February 26, 2024

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane
Room 1061, (HFA-305)
Rockville, MD 20852

Dear Dockets Management Staff:

The Coalition of PET Drug Manufacturers (“the Coalition”) was organized in November 2010 to help manufacturers of drugs for positron emission tomography (PET) understand requirements related to the implementation of 21 CFR part 212, and to communicate with the Food and Drug Administration (FDA) on behalf of this community. Since that time, the Coalition has played an instrumental role in numerous policy issues on the behalf of PET drug manufacturers. Coalition members represent the majority of the PET drug manufacturing facilities in the US and strive to represent the interests of the entire PET community. We appreciate the opportunity to provide comments on the FDA’s Draft Report and Plan on Best Practices for Guidance (Docket No. FDA-2023-N-5653).

A> Preamble

The Coalition is hereby providing formal comments to the January 3, 2024, posting in the Federal Register of the FDA’s “Draft Report and Plan on Best Practice for Guidance,” published in partial fulfillment of the regulatory requirements found under section 2505(a) of the Consolidated Appropriations Act of 2023 (Pub. L. 177-328). The submission of our comments is made within the comment deadline of March 4, 2024. The comments reflect the needs and priorities of the Coalition, which represents academic and commercial manufacturers of drugs for positron emission tomography (PET) in the US. As a result, our comments are aimed at optimizing the Guidance process in support of the development, regulatory approval, and production of diagnostic PET radiopharmaceuticals.

B> General Comments

As an opening statement, the Coalition appreciates the Agency for providing a retrospective view of its efforts over the last 10-year period, describing its approach to Guidance implementation across routine and health emergency conditions, and providing forward looking perspectives and priorities. By providing a comprehensive and substantive backdrop to its stakeholders, the Agency greatly facilitates the review process and the value of feedback generated.

The Coalition recognizes the critical role played by Guidance Documents in the development and production of PET drugs, as well as in defining and supporting compliance considerations and approaches to regulatory enforcement by the Agency. Within this context, the Coalition offers the following comments for consideration, and seeks to continue a genuine dialogue with the Agency.

1. General Comments on FDA’s latest efforts and outcomes

*FDA document sections covered: I. Executive Summary; III. Background; IV. Improving Efficiency and Transparency; V. – Guidance Plan, P. 24.*

The Coalition acknowledges the significant increase in Guidance issuance since 2011, nearly doubling the number of documents issued per fiscal year. Thanks to the level of detail provided, we understand that this outcome has been achieved through numerous initiatives within the Agency, such as (a) the creation of comprehensive teams with representatives from relevant divisions; (b) the adoption of program/project management principles, including assigned project managers, use of
tracking software, routine pre-defined review cycles, and the adoption of templated documentation approaches; (c) the increased use of Web-based informational tools, such as searchable databases and updated lists of planned and completed guidance initiatives; (d) the expanded use of Level 1 issuance without review under Public Health Emergency (PHE) decree during the COVID Pandemic.

The Coalition commends the Agency for the significant internal gains in efficiency and the resulting increased guidance issuance output. Generally, the Coalition believes that these efforts drive better communication among stakeholders and increase effectiveness and efficiencies across all main drug development and manufacturing business areas. We recognize these as significant successes consistent with the longer vision expressed under the 21st Century Initiatives.

2. Comments on FDA’s Proposed Revised Communication Modalities

*FDA document sections covered: V. Draft Section 2505 Guidance Plan, subsections A & B.1, p 24-25.*

*FDA’s Proposal:*
- provide for publication of the annual Guidance Agenda on the Internet only
- provide information to ease the process for individuals and firms to suggest topics for new guidance documents or to suggest that a particular guidance document be revised or withdrawn
- make guidance documents available on the “Search for FDA Guidance Documents” web page and make paper copies of guidance documents available only upon request

The Coalition acknowledges the above Agency proposals in support of improved communication modalities, and is supportive of the Agency’s goals and proposed means. Specifically,
- The Coalition supports publication of the annual Agenda on the Internet only.
  - As a result, we look forward to the Agency’s periodic updates of the Agenda through the fiscal year to maximize the web-based tool.
- The Coalition looks forward to learning about the specific tools and initiatives the Agency intends to deploy regarding receiving feedback on existing Guidance and suggestions regarding new guidance/guidance topics.
  - We would find useful any clarification regarding whether these new tools are intended to be supplemental or in (partial) replacement of current practices.
- The Coalition strongly supports the expanded use of any web-based database search tools that allow queries along categorical as well as specific terms, including term combinations (“Boolean approach”). The Coalition acknowledges the need for stakeholders to generate themselves paper-based versions according to needs.
  - We suggest that dialogue be maintained regarding search-based approaches to best serve a broad constituency.

Generally, the Coalition is in agreement with the Agency’s approach and supports the expanded use of Web-based tools, provided frequent updates and easier feedback remain the primary drivers behind the Agency initiatives.

3. Comments on FDA’s Proposed Guidance Issuance Modalities

*FDA document sections covered: V.B 2. Use of Level 1 Guidance “for Immediate Implementation” (P. 25)*

The Agency considers expanding its historically conservative practice of issuing level 1 guidance for immediate implementation, as well as developing new categories of Guidance as Level 2 that are inherently more appropriate for immediate implementation. The Agency restated the benefits provided by immediate implementation during the COVID-19 pandemic.
The Coalition has developed its position based on three independent areas of concern discussed below.

a) The Coalition membership consensus is that the regulatory landscape for PET drug approval and manufacturing compliance oversight is still new. This is especially relevant when considering diagnostic radiopharmaceuticals in comparison to other regulated categories of drugs and medical devices. The PET Good Manufacturing Practices (GMP) published in 21.CFR.212 became effective in 2012, along with Guidance supporting PET drug regulatory submissions and interpretation of manufacturing new regulations, whereas the regulatory landscape of other drugs and medical devices have been in place for about 50 years.

b) Thus, the compliance landscape for PET drugs is still maturing, as seen through the impending issuance of a revised chapter 21.CFR.212 that will incorporate learnings from manufacturing site inspections and other forms of regulatory oversight. This has been extensively documented by the PET community at radiopharmaceutical conferences and FDA attended forums, such as the latest FDA-hosted PET Drugs Workshop on November 13-14, 2023 at the FDA’s White Oak campus in Virginia. At this forum, the Agency acknowledged recent changes in its interpretation of its own Guidance framework for PET drugs, including admission of inconsistencies between regulatory and quality compliance policy interpretations.

c) We understand that the “FDA periodically reviews all comments and revises guidance documents based on comments when appropriate.” To that end, the Coalition has expended significant resources to ensure prompt review of FDA draft documents, and it has been a timely partner. The Agency has acknowledged – and appreciated – the interactive and communicative attitude of all PET-related manufacturers on several occasions, including recently at the November 2023 FDA-PET Industry Workshop. It was recognized that the finalization and release of some of the most awaited regulatory and Guidance documents, such as the revised 21.CFR.212, are not being controlled by – or contingent to – PET community feedback. Because stakeholder review cycles are not rate limiting to documentation issuance, cooperation and communication should remain the default modality.

Because the PET regulatory framework is still relatively new and several conflicts and inconsistencies remain, and because the PET Community has demonstrated a high level of timely engagement, we believe that an on-going dynamic and open communication must remain in place between the stakeholders at this time. As a result, the PET Coalition requests the following:

- Both Level 1 and 2 Guidance documents pertaining to diagnostic radiopharmaceuticals be subject to all PET stakeholders (especially drug manufacturers) review prior to Agency implementation.
- The Coalition and the PET Community be kept abreast of Level 1/2 guidance classification considerations by the Agency, and allowed the opportunity for feedback prior to firming any classification.

The Coalition recognizes the Agency’s authorities and powers within the Public Health Emergency regulatory landscape, and the above requests are not meant to restrict or conflict with such authorities in any way.

4. Comments on FDA’s Proposal for Streamlining Regulatory Submissions


The Agency describes its intent to create and revise Guidance documentation designed to facilitate submission and reviews of applications. The FDA may publish the intended scope of Guidance under the Guidance Agenda. The Agency also intends to develop further template and conformance and guides along Guidance document.

The Coalition supports all of the above Agency’s objectives. The Coalition also has the following requests:
• The Agency carefully considers the awareness – and whenever possible engagement – of specific (e.g. most effected) audiences, including the opportunity for feedback through the review period.

• The Agency considers sharing templates, especially when considered “checklists” during compliance enforcement activities. This would include sharing approaches to electronic data capture about forms/tables/templates with regulated parties.

In agreement with the Agency, the Coalition also supports the development of Guidance aimed at reducing a regulatory reporting category by defining upfront the concepts and conditions of “sameness” or “equivalency”, and the studies (types and scope) that would support such determination.

5. Comments on FDA’s Proposal for Issuance of Guidance Agenda within the Office of the Commissioner


The Agency proposes to publish within the Office of the Commissioner an annual agenda that better reflects the annual agenda of the various FDA Centers.

The Coalition supports any internal process improvement that provides the Agency a more accurate view of its own annual priorities within the Centers, as well as reduces the potential for conflicts and misalignments between the stakeholders.

> Conclusion

In conclusion, the Coalition appreciates the Agency’s efforts and progress since the 2011 Good Documentation Practice (GDP) report. The Coalition is also encouraged by continuing initiatives regarding communication simplification and information sharing, especially through the expanded use of web-based tools, templates and searchable databases, as well as the periodic review and publication of agendas. In all of these areas, the Coalition supports the proposed plans from the Agency. However, upon careful considerations of the evolving nature of the regulatory and compliance landscape of diagnostic radiopharmaceuticals, the Coalition does not support automatic implementation of Level 1 and 2 Guidance that can impact the manufacturing and/or regulatory submission of PET/diagnostic drugs at this time. Instead, the Coalition requests continuing engagement through Guidance review cycles and the use of comment periods.

The community has demonstrated its commitment to meeting review cycles over the last decade, and it is committed to maintaining timely and effective processes that will support the continued development of diagnostic radiopharmaceutical that are safe, effective and available to providers and patients. We look forward to supporting the Agency’s efforts towards achieving the proposed goals of the new Guidance process.

Best regards,

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