Overview of Generic PET Applications

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

What kind of an application should be submitted

- An applicant seeking approval for a PET drug may submit an ANDA, depending on the specific drug and the indications.
- ANDA applications submitted based on previously approved drug product (RLD).

The current products reviewed by the OGD

- FDG F-18 injection, USP
- Sodium Fluoride F 18 injection, USP
- Ammonia N 13 injection, USP

The Review Formats

- Electronic CTD Review Format
- QbR Review Format (not common)
- PET Review Samples listed in the PET Guidelines in the CMC Section.

The Important Changes In The PET Reviews

- Regulations revised for PET applications and multiple formulations in a single PET ANDA is acceptable. This was approved on 9-13-2011.
- The firm should provide the final release and stability test results for three lots of the highest strength.
- For the additional manufacturing facilities, the firm should provide stability data on one batch from each facility.

Drug Master Files

- The Type V DMFs for Cyclotrons will be reviewed as applicable by the ONDQA and CDRH. Some information is recommended to be included in the ANDA.
- The Type III DMFs for container/closure information will be reviewed by OGD reviewers.
- The Type II DMFs for starting material (Mannose Triflate) for FDG will be reviewed by ONDQA or OGD.
- The other starting materials such as water O 16 or O 18 will be reviewed during the CMC review.

Mannose Triflate

- If there are multiple suppliers for mannose triflate, do the materials from each of these suppliers meet the applicant's specifications?

- Some batches of Fludeoxyglucose F 18 Injection should be made from mannose triflate from each supplier

Specification for O-18 water

- Suppliers generally have enrichment acceptance criterion of > 90%.
- If a PET drug producer proposes enrichment acceptance criterion that is less then supplier's criterion, then it should be justified.
  - Less enrichment with O-18 means more O-16 water. O-16 During cyclotron bombardment produces N-13.
  - Applicant needs to show that the excess N 13 can be removed from product or will not be present in excessive amounts in the product.
- In general, if proposed acceptance criteria are more relaxed (inferior) to supplier's criteria, it should be justified by the applicant (with some data or scientific explanation).
- Important attributes for O-18 water:
  - O-18 enrichment
  - Fluoride content
  - Conductivity
- If there are multiple suppliers listed, identify the O-18 water from each equivalent supplier to the one qualified (from which batches were made)?

The Release Specifications

- Appearance
- Specific activity
- Radiochemical identity
- Radiochemical purity
- Radionuclidic identity
- Radionuclidic purity (USP <821>using gamma-ray spectrometer)
- Chemical purity
- pH
- BET
- Sterility
- Osmolality
- Requirements listed under injections <1>

Testing

- Tests routinely conducted vs. tests conducted periodically
  - Tests routinely conducted for every batch are to be listed in specification table.
    - Testing listed in specification table (except for sterility) must be completed before final release of the batch.
  - Tests conducted periodically should be listed separately from specification with specific schedule described (specific batch that will be periodically tested should be identified in the application)
    - Acceptable to perform periodic testing on:
      - 2 Chloro-2-deoxy-D-glucose in FDG
      - Radionuclidic purity

Reference Standards

- The firm should use non-radioactive standard related to the analytical testing.
- The radioactive standard using the determination of radionuclidic purity or calibration of the equipment should be provided.

Impurities For FDG F 18 injection

- 2-chloro-2-deoxy-D-glucose (Related Compound B)
  - NMT 1 mg per dose.
- Kryptofix (aminopolyether; Related Compound A) :
  - 50µg/mL

Impurities for Ammonia N 13 Injection

- The concentration of aluminum ion in the injection is NMT 10 µg/mL.

- These limits are per USP monograph.

Reprocessing of Drug Products

- Generally the final product is not to be reprocessed. But, if you reprocess the product, provide what is the procedure, why are you reprocessing.

Recovery

- Recovery of the water O 16 and water O 18 used in the manufacturing should be addressed in the application.

Recycled O-18 Water

- If O-18 water is recycled, the reprocessing procedure should be provided.
- Should have acceptance specifications for reprocessed water.
  - Preferably these should be similar to virgin water.
  - If not, these should be justified.
  - Should have data for some reprocessed lots

Fludeoxyglucose F 18 Injection

- Nucleophilic substitution of the triflate-leaving group by $^{18}F^-$ from the precursor mannose triflate in presence of a phase transfer agent (kryptofix) - 1,3,4,6-tetra-O-acetyl-2-fluoro-2-deoxyglucose.
- Base hydrolysis may lead to epimerization of FDG to a radiochemical impurity of 2-[^{18}F]fluoro-2-deoxy-D-mannose (FDM).
- Radiochemical purity test may not detect this impurity.
- Applicant needs to show (validate) that under the hydrolysis conditions they employ, this epimerization does not occur.

Stability

- Stability summary, pre-approval stability protocol
- Post-approval stability protocol
- Stability data should be provided.

Stability

- We require a minimum of 3 batches at or near the upper end of the proposed radio-concentration.
  - If different synthesizers (methods of synthesis) are used, 3 batches from each method of synthesis at near the upper end of the proposed radio-concentration are recommended.
- Batches do not have to be made in same facility. For the additional manufacturing facilities, the firm should provide stability data on one batch from each facility.

Microbiology Review

- Part of CMC
- Separate Discipline from Chemistry
- Focus on Product Sterility and Pyrogenicity
- Review of New Applications (INDs, NDAs & ANDAs) and Supplements
- INDs and NDAs reviewed by OPS/New Drug Microbiology Group
- ANDAs reviewed by OGD Division of Microbiology

Unique Aspects of PET Manufacturing

- Extremely small batches/sub-batches
- Purchased pre-sterilized/depyrogenated, sealed components
- Filter sterilized
- Aseptically Filled
- Unique testing/“release” requirements
  - Sterilizing filter integrity critical
  - Bacterial endotoxins testing
  - Sterility testing

Sterility Assurance issues to be described in ANDA:

- Product information
- Facility description
- Manufacturing Process
- Environmental Monitoring
- Media fills
- Product release tests

PET Application Improvement Recommendations

- **Description of Overall Manufacturing Process**
  - Describe address, manufacturing area (including environmental controls, such as laminar air flow hoods, biosafety cabinets, etc.)
  - Batch records

- **Environmental Monitoring**
  - Routine and/or periodic monitoring of personnel, surfaces & air during sterility testing and critical aseptic manipulations
  - Sampling methods & frequency
    - Cultivation: Media & incubation details
    - Action levels
    - Actions following exceeded limits

PET Application Improvement Recommendations (2)

- **Media Fills**
  - Qualification of operators including simulation of production methods
- **Actions Taken in Response to Failed Product Tests**
  - Sterility
    - Notification of adminstering facility and/or physician
  - Endotoxins
    - Repeat testing?
- **Validation of Release Tests**
  - Sterility test validation data
  - Endotoxins test validation data

Microbiology Release Tests

- Sterility
- Endotoxins
- Testing is required: 21 CFR 212. 70(e)

Product Sterility Testing

- Product may be released/administered before the test is finished (21CFR 211.165(a) and 21 CFR 212.70(c))
- Initiate test within 30 hours after completion of production*
  - *30-hour requirement may be exceeded due to a weekend or holiday, if demonstrated that longer period does not adversely affect the sample or test results and sample is stored appropriately (e.g.,under refrigeration).
- Individually tested product samples, not pooled
- After successful sterility test record is established for a particular PET drug, it is only necessary to test the first batch prepared each day (sub-batch testing not necessarily required)

Product Sterility Testing (2)

- Method
  - Include Materials, Controls & Validation
  - Reference USP <71> or equivalent (provide SOP)
  - Sample Type, Size, Time & Storage
    - Growth Media, Incubation Parameters and Examination Time Points
- Identify the Testing Laboratory
- Actions Following a Test Failure
    - Notifications, Investigation and Corrective Action Plans

Product Endotoxins Test

- Product Specification
  - NMT 175 EU/V, where V is the maximum volume of patient dose (mL)
  - Testing performed and completed prior to release for human use

Product Endotoxins Test (2)

- Identify the Testing Laboratory
- Method
  - Include Materials, Controls & Validation
  - Reference USP <85> or equivalent (provide SOP)
    - Modified Gel-Clot or Rapid Photometric
- Actions Following a Test Failure
  - Notifications, Investigation and Corrective Action Plans

PET References

- USP <823> -Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses – 2012

- 21 CFR 212 – effective 12/12/11

PET Guidances

- *Guidance: PET Drug Applications – Content and format for NDAs and ANDAs-* 8/11
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078738.pdf
- *Guidance: PET Drugs – Current Good Manufacturing Practice (CGMP) –* 12/09
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070306.pdf
- *Guidance: Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs –* 4/12
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273766.pdf
- *Guidance: FDA Oversight of PET Drug Products – Questions and Answers* – 2/12
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM290024.pdf

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