Bench to Bedside - The Roadmap
Chemistry, Manufacturing, and Controls
Issues in Radiopharmaceutical Applications

55th Annual Meeting of the Society of Nuclear Medicine
New Orleans, LA, June 14-18, 2008

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V, DPAMS
Office of New Drug Quality Assessment
CDER-FDA
Presentation Outline

- Radiopharmaceutical INDs
  - Exploratory INDs, Traditional INDs, cGMPs for INDs

- PET Radiopharmaceutical NDAs
  - FDG F 18 Injection, Ammonia N 13 Injection,
  - Sodium Fluoride F 18 Injection
  - PET cGMPs for NDAs

- PET Radiopharmaceutical Drug Master Files
  - Radionuclide production
  - Precursors and Final intermediates
  - Automated synthesis units

- Summary
Radiopharmaceutical INDs
Investigational PET Agents

- Limited availability
- Potential biomarkers in the development of therapeutic drugs
- Critical path initiative by FDA
- Institute of Medicine workshop (October 4-5, 2007) report
  [http://www.iom.edu/CMS/26765/41279.aspx](http://www.iom.edu/CMS/26765/41279.aspx)
- Leveraging resources to address expanded availability.
Workshop on Investigational PET Agents

- Planned by RSNA and SNM this year
  - FDA as an enabler
  - NCI and other key stakeholders
- Evaluate supply issues
- Restricted supply of PET imaging agents
  - Non-standardized CMC issues and product quality
  - Cooperation throughout the supply line to facilitate supply of PET imaging agents
- Streamline regulatory expectations and process
CMC Information in INDs

- IND Regulations: 21CFR 312
- IND Content and Format: 21CFR 312.23
- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs - [http://www.fda.gov/cder/guidance](http://www.fda.gov/cder/guidance).
- ICH Common Technical Document (CTD) format may be used.
CMC Information in INDs

- **21CFR312.22**: “…FDA’s review of phase 1 submissions will focus on assessing the safety…”

- **21CFR 312.23(a)(7)(i)**- Graded nature of CMC information needed as IND progresses.

- Progressive expectations of cGMPs

- Sufficient information needed to ensure identity, strength, quality, purity, and potency.
Exploratory IND

- A critical path initiative to identify promising drugs
- Facilitates lead optimization
- Reduces number of human subjects and resources
- Very limited human exposure
  - Sub-pharmacologic non-toxic dose
  - Not a traditional dose escalation, safety, and tolerance study
Exploratory IND Contd..

- No therapeutic or diagnostic intent
  - Screening studies/Microdose studies
- Upon completion, E-IND is withdrawn
- Traditional IND submitted for further development
CMC Information in Exploratory IND

- Adequate to ensure subjects will not face undue risk of harm.
- Type and extent of CMC information needed is similar to that for traditional INDs.
- E-IND drug candidates should be related – structurally and by pharmacological class.
- CMC information can be provided in summary tables for each drug candidate.
Content and Format of INDs

Introduction

- Any potential for human risk?
  - Specific preclinical findings
  - Potential risks and steps proposed to monitor for such risks

- CMC differences, if any, between drug product proposed for clinical use and the drug product used in the animal toxicology studies.
Drug Substance

- Physical, chemical, or biological characteristics:
  - Source (synthetic, animal, plant, biotech)
- Therapeutic class
- Structure elucidation
- General properties
  - Non-radioactive portion
  - Radionuclide
  - Specific activity
Drug Substance Contd..

- Impurities
  - Radionuclidic, radiochemical
  - Chemical (organic, inorganic, other)

- Reference standards, including lot numbers, data and certificates of analysis
Drug Substance Contd.

- Name and Address of the Manufacturer
- Synthesis of final intermediate
- Method of preparation of radioactive drug
  - Radiolabeling, purification, etc.
- Specifications (Test, procedure, acceptance criteria)
- Batch data and / or COA
- Container closure and stability information
Drug Substance Contd.

Reference standard for drug substance

Sources:
- Official source, such as USP / NF
- Commercial, non-official source
- Synthesized in-house
Drug Substance Contd.

Reference standard from an official source, such as USP / NF

- Requires no further identity / structure characterization
- Should be an official statement certifying it as a standard
- User should ensure that it will fulfill the intended purpose when used with the chosen procedures
Drug Substance Contd.

Reference standard from a commercial, non-official source

- Certificate of analysis (COA)
  - Assay
  - Purity
  - How is identity known?
- Stored as recommended by vendor
- Expiration date
Drug Substance Contd.

Reference Standard Synthesized In-house

- Structural elucidation data
  - Elemental analysis
  - Mass Spectrometry
  - NMR, IR Spectroscopy
  - X-Ray Crystallography

Etc.
Drug Product
Components and Composition

- Drug substance: mass and the amount of radioactivity
  - Specific activity
  - Radioactivity concentration (mCi/mL)
  - Total radioactivity

- Excipients (e.g., buffers, diluents, stabilizers/antioxidants and preservatives), their grades, quantities
Drug Product Contd.

- Justification for each component
- The Certificates of Analyses (COA).
- Novel excipients need preclinical qualification.
  - Route of administration, amount, and duration of exposure
- Inactive Ingredients Guide (IIG) at www.fda.gov/drugs
Drug Product Contd.

- The name and address of the drug product manufacturer
- Method of manufacturing and packaging
- Specifications
  - test attributes
  - analytical procedures
  - acceptance criteria
# Drug Product Test Attributes

<table>
<thead>
<tr>
<th>Color and appearance, Animal biodistribution (if necessary to control the quality of the product)</th>
<th>Radionuclidic identity/purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiochemical identity</td>
<td>Radiochemical purity</td>
</tr>
<tr>
<td>Specific activity</td>
<td>Assay</td>
</tr>
<tr>
<td>pH</td>
<td>Osmolality</td>
</tr>
<tr>
<td>Chemical impurities, Residual solvents</td>
<td>Biological activity</td>
</tr>
<tr>
<td>Stabilizers and preservatives</td>
<td>Sterility, Membrane filter integrity and endotoxins</td>
</tr>
</tbody>
</table>
Drug Product Contd.

- Information to support the stability of the drug product
- Container closure systems
- Radiolysis and chemical degradation
- Labels must carry a "caution" statement as required by 21 CFR 312.6(a):
  "Caution: New Drug - Limited by Federal (or United States) law to investigational use"
## Typical Drug Product Label

<table>
<thead>
<tr>
<th>Name and address of the Institution or Company</th>
<th>Product name and dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition description</td>
<td>Route of administration</td>
</tr>
<tr>
<td>Half-life of the radionuclide</td>
<td>Expiration period</td>
</tr>
<tr>
<td>Radioactive concentration / unit volume, net content and the calibration time</td>
<td>Lot number</td>
</tr>
<tr>
<td>Radioactivity cautionary sign</td>
<td>Storage conditions</td>
</tr>
</tbody>
</table>

Patient and Physician Information, and Study Protocol # etc.
IND- Environmental Assessment

- A claim for categorical exclusion from or submission of an environmental assessment [21 CFR 12.23(a)(7)(iv)(e)]
GMPs for INDs

- **FD&C Act 501(a)(2)(B):**
  - cGMP requirement for all drugs
  - [including INDs]
    - Incremental approach during IND stages
    - Enforcement discretion

- **21 CFR 211/212 requirements**
  - Commercial manufacture
  - Phase 2/3 drugs
  - Not for E-INDs/Phase 1 INDs.
GMPs for INDs Contd..

- Draft cGMP guidance for Phase 1/E-INDs
  - Quality control principles to the production
  - Well defined written procedures
  - Adequately controlled equipment
  - Accurate and consistent data recording
  - QC function independent of production function
GMPs for INDs Contd.

- USP<823> for investigational PET drugs
  - Pre-release testing requirements for endotoxins ($T_{1/2} > 20$ min) and residual solvents
  - Regulatory discretion based on scientific justification, GMP standing, batch history, and other controls
Inspection Triggers for E-IND/Phase 1

- Insufficient information to assess the risks to subjects
- Subjects likely exposed to unreasonable and significant risk
- Compromised safety due to inadequate QC procedures
- Manufacturing causalities related to safety
Investigator INDs: A Challenge!

- CMC Information is a requirement
- Attention to the format and organization
- Straight pathway to the information
- Index listing all parts with page numbers
- Paginated sequentially, including appendices
- Lab/Research grade chemicals from fine chemical suppliers for investigation
  – May not be adequate
Investigator INDs Contd.

- Adequate synthetic information
- In-house purification of research-grade chemicals under GMPs
- Chromatograms, spectra should be identified, clearly labeled and legible
- Tables and flow diagrams for clear conveyance of information
- A well-thought out CMC plan, organized, and structured
PET Radiopharmaceutical NDAs
Guidance on PET Drug Product Submissions

- **PET Drug Products: Safety and Effectiveness of Certain PET Drugs for Specific Indications**
  - FR: March 10, 2000 (Volume 65, Number 48), Pages 12999-13010.

- **Draft Guidance on the Content and Format of NDAs/ANDAs for Certain PET Drug Products**
  - FR: March 10, 2000 (Volume 65, Number 48), Pages 13010-13012.
  - FDG F 18 Injection, Ammonia N 13 Injection, Sodium Fluoride F 18 Injection
Format of NDAs and ANDAs for PET Drug Products

- CMC section for the three radiopharmaceuticals may be formatted as described in the draft sample formats.

- Other new PET drugs should follow the ICH Common Technical Document (CTD) format:

- CMC and ICH guidance are available at:
B2 or Not to B2?

- NDA (505)(b)(2) or (505)(b)(1) or ANDA (505)(j) ???
- Agency will determine suitability of regulatory pathway.
- ANDA - for a drug product that is the *same as a listed drug.
  - *Identical* active ingredient(s), strength, dosage form, route of administration
B2 or Not to B2? Contd.

- ANDA permitted inactive ingredient changes in parenteral drug products:
  - Preservative
  - Buffer
  - Antioxidant
  - Other Justified Changes

- The difference must not affect the safety or efficacy of the proposed drug product.

- FDA Orange Book lists RLDs for which ANDAs may be submitted:
  
  http://www.fda.gov/cder/orange/default.htm
Guidance on PET Drug Product GMPs

- **Proposed Rule on cGMPs for PET Drugs**
  - Federal Register: September 20, 2005 (Volume 70, Number 181), Pages 55038 – 55062.

- **Draft Guidance on cGMPs for PET Drug Products**
  - Federal Register: September 20, 2005 (Volume 70, Number 181), Page 55145.

- **Documents are being revised based on the received feedback**
  - Final regulations and guidance to be published soon
Proposed Rule for CGMP
(21 CFR 212) for PET Drug Products

- Proposed 21 CFR 212 regulations apply to commercial PET drug products.

- USP Chapter <823> “Radiopharmaceuticals for Positron Emission Compounding” for investigational and research PET drugs.

- For investigational PET drug products being developed for a future marketing application (NDA) - recommend that 21 CFR 212 be followed (after they are implemented).
PET Drug Product Application Contacts

- **NDA – Division of Medical Imaging and Hematology Products**
  Thuy Nguyen, M.P.H.
  Regulatory Health Project Manager
  Office: (301) 796-2050
  thuy.nguyen@fda.hhs.gov

- **ANDA – Office of Generic Drugs**
  Martin H. Shimer
  Branch Chief, Regulatory Support Branch
  FDA, Office of Generic Drugs
  (301) 827-0503
  martin.shimer@fda.hhs.gov
Radiopharmaceutical
DMFs
Drug Master File (DMF)

- 21CFR 314.420(a)
- A submission to the FDA of confidential information by a DMF Holder
- Allows a reference to be made to information in support of an IND or NDA/ANDA
- Submitted under different cover, separate from the IND or NDA/ANDA
- Prevents proprietary information from being disclosed to sponsor or applicant
DMF Contd.

- A DMF (Type II) can be used to provide information on the following:
  - Drug substance
  - Final Intermediates
  - Precursors
  - Radionuclide production and controls
  - Automated synthesis units (Type V)
- A letter of authorization from the DMF holder
- Guidance
DMFs for Radionuclides

- Radionuclide characterization
  - Radionuclide decay schemes
  - Radiation type, energy, and % abundance

- Radionuclide synthesis
  - Target preparation and controls
  - Description of cyclotron/Reactor/Accelerator, maintenance and controls
  - Nuclear reaction and irradiation cross section
  - Isolation/purification of radionuclide
  - Characterization of radionuclide
DMFs for Radionuclides Contd.

- Radionuclide specifications
  - Radionuclidic identity and assay
  - Gamma impurities by $\gamma$-spectroscopy
  - Beta impurities by Cerenkov
  - Alpha impurities by $\alpha$-spectroscopy
  - NIST traceable reference standards

- Container closure system and stability assessments
  - Metallic leachables from glasses
  - Stopper interactions
DMFs for Precursors/Final Intermediates

- **Examples:**
  - Mannose triflate for F-18 FDG
  - Trimethylstannyl derivatives for I-123/I-131
  - Ligand-containing chemicals for radiometal complexation with Tc-99m, Y-90, In-111, Cu-67, etc.
  - Anhydrothymidine and BNBT precursors for F-18 FLT
DMFs For Precursors Contd.

- Drug substance-like Quality is expected
  - Adequate synthesis description
    - Choice and purity of starting materials and reagents
    - In-process tests and process controls
    - Work up, isolation, purification
  - Specifications with justifications
    - Impact of impurities on radiolabeling
  - Well characterized reference standards
  - Container closure systems and stability assessments
## Typical Quality Attributes for Precursors and Final Intermediates

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>Impurities/Degradation products</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>Endotoxins</td>
</tr>
<tr>
<td>Organic volatile impurities</td>
<td>Trace reagents, metal catalysts, etc.</td>
</tr>
</tbody>
</table>
DMFs for Automated Synthesis Units (ASUs)

- Equipment description and principle of operation.
- Equipment specifications.
- Development reports
  - Design controls
  - Performance standards essential requirements
  - Risk evaluation and mitigation strategies
- Design verification testing
  - Programming logic/software testing (21CFR Part 11)
Automated Synthesis Units (Contd.)

- Bench Testing
  - Functional and electrical testing
  - Normal conditions of operation in a hospital
  - Stressed conditions (power disruptions, humidity and temperature changes, etc.)
  - Extraneous environment

- Installation and Operation qualification
- Performance verification studies
- Equipment maintenance schedule and shelf-life
Summary

- Exploratory INDs as enablers
- CMC information in traditional INDs
- cGMP requirements for INDs
- Regulatory pathway for PET NDAs
- PET GMPs and guidance
- DMFs as enablers
Acknowledgement

- Eldon Leutzinger, Ph.D., ONDQA
- Ravindra Kasliwal, Ph.D., ONDQA
- Rafel Rieves, M.D., DMIHP
- Libero Marzella, M.D., DMIHP
- Alex Gorovets, M.D., DMIHP
- Kaye Kang, Pharm.D., DMIHP
- Monica Caphart, Office of Compliance