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1300 North 17th Street ▪ Suite 900
Arlington, Virginia 22209
Tel: 703.841.3200
Fax: 703.841.3392
www.medicalimaging.org

September 13, 2024

Via Electronic Mail

Libero (Louis) Marzella MD, PhD
Director, Division of Imaging and Radiation Medicine
Office of Specialty Medicine
Food and Drug Administration - CDER
10903 New Hampshire Ave., Bldg. 22, Rm. 5482,
Silver Spring MD 20993-0002

Re: Recent FDA Policy Changes on Stability Studies for PET Drugs

Dear Dr. Marzella,

As the premier trade association representing the manufacturers of medical imaging equipment and radiopharmaceuticals, the Medical Imaging & Technology Alliance (MITA) is contacting you on behalf of our member organizations related to recent FDA Policy Changes on Stability Studies for PET Drugs.

MITA in conjunction with the Coalition of PET Drug Manufactures has recently created a position paper on this topic. This paper is available at: https://www.petdrugmanufacturers.org/latest-efforts.

FDA's regulations on stability testing for PET drugs state that a PET drug manufacturer "must establish, follow, and maintain a written testing program to assess the stability characteristics of [the] PET drug products," the test methods "must be reliable, meaningful, and specific," and the samples "must be representative of the lot or batch from which they were obtained and must be stored under suitable conditions." 21 C.F.R. 212.61. These regulations have not changed since they were finalized in 2009. Manufacturers of PET drugs are required to include stability testing information in their new drug applications (NDAs) or abbreviated new drug applications (ANDAs), which also include post-approval commitments to provide testing data to FDA in an annual report in accordance with the submitted protocol.

As explained more fully in the position paper, applications for PET drug products have typically included protocols for annual stability testing performed at a single manufacturing facility because such results are considered representative of batches produced at other facilities in the approved application using the same equipment, materials, and processing procedures. PET drug manufacturers have justifiably relied upon this "one stability, one facility" approach, which had been accepted by the FDA and has been the *de facto* standard in the PET drug manufacturing industry for years.

The “one stability, one facility” approach is predicated on the practice that all facilities in an approved application use the identical raw materials, components, container-closure, equipment, product synthesis, production and analytical procedures, personnel qualification, and change controls. In essence, all facilities in an application operate under a single quality management system with the same production and process controls. The only differences lie in different staff working in different facilities. This is equivalent to the same product being produced by different staff working on different operating shifts and or processing lines using identical equipment within the same facility. This approach also reflects the uniformity of PET drugs and, by definition, is a requirement for nationwide product uniformity.

For reasons that have not been made clear to the industry, some FDA inspectors have recently attempted to issue observations to PET drug manufacturers for failing to perform stability testing at every manufacturing facility on an annual basis — despite the absence of any regulations or written guidelines specifying a change in the agency’s expectations regarding stability testing for PET drugs and despite “one stability, one facility” protocols being approved by FDA in multiple PET drug applications across multiple organizations. FDA speakers in the November 2023 workshop seem to have adopted this revised approach and characterized it as a “clarification” of the agency’s PET drug manufacturing GMP regulations.

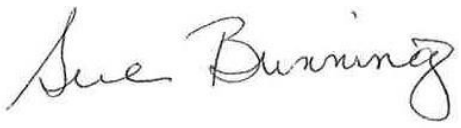
Because of PET radiopharmaceutical shelf-life constraints, unlike traditional pharmaceutical products, stability batches are not salable. In addition, as noted in the position paper, this change would have a significant impact on patient access to PET drugs and will result in additional costs to PET manufacturers. Of course, changes to the supply chain for PET drugs are always justified in the interest of product safety. First and foremost, PET drugs must be safe and efficacious. However, the FDA’s policy change regarding the “one stability, one facility” model does not seem to be linked to product safety concerns or other product performance attributes, individually or as a product category. Absent a product performance driver, a change of this magnitude should be generally based on science-based risk assessments. Based on the lack of publicly available information, no such risk assessment is readily available to the PET manufacturing community.

MITA members are deeply concerned that FDA appears to have changed course and has embraced an onerous new requirement for PET drug manufacturers without providing any reasonable justification for revising its position with respect to stability testing for PET drug products and without having first provided the opportunity for notice and comment. Moreover, the agency appears to be retroactively, albeit inconsistently, imposing these standards on approved products that have established their stability testing protocols in their marketing applications without fair warning. We believe that such actions run afoul of an essential tenet of administrative law: that agencies are required to “give notice of conduct that the agency prohibits or requires” and must “avoid surprising a party by penalizing it for good faith reliance on the agency’s prior positions.” *R.J. Reynolds v. FDA*, 65 F. 4th 182 at 189 (5th Cir. 2023) (citing *Christopher v. Smithkline Beecham Corp.*, 567 U.S. 142, 156-57 (2012)). Unexplained inconsistency in agency practice is a reason for holding a policy reversal arbitrary and capricious under the Administrative Procedure Act. 5 U.S.C. 706. See, *Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967 (2005). Given that the FDA has long accepted the one stability, one facility approach for PET manufacturing, “it cannot change this well-established course of action without supplying notice of and a reasoned explanation for its policy departure.” *CBS Corp. v. FCC*, 663 F.3d 122 at 138 (3d Cir. 2011).

We look forward to working with FDA related to any current or future proposed changes in the GMP regulations governing our industry. If you have any questions, please contact me at 703-340-4100 or by email at sbunning@medicalimaging.org.

Thank you for your consideration.

Sincerely,



Sue Bunning
Managing Director, MITA PET Group

MITA is the collective voice of medical imaging equipment and radiopharmaceutical manufacturers, innovators and product developers. Advancements in medical imaging are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. The industry is extremely important to American healthcare and noted for its continual drive for innovation, fast-as-possible product introduction cycles, complex technologies, and multifaceted supply chains. Individually and collectively, these attributes result in unique concerns as the industry strives toward the goal of providing patients with the safest, most advanced medical imaging currently available.