Safety and Benefit/Risk Considerations at Various Stages of Product Development
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Positron Emission Tomography Drugs: Product Quality, Regulatory Submissions, Facility Inspections, and Benefit-Risk Considerations

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No Conflicts of Interest.
Focus

Nonclinical study recommendations to support radio-pharmaceutical diagnostic or PET drug development from pre-IND stage, to INDs and future marketing applications

- What nonclinical and clinical data can be relied upon to support development of PET drugs?
- How to optimize nonclinical studies to ensure efficiency of clinical development program without jeopardizing safety for FIH studies?
- PET drug quality attributes (impurities and degradants, excipients) and safety throughout development

Statement on Guidance Documents

“FDA guidance documents do not establish legally enforceable responsibilities. Instead, a guidance describes the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited”
Regulatory Flexibility

- Current regulations allow for flexibility in nonclinical study requirements
- Sponsors are encouraged to meet with the FDA early in product development phase
- The FDA view is that there is value in early communication and agreement on IND enabling studies

Request a pre-IND meeting with the Review Division to ensure adequacy of the nonclinical package for future IND submissions

PET Drugs

Administered at low mass dose, 1/100th of a dose that elicits a pharmacologic effect, “sub-pharmacologic”

Mass dose ≤ 100 µg for small molecules or ≤ 30 nmol for protein products

Nonclinical study recommendations are more limited based on products’ unique characteristics and Division experience:

- Microdose and radiolabeled
- Single or infrequent use
- Clinical use setting

FDA guidance and regulations include eIND guidance, ICH M3(R2), RDRC (21 CFR 361.1) and implementing the 3 R’s
Recommended Nonclinical Studies Prior to Phase 1

Proof-of-concept studies:
- In vitro and in vivo characterization (receptor/target- and off-target profiling)
- Evidence that radiolabeling does not significantly alter pharmacologic characteristics
- Biodistribution, imaging and radiation dosimetry

Pharmacokinetics (PK) studies:
- PK information in a test species (exposure, t\(_{1/2}\))
- Biochemical information relevant to potential drug interactions

Single-dose toxicity study
- Conducted in a single mammalian species (typically a rodent)
- Both sexes (unless justification provided)
- Clinical route of administration
- Doses evaluated should provide an adequate safety margin

Studies Not Recommended
- Safety pharmacology
- Genotoxicity
- Repeat-dose toxicity
- DART studies (CFR 312.10 with adequate justification)
Comment on Toxicity Study Requirements

- Nonclinical guidance for diagnostic imaging agents differs from that of oncology drug products
- Consideration of the study design for the single dose toxicity study:
  - Adequate number of healthy animals per treatment group and controls
  - Extended, single dose toxicity studies should include interim and recovery groups with evaluation of clinical signs, hematology, clinical chemistry, body/organ weight, macroscopic and histopathology analysis
- Please provide all pivotal nonclinical safety study reports in your submissions

GLP Study Requirements

- ICH M3(R2) recommends that general toxicity studies supporting safety of an IND be conducted according to GLP regulations (21 CFR Part 58)
- GLP regulations ensure data quality and integrity
- However, if scientifically justified, deviations that would not have significant impact on the quality and integrity of studies may be acceptable on a case-by-case basis
Please Note!

- If a Sponsor determines that nonclinical pharmacology or toxicology studies are not needed, at any stage of development, FDA will consider request for not conducting studies if adequate justification is provided (21 CFR § 312.10)

What is considered adequate justification?

- Leveraging existing data and literature to support an IND
  - Close structural analogs with a toxicology assessment
  - Letters of Authorization to cross-reference IND for nonclinical support (same drug or theranostic pair)
- Please provide key cited literature in your submissions

Exceptions to Microdose Guidance

- Scenarios where additional nonclinical studies may be recommended
  - PET drug with pharmacologic activity at microdose levels (e.g., high affinity ligands or toxins)
  - PET drug clinical dose level exceeds a microdose
  - Presence of drug impurities that may be a greater safety concern than the investigational agent
  - Change in product formulation (e.g., excipient)

Meeting with the Review Division early to determine recommended studies
PET Drug Quality

- Impurities controlled according to ICH guidelines, e.g., ICH Q3A and Q3B
  - For microdose: reporting at 0.1%, identification at 1% (or 5 mcg), qualification at 1% (or 50 mcg)
  - Higher thresholds should be scientifically justified
  - Qualification may require conduct of new toxicity study or published literature (when appropriate)
  - Specifications should be supported by available data and ALARA principle

CMC and Pharm/Tox will evaluate PET drug throughout clinical development

PET Drug Quality cont.

- Radionuclide Generators
  - Examples include Rb-82 (from Sr-82) and Ga-68 (from Ge-68)
  - Safety concern with breakthrough
  - Presence of radionuclide impurities and other impurities

- F-18 PET Drugs
  - F-18 AlF radiochemistry; elemental impurities
  - Change in purification methodologies

CMC and Pharm/Tox will evaluate PET drug throughout clinical development
Lifecycle of PET Drug

Phase 1
- Control of impurities, qualification for later clinical phase

Clinical Phase
- Phase 2
- Change in method, formulation, radionuclide
- Any safety or efficacy concern? (toxicological risk assessment, bridging studies)

Phase 3
- NDA or BLA

Significant changes in PET drug quality may require additional data to support an NDA/BLA

Summary
- A more focused nonclinical safety evaluation
- Early communication with the Review Division to optimize the nonclinical program
- A flexible approach that allows innovative products to move safely and quickly through nonclinical development
- Control of PET drug quality specifications, supported by nonclinical studies and literature (when appropriate)
Thank You!

**Guidance Documents:**

- ICH Q3A Impurities in New Drug Substances: https://www.fda.gov/media/71727/download
- ICH Q3B Impurities in New Drug Products: https://www.fda.gov/media/71733/download
- M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: https://www.fda.gov/media/71542/download
- Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations: https://www.fda.gov/media/107641/download
- Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry: https://www.fda.gov/media/129547/download