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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

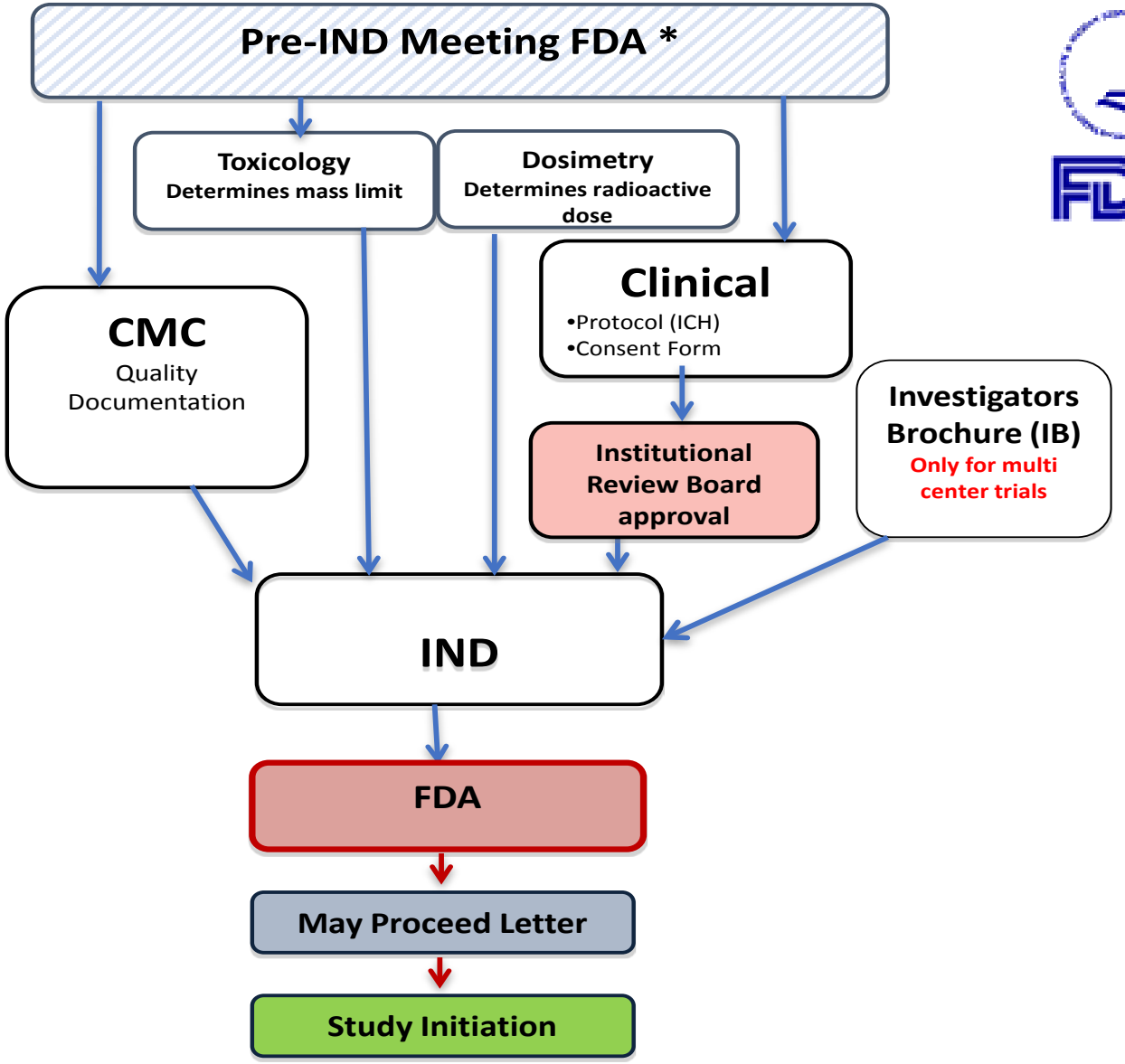
FDA requires filing an IND (FDA 21 CFR Part 312)
(https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312)

- 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



Clinical Trial Phases

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
   - Phase 2-3: must follow Part 211 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=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

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)

Exploratory IND Guidance 2006

- Microdose: 1/100th of the dose calculated to yield a pharmacologic effect
- **Mass dose ≤ 100 µg** (protein products ≤ 30 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
- 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
  - General Chapters - under 1000 are enforceable
  - 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

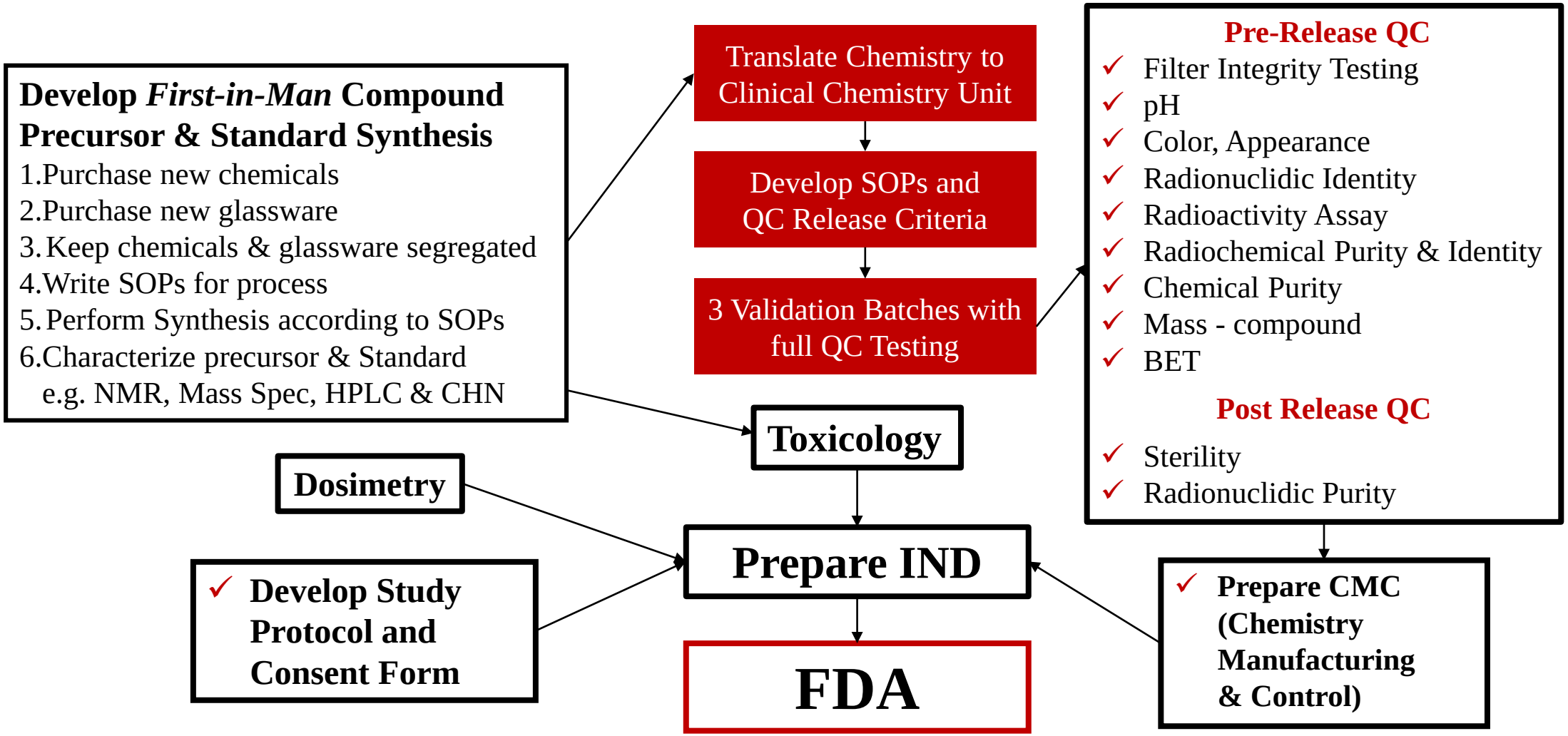
IND or Exploratory IND Chemistry Manufacturing & Controls (CMC)

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



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

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Cyclotron Facility

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 Visually inspect bottle for proper labeling.	Each container
2. Description Visual inspection matches description above.	Each container
3. Specifications Check manufacturer's C of A.	Each lot

Approved by (RPh.): _____ Date Issued: _____

Raw Material Acceptance Testing RM-528 L-Ascorbic Acid (Ver. 2: 8/2018) Page 1 of 1
G:\radsci\Cyclotron Facilities\Raw Material Spec Sheets

Checklist for In-house Produced Precursors

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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 check mark to indicate the data is submitted.

Appearance: _____

( ) HPLC Chromatogram (Purity by Area Percent)

( ) Elemental Analysis

( ) ^{1}H-NMR

( ) ^{13}C-NMR

( ) LC/MS

( ) Copy of Lab Logbook page

Handling and Storage

_____

Comments:

_____

_____

Raw Material Acceptance Testing: RM-133 PIB Methyl Triflate Precursor

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Raw Material Acceptance Testing

Raw Material: Precursor for C-11 PIB, Methyl Triflate

MIR Code: RM- 133

Identification:
Labeled 6-OH-BTA-0 (synonym: 2-(4'-Aminophenyl)-6-hydroxybenzothiazole).
CAS# 178804-18-7. Molecular weight: 242.30. Formula: $C_{13}H_{10}N_2OS$.

Description:
Yellowish to green solid (1 mg each) packed under argon, in sealed amber glass vials with tear-off crimp tops. Should be stored desiccated at 2-8°C (refrigerate).

Specifications:
Purity ≥ 95%
Complete Raw Material QC Acceptance Testing according to SOP# 516.

Acceptable Supplier(s):
A. ABX Advanced Biochemical Compounds, ABX GmbH Dresden, Chemical Division, Wilhelm-Roensch-Strasse-9, D-01454 Radeberg, Germany [49-3528-404160], catalog# 5100.0001

B.

Acceptance Test:	**Sample Size:**
1. Identification Visually inspect bottle for proper labeling.	Each bottle
2. Description Visual inspection matches description above.	Each lot
3. Specifications Check manufacturer's C of A, and complete QC Acceptance Testing form.	Each lot

Approved by (RPh.): _____ Date Issued: 8/10/16

JM/RO rev. 8/10/16

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RM-133 Precursor for C-11 PIB Methyl Triflate Receipt Log-In

Raw Material: Precursor for C-11 BTA(PIB) Methyl Triflate

RM# 133-	PO #	Date Received	# Rec'd	Supplier Name	Supplier Lot#	Date Expires	Acceptance Tests (initial when complete) 1	2	3	Checked By
22	3758074 M	8-15-14	60	A	20140401	2-26-2015	MK	MK	MK	SM
23	3809009 M	12-22-14	60	A	20140701	7-7-2015	MK	MK	MK	AJ
24	3867244 M	5-20-15	60	A	20140701	1-22-2015	MK	MK	MK	AJ
25	3904490 M	8-20-15	60	A	20150301	3-1-2016	BD	BD	BD	SM
26	3945498M	12-14-15	60	A	20151001	7-7-16				RO
27	4039928M	8-10-16	30	A	20160601	6-30-19				RO
RM 133-26 Expiration date was extended to 1-7-17. R.Orama 9-2-16										
133-28	4141065M	4-5-17	30	A	20161201	12/2019				RO
133-29	4194050M	8-7-17	30	A	20170601	6/2020				RO
133-30	4248282M	12-21-17	40	A	20170601	6/2020				RO
133-31	4298038M	4-16-18	40	A	20170601	6/2020				JLP
133-32	4357996 M	9-6-18	60	A	20180301	03/2021	JLP	JLP	JLP	JLP
33	4394284M	11-30-18	60	A	20180301	03-31-21	JLP	JLP	JLP	JLP
34	4417899M	1/31/19	60	A	20180301	03-31-21	JLP	JLP	JLP	JLP
35	4450592M	4-12-19	60	A	20181201	12-31-21	JLP	JLP	JLP	JLP
36	4475853M	6-18-19	60	A	20181201	12-31-21	JLP	JLP	JLP	JLP
37	45 11395 M	9/17/19	60	A	20181201	12/31/21	BT	BT	BT	RO
38	4545128M	11-12-19	60	A	20190501	05/31/22	JLP for BD	JLP for BD	JLP for BD	JLP
39	4553805M	12-18-19	60	A	20190801	08-31-22	JLP	JLP	JLP	JLP

4/16/2014

Example Batch Record page 1

MIR WUSM
Cyclotron Facility & Nuclear Pharmacy
RaPh Master Batch Record
Name
Production Location

Date: _____

Prepared by: _____

Batch ID: ___CSP_____

Affix Label Here

Final Product Vial Set-Up

Prepared by:_____ Date: _____ Time: _____

Empty vial weight: _____g

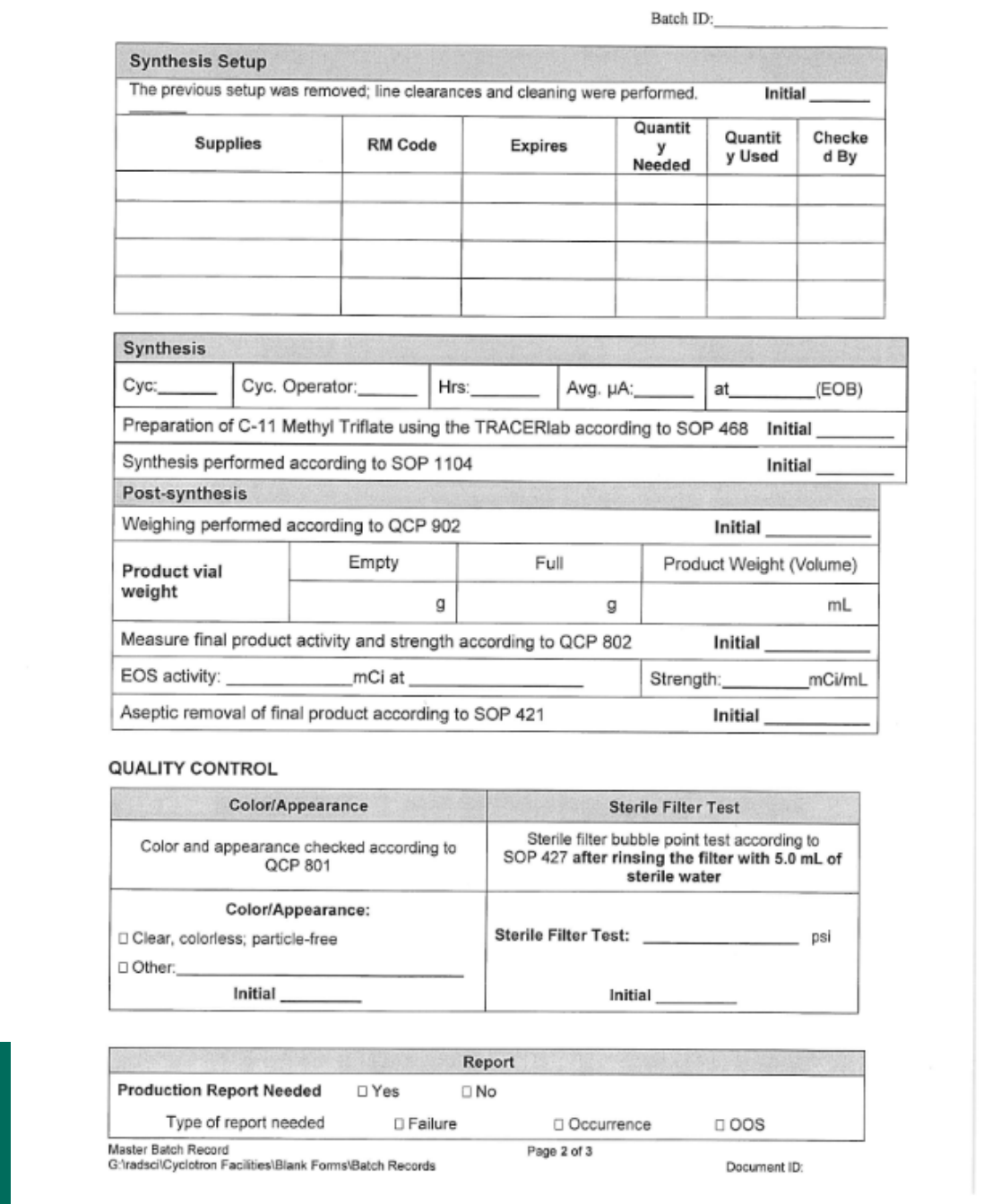
The ISO class 5 Laminar Airflow Hood (ID:_____) was cleaned according to SOP 712	**Checked by:**_____
Balance(s) (ID#_____; ID#_____) checked according to QCP 902 & 906	**Checked by:**_____
Sterile final product vial prepared according to SOP 420	**Checked by:**_____

Supplies	RM #	Expires	Quantity Needed	Quantity Used	Checked By
Sterile 18 Gauge Needle	RM 19 -		4		
10 mL clear, colorless glass Sterile Vial	RM 22 -		1		
Sterilizing Filter, 0.2 µm, Air-eliminating	RM 180 -		1		
Sterile vent filter, 0.22 µm	RM 337 -		1		
Sterile filter, 0.2 µm	RM 139 -		1		
0.9% Sodium Chloride	RM 8 -		1		
_____ mL Sterile Syringe			1		
Sterile Red Cap	RM 86 -		1		

- Prepare the FPV with sterile empty 10 mL vial (RM-22), sterilizing filter (RM-180), and sterile vent filter (RM-337).
- Add 9 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 FPV, 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: _____ psi

Example
Batch Record page 2



Batch ID:_____

Synthesis Setup

The previous setup was removed; line clearances and cleaning were performed. **Initial** _____

Supplies	RM Code	Expires	Quantity Needed	Quantity Used	Checked By

Synthesis

Cyc:_____	Cyc. Operator:_____	Hrs:_____	Avg. µA:_____	at_____(EOB)

Preparation of C-11 Methyl Triflate using the TRACERlab according to SOP 468 **Initial** _____

Synthesis performed according to SOP 1104 **Initial** _____

Post-synthesis

Weighing performed according to QCP 902 **Initial** _____

Product vial weight	Empty	Full	Product Weight (Volume)
	g	g	mL

Measure final product activity and strength according to QCP 802 **Initial** _____

EOS activity: _____mCi at _____ Strength:_____mCi/mL

Aseptic removal of final product according to SOP 421 **Initial** _____

QUALITY CONTROL

Color/Appearance	Sterile Filter Test
Color and appearance checked according to QCP 801	Sterile filter bubble point test according to SOP 427 **after rinsing the filter with 5.0 mL of sterile water**
Color/Appearance: ☐ Clear, colorless; particle-free ☐ Other:_____ **Initial** _____	**Sterile Filter Test:** _____ psi **Initial** _____

Report

Production Report Needed ☐ Yes ☐ No

Type of report needed ☐ Failure ☐ Occurrence ☐ OOS

Master Batch Record
G:\radsci\Cyclotron Facilities\Blank Forms\Batch Records

Page 2 of 3

Document ID:

Example Batch Record page 3

Batch ID:_____

QC Report Needed	☐ Yes	☐ No	
Type of report needed	☐ Failure	☐ Occurrence	☐ OOS

Comments: _____

_____

Dose Accountability

Released_____mCi in_____mL @_____to_____

Signed Off

Checked by (R.Ph.): _____ Date:_____

Master Batch Record
G:\radsci\Cyclotron Facilities\Blank Forms\Batch Records

Page 3 of 3

Document ID:

QC Release Specifications

Radiopharmaceutical Product Specification SP# 53.2

Cu-64 ABC

TEST	ACCEPTANCE CRITERIA	PROCEDURE	TESTING SCHEDULE
Filter Membrane Integrity Test	≥ 50 psi	Bubble Point Test (see SOP 427)	Pre-release; each batch
pH	5.0 to 6.5	Narrow range pH paper (see QCP 801)	Pre-release; each batch
Appearance; Color	Clear and particulate free, Colorless	Visual observation (see QCP 801)	Pre-release; each batch
Strength	1.07 – 1.16 (mCi/mL) (Information Only)	Dose calibrator (see QCP 802)	Pre-release; each batch
Radionuclidic Identity	Major photopeaks at 511.00 keV and 1345.77 keV	Gamma spectroscopy (see QCP 204)	Pre-release; each batch Each Batch of $^{64}CuCl_2$
Radiochemical Purity	≥90 %	HPLC analysis (see QCP 106)	Pre-release; each batch
Radiochemical Identity	Radioactive peak and standard (or co-injection) mass peak retention times must agree by ± 10%	HPLC analysis (see QCP 106)	Pre-release; each batch
Specific Activity	≥ 600 µCi/µg	Dose calibrator assay divided by peptide conjugate ^{64}Cu-LLP2A mass (15 µg)	Pre-release; each batch
Bacterial Endotoxin	≤ 175 EU/V (where V is the maximum total dose)	Chromogenic method (see QCP 501)	Pre-release; each batch
Sterility	Sterile (No visible growth)	Visual observation (see QCP 502)	Post-release; each batch
Cell Binding	Blocking to be ≥ 65 %	Cell binding assay (see QCP 1011)	Post-release; each batch
Radionuclidic Purity	≥ 99.0%	Gamma spectroscopy (see QCP 204)	Annual

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
  - Pre-clinical safety testing performed in animals an in vitro
  - Pharmacological studies include target/receptor profiling
  - Characterization of primary pharmacology in a relevant model
  - If sufficient information is known about a class of compounds, a careful literature search can reduce the need for additional studies.
  - Toxicology for the eIND more limited than traditional IND since microdose studies ($\leq$ 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
  - Single-use products can omit long-term, repeat dose safety studies
  - Biological imaging agents require pharmacokinetic data, HAMA, HAHA, or HACA levels
- Nonclinical Safety Assessments: e.g. contrast agents
  - Safety pharmacology studies: Pre-IND meeting with FDA prior to IND submission
  - Reproductive toxicology can be limited - Pre-IND meeting
  - Carcinogenicity studies – Pre-IND meeting

- Plan Pre-IND meeting with FDA

https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-and-industry-assistance-frequently-asked-questions-pre-investigational-new-drug-ind

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
  - Alternates could be University departments
    e.g. WU Comparative Medicine
  - University of Missouri Veterinary Medicine—performs toxicology studies
  - 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
  - NIC Experimental Therapeutics (NEXT) http://next.cancer.gov/
  - Bridging Interventional Development Gaps https://search.usa.gov/search?utf8=%E2%9C%93&affiliate=commonfund&query=grants+for+toxicology+studies&commit=Search

WU Comparative Anatomy Lab

- Follow FDA and ICH Guidance:
  - ICH Guidelines M3 (2R) 2009 https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-2.pdf
- FDA Guidance M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals 2013 Questions and Answers(R2)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization

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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