Safety and Risk Management of PET Drugs

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The 2020 workshop


Risk Management

• Risk is inherent in the pharmaceutical sciences
• Risk can never be eliminated but only managed
• Gained attention in the 2000s when FDA undertook a variety of initiatives focused on risk management
Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century

• One component was to “encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas”
• Ultimately led to a risk-based model for prioritization of surveillance inspections
• Also catalyzed the application of quality systems in the pharmaceutical industry and within the FDA

PDUFA V and VI: Structured approach to benefit-risk assessment in regulatory decision-making

• Aimed to develop a more systematic and transparent approach to the benefit-risk framework employed in review and approval of drug marketing applications
• Summarized in a series of white papers, workshops, guidance documents, and other publications


4FDA Public Workshops on Benefit-Risk Considerations (2017).
None of these initiatives specifically address risk from the perspective of the manufacturing techniques used for PET drugs

Notable documents dedicated to PET drugs have minimal information regarding risk management

• A keyword search of PET GMP regulations and guidance documents reveals that “risk” occurs four times¹⁻⁴
• Manual for inspection of PET drug facilities uses “risk” twice⁵
• Publicly-available (redacted) review of the most recently approved PET drug evaluates risk from a clinical perspective⁶
• Non-redacted portions of the review do not discuss risk in the context of the microbiology, chemistry, CMC, facilities sections⁶

²CDER. PET Drugs—Current Good Manufacturing Practice (CGMP); Small Entity Compliance Guide (2020).
³CDER. PET Drug Products - Current Good Manufacturing Practice (CGMP) (2020).
⁴CDER. Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (2012).
⁶Drug Approval Package: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216023Orig1s000TOC.cfm.
Clarity and transparency

• The goals of the benefit-risk framework\(^1\) are:
  1. Improve clarity and consistency in communicating regulatory decisions
  2. Ensure assessments can be readily understood in the larger patient care and public health context

\(^1\)Benefit-Risk Assessment in Drug Regulatory Decision-Making - PDUFA VI, March 2018, p.3.

Conclusion

Scarcity of publicly-available data suggests that a structured, science-based risk assessment focused on manufacturing techniques for PET drugs has not been elaborated either by the PET community or FDA
Moving forward

- To fill this gap, we have initiated a risk assessment focused on manufacturing techniques for PET drugs
- Based on a modified Failure Mode Effects Analysis (FMEA)\(^1\)
- Adapted for the characteristics of PET drugs and prototypical manufacturing techniques
- Not intended as guidance or policy, only to present a method for risk assessment of manufacturing techniques with the goal of improved risk-based decision-making


Challenges and methodologies

**Challenges—**
- Subjectivity
- Uncertainty
- Complexity
- Importance
- Relevance

**Methodologies—**
- Acknowledge and manage bias
- Multi-disciplinary stakeholders
- Initially limit scope to one process
- Initially focus on sterility assurance
- Corroborate with independent data, e.g., surveys, adverse events
Step 1: Define the process

Prototypical process (Fludeoxyglucose F 18)

- Radionuclide Production
- Radiochemical Synthesis/Purification
- Membrane Filtration
- Quality Control
- Released Product
Focus on sterility assurance: the final product vial

**Critical Design Elements**
- Membrane filtration, but not traditional aseptic processing
- Closed system downstream of filter
- Commercially sterilized components assembled aseptically
- Small batch scale, typically one batch = one vial
- 100% sampling plan for QC

**Components**
(a) Product inlet  
(b) Membrane filter  
(c) QC sampling syringe  
(d) Filtered vent  
(e) Product vial

Step 2: Identify failure modes and sources of contamination
Two failure modes for product non-sterility

Contaminated final product vial

Sources of contamination:
1. Personnel
2. Aseptic techniques
3. LFH/BSC
4. Materials/components
5. Process design

Ineffective membrane filtration

Sources of contamination:
1. During routine operations
2. Process design

Step 3: For each contamination source, define failure mechanisms and controls
Example: Personnel

• Failure mechanisms include:
  – Operator touch contamination
  – Airborne contamination from operator and non-operators
  – Poor operator technique

• Controls include:
  – Hygiene, garb, disinfection, etc.

Step 4: Calculate risk levels
Risk level calculation

• For each failure mechanism and existing control, assess the following (H/M/L):
  – Severity of a potential failure
  – Likelihood of failure (occurrence)
  – Probability of detection
• Determine overall risk level from sum of S/L/P

Step 5: Evaluate acceptability of resulting risk level
How effective are existing control mechanisms for sterility quality assurance?
# Approved PET drug applications

<table>
<thead>
<tr>
<th>PET Drug Product (Generic Name)</th>
<th>Date First Approved</th>
<th>Approved Applications</th>
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<tr>
<td>Sodium Fluoride F 18</td>
<td>February 24, 1972</td>
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<td>Rubidium Chloride Rb 82</td>
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<td>Florbetapir F 18</td>
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<td>Fluorodopa F 18</td>
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#### Silberstein and the SNM Pharmacopeia Committee

**Prevalence of Adverse Reactions in Nuclear Medicine**

Edward B. Silberstein, Janet Ryan and the Pharmacopeia Committee of the Society of Nuclear Medicine

The Eugene L. Saenger Radiotracer Laboratory, Division of Nuclear Medicine, Department of Radiology, University of Cincinnati Hospital, Cincinnati, Ohio

**Prevalence of Adverse Reactions to Positron Emitting Radiopharmaceuticals in Nuclear Medicine**

Edward B. Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine

Eugene L. Saenger Radiotracer Laboratory, Division of Nuclear Medicine, Department of Radiology, University of Cincinnati Hospital, Cincinnati, Ohio

**Brief Communication**

Prevalence of Adverse Events to Radiopharmaceuticals from 2007 to 2011

Edward B. Silberstein

Departments of Radiology and Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio
Pharmacopeia Committee Operational Definition of AE\textsuperscript{1}

1. The reaction is a noxious and unintended clinical manifestation (symptoms, signs, laboratory data abnormalities) following the administration of a radiopharmaceutical or nonradioactive adjunct pharmaceutical.
2. The reaction is unanticipated from the known pharmacologic action of the nonradioactive pharmaceutical.
3. The reaction is not the result of an overdose (which is a misadministration).
4. The reaction is not the result of injury caused by poor injection technique.
5. The reaction is not caused by a vasovagal response (slow pulse and low blood pressure).
6. The reaction is not caused by deterministic effects of radiopharmaceuticals intended for therapeutic uses.
7. The definition excludes altered biodistribution which causes no symptoms, signs or laboratory abnormalities.


AE Prevalence for PET and non-PET Radiopharmaceuticals\textsuperscript{1-3}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{ae-prevalence.png}
\caption{AE prevalence for PET and non-PET radiopharmaceuticals.}
\end{figure}

Reported batches and PET scans

Reported Number of Batches\(^1\)

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Number of PET Scans (1000s)\(^2\)

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\(^1\)PET Drug Manufacturers Surveys, SNMMI/MITA/Coalition, 2020/2023.  

AE Prevalence for PET and non-PET Radiopharmaceuticals\(^1-4\)

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Ten-year Summary

- 20.4 million PET scans\(^1\)
- 559,000 reported\(^2\) batches of PET drugs produced
- 78 sterility test OOS results (0.014% of batches)
  - Nearly all OOS investigations conclude accidental contamination (laboratory error; false positives)
  - Compares favorably to expected 0.05% sterility test failure (not OOS)\(^3\)

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\(^1\) IMV 2023 PET Imaging Market Summary Report, 2023.
\(^2\) Does not represent all batches produced in US due to non-respondents.
\(^3\) PET GMP Final rule, Federal Register, vol. 74, no. 236, December 10, 2009.
Existing Control Mechanisms are Effective

Current
Adverse Events
0 – 0.06/10^5 doses

Future
Decreased Supply Chain
Limits Patient Access

Increased Regulatory Burden
through inspection or regulations without risk assessment

Closing Thoughts

• PET drugs have a proven track record under existing standards and regulations
• Current standards and regulations
  • Can safely maintain existing supply chain of PET drugs
  • Accommodate expansion of new PET drugs as they come onto the market
• Increased costs associated with new regulatory requirements will place pressure on
  PET drug manufacturers and threaten new product implementation
• The PET community is concerned that potential increased costs with no change in
  CMS reimbursement could lead some PET drug manufacturers to exit the market,
  resulting in reduced patient access

Non-Sustainable PET manufacturing business

Added cost due to new regulations
+ Declining market price
Open Questions

• Can the PET community and the FDA work together to develop an effective framework for collecting and assessing AE and sterility OOS data?
• Can the PET community work with the FDA to maintain compliance without increased regulatory burden?
• Can the PET community and the FDA work together to develop an effective risk management framework for PET drug manufacturing?
• Can we accept the conclusions of the resulting risk assessments?