specialists with expertise in PET drug manufacturing. Attendees represented academic institutions, commercial suppliers, contract manufacturers, and innovators involved in the development of new PET drugs. Many representatives from the FDA also attended. Approximately 150 attendees participated in-person and numerous participants joined in a live video broadcast of the event. The presentations and a recording of the workshop are currently available on the FDA’s website (2). The organizers defined four sessions for the workshop agenda:

Session I: Considerations and Trends in Inspections and Compliance

Session II: Lifecycle Management of PET Drug Applications

Session III: Chemistry and Product Quality Assurance

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

This paper describes the workshop highlights. The full agenda as well as a complete account of each presentation and the panel discussions appears in the supplementary materials that accompany this paper (3-33).

OPENING REMARKS

Louis Marzella, Division Director for Medical Imaging and Radiation Medicine, opened the workshop, noting that “the first principle is that the risk-benefit approach is applicable to the development of standards for quality of products...to ensure that safe and effective products are consistently administered to patients.” Reflecting the fact that specific GMP regulations (34) apply to the manufacturing of PET drugs, Marzella also noted, “we agree that specific considerations apply to different products including PET drugs.” Although there was recognition that standards evolve, Marzella stressed “the importance...of ensuring there is a consistency of approach regarding product quality expectations during the application review process and during the inspectional process. To this end, I think that the collaboration and cross talk between the review staff and the inspectional staff is an important topic.”

Sally Schwarz, co-chair of the Coalition, provided the Society of Nuclear Medicine and Molecular Imaging perspective on the workshop. The short shelf life and very low injected mass 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 PET drug batches annually required to meet nationwide demand (approximately 50% of the market for PET drugs is represented in this data) (3). The practical ramifications of these characteristics have resulted in negligible rates of patient adverse events following the administration of PET drugs (4-8). 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.

Sue Bunning, Industry Director for PET, provided the Medical Imaging Technology Alliance perspective. 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. According to market research data, slightly more than 2 million PET scans were performed in the US in 2018 (9). 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.

Henry VanBrocklin, co-chair of the Coalition, provided the WMIS perspective on the future of PET imaging. New PET scanner technologies hold the promise of greater sensitivity and earlier detection of disease states. However, the expected benefits from the underlying investments in new scanner technologies will be unrealized without the continued supply of PET drugs. New PET drug approvals in the last decade have exceeded the number of approvals in the previous thirty years, but the future of PET imaging may be jeopardized if the regulatory burden on routine manufacturing undermines a sustainable supply of PET drugs.

The goals for the workshop were to:

- Discuss regulatory compliance for the development and manufacturing of PET drugs
- Identify pathways for PET drug application approvals, application maintenance, and inspections based on the PET GMP regulations
- Share perspectives from industry, academia, investigators, and regulators on inspectional findings and trends
- Provide information on the management of PET GMP inspections and maintenance of PET NDAs and ANDAs

SESSION I – CONSIDERATIONS AND TRENDS IN INSPECTIONS AND COMPLIANCE

Steve Zigler, Chief Technical Officer for PETNET Solutions, introduced the first session by encouraging attendees to think beyond the half-life and to consider the practical ramifications that define the time-critical supply chain and the distributed manufacturing model for PET drugs. Decades after the first FDA approval of a PET drug, half-life constraints and their ramifications continue to define and re-define regulatory expectations in unforeseen ways. The core principle of the workshop was to provide a forum to discuss these unforeseen ramifications.

Manufacturing Process Assessment and Pre-approval Inspections

Krishna Ghosh, Senior Policy Advisor in CDER's Office of Pharmaceutical Quality (OPQ), provided the FDA perspective on this topic. As part of their fulfillment of the requirements in the 1997 FDA Modernization Act (FDAMA) (35), the FDA conducted inspections at all PET manufacturing facilities and approved all ANDAs by December 2015. The inspections consisted of a mixture of pre-approval and surveillance inspections. Also in 2015, the FDA underwent a reorganization to create the OPQ, which led to a separation of the offices that manage pre-approval and surveillance inspections. Consequently, since the reorganization, pre-approval inspections (PAIs) have been managed by the Office of Pharmaceutical Manufacturing Assessment (OPMA) and the Office of Regulatory Affairs (ORA), while surveillance inspections have been managed by ORA in conjunction with the Office of Surveillance (OS) and the Office of Compliance (OC). The Agency's review of inspection history since 2015 indicates a need to mature some of its original guidance documentation, which should be supported by a common level of understanding across stakeholders.

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, OS and 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 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.

Recent Experience with cGMP Surveillance Inspections of Commercial PET Manufacturers

Rick Friedman, Deputy Director, Office of Manufacturing Quality, CDER Office of Compliance, gave this presentation, which began with an overview of the inspection process as conducted by the Office of Regulatory Affairs (ORA). 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.

Between June 2018 and January 2020, the ORA finalized the classification of 45 PET facility inspections. The breakdown of the classifications was: NAI (n = 17, 38%), VAI (n = 24, 53%) and OAI (n = 4, 9%). A total of 6 PET inspections were classified as OAI from January 2018 to January 2020. Three OAI inspections resulted in the issuance of a warning letter and three resulted in regulatory meetings. All three warning letters were issued to non-academic, non-hospital manufacturers. Two of the regulatory meetings were held with academic or hospital-based manufacturers and the third regulatory meeting was held with an undisclosed type of manufacturer. Friedman did not discuss the FDA’s criteria for the issuance of warning letters versus regulatory meetings. All six OAI classifications resulted from failure to maintain a suitable environment for aseptic processing operations according to 21 CFR 212.30(a).

Since inspections are a snapshot in time, the FDA uses field alert reports (FARs) to augment their assessment of quality trends over a longer time horizon. From 2016 to 2019, the FDA analyzed FARs from PET manufacturers and found that 27% of commercial manufacturers submitted a FAR during this 4-year period (n=141). Friedman did not comment on the submittal of FARs from academic manufacturers. 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 (11).

Current Trends and Observations on Inspections – the PET Community Perspective

Sally Schwarz, Professor of Radiology at Washington University School of Medicine, provided the academic perspective on FDA inspections of PET manufacturers. The presentation included experiences from numerous PET manufacturing facilities and addressed questions that had been collected from the PET community before the workshop. Based on this feedback, several examples were provided to illustrate the inconsistent enforcement that sometimes occurs between FDA inspections and FDA regulations (34), guidance documents (13), and policy guides (14).

Peter Webner, CEO of Zionexa USA, provided the commercial perspective on FDA inspections of PET manufacturers, noting 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. As evidenced by the numerous recent approvals of new PET drugs, the existence of the PET GMP regulations has spurred significant innovation in this domain. The PET GMP regulations provide a platform for which investors and small companies can rely upon over the time horizon required for investment in the development of new products. Inconsistent enforcement of the PET GMP regulations creates uncertainty in development costs and timelines and thus hinders innovation in the development of new PET drugs. Changes to FDA policies that only come to light during a pre-approval inspection threaten the viability of a new product just as it almost reaches the finish line, but now must go through additional regulatory obstacles.

Office of Regulatory Affairs (ORA) PET Surveillance Inspections

Ileana Barreto-Pettit, National Drug Expert from the FDA Office of Pharmaceutical Quality Operations in the ORA, provided an update on FDA surveillance inspections. Based on the current organization chart for the ORA, the FDA manages surveillance inspections through a tiered system of offices that include four geographic divisions where inspections are conducted at the local level. The geographic divisions were formerly known as districts.

The FDA uses a risk-based site selection model to identify manufacturing facilities for surveillance inspections (16). 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. Barreto-Pettit did not discuss the FDA's criteria for assigning a risk score for type of facility, patient exposure, or the inherent product risk.

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.

FDA Pilot Program for Tablet-Based Inspections for PET Drugs

Binh Nguyen, Educator for Pharmaceutical Programs in the ORA, described the new inspection protocol project and the eNSpect electronic management tool for the inspection of PET manufacturers.

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. 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.

SESSION II – LIFECYCLE MANAGEMENT OF PET DRUG APPLICATIONS

Lifecycle Management of PET Drugs – the FDA Perspective

Ramesh Raghavachari, Branch Chief in CDER's OPQ, provided an overview of the lifecycle of FDA approved drug products. The typical lifecycle of a drug begins the discovery and development phases and continues with clinical development (investigational new drug or IND) and ultimately with FDA marketing approval (NDA) and finally with generic drug approval (ANDA).

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 (Pre-approval Supplement) – 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

Specific details about the risk levels for changes to approved applications were not provided.

Management of PET Drug Applications – the PET Community Perspective

Peter Scott, Associate Professor of Radiology at the University of Michigan, described the workload for a busy academic PET manufacturing facility with more than 30 different PET drugs available for clinical use. Experience at the University of Michigan during 15 years of operation with approximately 8,000 to 10,000 PET scans each year indicates no adverse events occurred during this time. This is consistent with the experience of the overall PET community, which was discussed earlier in the opening comments for the workshop wherein a recent survey found that six sterility test failures (including false positives) occurred in more than 58,000 batches produced in 2019 (3). In addition, the incidence of adverse events for radiopharmaceuticals was reported as 1.6 in 100,000 diagnostic studies (8).

SESSION III – CHEMISTRY AND PRODUCT QUALITY ASSURANCE

Product Quality Assurance: Microbiological Regulatory Perspective

Laura Wasil, Review Microbiologist in CDER's OPO, provided the FDA's microbiological perspective on product quality assurance for PET drugs.

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

The components used in the final product vial assembly consist of needles, syringes, membrane filters, and the container. All items are commercially available as pre-sterilized components and are aseptically assembled in the ISO 5 air environment. The components and assembly process should be described in the NDA or ANDA, as well as the storage conditions and expiration date of assembled product vials. [Figure](#) illustrates a final product vial assembly commonly used in PET drug manufacturing.

Microbiological tests for PET drugs include filter integrity, bacterial endotoxins, and sterility. For all PET drugs, the filter integrity must be evaluated after completion of membrane filtration but before release for administration. 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. Sterility testing cannot be completed before the release and administration of PET drugs.

Microbiological Considerations for PET Drugs – the PET Community Perspective

David Hussong, Chief Technology Officer of Eagle Analytical Services and former FDA Review Microbiologist, provided a perspective on the historical regulation of PET drugs and the microbiological risk factors associated with them. Sterility is notoriously difficult to prove and cannot be measured, even for non-PET drugs, due to statistical and microbiological limitations in test methods ([20-22](#)). Sampling for sterility testing of pharmaceuticals can only detect contaminated units when 10% or more of the batch is contaminated ([23](#)). 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.

Henry VanBrocklin, Professor of Radiology and Biomedical Imaging at the University of California San Francisco, summarized this presentation by noting that these controls have effectively minimized the risk of microbial contamination in PET drugs. 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%.

Christopher Ignace, Head of Scientific and Regulatory Affairs for Nuclear and Precision Health Solutions (NPHS) at Cardinal Health, discussed product quality assurance from the perspective of a commercial network of PET drug manufacturing facilities.

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.

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.

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.

SESSION IV – CHANGING LANDSCAPE OF PET DRUGS, LABELING REQUIREMENTS, AND ELECTRONIC FILING REQUIREMENTS

Ravi Kasliwal, Review Chemist in CDER's Office of Pharmaceutical Quality (OPQ), provided the FDA's perspective on the evolution of 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 $^{68}\text{Ga}\text{-GaCl}_3$ eluted from a $^{68}\text{Ge}/^{68}\text{Ga}$ 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. The radiolabeling of the kit with the generator eluate is performed under the practice of pharmacy according to instructions provided in the package insert.

CLOSING REMARKS

Closing remarks for the workshop were presented by Louis Marzella and Steve Zigler as personal observations on behalf of the organizing committee. It is clear that non-uniform inspections create confusion in the PET community concerning which regulations to follow or what guidance is applicable. This in turn jeopardizes the uniformity of the PET drug supply in the US. A comprehensive risk profile based on the inherent characteristics of positron-emitting radionuclides and PET drug manufacturing processes does not currently exist. The little that is known in this area is not uniformly understood across the PET community and within the FDA. A comprehensive training program for PET drug manufacturing and associated regulatory sciences does not currently exist in any pharmacy or university curriculum.

In closing the workshop, the PET community and the FDA aim to:

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

DISCUSSION: WORKSHOP SUMMARY AND RECOMMENDATIONS FROM PET MANUFACTURING STAKEHOLDERS

Four predominant themes emerged throughout the workshop. These themes may be summarized as follows:

- The uniformity of FDA inspections of PET manufacturing facilities
- A science-based risk profile for PET drugs
- Improvements to training for FDA investigators and the regulated community
- 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.

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.

Consequently, it seems self-evident that FDA inspections of PET drug manufacturing facilities should be uniform. 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 pharmaceutical 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 applicable FDA policies and procedures, *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. On 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 (32). To continue to realize this goal, it is critical that the FDA inspection process is uniformly implemented across all PET manufacturers.

Therefore, the FDA must 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.
- 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 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. 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 ORA, 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. This would minimally identify variations in regulatory interpretation and provide material support to the Guidance upgrade process.

A Science-based Risk Profile for PET drugs

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 FDA should 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 (33). 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 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.

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.

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.

CONCLUSIONS

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 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.

Acknowledgments

The authors thank SNMMI, WMIS, MITA and FDA for sponsoring the Workshop.

Disclosures

Christopher Ignace is an employee of Cardinal Health. Sally W. Schwarz is employed by Travarex Biomedical part time. Peter J. H. Scott has active research grants from Bristol Myers Squibb, GE Healthcare, AbbVie, Gossamer Bio Inc, IMRA America Inc, and clinical trials support from Bristol Myers Squibb. He is an owner of SynFAST Consulting LLC, and receives editorial royalties from John Wiley and Sons. He is an ad hoc consultant for GE Healthcare, the International Atomic Energy Agency, and holds leadership roles at the Society of Nuclear Medicine and Molecular Imaging and the Society of Radiopharmaceutical Sciences. Steven S. Zigler is an employee of Siemens PETNET Solutions. Sue Bunning, Steve Mattmuller and Henry F. VanBrocklin have no disclosures. No other potential conflicts of interest relevant to this article exist.

References

1. FDA Orange Book: Approved drug products with therapeutic equivalence evaluations. U.S. Food and Drug Administration website. www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed Dec 21, 2021.
2. PET Drugs: A workshop on inspections management and regulatory considerations. U.S. Food and Drug Administration website. www.fda.gov/drugs/pet-drugs-workshop-inspections-management-and-regulatory-considerations-02212020-02212020. Dec 21, 2021.
3. 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.
4. Silberstein, EB. Prevalence of adverse events to radiopharmaceuticals from 2007 to 2011. *J Nucl Med*. 2014;55:1308-1310.
5. Silberstein, EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. *J Nucl Med*. 1998;39:2190-2192.
6. 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.
7. 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.
8. 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.
9. Global imaging market outlook report, IMV Medical Information Division, Arlington VA, 2019.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.

-
15. 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.
 16. 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.
 17. 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.
 18. 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.
 19. 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.
 20. Halvorson, HO, Ziegler, NR. Application of statistics to problems in bacteriology. *J Bacteriol.* 1933;26:559-567.
 21. Bowman, FW. The sterility testing of pharmaceuticals. *J Pharm Sci.* 1969;58:1301-1308.
 22. Bryce, DM. Tests for the sterility of pharmaceutical preparations; the design and interpretation of sterility tests. *J Pharm Pharmacol.* 1956;8:561–572.
 23. Sutton, S. The sterility tests. In: rapid sterility testing, Moldenhauer, J. ed., PDA, Bethesda, 2011.
 24. ISO Technical Standard 14698-1, Cleanrooms and associated controlled environments— Biocontamination control, Part 1: General principles and methods. *Geneva: ISO, 2003: 32.*
 25. 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.
 26. 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.
 27. 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.
 28. 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.
 29. 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.

30. 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.
31. 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=SBI%3A%20OPQ%20Issues%20Annual%20Report%20for%202019&utm_medium=email&utm_source=Eloqua. Accessed Dec 21, 2021.
32. 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-snmami-annual-meeting/>. Accessed December 21, 2021.
33. 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.
34. Current good manufacturing practice for positron emission tomography drugs: final rule. *Federal Register*, December 10, 2009;74:65409-65436. <https://www.federalregister.gov/documents/2009/12/10/E9-29285/current-good-manufacturing-practice-for-positron-emission-tomography-drugs>. Accessed December 21, 2021.
35. FDA modernization act of 1997, Section 121, Positron emission tomography. Public Law No. 105-115. <https://www.govinfo.gov/content/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf>. Accessed December 21, 2021.

Figure Legend

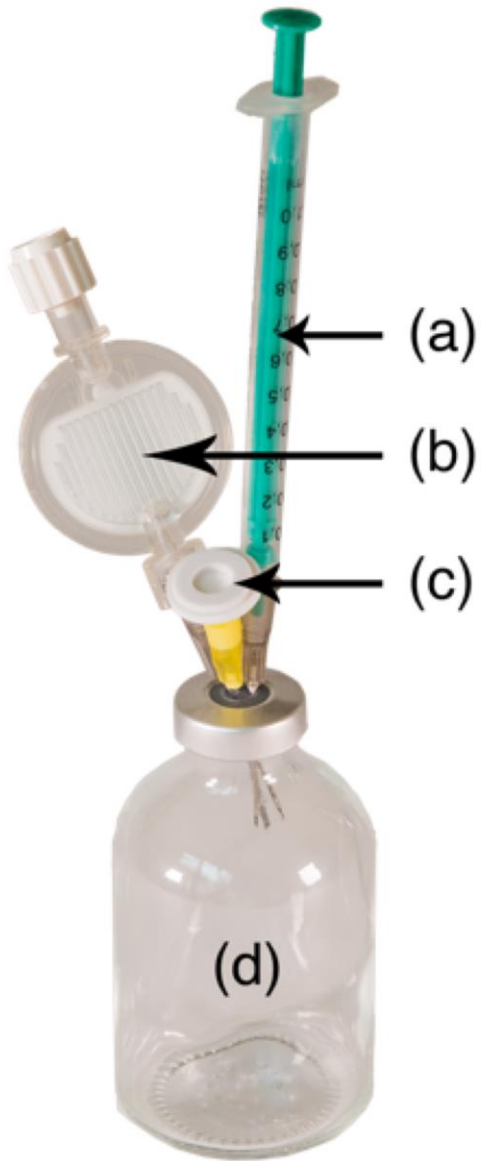


Figure 1. Assembled final product vial commonly used in PET manufacturing. (a) QC syringe, (b) membrane sterilizing filter, (c) filter vent, (d) product vial.