FDA Inspections: Academic Perspective

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DISCLAIMER

Data presented and discussed does not represent University of California San Francisco. Data from this talk was provided by the Coalition of PET Drug Manufacturers through a survey of PET drug manufactures, as well as through verbal communication with academic PET drug manufacturing facility personnel.
SURVEY PARTICIPANTS: MAJORITY ACADEMIC

MANUFACTURING LANDSCAPE

- Since PET has been regulated, landscape has changed from initially academic centers to current commercially dominated supply.

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<tr>
<th>PET drug</th>
<th>NDA #</th>
<th>Institution</th>
<th>Approval year</th>
<th>No. of active ANDAs</th>
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Dick, Handbook of Radiopharmaceuticals, page 499, 2021
MANUFACTURING LANDSCAPE

• Since PET was been regulated, landscape has changed from initially academic centers to current commercially dominated supply.
  • Manufacturing currently a mix of academic and commercial
  • >100 commercial and ~30 academic manufacturing sites

• Still major differences between academic and industry

• The PET Manufacturing community must work together for a **uniform** set of procedures to enable manufacturing to continue safely and provide patient care
  • *Need to work with the FDA to ensure that the regulations are consistently applied across all sites and are consistent with the risk and needs in order provide patient access*

ACADEMIC OPPORTUNITIES

• Distribution
  • Academic facilities often do not distribute beyond their own clinic
    • Supplying fewer doses
    • Overall reduced risk
  • Often fill critical gaps in PET drug availability

• Ability to collaborate with cross-functional experts
  • In-house expertise

• **Crucial for innovation**
  • *Work collaboratively with industry partners*
  • *Goal is to continue to work with the FDA to ensure regulations and policies do not present barriers to innovation*
ACADEMIC CHALLENGES

• Vendor auditing
  • Academic institutions lack the infrastructure and resources for vendor audits
  • Potential to leverage Coalition for vendors of commonly used components
    • ALK vials, ABX precursors
    • Establishment of SOP is essential for academics to qualify vendors
• Supplies and Purchasing
  • Central purchasing through University
    • Limited vendors
    • Long timelines to add a new vendor into system
  • Shipping of incoming components
    • Often ship to a central receiving location on campus
      • Chain of custody often difficult to impossible

ACADEMIC CHALLENGES

• Organizational Structure
  • Top level (Board of Trustees, etc) often very removed from radiopharmaceutical facilities
    • Important to contact regulatory personnel for support
• IT challenges
  • Hardware and software updates often mandatory
  • If no update, no institutional support
  • Potential loss of electronic data – perceived data integrity issues
• Facility constraints for existing facilities
  • Resources for altering infrastructure very limited
  • Lengthy timelines to complete upgrades/changes
    • Potential to prohibit patient access
5. Do FDA inspectors pre-announce inspections?
18 responses

- Always: 33.3%
- Sometimes: 16.7%
- Never: 11.1%
- N/A - never been inspected: 38.9%

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| 1 | - Organization Chart  
- Identify the personnel associated and trained for PET drug manufacturing with roles and responsibilities |
| 2 | Batch Release procedure(s)- Final QA release  
- Include the procedure for conditional final release for PET drugs if a separate procedure |
| 3 | Procedure(s) related to agency communication (e.g. FARs) |
| 4 | SOP for Recalls |
| 5 | Change Control or Change Management procedure(s) |
| 6 | Please explain UCSF’s history with PET manufacturing  
- How long have you been working with PET?  
  - Provide a list of IND and RDRC drugs currently being produced in the laboratory  
- What other approved PET products do you have experience with?  
  - Please list |
| 7 | List of procedures specific to PET production  
- Procedure for sample retention plan for PET drugs for (conditional release)  
- Provide procedure for sterility investigations  
- Procedure for PET stability program and protocol for PSMA 11-Ga68Injection |
| 8 | Change Controls to introduce PSMA 11-Ga68Injection into the facility |
| 9 | List of all material suppliers for the PSMA 11-Ga68Injection |
Survey results: Number of 483s related to an observation of a QC test method or manufacturing process that you were following without deviation according to approved NDA or ANDA

- Invalid Endotox test result- SOP indicated to retest sample
  - 483 given for not reporting as OOS and for releasing upon retesting
- Mandatory use of sterile gloves and wipes
**PRECURSOR ACCEPTANCE TESTING**

(1) If you conduct finished-product testing of a PET drug product that includes testing to ensure that the correct components have been used, you must determine that each lot of incoming components used in that PET drug product complies with written specifications by examining a certificate of analysis provided by the supplier. You are not required to perform a specific identity test on any of those components.

- 2 separate institutions received 483 observations for not doing additional identity testing (beyond CoA) on precursor from known and trusted vendor (ABX)
- Difference in the way regulation is being interpreted
  - CoA for precursor was not deemed sufficient for identity testing
- PET community needs to understand the **expectation** from the FDA
  - Appropriate SOPs based on the FDA expectations

**EXAMPLES OF ACADEMIC 483**

- IT software upgrade caused loss of electronic data
  - A unique challenge for academic institutions
- Observations to monitor non-classified areas (syntheses hotcells, non-classified rooms)
  - Regulations do not specify this is required
- Quality Systems
  - Need for implementation of a robust quality management system
    - Can be lacking in academic setting
  - Typically no dedicated QA group
    - Industry has central QA team for multiple sites
SURVEY RESULTS: FDA INSPECTOR TRAINING

- Critical that FDA inspectors are trained in 21CFR212 prior to inspections
  - Consistency amongst all sites
- Work with the Coalition to develop and implement uniform manufacturing practices (and inspections) across all PET manufacturers

SUMMARY

- Academic institutions represent an important portion of PET Drug Manufacturers in the United States
  - Academics face unique challenges
    - Infrastructure and resources
    - **Academics are essential for innovation and patient care**
- Appropriate regulatory environment that supports the **breadth** of manufacturing sites
- It is critical that we achieve manufacturing and **inspection uniformity** to maintain the **patient access** to critical imaging agents