US First-in-Human Regulatory Requirements
Nuts and Bolts for CMC Preparation
Overview

• First-in-human radiopharmaceutical studies
• Investigational New Drug (IND) or Exploratory IND
  ✓ Investigational Plan and Protocol
  ✓ CMC Section
  ✓ Dosimetry
  ✓ Toxicology—1 or 2 mammalian species
• Radioactive Drug Research Committee (RDRC)
PET and SPECT Clinical Research Production

1) New Drugs—First in Human: require Investigational New Drug Application (IND or Exploratory IND (Rule: FDA 21 CFR Part 312)

2) Drugs with known human pharmacology may be produced under approval from a local Radioactive Drug Research Committee (RDRC) (21 CFR Part 361.1)
First-In-Man
Investigational New Drug (IND) Application

FDA requires filing an IND (FDA 21 CFR Part 312)

- Exploratory IND: Phase 0 (PET & SPECT)
- IND Phase 1: Tolerability studies - metabolism and pharmacologic action, side effects, structure-activity-relation, explore biological phenomena or disease process
- IND Phase 2: Evaluate effectiveness
- IND Phase 3: Effectiveness and safety - commercialization
US Regulatory Pathway for First-In-Man Radiopharmaceuticals (RPs)

Radiopharmaceuticals subject to same process as development of new therapeutic pharmaceuticals

* Recommended, not required
Phase 0
Exploratory studies used to demonstrate proof of concept, to establish if a new RP will work as desired in humans. Enables decisions to be based on human studies rather than on preliminary animal data.

Phase 1
The primary goal is safety - determine the drug's side effects and how the RP is metabolized and excreted. It is usually conducted in healthy volunteers and subjects with disease.

Phase 2
The primary goal is effectiveness - obtain data to demonstrate the RP is effective for people with a certain type of disease

Phase 3
Studies to demonstrate efficacy and continued safety in a larger sample of human subjects, usually in comparison to the current standard.
Clinical Research Radiopharmaceuticals, SPECT and PET

1) SPECT RP, Part 211:
• Phase 0 and 1: *in vivo* diagnostics are exempt from 21 CFR Part 211 requirements
• Production of Phase 1 Part 211 drugs: FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008; [https://www.fda.gov/media/70975/download](https://www.fda.gov/media/70975/download)
• Phase 2-3: must follow Part 211

2) PET RP, Part 212:
• Phase 0, 1 and 2: allows production of Investigational PET drugs according to either USP Chapter <823> or Part 212
• Phase 3: must follow Part 212
• FDA Guidance: IND Applications for PET Drugs, December 2012 [https://www.fda.gov/media/83077/download](https://www.fda.gov/media/83077/download)

3) *Drugs with known human pharmacology may be produced under Radioactive Drug Research Committee (RDRC) (21 CFR Part 361.1)***
21 CFR Part 212; Final Rule current Good Manufacturing Practice (CGMP) for PET Drug Production

• The rule §212.5(b) also 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 42 General Chapter <823> “Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses”
  ✓ Includes:
    1. PET Drugs produced under Investigational New Drug (IND) Application in accordance with Part 312 of this chapter or
    2. PET Drugs approved through a Radioactive Drug Research Committee (RDRC) in accordance with Part 361 of this chapter
  ✓ FDA has indicated that IND Phase 0-1-2 are research. Phase 3 usually indicates moving to commercialization & must follow Part 212.
The Radioactive Drug Research Committee (RDRC)

• Title 21 Code of Federal Regulations (CFR) 361.1
• Conditions for RDRC Research:
  ✓ Generally Recognized as Safe and Effective (GRASE)
  ✓ Basic Science Research -- Not intended for therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug
  ✓ No Pharmacologic Effect
  ✓ Radiation Dose Limits
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
- Protocol(s): Phase 1 less detailed than Phase 2 & 3
- Investigator’s brochure
  - Not required for a single site study
- Chemistry Manufacturing & Controls (CMC)
  - Production Process
  - Quality Control Process
- Pharmacology and Toxicology - 2 species
- Previous human experience
- Case Report Forms
- Dosimetry Estimates (not a specified section)
Microdose: 1/100th of the dose calculated to yield a pharmacologic effect

- **Mass dose $\leq 100 \, \mu g$** (protein products $\leq 30 \, \text{nanomole}$)
- 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 [https://www.fda.gov/media/72325/download](https://www.fda.gov/media/72325/download)

- Transition to traditional IND, Phase 1
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 pharmacokinetics, PK
- Initial safety studies
- Select most promising lead candidate RP from a group of the same chemical class with single pharm/toxicology study
Investigational Clinical Plan and Protocol

• Physician investigator develops the general investigational plan and the protocol

• Phase 0 - early Phase 1: investigational plan more limited in scope & number of subjects, but may be more detailed in some areas (e.g. first in human study can include limited safety evaluation such as continuous EKG)

• Phase 1-3: safety and effectiveness
What is the United States Pharmacopeia? (USP)

United States Pharmacopeia (USP):
• Sets legal, enforceable standards for drugs (including radiopharmaceuticals) in the United States
  o General Chapters - under 1000 are enforceable
  o General Chapters over 1000 are for information
USP Chapter <823>

Positron Emission Tomography Drugs For Compounding, Investigational & Research Uses

USP Chapter 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
USP Chapter <1823> Positron Emission Tomography Drugs—information chapter

1. Information
2. Techniques for production and quality control
3. Quality assurance
4. Production
5. Quality Control
6. Analytical Methodologies
7. Quality Attributes
8. Sterility Assurance
1. Written raw materials specifications:
   a. Specify Grade (e.g. HPLC Grade)
   b. Certificate Of Analysis (COA)-specify receipt from manufacturer

2. Order/Receipt of raw materials
   a. Control of raw materials-segregated area

3. Written Standard Operating Procedure (SOP)

4. Written batch record: list of materials (ingredients)

5. QC Release Specifications

6. Equipment verification (e.g. balance)
   a. Standard weights, covering range of use
   b. Record Day of Use –instrument log book
   c. Maintenance—record instrument history in writing

7. Written precursor characterization requirements
   --NMR, Mass Spec, HPLC, CHN or Mfg. COA

8. Three (3) Consecutive validation runs

9. Stability analysis for 3 runs – establish expiration

10. Prepare written CMC
Documentation Requirements

- Process Validation
- Paperwork Correction
  - Daily Tasks
  - Batch Record Entries
- Labeling
  - Lot number
  - Date
  - Open date

- Precursor Documentation
  - Materials
  - Segregation
  - Notebook
  - Written Documentation—NMR, Mass Spec, HPLC, CHN analysis
  - Labeling
  - Stability
Synthesis flowchart for preparation of IND or EIND

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 e.g. NMR, Mass Spec, HPLC & CHN

Develop SOPs and QC Release Criteria
3 Validation Batches with full QC Testing

Translate Chemistry to Clinical Chemistry Unit

Toxicology

Prepare IND

FDA

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

Post Release QC
✓ Sterility
✓ Radionuclidic Purity

✓ Develop Study Protocol and Consent Form
✓ Prepare CMC (Chemistry Manufacturing & Control)

Dosimetry

MIR Mallinckrodt Institute of Radiology
Precursor & Standard In-house Synthesis

- Purchase new chemicals—assign raw material numbers (RMs) for the chemicals
- Purchase new glassware
- Keep chemicals & glassware segregated from routine use
- Write SOPs for process
- Perform Synthesis according to SOPs
- Label product: Product Name, Lot number, Date of preparation
- Characterize precursor & Standard: possible analyses are
  - NMR
  - Mass Spec
  - HPLC
- Maintain the records in writing
- Perform Stability Analysis
Raw Material (RM-528)
L-Ascorbic Acid

Raw Material Acceptance Testing

Raw Material:  L-Ascorbic Acid
MIR Code:  RM-528

Identification:
Labeled L-Ascorbic acid – ACS reagent ≥ 99%

Description:
Supplied as a white powder in a plastic container.

Specifications:
Titration by iodine ≥ 99.0 %

Storage:
Store at room temperature.

Acceptable Supplier(s):
A. Sigma-Aldrich, PO Box 14508, St. Louis, MO 63178 [1-800-558-9160]

Acceptance Test:                      Sample Size:
1. Identification                      Each container
   Visually inspect bottle for proper labeling.

2. Description                        Each container
   Visual inspection matches description above.

3. Specifications                     Each lot
   Check manufacturer’s C of A.

Approved by: ___________________________  Date Issued: ____________
Checklist for In-house Produced Precursors

Checklist for accepting in-house produced precursor

Precursor's chemical name: ____________________________

Precursor's lot#: ____________________________

Used in production of __________________________________ Radiopharmaceutical.

Prepared By: ___________________________________________

Prepared Date: _________________________________________

Preparer's Log Book page#: ____________________________

Preparer's contact #: ____________________________

Analytical Data
(Preparer should write comments for Elemental Analysis, NMR & LC/MS data.)
Write a checkmark to indicate the data is submitted.

Appearance: ____________________________________________

( ) HPLC Chromatogram (Purity by Area Percent)
( ) Elemental Analysis
( ) 1H-NMR
( ) 13C-NMR
( ) LC/MS
( ) Copy of Lab Logbook page

Handling and Storage

Comments: ____________________________________________
Raw Material Acceptance Testing:
RM-133
PIB Methyl Triflate Precursor
### RM-133
Precursor for C-11 PIB Methyl Triflate
Receipt Log-In

<table>
<thead>
<tr>
<th>RM#</th>
<th>PO #</th>
<th>Date Received</th>
<th># Rec'd</th>
<th>Name</th>
<th>Supplier Lot#</th>
<th>Date Expires</th>
<th>Acceptance Tests (initial when complete)</th>
<th>Checked By</th>
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<tr>
<td>25</td>
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<td>33</td>
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<td>1-23-19</td>
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<td>A</td>
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<td>36</td>
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<td>37</td>
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<td>9-17-16</td>
<td>60</td>
<td>A</td>
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<td>12-31-18</td>
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<td>11-21-18</td>
<td>60</td>
<td>A</td>
<td>2019-02-01</td>
<td>12-31-18</td>
<td>12-31-18</td>
<td>12-31-18</td>
</tr>
</tbody>
</table>

4/16/2014
**Final Product Vial Set-Up**

<table>
<thead>
<tr>
<th>Prepared by</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Empty vial weight: 9 g

The ISO class 5 Laminar Airflow Hood (ID: _________) was cleaned according to SOP 712

Checked by: [Signature]

Balance(s) (ID# _________) checked according to CCP 902 & 906

Checked by: [Signature]

Sterile final product vial prepared according to SOP 420

Checked by: [Signature]

<table>
<thead>
<tr>
<th>Supplies</th>
<th>RM #</th>
<th>Expires</th>
<th>Quantity Needed</th>
<th>Quantity Used</th>
<th>Checked By</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile 18 Gauge Needle</td>
<td>RM 16-</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mL clear, colorless glass Sterile Vial</td>
<td>RM 22-</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterilizing Filter, 0.2 µm, Air-eliminating</td>
<td>RM 160-</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile vent filter, 0.22 µm</td>
<td>RM 337-</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile filter, 0.2 µm</td>
<td>RM 139-</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9% Sodium Chloride</td>
<td>RM 8-</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>______ ml Sterile Syringe</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile Red Cap</td>
<td>RM 86-</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Prepare the FPPV with sterile empty 10 mL vial (RM-22), sterilizing filter (RM-160), and sterile vent filter (RM-337).
- Add 5 mL of 0.9% Sodium Chloride through the sterilizing filter.
- Remove the sterilizing filter used for 0.9% Sodium Chloride. Set it aside for bubble point test.
- Insert another sterilizing filter (RM-139) into the FPPV, and attach the sterile cap.
- Perform bubble point test for the filter used for 0.9% Sodium Chloride. Record the result in the batch record.

Bubble point test result: 5 psi
Example
Batch Record page 2

Synthesis Setup
The previous setup was removed, line clearances and cleaning were performed. Initial

<table>
<thead>
<tr>
<th>Supplies</th>
<th>Rinse Code</th>
<th>Expires</th>
<th>Quantity Needed</th>
<th>Quantity Used</th>
<th>Checked By</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Synthesis
Preparation of C-11 Methyl Trifluoroacetate using the TRACERlab according to SOP 468 Initial
Synthesis performed according to SOP 1104 Initial

Post-synthesis
Weighing performed according to QCP 802 Initial

<table>
<thead>
<tr>
<th>Product vial weight (Empty) g</th>
<th>Full g</th>
<th>Product Weight (Volume) mL</th>
</tr>
</thead>
</table>

Measure final product activity and strength according to QCP 802 Initial

ECS activity: _____ mCi at: ____________  Strength: _____ mCi/mL
Aseptic removal of final product according to SOP 421 Initial

QUALITY CONTROL

<table>
<thead>
<tr>
<th>Color/Appearance</th>
<th>Sterile Filter Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color and appearance checked according to QCP 801</td>
<td>Sterile filter bubble point test according to SOP 427 after rinsing the filter with 5.0 mL of sterile water</td>
</tr>
<tr>
<td>Color/Appearance:</td>
<td>Sterile Filter Test: _____ psi</td>
</tr>
<tr>
<td>□ Clear, colorless, particle-free</td>
<td></td>
</tr>
<tr>
<td>□ Other:</td>
<td></td>
</tr>
<tr>
<td>Initial:</td>
<td>Initial:</td>
</tr>
</tbody>
</table>

Report
Production Report Needed: □ Yes □ No

<table>
<thead>
<tr>
<th>Type of report needed</th>
<th>Failure</th>
<th>Occurrence</th>
<th>OOS</th>
</tr>
</thead>
</table>

[Image of Batch Record page 2 of 3]
### Example Batch Record

### Batch ID:

<table>
<thead>
<tr>
<th>QC Report Needed</th>
<th>Type of report needed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Yes</td>
<td>☐ Failure</td>
<td>☐ Occurrence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Accountability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Released:___________ mCi in:__________ mL @:______ ks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signed Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checked by (R.Ph.):_________________________ Date:_________________________</td>
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## QC Release Specifications

<table>
<thead>
<tr>
<th>TEST</th>
<th>ACCEPTANCE CRITERIA</th>
<th>PROCEDURE</th>
<th>TESTING SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filler Membrane Integrity Test</td>
<td>≥ 50 psi</td>
<td>Bubble Point Test (see SOP 427)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>pH</td>
<td>5.0 to 6.5</td>
<td>Narrow range pH paper (see QCP 801)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Appearance; Color</td>
<td>Clear and particulate free. Colorless</td>
<td>Visual observation (see QCP 801)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Strength</td>
<td>1.67 – 1.16 (μG/mL) (Information Only)</td>
<td>Dose calibrator (see QCP 802)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Radiometric Identity</td>
<td>Major photopeaks at 511.00 keV and 1345.77 keV</td>
<td>Gamma spectroscopy (see QCP 204)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Radiochemical Purity</td>
<td>≥90 %</td>
<td>HPLC analysis (see QCP 105)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Radiochemical Identity</td>
<td>Radioactive peak and standard (or co-injection) mass peak retention times must agree by ± 10%</td>
<td>HPLC analysis (see QCP 105)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Specific Activity</td>
<td>≥ 600 μCi/μg</td>
<td>Dose calibrator assay divided by peptide conjugate 86Cu-LLP2A mass (15 μg)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Bacterial Endotoxin</td>
<td>≤ 175 EUV (where V is the maximum total dose)</td>
<td>Chromogenic method (see QCP 801)</td>
<td>Pre-release; each batch</td>
</tr>
<tr>
<td>Sterility</td>
<td>Sterile (No visible growth)</td>
<td>Visual observation (see QCP 802)</td>
<td>Post-release; each batch</td>
</tr>
<tr>
<td>Cell Binding</td>
<td>Blocking to be ≥ 65 %</td>
<td>Cell binding assay (see QCP 1011)</td>
<td>Post-release; each batch</td>
</tr>
<tr>
<td>Radiometric Purity</td>
<td>≥ 95.0%</td>
<td>Gamma spectroscopy (see QCP 204)</td>
<td>Annual</td>
</tr>
</tbody>
</table>

Approved By: ___________________ Date Issued: ___________
Dosimetry Studies

- Biodistribution study performed in rats or mice
- Human radiation dose estimates are then calculated
- Provides safety assessment of the candidate RP at the radioactive dose proposed for the research protocol
- Human dosimetry usually performed in Phase 1 study
Pharmacology & Toxicology

• Pharmacology
  o Pre-clinical safety testing performed in animals an in vitro
  o Pharmacological studies include target/receptor profiling
  o Characterization of primary pharmacology in a relevant model
  o If sufficient information is known about a class of compounds, a careful
    literature search can reduce the need for additional studies.
  o Toxicology for the eIND more limited than traditional IND since microdose
    studies (≤ 100 µg) designed not to induce pharmacologic effects
Traditional IND Toxicology Requirements

• Toxicology: single dose studies in 2 mammalian (one non-rodent) species, clinical route and parenteral route of administration
  Non-radiolabeled contrast agents generally treated like therapeutic agents

• Frequency of Use
  o Single-use products can omit long-term, repeat dose safety studies
  o Biological imaging agents require pharmacokinetic data, HAMA, HAHA, or HACA levels

• Nonclinical Safety Assessments: e.g. contrast agents
  o Safety pharmacology studies: Pre-IND meeting with FDA prior to IND submission
  o Reproductive toxicology can be limited - Pre-IND meeting
  o Carcinogenicity studies – Pre-IND meeting

• Plan Pre-IND meeting with FDA
What needs to be done for a single-dose microdose toxicology study?

- For imaging agents dose ≤ 100 µg (for protein products ≤ 30 nanomole)
- Single mammalian species (both sexes), usually mice/rats
- Animals: 15 animals per sex per group
- Route of administration should be intended clinical route
- Animals should be observed for 14 days post-dosing (5 animals/sex/group) with an interim necropsy, typically on day 2 (10 animals/sex/group)--total of 30 animals/dose & control group [60 animals total for one dose level]
- Endpoints evaluated should include body weights, clinical signs, clinical chemistries, hematology & histopathology
- Dose multiple should be large multiple--100X proposed human dose (mg/kg basis)
- Scale from animals to humans based on body surface area
Toxicology Labs

• GLP Lab—FDA recommends GLP lab should be used
  o Alternates could be University departments
e.g. WU Comparative Medicine
  o University of Missouri Veterinary Medicine—performs toxicology studies
  o Pre-IND meeting with the FDA

• Work with an outside lab to provide part of the service – e.g. dose preparation and verification

• Have found that GLP labs are more price competitive due to use of other non-GLP labs

• NIH has programs to offer assistance for certain toxicology studies
  o NIC Experimental Therapeutics (NEXT) http://next.cancer.gov/
  o Bridging Interventional Development Gaps
    https://search.usa.gov/search?utf8=%E2%9C%93&amp;affiliate=commonfund&amp;query=grants+for+toxicology+studies&amp;commit=Search
WU Comparative Anatomy Lab

- Follow FDA and ICH Guidance:
Cost of Toxicology Studies

- Single toxicity rodent study: $60-140K
- Developing new animal models: swine (U of Missouri)
- Finding that swine acquire similar diseases as humans
- Cost of swine toxicity study is similar to rats
- Could use swine as 2nd non-rodent species
- Other species for a traditional IND
  - Dogs
  - Rabbits
Conclusion

• First-in-man Regulatory Requirements
• IND or EIND
  ✓ Investigational Plan and Protocol
  ✓ CMC Section
  ✓ Dosimetry
  ✓ Toxicology—1 or 2 mammalian species
Thank you!

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