US Production of PET Drugs for Clinical and Research Uses

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Overview

I. Clinical Drug Regulatory Oversight
   21 CFR Part 212
   PET Drugs

II. PET Clinical Research Translation
    First-in-Man Compounds
    1. Investigational New Drug (IND) Application or
    2. Exploratory IND

III. Radioactive Drug Research Committee

IV. International Clinical Trial; Use of C-11 PIB
Current Good Manufacturing Practice (CGMP) for PET Drugs

What are CGMP Standards for PET Drugs? [21 CFR 212 (PET)]

• A rule (or regulation) that contains binding requirements that manufacturers must follow, and is enforceable in the courts.
• CGMP is the minimum standard that each manufacturer must follow to produce the drug to help ensure a drug remains safe and effective over its labeled shelf-life.
  ✓ Broad requirements - what you must do
  ✓ How to do, the details of compliance is detailed in manufacturer’s SOPs

C = current practices employing up-to-date technology and the up to date version of the regulation
G = good: of a favorable character; adequate, satisfactory
MP = manufacturing practices: methods, facilities, and controls used in the preparation, processing, testing, packaging, or holding of a drug
(FD&C Act)
PET Drugs are Unique

• Short half-life, usually minutes to hours
• High energy emitting radionuclides (511 keV)
• Batch produced provides a limited supply - usually hours - and can be produced for a single dose
• Mass contained in the final product is usually nanogram-microgram
• Quality control issues due to short half-life
• Complete quality control testing performed for every batch, all but sterility testing is pre-release
21 CFR Part 212 Clinical PET Manufacturing (CGMP)

- 21 CFR Part 212 - as of June 2012
- The regulation contains the minimum Current Good Manufacturing Practice (CGMP) for preparation of PET drugs for administration to humans
- Air Quality only defined for Laminar Flow Hood (ISO Class 5)
- Testing requirements different than Part 211 - unique quality of PET drugs
- Must file New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) with FDA
- Examples of FDA Approved Drugs:
  - F-18 FDG Injection
  - F-18 Fluoride Injection
  - N-13 Ammonia Injection
  - C-11 Choline
Controlled PET Manufacturing Facility

Production area:
Hotcell & ante-chamber
Room air non-classified
~ISO Class 8

ISO Class 5
Laminar Air Flow Hood

Quality Control Area
ISO 7 Production Facility Hand Washing & Gowning

Handwashing

Garbing

Airlock Entrance

Production Hotcells & Biosafety Cabinets
ISO Class 7 Facility

- Biosafety Cabinets
- ISO 5 Dispensing Hotcell
- Pass through QC Laboratory
- Shipping Area
Raw Materials Specifications: Receipt & Release (green sticker)
PET Dispensing ISO Class 5
Laminar Flow Hotcell

- USP Chapter <797>
- Dispensing often requires use of laminar airflow hotcells
- Manipulator arms
- Due to exposure rate from PET 511 kev photons
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USA Regulatory Pathway for First-In-Man Radiotracers

Radiotracers subject to same process as development of new therapeutic pharmaceutical:

1. Exploratory IND - Phase 0
2. IND
3. Clinical Phase 1, 2, & 3
4. FDA Approval

- First-in-Man? Yes
Part 212 Investigational and Research PET Production

The rule §212.5(b) provides that investigational and research PET drugs, CGMP may be met by producing PET drugs:

- in accordance with Part 212 or
- in accordance with USP General Chapter <823> “Radiopharmaceuticals for Positron Emission Tomography – Compounding,” May 1, 2009, 32nd Edition

1. PET Drugs produced under IND Application in accordance with 21 CFR Part 312
2. PET Drugs approved through RDRC in accordance with 21 CFR Part 361

FDA has indicated that IND Phase 0, 1 and 2 are research. Phase 3 usually indicates moving to commercialization & must follow Part 212.
Overview 21 CFR Part 212

Subpart A: General Provisions
Subpart B: Personnel and Resources
Subpart C: Quality Assurance
Subpart D: Facilities & Equipment
Subpart E: Control of Components, Containers, & Closures
Subpart F: Production & Process Controls
Subpart G: Laboratory Controls
Subpart H: Finished Drug Product Controls & Acceptance
Subpart I: Packaging and Labeling
Subpart J: Distribution
Subpart K: Complaint Handling
Subpart L: Records
United States Pharmacopoeia

- **United States Pharmacopoeia (USP):**
  - Sets legal, enforceable standards for drugs in the United States
    - General Chapter <823>, PET Drugs for Compounding, Investigational & Research Uses
    - General Chapter <797> Pharmaceutical Compounding Sterile Products

- **USP Chapter <823>**
  - Contains many essential elements of cGMP
    - The organization of USP <823> provides more specifics than Part 212
    - Part 212 regulation leaves many of the specifics to the Part 212 Guidance
  - **Does not have a guidance document**
    - Contains specifics similar to those found in the Guidance

- **USP Chapter <797>**
  - Dispensing for all radio(pharmaceuticals)
**USP <823>**

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### Investigational PET radiotracers
- IND = Clinical Trial/Research
- RDRC
  - Basic science only
  - Not for diagnosis or therapy
  - Not for safety or efficacy
  - Pharmacology must be known in humans
  - Mass dose—no pharmacological effect
  - Radioactive dose limit

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### Clinical PET radiopharmaceuticals
- Drugs administered as part of clinical care
- Information used to guide patient care decisions
- Approved under NDA/ANDA
- Legally marketed
  - For sale
  - Interstate distribution

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**Part 212 PET CGMPs**
Revised Chapter 823

Positron Emission Tomography Drugs For Compounding, Investigational, And Research Uses

Sections reflect organizational layout of 21 CFR 212

1. Definitions
2. Personnel
3. Quality Assurance
4. Facilities and Equipment
5. Control of Components, Materials, and Supplies
6. Process and Operational Controls
7. Stability
8. Controls and Acceptance Criteria for Finished PET Drug Products
9. If a PET Drug Does Not Conform to Specifications
10. Reprocessing
11. Labeling and Packaging
C. Personnel Qualifications

- Qualified and trained in PET drug production and QC methods
- Aseptic Technique
  - ✔️ Training in aseptic technique
  - ✔️ Training in proper garbing & gloving
  - ✔️ Media Fill Testing: 3 times initially then annually
What are the components of an Investigational New Drug (IND) 21 CFR Part 312 Application?

- FDA Application 1571
- Table of Contents - hyperlinked to the document sections
- General investigational plan
- Investigator’s brochure, if required
- Protocol(s): Phase 1 less detailed than Phase 2 & 3
- Chemistry Manufacturing & Controls (CMC)
  - Production Process
  - Quality Control Process
- Pharmacology and Toxicology - 2 species
- Previous human experience
- Case Report Forms
- Dosimetry Estimates (not specified section)
Exploratory IND Guidance 2006

- Introduced in European Union, 2004
- Microdose: 1/100th of the dose calculated to yield a pharmacologic effect
- **Mass dose \( \leq 100 \, \mu g \)** (protein products \( \leq 30 \) nmoles)
- Reduced pharmacology, toxicology requirements
  - One mammalian species (both sexes)
  - 100 times human dose
  - Study period 14 days
- Phase 0 studies
- Subject enrollment: number not stated in the guidance
- Exploratory IND guidance
- Transition to Phase 1 IND
Exploratory IND Objectives

- Facilitates “First-in-Man” imaging studies
  - Biologics
  - Drugs
- Bridges preclinical - Phase 0 to early Phase 1
- Ideal for clinical investigations of the mechanism of action (MOA) in humans—is it the same as defined in experimental systems, proof of concept
- Provide information on PK
- Initial safety studies
- Select most promising lead candidate RP from a group of the same chemical class with single pharm/tox study
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### EU IMPD
Investigational Medical Product Dossier

- Manufacturing Process & Process Controls
  - Nuclear reaction
  - Irradiation conditions
- Cleaning & segregation
- Active pharmaceutical ingredient (API) including radionuclide
- Process Validation
  - cleaning, preparation, production & QC
- QC tests: pre/post
- 3 validation runs
- Stability testing

### US IND CMC
Chemistry Manufacturing Control

- Components/Raw Materials
- Production of Radionuclide
- Drug Process Evaluation
- Production Process
  - Equipment
  - Synthesis & Purification
  - In-Process Controls
  - Post Synthesis procedures
- QC testing for finished drug
  - Pre/Post
- 3 Validation runs
- 3 Stability tests

EANM Guideline on Preparation of IMPD EJNM Todde S 8-1-14
In-house Synthesis
Precursor & Standard

1. Purchase new chemicals
2. Purchase new glassware
3. Keep chemicals & glassware segregated from routine use
4. Write SOPs for process
5. Perform Synthesis according to SOPs
6. Label product: Product Name, Lot number, date of preparation
7. Characterize precursor & Standard
   a) NMR
   b) Mass Spec
   c) CHN
   d) HPLC
8. Deliver to Document Control Person
9. Perform stability Analysis
Develop *First-in-Man* Compound

**Precursor & Standard Synthesis**
1. Purchase new chemicals
2. Purchase new glassware
3. Keep chemicals & glassware segregated
4. Write SOPs for process
5. Perform Synthesis according to SOPs
6. Characterize precursor & Standard eg NMR, Mass Spec, CHN & HPLC

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**Translate Chemistry to Clinical Chemistry Unit**

**Develop SOPs and QC Release Criteria**

**3 Validation Batches with full QC Testing**

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**Toxicology**

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**Prepare IND**

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**Pre-Release QC**
- Filter Integrity Testing
- pH
- Color, Appearance
- Radionuclidic Identity
- Radioactivity Assay
- Radiochemical Purity
- Chemical Purity
- Mass - compound
- BET

**Post Release QC**
- Sterility
- Radionuclidic Purity

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**Prepare CMC (Chemistry Manufacturing & Control)**

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**FDA**
IND Toxicology Requirements

- Toxicology: 2 mammalian (one non-rodent) species, clinical route and parenteral route of administration
  [link]
- Frequency of Use
  - Single-use products can omit long-term, repeat dose safety studies
  - Biological imaging agents require pharmacokinetic data, HAMA, HAHA, or HACA levels
- Plan Pre-IND meeting with FDA
  [link]
Dosimetry Studies

- Biodistribution study performed in rats or mice
- Imaging may provide additional information
- Calculations performed fitting animal data to models, and performing theoretical calculations using OLINDA software
- Provides human radiation dose estimates for all normal organs
Radioactive Drug Research Committee (RDRC) 21 CFR Part 361

• Purpose: to study basic research
  (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=361)
• No clinical decisions allowed
• Pharmacology must be known in humans
  ✓ Drug generally recognized as safe and effective (GRASE)
• No observed pharmacological effect can be noted from mass dose administered (NOEL)
• No ‘First-in-Man’ Studies
• Radiation Dose Limits: adults and children (10% of adult radiation dose is maximum, often not adequate)
  ✓ Regulatory revisions needed in pediatric dose limits
  ✓ Federal funding requires children be included in studies
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Dominantly Inherited Alzheimer’s Network Trials Unit Clinical Trial (DIAN-TU)

Investigator: Randy Bateman, MD (Imaging PI Tammie Benzinger, MD)
Countries: 8 (31 study sites, 22 PIB sites)
Two therapeutic agents, currently
Trial Imaging Biomarker: C-11 PIB
  1. No monograph in any Pharmacopeia
  2. Not approved for MA
  3. Therefore classified as an IMP
  4. Covered by Regulations on clinical trials

Each application requires:
1. Clinical Trials Agreement (CTA) submit to each country
2. Country (National) Approval--IMPD
3. C-11 PIB IND Production review and approval at each site, by Washington University (Certus International)
Clinical Trial C-11 PIB
PET Center Readiness Evaluation

- International Trial
  - US, Puerto Rico, Canada, France, Italy, Spain, UK, Australia
- Required a CTA for each site
- PET Production Center Evaluation Criteria (USP Chapter 823—basis for review)
  - Personnel education, qualification & training (includes media fill testing)
  - Facility design, and layout
  - Raw material receiving: components, closures, containers & material controls
  - Production & process control
  - Aseptic processing & sterilizing filtration
  - Quality Control/Quality Assurance
  - Process validation & computer control
  - Finished product acceptance criteria
  - 3 Validation runs
  - Stability testing
  - Labeling
  - Records
Validation, Stability Testing & Expiration Dating

1. Three validation runs
2. Expiration dating and storage conditions must be established
3. Perform stability testing at highest radioactive concentration
   a) Withdraw sample from the intended final container/closure
   b) Parameters to evaluate for stability:
      ✓ Radiochemical identity & purity (including levels of radiochemical impurities)
      ✓ Appearance
      ✓ pH
      ✓ Chemical purity

Must meet all acceptance criteria at expiration
Conclusion

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Thank you!

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New Regulation on EU Clinical Trials

Legislative Proposal published 17/07/2012 by European Commission (Health & Consumers)

Discussion in National Parliaments

modification in discussion with European Parliament and the Council Working Group

April 2nd 2014 passed European Parliament, will come into effect 1.1.2016
Article 63
Manufacturing and import
1. **Investigational medicinal products shall be manufactured by applying** manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial (**‘good manufacturing practice’**). The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to specify the principles and guidelines of good manufacturing practice and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products, taking account of subject safety or data reliability and robustness, technical progress and global regulatory developments in which the Union or the Member States are involved.

In addition, **the Commission shall also adopt and publish detailed guidelines** in line with those principles of good manufacturing practice and revise them when necessary in order to take account of technical and scientific progress.
Paragraph 1 shall not apply to any of the following processes:

(a) re-labelling or re-packaging …..

(b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;

(c) the preparation of medicinal products referred to in points (1) and (2) of Article 3 of Directive 2001/83/EC for use as investigational medicinal products, where this process is carried out in hospitals, health centres or clinics legally authorised in the Member State concerned to carry out such process and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State.

Same exemption for authorization for manufacturing
Exemption /simplification for labelling of in-house radiopharmaceuticals

Radiopharmaceuticals are special, but is this recognized?
The possible impact of the new Clinical Trials Regulation on the preparation of radiopharmaceuticals

C. Deeristoforo · I. Penuelas · P. Elsinga · J. Ballinger · A. D. Winhorst · A. Verbruggen · F. Verzijlbergen · A. Chiti
ISO Class 5 Laminar Flow Hood
Environmental & Personnel Monitoring

Microbiological Testing Requirements:
During Final Product Set-Up and Sterility Testing

Final Product Vial Set-up

Contact Plate

Finger Touch Plate

Air Sampling Plate