Coalition of PET Drug Manufacturers' Position Paper

Recent FDA Policy Changes on Stability Studies for PET Drugs

Introduction

A workshop on regulatory and compliance topics associated with the manufacture of drugs for positron emission tomography (PET) took place on November 13-14, 2023. The title of the workshop was "Positron Emission Tomography: Product Quality, Regulatory Submissions, Facility Inspections, and Benefit-Risk Considerations." Jointly sponsored by the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the Medical Imaging and Technology Alliance (MITA), the Coalition of PET Drug Manufacturers (the Coalition), and the Food and Drug Administration (FDA), the workshop took place at the FDA's Silver Springs campus in Maryland. Approximately 150 participants attended in person and 350 joined via the live stream broadcast. The workshop was recorded and is available on the FDA's website.[1]

The workshop consisted of four sessions focused on the topics defined in the workshop title. Members of the PET manufacturing community and FDA staff provided information and perspectives through presentations and Q&A sessions. One topic that garnered much attention during the workshop was the stability testing performed on PET drugs and the FDA's recent policy changes in this area. This article discusses these changes, which, if implemented, will have a profound impact on the supply of PET drugs in the USA.

Background

During the development and FDA approval process for a new PET drug, the stability of the product is assessed to ensure that the purity and quality of the product are suitable both at the time of release and at product expiry. Thus, stability studies define the shelf life for the product. Due to the short half-lives of most positron-emitting radionuclides (typically minutes to hours), the shelf life of a PET drug is typically measured in hours.

Stability studies are described in a protocol that is included in the new drug (NDA) or abbreviated new drug (ANDA) application for the product of interest. The protocol defines quality attributes and associated analytical methods that reflect the stability of the product. Known as stability indicating assays, these tests primarily rely on the radiochemical purity of the product, but also may include chemical purity, pH, specific and/or molar activity, stabilizer content, appearance, and other attributes. The protocol also describes the concentration of the active radiopharmaceutical ingredient, the formulation, stabilizer content, sampling times, vial configuration (e.g., upright or inverted), and storage conditions (e.g. temperature). Stability studies are typically performed for each vial size and chemistry synthesizer described in the NDA/ANDA. The regional section of the initial application submission contains facility-specific stability data. Although each facility executes the stability protocol at the time of the initial submission, it is typical to include detailed data sets for one facility and a tabulated summary of

[1] See: https://www.fda.gov/drugs/news-events-human-drugs/positron-emission-tomography-product-quality-regulatory-submissions-facility-inspections-and-benefit. Accessed May 21, 2024.

test results for additional manufacturing facilities. The results of the studies must support the proposed shelf life of the product.

After FDA approval, product stability is tested periodically (in most cases annually) to demonstrate that the stability (and thus the shelf life) of the product has not changed since FDA approval. This ongoing commitment is also defined in the stability study protocol included in the approved NDA/ANDA. Historically, NDA/ANDA holders with more than one manufacturing facility have included the commitment to perform stability studies at a single manufacturing facility and consider the results representative of other manufacturing facilities listed in the approved application. From a chemistry perspective, this approach is based on the fact that product stability is defined by the physicochemical properties of the active radiopharmaceutical ingredient and the product matrix, both of which are the same for batches of product manufactured at different facilities. Further, this "one stability, one facility" approach is predicated on the practice that all facilities in the approved application use the same raw materials, components, equipment type, synthesis and analytical procedures, personnel qualification, change controls, and quality system. In essence, this strategy reflects the uniformity of a PET drug manufactured using the same equipment and processes, regardless of the facility and personnel involved in preparation. By definition, this is a requirement for nationwide product uniformity.

Virtually all network-based commercial PET manufacturers have included the "one stability, one facility" approach in the stability protocols defined in their approved NDA/ANDAs. The FDA recognized this approach in a public meeting in 2011 when it stated, "*We are not looking for site-specific stability. So long as your manufacturing process is the same, uses the same synthesizer, the data from that site should be okay. You don't need to generate stability data at each site*."[2] Further, the FDA has approved the "one stability, one facility" approach in numerous PET drug applications and application supplements going back to the early 2010s. Even as recently as two days after the November 2023 workshop, the agency approved an application supplement describing the "one stability, one facility" approach. Since 2011, the number of batches of PET drugs produced according to these approved applications is not known with certainty; however, estimates based on industry data presented at the November 2023 workshop[1] place the total number of batches produced under the "one stability, one facility" model well in excess of 700,000. Finally, the "one stability, one facility" model has not been deemed objectionable in hundreds of FDA inspections at commercial PET manufacturing facilities. Together, the FDA's long term and widespread recognition of the "one stability, one facility" model has resulted in a *de facto* standard that has existed for years in the supply of PET drugs in the USA.

[2] Transcript, "Positron Emission Tomography (PET) Drugs: Submitting an Application for PET Drugs Currently in Clinical Use," FDA White Oak Campus, Wednesday, March 2, 2011, page 147. See: https://web.archive.org/web/20111229210542/http://www.fda.gov/Drugs/NewsEvents/ucm236825.htm. Accessed May 21, 2024.

Recent FDA Policy Changes regarding the "One Stability, One Facility" Model

Based on this history, it is surprising to note that, beginning in 2023, some FDA inspections highlighted the requirement for PET manufacturers to perform stability testing at *every* manufacturing facility on an annual basis. Initially, this appeared to be erroneous since the inspections occurred at facilities listed in approved applications with a stability protocol that described the "one stability, one facility" approach. The PET community was further surprised during the November 2023 FDA workshop when the agency repeatedly noted the need to clarify the PET GMPs and stressed that the regulations require stability testing at each facility annually. However, in fact, careful examination of the PET GMP regulations,[3] PET guidance documents,[4] and the general regulations for drug marketing[5] reveals that this requirement does not appear to be explicitly stated. The only readily available reference that specifically mentions facility-specific requirements for stability is a guidance document focused on stability in ANDAs, which notes, *"…if different synthesizers (methods of synthesis) are used, three batches from each method of synthesis at or near the upper end of the proposed radio-concentration are recommended. Batches do not have to be made in the same facility. For any additional manufacturing facilities, applicants should provide stability data on at least one batch at or near the upper end of the proposed radio-concentration from each facility, although bracketing approaches may be submitted for review*."[6] Notably, this guidance does not suggest the requirement for annual stability studies at each facility.[6] Thus, it seems clear that the PET GMPs and associated guidance documents do not explicitly require annual stability testing at each facility.

Consequently, one can only conclude that the FDA's position has changed since 2011 and, further, the agency's new position appears to be an interpretation of the regulations instead of a literal translation. The basis for the FDA's policy change and interpretation is unknown but may stem from multiple factors.

First, the FDA's experience with vertically integrated manufacturing models used in the traditional non-PET pharmaceutical industry may influence the agency's perspective regarding facility-based stability. Traditional pharmaceutical manufacturing may include facilities that manufacture the same product at different locations, often with different equipment and manufacturing conditions as dictated by legacy systems at each facility. This requires disparate manufacturing instructions and personnel training in order to maintain consistent product quality at each facility. In this model, it may not be possible for stability data from one facility to represent other facilities. In contrast, network-based PET manufacturers employ identical chemistry synthesizers, components, closed product vial systems, software instructions, and

[3] Code of Federal Regulations, Title 21, Part 212, "Current Good Manufacturing Practice for Positron Emission Tomography Drugs."
[4] PET Drug Products - Current Good Manufacturing Practice (CGMP), FDA Center for Drug Evaluation and Research, December 2009.
[5] Code of Federal Regulations, Title 21, Part 314, "Applications for FDA Approval to Market a New Drug."
[6] Guidance for Industry, ANDAs: Stability Testing of Drug Substances and Products-Questions and Answers, Office of Generic Drugs, May 2014.

procedures for a given PET drug product. In this case, stability data from one facility represents all facilities with identical configurations. If a different chemistry synthesizer or product vial system is used within a network-based manufacturer, stability data is generated for each unique configuration. Thus, network-based PET manufacturers operate in a truly standardized manner controlled by an effective quality system.

Second, based on discussions at the November 2023 workshop, the agency does not appear to be internally aligned on these policy changes and interpretations,[1] perhaps reflecting the possibility that the changes have evolved out of FDA inspections (i.e., "regulation by inspection"). Although occasionally employed during FDA inspections of traditional manufacturing facilities, this inspectional strategy may lead to nonuniform standards employed in PET manufacturing and thus undermine the framework that ensures PET drug uniformity.[7]

Several times during the November 2023 workshop, questions arose from the audience in an effort to understand the basis for the FDA's recent policy change and new interpretation.[1] After lengthy discussions and attempts by the FDA to describe the change as clarification, the agency noted that *"…there is a lot of stuff in an application and not everything that is in an application is necessarily approved*" and that an approved application is *"…not a green light for everything in [the application]*." This confusing message is inconsistent with the agency's longstanding support of the "one stability, one facility" model. Further this message erodes the presumption that an FDA action on an approved application represents the "conditions of approval" for a product, which in turn forms the regulatory basis for enforcement. Ultimately, the FDA acknowledged that oversights had occurred in the review of numerous NDA/ANDAs, application supplements, and FDA inspections since 2011 and this in turn has led to a disconnect between the agency and the regulated community.[1]

Implications of the FDA Policy Change

As already noted, the widespread approval of stability protocols, the preparation of hundreds of thousands of batches, and the completion of hundreds of FDA inspections based on the "one stability, one facility" approach has resulted in a longstanding *de facto* standard for the supply of PET drugs. In turn, this has shaped the very nature of the just in time supply chain for PET drugs in the USA. Staffing levels, equipment, resources, workflows, product availability, and imaging center expectations have evolved according to this standard.

At first, it may seem surprising that the simple addition of annual stability studies at each facility has a significant impact on the supply chain for PET drugs. However, a simple analysis[8] reveals

[7] Bunning, S., et al., Proceedings: PET Drugs—A Workshop on Inspections Management and Regulatory Considerations, J Nucl Med, 2022, 63, 1117-1123.

[8] The number of products, commercial suppliers, and facilities is not known with certainty. For purposes of this analysis, the following values are used: 11 total FDA approved PET drugs, 4 commercial suppliers with networks of facilities, 100 commercial manufacturing facilities, maximum of 6 products manufactured at each facility. Under the "one stability, one facility" model, this requires 11 products x 4 suppliers or 44 stability batches per year. The adoption of the "stability at every facility" model will require 6 products x 100 facilities, or 600 stability batches per year. This represents an increase of 600/44 or 1400%. The execution of a 12-hour stability study requires a minimum of 24 hours of labor for each stability batch (including preparation, synthesis, testing, documentation,

that this additional requirement amounts to an increase of 1400% in the number of stability batches and additional costs of approximately $3 million each year across the commercial manufacturing supply chain. These additional costs do not account for lost revenue caused by supply interruptions due to stability studies. Since the commercial market for PET drugs is approximately $400 million/year,[9] the cost for the additional stability studies represents 0.8% of the total market. To put this into perspective, if a similar cost for stability studies was applied to the traditional USA drug market of $510 billion,[10] it would represent an additional cost of almost $4 billion.

Beyond simple economics, the FDA's policy change will significantly and negatively impact people, including both the patients who require access to PET drugs and the personnel involved in PET drug manufacturing. The execution of stability studies at each PET facility will require the complex coordination of resources, stakeholders, patient scheduling, and transfers of doses between PET facilities. In order to implement the "stability at every facility" model, the most likely scenario will result in the complete disruption of patient doses on days when stability studies are executed at a PET facility. A simple analysis[11] reveals that this will result in a disruption of up to 600 or 2.3% of the available manufacturing days for commercial PET manufacturers each year. In addition to the significant economic impact due to lost revenue, a disruption of this magnitude will strain the existing supply chain and increase wait times for patients in need of PET scans.

The increased strain in the supply chain will also increase stress on the workforce and degrade the work environment associated with PET drug manufacturing. Human factors such as more complex workflows, scheduling, hours of operation, and supply management will lead to more overtime, turnover, and increased quality issues. In turn, this will add pressure to a strained labor market thereby compounding the potential for reduced patient access and higher costs.

Conclusions

The implementation of stability studies at each commercial PET manufacturing facility will have a surprisingly large 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

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quality review, etc.). Thus, the "one stability, one facility" model requires 44 batches x 24 hours of labor/batch, or 1056 hours of labor per year. The "stability at every facility" model will require 600 batches x 24 hours of labor/batch, or 14,400 hours of labor per year. This is a net increase of 13,344 hours of labor. Assuming a fully loaded labor rate of $150/hour, this represents an additional $2 million in labor costs each year. Additional material and indirect costs will add $1 million in expenditures, resulting in an estimated additional cost of $3 million.

[9] Estimate from "PET Imaging Market Summary Report," IMV Market Research (2023). For purposes of the analysis presented herein, the data in the IMV report has been adjusted to reflect the market for commercial suppliers only.

[10] https://www.vantagemarketresearch.com/industry-report/pharmaceutical-manufacturing-market-2300. Accessed June 2, 2024.

[11] The total number of manufacturing days for commercial PET manufacturers is assumed to be 52 weeks x 5 manufacturing days/week x 100 manufacturing facilities, or 26,000 manufacturing days each year. Assuming six approved products are manufactured at each facility and that a 12-hour stability study requires a full day to complete, the number of disrupted days is 1 day/stability x 6 products x 100 facilities, or 600 disrupted days across all commercial facilities. This represents 600/26,000 or 2.3% of the total available manufacturing days.

the name of product safety. First and foremost, like all pharmaceutical products, 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 from the FDA, no such risk assessment is readily available to the PET manufacturing community. Instead, these new requirements appear to be driven by changes in the FDA's interpretation of existing regulations, possibly based on the agency's experience with vertically integrated non-PET manufacturing models and possibly complicated by variability in inspector enforcement and the consequent risk of "regulation by inspection" arising from FDA inspections.

The "one stability, one facility" model is consistent with the requirements for–and the demonstration of–product uniformity in the nationwide supply of PET drugs. This is due to the fact that product stability is based on the physicochemical properties of the active radiopharmaceutical ingredient and the product matrix. Raw material controls, equipment standardization, process and documentation controls, training, personnel qualification, quality control, change controls, and other aspects of an effective quality system ensure uniformity of the product matrix and thereby define the core of the risk assessment for the "one stability, one facility" model. Given the high degree of process standardization across a given manufacturing network, as well as the stability data obtained during product development and the extensive history of the "one stability, one facility" model, such impactful changes seem unwarranted from a product performance standpoint. The addition of facility-specific stability data for networked PET manufacturers will not improve product safety and will only reduce patient access while increasing the cost of PET drugs.

Importantly, these conclusions represent a snapshot of the current state of commercial PET manufacturing in the USA today. Given the anticipated growth in the number of diagnostic PET procedures[9] and the development of new PET drugs,[12] the number of approved PET drug applications and their corresponding manufacturing facilities may experience significant growth in the near future. Thus, the implementation of a "stability at every facility" model is likely to have increasingly negative consequences over time, which could slow innovation in nuclear medicine and therapeutic applications that rely on PET scans.

Recommendations

Based on this analysis, the following recommendations are offered.

1. The FDA should reaffirm its commitment to the "one stability, one facility" model for PET drug network manufacturers, as allowed under a risk-based approach in an application. The agency should honor the contracts made over the last decades in the approvals of numerous PET drug NDA/ANDAs, application supplements, and in hundreds of inspections of PET manufacturing facilities.

[12] See: SNMMI Annual Meeting, Opening Plenary Session, Toronto, June 8-11, 2024.

2. Going forward, the FDA should engage the regulated community of PET manufacturers before the implementation of major policy changes in PET manufacturing. The Coalition, MITA, and the SNMMI offer multiple sources of information and expertise that the agency may engage in the evaluation of such changes.
3. When clarifications to existing policies and regulations are required, the FDA should communicate these changes in a controlled fashion directly with NDA/ANDA holders. FDA should as much as possible provide the rationale for changes and references to authoritative sources, such as existing regulations and guidance. Change implementation through one-by-one inspections of PET facilities causes confusion among NDA/ANDA holders, contract manufacturers, and the PET community, which potentially leads to a non-uniform nationwide supply of PET drugs.