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

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

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

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

Key Words: quality assurance; radiochemistry; radiopharmaceuticals; 21 CFR §212; PET drug manufacture; regulatory oversight

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Over the last 2 decades, significant advances have been made in the development of new molecular imaging agents for 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 stood at 17 (*1*). Most of these approvals occurred within the last decade. Notwithstanding this success, the continued use of PET drugs for diagnostic imaging applications must be ensured by a sustainable supply chain of PET manufacturing facilities operating in accordance with FDA regulations on current good manufacturing practices (cGMPs) for PET drugs (title 21, *Code of Federal Regulations* [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, 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 representatives from academic and commercial PET manufacturers as well as FDA staff members.

The workshop was attended by radiopharmaceutical scientists, nuclear pharmacists, regulatory affairs professionals, and compliance specialists with expertise in PET drug manufacturing. Attendees represented academic institutions, commercial suppliers, contract manufacturers, and innovators involved in the development of PET drugs. Many representatives from the FDA also attended. Approximately 150 attendees participated in person, and numerous participants joined in a live video broadcast of the event. The presentations and a recording of the workshop are available on the FDA's website (*2*). The organizers defined 4 sessions for the workshop agenda: "Considerations and Trends in Inspections and Compliance," "Life Cycle Management of PET Drug Applications," "Chemistry and Product Quality Assurance," and "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 supplemental materials (available at http://jnm.snmjournals.org) (*3–33*).

OPENING REMARKS

Louis Marzella, the FDA's 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 good-manufacturing-practice (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."

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For correspondence or reprints, contact Peter J.H. Scott (pjhscott@umich.edu).
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Sally Schwarz, a cochair of the Coalition of PET Drug Manufacturers, 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, presterilized 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 microbiologic 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 (~50% of the market for PET drugs is represented in these data) (*3*). The practical ramifications of these characteristics have resulted in negligible rates of patient adverse events after 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, the 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, ^{18}F-FDG, accounted for more than 35 NDAs or ANDAs. According to market research data, slightly more than 2 million PET scans were performed in the United States in 2018 (*9*). Thus, the size of the U.S. market for PET drugs is quite small compared with the pharmaceutical industry. Considering these factors, the public health risk of PET drugs is miniscule compared with that of traditionally manufactured pharmaceutical products.

Henry VanBrocklin, a cochair of the Coalition of PET Drug Manufacturers provided the World Molecular Imaging Society 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 30 y, 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; and 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, the 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 redefine 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 Preapproval Inspections (PAIs)

Krishna Ghosh, a senior policy advisor in CDER's Office of Pharmaceutical Quality (OPQ), provided the FDA perspective on this topic. As part of its fulfillment of the requirements in the 1997 FDA Modernization Act (*35*), the FDA conducted inspections at all PET manufacturing facilities and approved all ANDAs by December 2015. The inspections consisted of a mixture of preapproval 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 preapproval and surveillance inspections. Consequently, since the reorganization, preapproval inspections (PAIs) have been managed by the Office of Pharmaceutical Manufacturing Assessment and the Office of Regulatory Affairs (ORA), whereas surveillance inspections have been managed by ORA in conjunction with the Office of Surveillance and the Office of Compliance. The FDA's review of inspection history since 2015 indicates a need to mature some of its original guidance documentation, a process that should be supported by a common level of understanding across stakeholders.

The FDA conducts 4 different types of inspections: PAIs, postapproval inspections, routine surveillance inspections, and for-cause inspections. PAIs 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 Office of Pharmaceutical Manufacturing Assessment and the ORA. Postapproval 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 Office of Pharmaceutical Manufacturing Assessment and the ORA. Routine surveillance inspections are routine periodic inspections of manufacturing facilities. These inspections are managed by the ORA, Office of Surveillance, and Office of Compliance. For-cause inspections result from a potential indication or evidence of noncompliance by the manufacturer. These inspections are managed by the Office of Compliance and the ORA.

The FDA considers at least 3 specific risk factors during the PAI process, including facility risks, process risks, and product risks. In the evaluation of facility risks, the FDA considers the compliance history of the facility, including whether 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, the deputy director of the Office of Manufacturing Quality, CDER Office of Compliance, gave a presentation on recent experience with cGMP surveillance inspections of commercial PET manufacturers. The presentation began with an overview of the inspection process as conducted by the ORA. On completion of a surveillance inspection, the ORA classifies the inspection

outcome into 1 of 3 categories: no action indicated, voluntary action indicated, and official action indicated. Inspections with minor findings are classified as no action indicated or voluntary action indicated, whereas inspections with the most problematic findings may be classified as official action indicated.

Between June 2018 and January 2020, the ORA finalized the classification of 45 PET facility inspections. The breakdown of the classifications was 17 cases of no action indicated (38%), 24 of voluntary action indicated (53%), and 4 of official action indicated (9%). A total of 6 PET inspections were classified as official action indicated from January 2018 to January 2020. Three official-action-indicated inspections resulted in the issuance of a warning letter, and 3 resulted in regulatory meetings. All 3 warning letters were issued to nonacademic, nonhospital manufacturers. Two of the regulatory meetings were held with academic or hospital-based manufacturers, and the third 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 6 official-action-indicated 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 to augment its assessment of quality trends over a longer time horizon. From 2016 to 2019, the FDA analyzed field alert reports from PET manufacturers and found that 27% of commercial manufacturers submitted a field alert report during this 4-y period ($n = 141$). Friedman did not comment on the submittal of field alert reports from academic manufacturers. On the basis of a review of inspection reports, the FDA found that not all sterility test failures were reported in a field alert report, even though the FDA requires PET manufacturers to immediately file a field alert report in the event of a positive sterility test result. 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, a 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. On the basis of 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, the chief executive officer of Zionexa USA, provided the commercial perspective on FDA inspections of PET manufacturers, noting that 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 on which investors and small companies can rely 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 come to light only during a PAI threaten the viability of a new product, making it go through additional regulatory obstacles just as it almost reaches the finish line.

ORA PET Surveillance Inspections

Ileana Barreto-Pettit, a national drug expert from the FDA OPQ Operations in the ORA, provided an update on FDA surveillance inspections. The current organization chart for the ORA shows that the FDA manages surveillance inspections through a tiered system of offices that include 4 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*). Ranking of drug manufacturing facilities for surveillance inspections by the FDA is 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 numeric 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 FDA acknowledged some gaps in training for PET GMPs. In addition, some investigators misunderstand 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, an 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 2 of the 6 quality systems requires 3–5 d for the actual inspection and an additional 5–7 d to write the establishment investigation report. A comprehensive PET inspection that covers 4 or more quality systems typically requires 3–7 d for the actual inspection and an additional 5–10 d to write the report. The new inspection protocol and the associated electronic tool (eNSpect) are designed to expedite the inspection process and preparation of the reports. 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 PAIs.

SESSION II: LIFE CYCLE MANAGEMENT OF PET DRUG APPLICATIONS

Life Cycle Management of PET Drugs: The FDA Perspective

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

Changes to approved applications and the life cycle of a drug can be achieved by a variety of mechanisms based on the risk of the change. The FDA has 4 defined risk categories: prior approval changes (preapproval supplement; high risk), changes being effected

in 30 d (moderate risk), changes being effected in 0 d (low risk), and 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, an 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 y of operation with approximately 8,000–10,000 PET scans each year indicates that 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 4 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: Microbiologic Regulatory Perspective

Laura Wasil, a review microbiologist in CDER's OPQ, provided the FDA's microbiologic perspective on product quality assurance for PET drugs.

Since PET drugs are administered to patients before the results of sterility testing are known, aseptic operations and procedures are critical to ensure the sterility of PET drug products. The following are critical operations that must be aseptically executed: assembly of the components used in the final product vial assembly, 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, and withdrawal of quality control samples), sterility testing, gowning and gloving procedures for personnel working in aseptic areas, environmental monitoring, and cleaning and disinfection of aseptic and 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 presterilized 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 1 illustrates a final product vial assembly commonly used in PET drug manufacturing.

Microbiologic 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 U.S. Pharmacopeia 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.

Microbiologic Considerations for PET Drugs: The PET Community Perspective

David Hussong, the chief technology officer of Eagle Analytic Services and a former FDA review microbiologist, provided a perspective on the historical regulation of PET drugs and the microbiologic risk factors associated with them. Sterility is notoriously difficult to prove and cannot be measured, even for non-PET drugs, because of statistical and microbiologic limitations in test methods (*20–22*). Sampling for sterility testing of pharmaceuticals can detect contaminated units only 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 indicates only 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.

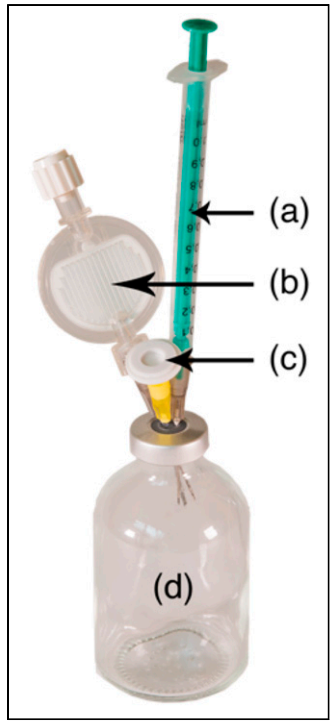

FIGURE 1. Assembled final product vial commonly used in PET manufacturing: quality control syringe (a), membrane-sterilizing filter (b), filter vent (c), and product vial (d).

Henry VanBrocklin, a 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 sterility test results was 18 batches, or 0.013% (*3*).

Christopher Ignace, the head of scientific and regulatory affairs for nuclear and precision health solutions 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 communicate only with local manufacturing staff or are unwilling to describe findings and the rationale for potential noncompliance before issuing an FDA form 483. This form's purpose is to notify the site's management of objectionable conditions found during the inspection. Investigators should always first discuss potential objectionable findings with the site's staff and if at a site of a large producer, include their corporate quality assurance staff before completing a 483.

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 nondegreed microbiologist was unacceptable. By this logic, other areas of training in PET manufacturing would require degreed chemists, pharmacists, and physicists.

The scope of preapproval and surveillance inspections should be well defined. The 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 renegotiation of the original approval commitments and the appearance that an investigator is enforcing his or her personal area of expertise.

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

Ravi Kasliwal, a review chemist in CDER's 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 nonradioactive kit for the preparation of the injectable PET drug. There are critical differences between these 2 classes of products. In the first case, exemplified by ^{18}F-FDG 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 ^{68}Ga-DOTATATE injection, which uses $^{68}GaCl_3$ eluted from 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. 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 nonuniform 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 United States. 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 had several aims: to enhance the effectiveness of inspections (ensuring the uniformity of PET drugs in the United States), to reach a consensus on a science-based risk profile for PET drugs, to create and implement training to enhance the consistency of FDA inspections, to periodically hold a workshop to continue the dialog between the FDA and PET stakeholders, and to hold interim informational meetings between the FDA and PET stakeholders to discuss ongoing issues with inspection of PET manufacturing facilities.

DISCUSSION: WORKSHOP SUMMARY AND RECOMMENDATIONS FROM PET MANUFACTURING STAKEHOLDERS

Four predominant themes emerged throughout the workshop: 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, and continued dialog between the FDA and the PET community.

Prior to the workshop, the organizing committee collectively defined the workshop as "a forum for the exchange of information and perspectives on the regulatory and compliance framework for PET drug manufacturing … thereby [improving] global understanding of issues and challenges facing PET manufacturers." In that spirit, the remainder of this paper discusses each of these 4 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 not to be the case. For example, some FDA investigators have used 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, and other aspects of manufacturing. Moreover, speakers at the workshop noted that the incidence of nonuniform inspections seems to have increased recently.

The nonuniformity in FDA inspections potentially results from various factors, including inadequate organizational controls within the FDA, 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 used 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 nonuniform 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 be 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 4 recommendations.

First, the FDA should organize a designated team of investigators to inspect 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 and the characteristics of the PET manufacturing supply chain.

Second, FDA investigators should use a prescribed checklist during inspections of PET manufacturers. This is imperative since deviations in inspectional approaches inevitably lead to nonuniform inspections. To this end, FDA speakers at the workshop described a tablet-based approach to managing inspectional checklists during PET inspections. The FDA should accelerate its efforts on this project and seek guidance on the program from the PET community. Although the FDA stated that sponsors will not be allowed to view screenshots of the tablet screen, the inspectional checklist should be publicly available to the PET community outside 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.

Third, 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 the FDA with 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 on the basis of whether a facility is academic or commercial.

Fourth, 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 often the only practical option in this situation is the issuance of a 483 observation. 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 quality assurance oversight for inspections, much like the second-person operational checks that ensure quality and prevent the inherent bias that occurs when operators perform quality control on their own work. This solution 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 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 the inspection of PET manufacturers. This approach is consistent with the pharmaceutical quality initiative described earlier in this paper. 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 be characterized only 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 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 pharmacologic response, radioactivity levels, and potential for repeat uses. These factors are already considered in regulatory assessments such as the exploratory investigational new-drug pathway (*33*). The risk analysis should also include mitigation strategies used in PET manufacturing as described throughout this workshop, including the use of closed systems, presterilized components, aseptic environments, microbiologically lethal processing steps, and other manufacturing steps. The analysis should be published in the peer-reviewed literature and openly available to the regulated community. The results of this exercise, done together with PET manufacturers, 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 said that the FDA is revising the PET GMP regulations and associated guidance documents. However, speakers from the PET community described the continued track record of safety associated with PET drugs, thus putting into question the immediate need for revision of the PET GMP regulations, which have been in use for only 10 y 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 (as described in the previous paragraph) and therefore may be delayed until this has been completed. This delay will allow for revisions 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 the 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 y old, and experiences with the FDA and the PET community will continue to evolve. 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 the formal channels of an application review or an inspection.

CONCLUSION

PET drugs have opened the door to molecular imaging and the 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, 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 lifesaving diagnoses available only through PET imaging.

DISCLOSURE

Christopher Ignace is an employee of Cardinal Health. Sally Schwarz is employed by Travarex Biomedical part-time. Peter Scott has active research grants from Bristol Myers Squibb, GE Healthcare, AbbVie, Gossamer Bio Inc., and IMRA America Inc.; has clinical trials support from Bristol Myers Squibb; is an owner of SynFAST Consulting LLC; receives editorial royalties from John Wiley and Sons; is an ad hoc consultant for GE Healthcare and the International Atomic Energy Agency; and holds leadership roles in the Society of Nuclear Medicine and Molecular Imaging and the Society of Radiopharmaceutical Sciences. Steven Zigler is an employee of Siemens PETNET Solutions. No other potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Orange book: approved drug products with therapeutic equivalence evaluations. FDA website. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed May 16, 2022.
2. PET drugs: a workshop on inspections management and regulatory considerations. FDA website. https://www.fda.gov/drugs/pet-drugs-workshop-inspections-management-and-regulatory-considerations-02212020-02212020. Published February 21, 2020. Accessed May 16, 2022.
3. SNMMI/MITA Survey of PET Drug Manufacturers, February 4–10, 2020, as described in Introduction to PET drugs. FDA website. https://www.fda.gov/media/136480/download. Published February 21, 2020. Accessed May 16, 2022.
4. Silberstein EB. Prevalence of adverse events to radiopharmaceuticals from 2007 to 2011. *J Nucl Med.* 2014;55:1308–1310.
5. Silberstein EB; Pharmacopeia Committee of the Society of Nuclear Medicine. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. *J Nucl Med.* 1998;39:2190–2192.
6. Laroche ML, Quelven I, Mazère 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; 2019.
10. FDA pharmaceutical quality oversight: one quality voice. FDA website. https://www.fda.gov/media/91721/download. Accessed May 16, 2022.
11. Other postmarketing reports. FDA website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.81. Updated March 29, 2022. Accessed May 16, 2022.
12. Current good manufacturing practice for positron emission tomography drugs. FDA website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=212. Accessed May 16, 2022.
13. Guidance: PET drugs—current good manufacturing practice (CGMP). FDA website. https://www.fda.gov/media/71013/download. Published December 2009. Accessed May 16, 2022.
14. Positron emission tomography (PET) cGMP drug process and pre-approval inspections/investigations. FDA website. https://www.fda.gov/media/82370/download. Published September 11, 2015. Accessed May 16, 2022.
15. Current Good Manufacturing Practice for Finished Pharmaceuticals. FDA website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211. Updated March 29, 2022. Accessed May 16, 2022.
16. Understanding CDER's risk-based site selection model. FDA website. https://www.fda.gov/media/116004/download. Published September 26, 2018. Accessed May 16, 2022.
17. Comparability protocols for human drugs and biologics: chemistry, manufacturing, and controls information. FDA website. https://www.fda.gov/media/97148/download. Published April 2016. Accessed May 16, 2022.
18. Electronic records; electronic signatures. FDA website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11. Updated March 29, 2022. Accessed May 16, 2022.
19. Guidance: media fills for validation of aseptic preparations for positron emission tomography (PET) drugs. FDA website. https://www.fda.gov/media/81974/download. Published April 2012. Accessed May 16, 2022.
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: Moldenhauer J, ed. *Rapid Sterility Testing.* Parenteral Drug Association; 2011:9–13.
24. *ISO Technical Standard 14698-1, Cleanrooms and Associated Controlled Environments—Biocontamination Control, Part 1: General Principles and Methods*. International Organization for Standardization; 2003:32.
25. Pharmaceutical CGMPs for the 21st century: a risk-based approach—final report. FDA website. https://www.fda.gov/media/77391/download. Published September 2004. Accessed May 16, 2022.
26. Guidance for industry: Q10 pharmaceutical quality system. FDA website. https://www.fda.gov/media/71553/download. Published April 2009. Accessed May 16, 2022.
27. General labeling provisions. FDA website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=201&showFR=1. Updated March 29, 2022. Accessed May 16, 2022.
28. Providing regulatory submissions in electronic format: certain human pharmaceutical product applications and related submissions using the eCTD specifications. FDA website. https://www.fda.gov/media/135373/download. Published February 2020. Accessed May 16, 2022.
29. M4 organization of the common technical document for the registration of pharmaceuticals for human use. FDA website. https://www.fda.gov/media/71551/download. Published October 2017. Accessed May 16, 2022.
30. Guidance for industry: integrated summaries of effectiveness and safety—location within the common technical document. FDA website. https://www.fda.gov/media/75783/download. Published April 2009. Accessed May 16, 2022.
31. CDER Office of Pharmaceutical Quality: report on the state of pharmaceutical quality—fiscal year 2019. FDA website. https://www.fda.gov/media/135046/download?utm_campaign=SBIA%3A%20OPQ%20Issues%20Annual%20Report%20for%202019&utm_medium=email&utm_source=Eloqua. Published June 2020. Accessed May 16, 2022.
32. Coalition for PET Drugs sponsors three sessions at SNMMI annual meeting. Coalition for PET Drug Manufacturers website. https://coalitionforpetdrugs.org/2017/07/11/coalition-for-pet-drugs-sponsors-three-sessions-at-snmmi-annual-meeting/. Published July 11, 2017. Accessed May 16, 2022.
33. Guidance for industry, investigators, and reviewers: exploratory IND studies. FDA website. https://www.fda.gov/media/72325/download. Published January 2006. Accessed May 16, 2022.
34. Current good manufacturing practice for positron emission tomography drugs. *Fed Regist.* 2009;74:65409–65436.
35. Food and Drug Administration Modernization Act of 1997. govinfo website. https://www.govinfo.gov/content/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf. Published November 21, 1997. Accessed May 16, 2022.