Best Chemistry Practices to Support the Development of PET Drugs

June 10, 2017
8:00 – 16:00

Organizers and Moderators:
Amy Vavere, Ph.D.
Steve Zigler, Ph.D.

Sponsors:
Radiopharmaceutical Sciences Council
Coalition for PET Drugs
Employee of Siemens-PETNET Solutions

I will not discuss investigational agents, nor will I discuss indications or uses of any approved products
Does anyone want to get their PET tracer into commercial production?

Does anyone want to get new PET tracers onto the market?
Does anyone want to get their tracer approved by the FDA?
The PET Challenge...

- There are more than 150 facilities in the US that produce PET drugs
- Some facilities only focus on basic research
- Some facilities only make commercial products
- Many facilities are involved in production activities across the spectrum from pre-clinical studies to the production of FDA-approved products for routine clinical purposes
Contrasting Manufacturing Models

Traditional drug model—

- Nationwide supply requires a relatively few number of large-scale batches
- Product inventory can moderate supply chain difficulties
- Large facilities staffed by large number of people
- Drug substance and product often produced separately

PET drug model—

- Nationwide supply requires a large number of small batches (1 batch = 1 vial)
- Product inventory not possible
- Small facilities with relatively small staff in a laboratory-like environment
- Typically not possible to isolate drug substance
The PET manufacturing model creates unique challenges across the product development spectrum.
How do I know the chemistry-related decisions I make here...

AND...

...won’t waste time and resources here?

...don’t waste time and resources here?

How do I know the chemistry-related decisions I make here...
Can we efficiently share best practices across the spectrum from the early phases of development to commercial production?
But it is not just about the manufacturing model...

- PET drugs themselves are unique
- Short half-life affects ability to complete QC testing
  - Ramifications for sterility testing, OOS investigations, process validation, etc.
- Sub-pharmacologic mass doses of the radioactive ingredient are administered in micro- to nano-molar quantities
- Patients typically not subjected to repeated doses
- Creates a unique risk profile that should inform chemistry-related topics such as reference standards, impurities, etc.
The Purpose of this Session...

- Provide a scientific forum to share information, experiences, and best practices
- Help attendees understand how others deal with key chemistry practices at various stages of development and commercialization
- All with a focus on chemistry, manufacturing, and controls information (CMC)
Some potential topics...
The Ultimate Goal...

- Stimulate dialog and actions that lead to improved chemistry practices associated with the development and commercialization of PET drugs
- Where it makes sense; not meant to imply that “one size fits all”
- *We need flexibility where we need flexibility*
- *We need rigor where we need rigor*
Economic challenges...

What was the size of the US pharmaceutical market in 2016?

$333 billion

Source: US Commerce Dept

What was the size of the US PET drug market in 2016?

$300 million

Source: Personal estimate
The combined FDG market is about 25% of the 100th top-selling drug in the US

(#100: Sutent by Pfizer $1.12 billion)

Regulatory challenges...

• PET drugs are a relatively new class of products
• Numerous applications and facilities for a small number of products
• Multiple INDs for the same investigational agent submitted by different sponsors
• Almost 90 ANDAs* for FDG, NaF, and ammonia
• More than 150 facilities

Source: FDA Orange Book
Our goal is to build a bridge...

Between the different stages of…

Between different stakeholders in…

…the development and commercialization of PET drugs
Target Audience...

*Chemists, pharmacists, scientists involved in:*

- The development of new PET drugs
- Routine production and testing of PET drugs
- Quality assurance and regulatory affairs
- FDA review of applications for PET drugs
To openly participate in this scientific forum
Share your experiences and ideas
Help set the course for future directions
How many PET Drugs have an Approved NDA?

As of May 9, 2017:

10
This session is an experiment...

- Topics based on feedback received from various stakeholders involved in the development and manufacturing of PET drugs, including academia, industry, and the FDA
- We continuously need to reach out and address top issues for all stakeholders
We need your feedback...

• Was it successful?
• Is it helpful to have future sessions like this?
• Should we do it again?
• If so, how should it be changed to better meet your needs?
• Are there other avenues for us to communicate and share this information?
• Give us your feedback
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  – steve.zigler@petnetsolutions.com
Food for thought...

• We are in the early stages in the development and commercialization of new PET drugs...many lessons learned, many more to learn

• Do we understand the chemistry challenges associated with the development and commercialization of PET drugs?

• Can we articulate these challenges to the appropriate audiences in a way that brings maximum value to the patient?

• Can we share ideas on the successful development and commercialization of new PET drugs?
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<td>8:00 – 8:30</td>
<td>Introduction and Overview of FDA Regulations and Guidance Documents related to PET Drug Chemistry</td>
<td>Steve Zigler</td>
<td>Siemens PETNET</td>
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<td>8:30 – 9:00</td>
<td>F-18 and C-11 Chemistry Challenges</td>
<td>Peter Scott</td>
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<td>Special Considerations for Tracers based on Proteins or Protein Fragments (include radiometals)</td>
<td>Serge Lyaschenko</td>
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<td>9:45 – 10:15</td>
<td>Field Notes #1 - Challenges behind the scenes of clinical PET tracer production</td>
<td>Ashley Mishoe</td>
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<td>Stability Studies to Support PET Drug Applications</td>
<td>Danny Bingham</td>
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<td>Common Deficiencies with Chemistry-Related Topics in PET Drug Applications</td>
<td>Ravi Kasliwal</td>
<td>CDER, FDA</td>
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<td>Role of USP monographs and general chapters</td>
<td>Steve Zigler</td>
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<td>Characterization of Active Ingredients, By-Products, Impurities, and Standards</td>
<td>Jeanne Link</td>
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<td>Amy Vavere</td>
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<td>System suitability for Analytical Methods</td>
<td>Mike Haka</td>
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<td>Transfer of Technology to Multiple Facilities - Pitfalls and Best Practices</td>
<td>Tyler Benedum</td>
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<td>Field Notes #3 - Experience from Inspections (212 &amp; 823)</td>
<td>David Dick</td>
<td>University of Iowa</td>
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<td>Future Directions, Moderated Discussion</td>
<td>Amy Vavere &amp; Steve Zigler</td>
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