Industry Perspective on the Impact of COVID-19 on FDA Inspections and Regulation of PET Drug Manufacturers

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Coalition Leadership Team

Website: coalitionforpetdrugs.org/
Overview

• Section I: Industry Site Inspections Observations
  • Industry PET Members
  • Current challenges
  • Coalition proposed support
  • Most recent FDA inspection findings

• Section II: Quality and Regulatory Compliance Factors
  • Inspectional standards/requirements under COVID-19
  • Alternative Inspections Methods: “remote/virtual” inspections?
  • Information Requests (704(a)(4)): confusing compliance language?
  • Remote Interactive Evaluations: what to expect?
Industry PET Drug Manufacturers

- 3D IMAGING DRUG DESIGN AND DEVELOPMENT LLC
- ADVANCED ACCELERATOR APPLICATIONS USA INC
- AVID RADIOPHARMACEUTICALS INC
- BIOMEDICAL RESEARCH FOUNDATION NORTHWEST LOUISIANA
- BLUE EARTH DIAGNOSTICS LTD
- BRACCO DIAGNOSTICS INC
- BRIGHAM AND WOMENS HOSP
- CARDINAL HEALTH NUCLEAR & PRECISION HEALTH SOLUTIONS
- CENTRE FOR PROBE DEVELOPMENT AND COMMERCIALIZATION
- CLARITY INC
- ESSENTIAL ISOTOPES LLC
- GE HEALTHCARE
- HOUSTON CYCLOTRON PARTNERS LP
- IBA
- IONETIX CORP
- JUBILANT DRAXIMAGE RADIOPHARMACIES INC
- LANTHEUS MEDICAL IMAGING INC
- LIFE MOLECULAR IMAGING SA (Piramal)
- MIDWEST MEDICAL ISOTOPES LLC CYCLOTRON DIV
- MIPS CYCLOTRON AND RADIOCHEMISTRY FACILITY
- NCM USA BRONX LLC
- NORTHLAND NUCLEAR MEDICINE LLC
- ORA
- PETNET SOLUTIONS INC
- PHARMALOGIC HOLDINGS CORP
- PRECISION NUCLEAR LLC
- RADIOMEDIX INC
- SHERTECH LABORATORIES LLC
- SOFIE CO DBA SOFIE (FKA ZEVACOR PHARMA INC)
- NUKEMED INC DBA SPECTRONRX
- THE GENERAL HOSPITAL CORP (MGH)
- TELIX PHARMACEUTICALS
- TRACE-ABILITY INC
- WISCONSIN MEDICAL CYCLOTRON LLC
- ZIONEXA US CORP
PET drug manufacturers face the following challenges:

- Increasing diversity of PET diagnostic molecules in development (isotopes and biomarkers), in part driven by new therapeutic drugs (theranostic)
- Increasing volume of PET drugs (clinical and commercial)
- Different manufacturing and testing methodologies
- Some confusion about site inspection modalities, made more acute by COVID-19 remote FDA practices and several new Guidance
- Ongoing challenges associated with COVID-19 pandemic
- Post-pandemic concerns: how to manage back-log/delayed inspections, especially for PET Networks
How can the Coalition help the PET Industry?

- Provide a primary and formal FDA interface for quality and regulatory compliance communications affecting the PET manufacturer community

- Enable the organization to represent PET across manufacturers at symposia, conferences and other meeting forums

- Help organize and prioritize issues important to PET

- Help ensure consistent interpretation of CGMP Guidance and Regulations, as well as consistent field implementation
Inspections During COVID-19

- Informal pooling of handful of PET businesses- Global to start-up (confidentiality/competitiveness)

- Qualitative analysis for March 2020-21:
  - Every respondent received Information Requests from FDA
  - Very few on site inspections, regardless of corporate size (as low as 0, or 1)
  - PET Networks had fewer on-site inspections than usual (3-5); for every on-site inspection there were 4 Information Requests
  - On-site inspections were of typical pre-pandemic scope and durations (few days)
  - On-site inspections still involves multiple inspectors for small PET locations (logistics difficult)
  - FDA site inspectors requested information “de novo”

  Overall consistent with FDA deferring most surveillance inspections during COVID-19 pandemic

- Comments on Information Request (704)
  - Extensive and resource intensive (2 weeks for site staff/corporate QA)
  - Occasional large/excessive number of requests by FDA (3 to 5) for same site over weeks/months
  - Multiple emails/snail mails to accommodate file size/lack of secure server
  - Information not provided to site inspectors
  - No feedback to sponsor (“black hole”) – no findings, no database update, no “closure”
  - Are these “in lieu of” site inspections?
  - General feedback: IRs provide no value to industry; FDA should stop if not used “in lieu of” inspection
Inspections During COVID-19

• Section II: Quality and Regulatory Compliance Factors

  • Inspectional standards/requirements under COVID-19
FDA Guidance – Requirements under COVID-19

Good manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing”, June 2020, FDA/CDER.

Section III: For positron emission tomography (PET) drugs, 21 CFR 212.30, “What requirements must my facilities and equipment meet?”, states: (a) Facilities. You must provide adequate facilities to ensure the orderly handling of materials and equipment, the prevention of mix-ups, and the prevention of contamination of equipment or product by substances, personnel, or environmental conditions that could reasonably be expected to have an adverse effect on product quality.


Q7 […] For products regulated by CBER, contact cbershortage@fda.hhs.gov. Except as described above, FDA intends to continue following the procedures outlined in relevant Manuals of Policies and Procedures (MAPPs) and Standard Operating Procedures and Policies (SOPPs).

Note: FDA MAPP 7346.832.
Ref. 5. “For current good manufacturing practice (CGMP) standards concerning (a) positron emission tomography (PET) drugs, refer to 21 CFR part 212 and compliance program 7356.002P—Positron Emission Tomography (PET) CGMP Drug Process and Pre-approval Inspections/Investigations; (b) […]

→ No change in inspectional standards/requirements under COVID-19 pandemic
→ 21.CFR.212 is adequate (“necessary and sufficient”)
Inspections During COVID-19

• Section II: Quality and Regulatory Compliance Factors

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  • Alternative Inspections Methods: “remote/virtual” inspections?
FDA Alternative Inspection Methods

Additional Questions from FDA-SNMMI Webinar (6/17/2020)

4. [WHY] FDA response: “FDA is utilizing alternative approaches to inspections, including re-inspections, where possible to mitigate the need or duration of inspections during the COVID-19 pandemic. […]”

7. [WHAT] FDA response: “FDA does not conduct “virtual” drug CGMP inspections, as inspections inherently include on-site activities as defined in the Food Drug and Cosmetic act. The alternative tools described […] are used to facilitate remote assessments of facilities if an inspection cannot be conducted”.

8. [HOW] FDA response: […] The process for issuing a records request under 704(a)(4) of the FD&C act does not currently utilize Form FDA 482. These requests are initiated using Form FDA 4003.

Synopsis from 6/2020 FDA communications:

→ During COVID-19 Pandemic FDA uses alternative methods to avert/avoid/defer site inspections
→ The alternative methods (including record requests) are not inspections (“No virtual GMP drug inspections”)
→ Alternative methods provide input for internal FDA compliance risk management program (priorities and criticality)
Inspections During COVID-19

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Q4: How will FDA ensure the quality of imported products while inspections are limited?  
A4: […] FDA is expanding the use of other tools and approaches, when possible […]. These may include physical examinations of products […] and requesting records directly from facilities “in advance of or in lieu of” certain drug inspections. […]  

Q5: How will limited inspection activity affect my application?  
[...] FDA is also working directly with facilities to communicate any issues identified through a review of records or other information requested. For example, for both CDER- and CBER-regulated products, interim processes have been implemented to communicate with manufacturing facilities regarding issues identified following a review of records or other information requested in advance of or in lieu of a pre-approval or pre-license inspection. Responses from the facility regarding these issues will, as feasible, be considered before taking an action on a pending application.
FDA Communication – Information Requests


PET Community Inferences:

- FDA IR can count towards an onsite inspection (“in lieu of” = substitute)
- A site providing an IR response/package expects feedback from FDA (“communicate with manufacturing facilities regarding issues identified”)
- There needs to be closure from FDA following fulfillment of IR request by a manufacturing site

→ conflicts with “no virtual inspections” (6/2020 SNMMI Meeting)
→ Confusing language about “in lieu of”
Inspections During COVID-19

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Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency

Guidance for Industry

April 2021

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Veterinary Medicine

Contains Nonbinding Recommendations
# FDA Communication – Remote Interactive Evaluation

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<td>FOI accessible</td>
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*COALITION OF PET DRUG MANUFACTURERS*
Closing Thoughts: Opportunities

1) Clarify expectations on “Alternative Inspectional Methods” (Guidance interpretation)
   a) IRs and RIEs are not considered “inspections” statutorily (under 510(h)(3))
   b) IRs and RIEs are tools for FDA compliance risk management and site inspection prioritization
   c) FDA may use knowledge gained through IRs and RIEs to make regulatory decisions on applications
   d) RIEs bring regulatory exposure considerations for sponsors (FOI access, database update)

2) Effectiveness of the IR process
   a) Site resource impact (opportunities for optimizing the process)
   b) Lack of feedback for sponsors (Academia and Industry) – how to create additional value/win-win?

3) Feedback of the RIE process
   a) Current experience over time (now if any)
   b) Opportunities for enhancement

4) Post-pandemic inspection management: how to return to “normal” and defining “normal”?