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

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Overview

• Introduction
• Inspections during covid-19
• Waiver of eCTD requirements for PET drug manufacturers
• Working with new radionuclides
• Discussion Items
Academic PET Drug Manufacturers

- Brigham and Women’s Hospital
- Children’s Hospital of Michigan
- Decatur Memorial Hospital
- Feinstein Institute of Medical Research
- Johns Hopkins University
- Kettering Medical Center
- Kreitchman PET Center (Columbia)
- Massachusetts General Hospital
- Mayo Clinic
- MD Anderson
- Memorial Sloan Kettering Cancer Center
- Molecular Imaging Program at Stanford

- Queen Hamamatsu PET Center
- The Methodist Hospital
- University of Pennsylvania
- UC Los Angeles
- UC San Francisco
- University of Iowa
- University of Michigan
- UT Southwestern
- University of Wisconsin
- University of Utah
- Washington University St. Louis
FDA Approved PET Drugs as of 2021

- FDG F18
- NaF F18
- Ammonia N13
- Neuraceq (Florbetaben F18)
- Vizamyl (Flutemetamol F18)
- Amyvid (Florbetapir F18)
- Choline C11
- Auxumin (FACBC, Fluciclovine F18)
- Cardiogen / Ruby-Fill (RbCl, Rb82)
- Netspot (DOTATATE, Ga68)
- DOTATOC Ga68
- Tauvid (Flortaucipir F18)
- Cerianna (Fluoroestradiol F18)
- Detectnet (DOTATATE, Cu64)
- PSMA-11 (Ga68)
- Fluoro-DOPA (F18)
- PYLARIFY® (piflufolastat F 18)

~15 approvals since 2012!
The PET drug workflow is built for FDG

- Cyclotron beam schedule
- Radiochemistry staffing and infrastructure (e.g. hot-cells, synthesis modules)
- Scanner availability
- Dispensing (e.g. Intego)
- Distribution
- QC Equipment

Coalition of PET Drug Manufacturers
Challenges

Thus, a number of challenges face PET drug manufacturers in 2021:

• More tracers are garnering FDA approval, including $^{11}$C, $^{18}$F, $^{68}$Ga and $^{64}$Cu tracers, mandating increased numbers of more diverse radiosyntheses per day;

• Demand for PET drugs is increasing overall (e.g. clinical throughput has doubled at UM in the last 5 years);

• There is a need to label more complex molecules (e.g. labeling tracers for new imaging targets or labeling complex pharmaceutical assets);

• cGMP is increasing regulatory burden (and cost) associated with PET drug manufacture;

• Ongoing challenges associated with covid-19 pandemic.
How can the Coalition help Academic PET Centers?

- Serve as a regulatory knowledge hub for academic PET drug manufacturers who typically don’t have the same resources or regulatory support as pharma;

- Function as a contact network for academic labs involved in PET drug manufacture;

- Assist academic PET Centers with GMP compliance and inspection challenges.
Inspections During Covid-19

- 23 academic sites surveyed, 12 responded;
- Majority of sites have not been inspected in the last 18 months;
- Inspections have been a mix of virtual and in person.
Inspection Considerations

• There have been some variation in covid inspections:
  • Most have not been inspected;
  • Some have had surveillance inspections postponed because of covid;
  • 2 in person PAIs occurred for NDAs;
  • 1 PAI for an ANDA is tabled: “We submitted an ANDA around March of 2020 and have received notification from FDA that we are awaiting an inspection. However, FDA is currently under COVID travel restrictions and will let us know when things change. I asked if they would consider “virtual” and was told that was not a consideration”.
  • Why inconsistencies? Is FDA conducting PAIs for NDAs, but not ANDAs?

• In person inspections involved standard covid precautions;

• Virtual inspections involved requests for documentation:
  • “Request for documentation was extensive, taking several weeks to complete. A selection of questions were specific for commercial PET operations and not academic sites.”
  • “I know of one non-PET facility that got FDA inspected, that was also remote.”
Inspection Considerations: 211 vs 212

There are ongoing variations in inspections:

- *Inspector brought up a lot of from 211 and they were not versed in 212*; “Their requests were very 211 oriented and it was mentioned several times during the week that they don’t follow 212 guidelines for most cases.

- They were very insistent on precursor check-in and validation procedures, even for commercially purchased (ABX) precursors. Another thing that came up quite often was vendor qualification. I am not sure how this is addressed in most academic labs, but it might be something worth bringing up with the community;

- They don’t allow end product testing as the means to identify the precursor integrity (212). They found the review of COA upon receipt and final end product testing unacceptable (got a 483 and a formal request to validate even if commercially available)

- They wanted forced degradation test for up to 3 h EOS for tracer that is injected right away (I opposed and I won, but I know others have got a 483 there).
Inspection Considerations: 211 vs 212 (cont.)

• They requested microbial identification with any CFU>0. So anytime we see growth, we should send the plates out for testing to identify species no matter what the origin. I opposed and we agreed upon a milder 483 that requires risk assessment first.

• They requested me to implement a system to keep track of UPS/FEDEX deliveries for everything that is delivered for clinical purposes. They are afraid that sensitive materials (e.g. precursors) are intercepted from a third party and damaged while in transit. Needless to say that I opposed.

• According to inspectors, generators are not to be considered as devices and breakthrough/inspection are not enough to accept a generator. The CoA would not suffice and they wanted us to do a validation for any incoming generator prior to acceptance. They initially requested 3 runs and complete metal contents assessment! After several hours, we agreed upon 1 chemistry test run with any approved $^{68}$Ga probe and no metals quantification.
Waiver of eCTD requirements for PET drug manufacturers

• At the February 2020 coalition workshop, FDA announced updated eCTD guidance document;

• The guidance includes a waiver criteria of electronic submissions for certain PET drug INDs, NDAs, ANDAs, and BLAs, and waiver criteria for certain Type II DMFs

• Coalition members have experience that this waiver process is working well and reduces the burden of sending regulatory filings to FDA.
I. Certain Positron Emission Tomography (PET)\textsuperscript{20} Drug Submissions

The requirement to comply with the eCTD requirement for certain PET IND, NDA, ANDA, or BLA submissions could adversely impact the development and availability of PET drugs. FDA may grant a waiver to a PET drug sponsor or applicant intending to submit an IND, NDA, ANDA, or BLA if \textit{all} of the following apply:

(a) The applicant produces PET drugs at a single PET drug facility.

(b) PET drugs are the only FDA-regulated drug products (other than noncommercial drug or biologic products) manufactured or produced by the sponsor or applicant.

(c) The sponsor or applicant explains that, because it meets the criteria above, it cannot achieve compliance with eCTD requirements.

A waiver request should be sent to FDA before submitting the document(s) for which this waiver is claimed,\textsuperscript{21} with an explanation regarding why the sponsor or applicant’s compliance with the requirement cannot be achieved, including that the sponsor or applicant is representing that (a) through (c) above are met\textsuperscript{22} and a description of the proposed alternative submission format\textsuperscript{23} the sponsor or applicant will be using during the duration of the waiver (e.g., PDF files following the CTD structure).

The information provided in the waiver request may be verified through inspection or through a records request in lieu of an inspection.
2. *Certain Type II DMF*\textsuperscript{24} *Submissions*

Holders of certain Type II DMFs that solely support an application for a PET drug or a noncommercial IND application may also qualify for a waiver. FDA recognizes that the holders of these Type II DMFs may be distinct from the holder of the application(s) in question. FDA may grant a waiver to a holder intending to submit a Type II DMF if the Type II DMF holder explains that it cannot achieve compliance with eCTD requirements because one of the following applies:

(a) The Type II DMF is intended to support an application for a PET drug (i.e., IND, NDA, ANDA, or BLA) and contains information regarding radiolabeled drug products or production of PET radionuclides, and the Type II DMF holder is an academic institution, government (state or federal) entity, or a non-profit\textsuperscript{25} research organization.

OR

(b) The Type II DMF is solely used to support a noncommercial IND application, and the Type II DMF holder is an academic institution, government (state or federal) entity, or a non-profit research organization.

A waiver request should be sent to FDA before submitting the document(s) for which this waiver is claimed,\textsuperscript{26} with an explanation regarding why the sponsor or applicant’s compliance with the eCTD requirement cannot be achieved (i.e., that the sponsor or applicant is representing that (a) or (b) above is met), including a description of the proposed alternative submission format\textsuperscript{27} the sponsor or applicant will be using during the duration of the waiver (e.g., PDF files following the CTD structure).

The information provided on the waiver request may be verified through inspection or through a records request in lieu of an inspection.
Working with New Radionuclides?

• Gallium Ga 68 DOTATATE, NETSPOT®
  o A radiopharmaceutical kit, originally approved with the Eckert & Ziegler Ge-68/Ga-68 generator, the IRE Ge-68/Ga-68 generator followed. Both generators have DMFs, both are listed on the product insert.

• Gallium Ga 68 PSMA-11 by UCLA and UCSF*
  o Drug product, prepared with gallium Ga-68 chloride from either a Ge-68/Ga-68 generator or from a cyclotron (UCSF only).

• Gallium Ga 68 PSMA-11 by Telix
  o A radiopharmaceutical kit, to be prepared with gallium Ga-68 chloride from either a Ge-68/Ga-68 generator or from a cyclotron. It is expected that the package insert will list acceptable Ge-68/Ga-68 generators as with NETSPOT® and cyclotron gallium Ga-68 chloride by GE Healthcare.
  o GE Healthcare will soon have a DMF for their gallium Ga-68 chloride FASTlab cassette.
Discussion Items

• Inspections;

• Regulatory filings;

• When should 212 apply? Should 212 regulations be revised to only include certain PET drugs (e.g. \( t_{1/2} < 120 \) min since Cu64 Detectnet is manufactured per 211 at a centralized location)?

• New radionuclides.
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