Product Quality Considerations for PET Regulatory Applications

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Outline

- Highlights of Critical Quality Considerations/Format in PET INDs
- Highlights of critical Quality Considerations/Format in PET NDAs
- Comparability protocols in PET Radiopharmaceutical NDAs

Quality data in an IND submission

- As required per 312.23 (a)(7)
  Drug product quantitative composition, controls to ensure the identity, potency, purity and quality, stability data, controls of raw materials, manufacturers.
  PET Radiopharmaceuticals:
  Three qualification batches at each site of manufacture with tabulated batch analysis results
  At least one executed batch record
  Certificates of analysis and expiry dates for chemical precursor, radionuclide and reference standard
Repeat Gaps in PET IND Submissions

• “Empty” CMC Section: No information as to who supplies PET drug for the IND study
• Lack of accurate Letters of Authorization (LoAs) or location of LoAs (e.g., state where submitted in previous protocol)
• Lack of identification of the production site that will supply the clinical site with PET drug
• Lack of qualification data for PET drug produced at the sponsor’s site, even though cross-referenced to another sponsor’s IND

Outcomes

Unsuccessful
• Insufficient quality information to assess risk to subjects may lead to a recommendation for clinical hold per 21 CFR 312.42(b)(1)(iv) for the clinical protocol

Successful
• A complete application at the time of submission that includes a complete quality and microbiology package
Multicenter Trials

- Identify product manufacturing sites that supply the clinical centers
- Opening trial: The qualification batches at the site of manufacture in the original submission, amend the IND with qualification batch data from subsequent sites
- Across sites/centers: Same range of specific activity, same formulation, same manufacturing process
- Accurate Letters of Authorization (LoA) and CMC data from the opening site(s) at the time of submission

Quality Content and Format

- “IND Applications for Clinical Investigations: Chemistry, Manufacturing, and Control (CMC) Information”
- “Providing Regulatory Submissions in Alternate Electronic Format”
- “Guidance for Industry M4Q: The CTD — Quality”

Refer to the FDA Guidance(s) at www.fda.gov
Drug Substance – CTD
(Precursor and Radioactive Drug Substance)

• 5.1 General Information: Nomenclature, Structure, General Properties
• 5.2 Manufacture
  – Manufacturers
  – Description of Manufacturing Process and Process Controls
    • Flow Diagram
    • Process Narrative
    • Process Controls
  – Control of Materials
    • Starting Materials
    • Reagents, Solvents, Auxiliary Materials
  – Control of Critical Steps and Intermediates
  – Manufacturing Process Development
• 5.3 Characterization
  – Elucidation of Structure
  – Other Characteristics
    • Physicochemical properties
    • Solid State Forms
  – Impurities
    • Types (organic, inorganic, residual solvents)
    • Classification (specified/unspecified, identified/unidentified)
    • Reporting, Identification and Qualification Thresholds
    • Acceptance Criteria
    • Qualification
• 5.4 Control of the Drug Substance
  – Specifications
  – Analytical Procedures
  – Validation of Analytical Procedures
  – Batch Analyses
  – Justification for Specifications
• 5.5 Reference Standards
• 5.6 Container Closure System
• 5.7 Stability
  – Stability Protocol and Data Evaluation
  – Forced Degradation/Stress Testing
  – Photo stability
  – Stability Summary and Conclusion
  – Post-approval Stability Protocol and Commitment
  – Stability Data

Drug Product – CTD

• Drug Product
• P.1 Description and Composition
• P.2 Pharmaceutical Development
  – Drug Substance
  – Excipients
  – Formulation Development
  – Manufacturing Process Development
  – Container Closure Suitability
  – Other
• P.3 Manufacture
  – Manufacturer
  – Batch Formula
  – Description of Manufacturing Process and Process Controls
  – Control of Critical Steps and Intermediates
• P.4 Control of Excipients
• P.5 Control of the Drug Product
  – Specifications (release, stability, in-house)
  – Analytical Procedures
  – Validation of Analytical Procedures
  – Batch Analyses
  – Justification of Specifications
• P.6 Reference Standards
• P.7 Container Closure Systems
  – Primary, Secondary, Functional and Non-Functional Secondary Packaging
• P.8 Stability
  – Stability Protocol and Data Evaluation
  – Forced Degradation/Stress Testing
  – Photo stability
  – Stability Summary and Conclusion
  – Post-approval Stability Protocol and Commitment
  – Stability Data
• Appendices (3.2.A)
  – Facilities and Equipment
  – Adventitious Agents Safety
• Regional Information (3.2.R)
  – Executed batch records, comparability protocols, methods validation package
Phase 3 studies

- Transfer of production sites from earlier stages
- Clear identification of suppliers of critical components, e.g., precursors (peptides, ligands), radionuclides (sources, e.g., generator, accelerator, and production methods), Letters of Authorization (LoA) to Drug Master Files (DMF), sterile components

Phase 3 studies

- Final drug product formulation or bridge pivotal clinical trial formulation to commercial product
- Drug Product Specification
- Presentation (single dose, multidose)
**NDA submission**

- Successful updates to the IND until Phase 3 lead to a successful NDA submission
- PET Diagnostic radiopharmaceutical: May be produced in a PET production facility, or the kit formulation may be radiolabeled at the radiopharmacy

**NDA submission**

- All manufacturing facilities ready for inspection current GMP compliance, listed accurately in 356h form
- All DMFs identified with LoAs
- Is the drug product formulation the same as used in Phase 3 clinical studies? Otherwise bridging information in the NDA 21 CFR 320.24
- Drug Product Release specifications and batch results for at least 3 exhibit batches
NDA submission

• Diagnostic radiopharmaceutical: A kit formulation should be demonstrated to radiolabel successfully by a radiochemical sourced from available different sources, e.g., generator, cyclotron, etc.
• Complete drug product specification should be included in the application with batch analysis test results

Labeling Considerations

• For a New Molecular Entity, what is the USAN name and has it been accepted by the USAN council?
• Strength: What is the radioactivity concentration or radioactivity amount?
• Radiolabeling instructions in the PI should be supported by CMC data submitted in the application, e.g., manipulations, reaction conditions, volumes etc.
• User Manuals: Safe use of complex products and accurate dose dispensing by the end user/operator
Comparability Protocols (CP)

- CP can be submitted in an original NDA application or in a Prior Approval Supplement (PAS) per 21 CFR 314.70(e)
- Effective knowledge of the product and manufacturing process
- Robust control strategy
- Robust pharmaceutical quality system
- Risk management activities over a product’s life cycle

Comparability Protocols in PET Radiopharmaceuticals

- PET drugs or radiopharmaceuticals with short half-lives are often produced by a large network of manufacturing sites to dispense to hospitals and radiology facilities in proximal geographic locations
- Multiple drug product manufacturing sites in the NDA application and/or expanded after approval and launch to market – Large number of sites in an application, supported by compliant GMP status and production data
- Alternate manufacturing sites with acceptable inspectional history and GMP requirements using the same validated manufacturing process to ensure the same drug product composition and purity profile may be submitted in a “Changes Being Effected” (CBE-30) supplement. The GMP status of a facility is a “live” system and the category of supplement may be re-assessed to PAS at the time of submission of the supplement if the facility is not cGMP compliant.
Successful Comparability Protocol Assessments

- Effective use of knowledge of the product and manufacturing process:
- Radiosynthesis has been validated in a defined range of specific activities
- Formulation of the drug product remains the same

These are considered major changes per 21 CFR 314.70:

- Change(s) in the precursor (different leaving group, different protecting group) or its manufacturer
- Change of equipment, e.g., synthesizer type and model, purification
- Change(s) of critical process parameters of the radiosynthesis and deprotection reaction
- Change of the purification method relating to the radiosynthesizer, e.g., HPLC to SPE
- Major change(s) in the analytical method analyzing impurities in the drug product (e.g., column, mobile phase, elution method (gradient-isocratic), run time)

Conclusions

- Product Quality (CMC) data are critical to successful NDA assessments and IND studies.
- FDA encourages innovation and engages with stakeholders and other government agencies working towards availability of new PET drugs and nuclear medicine technologies to patients