CIP/NCI Qualification Information

University of Wisconsin-Madison

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Table of Contents

SAMPLE

University of Wisconsin PET Tracer Program

There is a long history of PET radiotracer production in the Molecular Imaging Program at the University of Wisconsin School of Medicine and Public Health. Multiple Investigational New Drug (IND) applications have been held in the past, such as IND #28-571 for [F-18]-2-fluorodeoxyglucose used for CNS and tumor imaging, IND #30-456 for [N-13]-ammonium chloride used for cardiac perfusion imaging and IND #29-896 for [^{11}C]-carbon monoxide used for cardiac blood pool imaging. To date, we hold several active INDs and DMFs along with a number of new INDs and DMFs targeted for submission by the end of 2015. A list of active and anticipated FDA applications is provided in the Summary Table below.

In the next several months we will occupy a newly constructed Radiopharmaceutical Production Facility (RPF) of nearly 2000 sq. ft. in the Wisconsin Institutes for Medical Research building (WIMR). This new facility is designed to satisfy FDA's CGMP requirements for radiopharmaceutical production. The RPF is equipped with 6 hot cells connected to the cyclotron located across the hall, multiple laminar flow hoods for drug preparation, a separate area for quality control, and a USP <797> compliant Radiopharmacy to allow shipping CGMP compliant molecular imaging agents to other medical centers.

University of Wisconsin-Madison PET Tracer Specifications

We certify that our PET Tracers used in NCI sponsored multicenter human clinical studies meet the specifications as specified in the CIP/NCI INDs. To qualify, we are providing copies of the specifications contained in our Chemistry, Manufacturing, and Controls (CMC) Data that has been submitted to FDA either in a Type II Drug Master File (DMF) or Investigational New Drug Application (IND). Also included are copies of acknowledgment letters provided by U.S. FDA and any respective Letters of Authorization.

Summary of University of Wisconsin- Madison PET Tracers for Clinical Studies

	Tracer	Imaging/Indication	IND/DMF holder	IND/DMF #	Status (target date)
1	[^{18}F] FLT	Multiple	Perlman	DMF #28697	Active
	[^{18}F] FLT	Prostate and other solid malignancies	Perlman	IND #124753	Active
	[^{18}F] FLT	Adult Acute Myeloid Leukemia (EAI141)	LOA NCI	IND# 71,260	Active
2	[^{18}F] FES	Multiple	Perlman	DMF #29208	Active
	[^{18}F] FES	Metastatic breast cancer (EAI142)	Fowler	IND #127326	Active
3	[^{124} I] NM404	Lung, Glioblastoma, Other solid tumors	Perlman	IND #67287	Active
4	[^{18}F]Mefway Multiple	5HT1A serotonin	Christian	IND #118418	Active
5	[^{18}F]Nifene Multiple	Nicotinic acetylcholine	Christian	IND #119770	Active
FUTURE MOLECULAR AGENT IND/DMFs					
6	[^{18}F] DCFPyL	Multiple	Cho	DMF # TBD	(10/2015)
	[^{18}F] DCFPyL	Prostate imaging	Cho	IND # TBD	(10/2015)
7	[^{18}F] FFNP	Multiple	Perlman	DMF # TBD	(11/2015)
	[^{18}F] FFNP	Breast imaging	Fowler	IND # TBD	(11/2015)
8	[^{68}Ga] DOTATOC	Multiple	Cho	DMF # TBD	(12/2015)
	[^{68}Ga] DOTATOC	Prostate cancer	Cho	IND # TBD	(12/2015)

SAMPLE

University of Wisconsin-Madison PET Tracers for Clinical Studies

1. An FLT radiotracer is produced at the University of Wisconsin-Madison to support an IND (IND #124753) for FLT PET/CT in patients with multiple malignancies.

   A Type II DMF is on file at CDRH/FDA which contains Chemistry, Manufacturing, and Control Data and Specifications for the production of FLT. FDA acknowledgment letters are provided to demonstrate notification from FDA for the IND & DMF filing numbers.

   [^{18}F] FLT- Type II Drug Master File (DMF #28697) is on file at U.S. FDA
   a. Manufacturing process and final product specifications are on file with U.S. FDA
   b. Copy of the DMF (DMF #28697) acknowledgment letter is provided- *see* Attachment A
   c. Copy of the CIP/NCI LOA for FLT DMF #28687 will be obtained and provided
   d. Manufacturing/CMC Specifications for FLT is provided- *see* Attachment B

   [^{18}F] FLT- Investigational New Drug Application (IND #124753) is on file at U.S. FDA
   e. Copy of the IND (IND #124753) acknowledgment letter is provided- *see* Attachment C

   [^{18}F] FLT- will be used in our participation of the NCI ECOG-ACRIN trial (Protocol #: EAI141). The University of Wisconsin-Madison will participate in this multicenter study and manufacture [^{18}F] FLT under UW's active DMF (DMF #28697). A copy of the (DMF #28697) acknowledgment letter for FLT is provided in Attachment A. A copy of the letter of authorization for the FLT DMF has been submitted to FDA and NCI- *see* Attachment D. A copy of the Statement of Commitment Letter for NCI is provided- *see* Attachment E.

2. An FES radiotracer is produced at the University of Wisconsin-Madison and is intended for use in our participation of a NCI ECOG/ACRIN trial (Protocol #EAI142). A cross-reference letter of authorization from NCI has been provided to allow access Pharmacology/Toxicology information provided in NCI's IND (IND #79005) and is attached. A Type II DMF is on file at CDRH/FDA which contains Chemistry, Manufacturing, and Control Data and Specifications for the production of FES. FDA acknowledgment letters are provided to demonstrate notification from FDA for the IND & DMF filing numbers. We anticipate this to be an active IND after the 30 day FDA review period which extends until August 21, 2015.

   [^{18}F] FES- Type II Drug Master File (DMF #29208) is on file at U.S. FDA
   a. Manufacturing process and final product specifications are on file with U.S. FDA
   b. Copy of the DMF (DMF #29208) acknowledgment letter is provided- *see* Attachment F
   c. Copy of the CIP/NCI LOA for FES IND #79005 is provided- *see* Attachment G
   d. Manufacturing/CMC Specifications for FES is provided- *see* Attachment H

   [^{18}F] FES- Investigational New Drug Application (IND #127326) is on file at U.S. FDA
   e. Copy of the IND (IND #127326) acknowledgment letter is provided- *see* Attachment I

3. NM404 is a molecular imaging agent produced at the University of Wisconsin-Madison to support an IND (IND #67287) for lung, glioblastoma, and all other solid tumors.

   [^{124} I] NM404- Investigational New Drug Application (IND #67287) is on file at U.S. FDA.
   a. Manufacturing process and final product specifications are on file with U.S. FDA
   b. Copy NM404 IND (IND #67287) Annual Report is provided- *see* Attachment J

SAMPLE

4. [^{18}F]Mefway Multiple, is a serotonin 1A receptor (5HT1A) molecular imaging agent produced at the University of Wisconsin-Madison to support an IND (IND #118418) for brain imaging studies.

   [^{18}F]Mefway Multiple- Investigational New Drug Application (IND #118418) is on file at U.S. FDA.
   a. Manufacturing process and final product specifications are on file with U.S. FDA
   b. Copy of the IND (IND #118418) acknowledgment letter is provided- *see* Attachment K

5. [^{18}F]Nifene Multiple, is a nicotinic acetylcholine molecular imaging agent produced at the University of Wisconsin-Madison to support an IND (IND #119770) for brain imaging studies.

   [^{18}F]Nifene Multiple- Investigational New Drug Application (IND #119770) is on file at U.S. FDA.
   a. Manufacturing process and final product specifications are on file with U.S. FDA
   b. Copy of the IND (IND #119770) acknowledgment letter is provided- *see* Attachment L

FUTURE MOLECULAR AGENT IND/DMFs

6. A radiotracer, [^{18}F] DCFPyL will be produced at the University of Wisconsin-Madison and regulated under an IND to be used for the evaluation of patients requiring prostate imaging.

   A Type II DMF will be filed at CDRH/FDA which to contain Chemistry, Manufacturing, and Control Data and Specifications for the production of [^{18}F] DCFPyL. FDA acknowledgment letters will be provided to demonstrate FDA approval of the IND & DMF applications.
   a. Manufacturing process and final product specifications will be on file at U.S. FDA
   b. Copy of [^{18}F] DCFPyL Investigational New Drug acknowledgment letter to be provided
   c. Copy of [^{18}F] DCFPyL Type II Drug Master File acknowledgment letter to be provided

   The supporting FDA applications are targeted for submission in October 2015.

7. A molecular imaging agent, [^{18}F] FFNP will be produced at the University of Wisconsin-Madison and regulated under an IND to be used for breast cancer imaging.
   a. Manufacturing process and final product specifications will be on file at U.S. FDA
   b. Copy of [^{18}F] FFNP Investigational New Drug acknowledgment letter to be provided
   c. Copy of [^{18}F] FFNP Type II Drug Master File acknowledgment letter to be provided

   The supporting FDA applications are targeted for submission in November 2015.

8. Use of [^{68}Ga] DOTATOC for detection of recurrence prostate cancer post-prostatectomy will be produced at the University of Wisconsin-Madison and regulated under an IND.
   a. Manufacturing process and final product specifications will be on file at U.S. FDA
   b. Copy of [^{68}Ga] DOTATOC IND acknowledgment letter will be provided
   c. Copy of [^{68}Ga] DOTATOC Type II DMF acknowledgment letter will be provided

   The supporting FDA applications are targeted for submission in December 2015.

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Checklist for Approval of Manufacturing Site for [F-18]FLT

Checklist for Approval of Manufacturing Site Not Previously Approved by NCI CIP to Manufacture a Specific PET agent.

This Checklist can be used to submit updates or corrections.

Documents to be submitted by the trial PI through CTEP PIO to the CIP/NCI	**Included**	**Comment[1]**
1. Site has successfully filed PET NDA or ANDA for clinical use or has ≥ 3 active PET INDs (not RDRC). Cover sheet for the most recent Annual Reports submitted for each one. If none yet, FDA acknowledgement letter provided to CIP.	□ Yes □ No	Pages 3-6, 11, 17, 27, 35, 47, 83, 87
2. Site has submitted latest FDA inspection report (Establishment Inspection Reports (EIR) and/or Form FDA-483) for their INDs, NDA or ANDA to CIP if any have been conducted.	□ Yes □ No	N/A
3. Site has an active DMF or IND for this PET agent. Copy of last Annual Report submitted to CIP. If none yet, FDA acknowledgement letter provided to CIP.	□ Yes □ No	Page 11 & 13
4. Site can meet the same specifications in the NCI IND including expiration dating. Specification Sheet submitted to CIP with a comparison of the specifications	□ Yes □ No	Page 7
5. Site makes consistent product. Analytical Test Results submitted for last 12 months batch analyses, passed or failed. At least three lots must pass and no more than 10% fail for other than equipment failure.	□ Yes □ No	Page 11
6. Site commits to PET manufacturing stipulations (NCTN Group/Consortium/ ETCTN Study PI/CIP Pre-qualification Steps) for lifecycle of IND trial(s). Statement of Commitment on official letterhead provided to CIP.	□ Yes □ No	Page 15
7. Site provides CIP through trial PI with Letter of Authorization to Cross Reference to Site's DMF or IND, in order to include reference to this new/additional manufacturing information in CIP's IND. Site files letter with their application. CIP files letter with their IND for the Clinical Trial.	□ Yes □ No	Page 14
8. NCTN group/Consortium/ETCTN Study PI notifies CIP that they are satisfied with Site's manufacturing qualifications and commitment to compliance responsibilities and submits all of this documentation through CTEP PIO. *(**Stipulation list to be created by Group/CIP* See Points to Consider, on following page.**)*	□ Yes □ No	
9. CIP notifies site that the site is approved to supply PET agent for IND clinical trial.	□ Yes □ No	

*Key Points of Reference for Stipulation List:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM266640.pdf
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm
http://www.gpo.gov/fdsys/granule/CFR-2010-title21-vol4/CFR-2010-title21-vol4-part212/content-detail.html
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM277416.pdf
http://www.gpo.gov/fdsys/pkg/CFR-2010-title21-vol4/pdf/CFR-2010-title21-vol4-part212.pdf

[1]See respective pages of this NCI CIP Qualification Information Package.

SAMPLE

Product Specifications for [F-18]FLT

[^{18}F]FLT FOR INJECTION- 18F-3'-Fluoro-3'-deoxythymidine in Phosphate Buffered Saline, for injection, containing 8% Ethanol, 0.01M Phosphate and 0.15M Saline.

NOTE: University of Wisconsin-Madison maximum injection volume (or total dose) for FLT is ≤ 10 mL.

Product Specifications for [F-18]FLT

Test	Specification	Proposed site specifications	Comments
Radiochemical Purity (TLC):	Rf = 0.4—0.7 Purity ≥ 95%	N/A	See footnote[1]
Residual Solvent Levels:	Acetone < 5000 ppm Acetonitrile < 410 ppm DMSO < 5000 ppm	N/A < 400 ppm N/A	See footnote[2] See footnote[3] See footnote[2]
Radionuclidic Purity:	Measure half-life 100 – 120 minutes	Measure half-life 100 – 120 minutes	Identical
Bacterial Endotoxin Levels:	< 175 EU per dose	< 175 EU per dose	Identical
pH:	4.5– 8	6 – 8	See footnote[3]
Sterility:	no growth observed in 14 days	no growth observed in 14 days	Identical
Residual Kryptofix® [2.2.2]:	< 50 µg/ mL Kryptofix®	< 50 µg/ mL Kryptofix®	Identical
Radiochemical Purity (HPLC):	> 95%	≥ 95% of the sum of all radioactive peaks	Identical
Chemical Purity (HPLC):	FLT < 0.61 µg/ml l	FLT < 6.1 µg/dose	UW has a more stringent specification; See footnote[3]
Chemical Purity (particulates)	Clear and Colorless	Clear, colorless and particulate free	Identical
Store at room temperature in a septum sealed, sterile, pyrogen-free glass vial with an expiration time of 8 hours		Store at room temperature in a septum sealed, sterile, pyrogen-free glass vial; expiry time of 6 hours	UW has adopted a more stringent expiration period

[1] UW relies on HPLC method to determine radiochemical purity.

[2] This solvent is not used in the UW production process for FLT and therefore no specification is established and this residual solvent is not tested for in the final product.

[3] UW specification for chemical purity is more stringent than that of NCIs. UW maximum infusible volume or dose is not to exceed 10 mL. Chemical Purity by HPLC presented as µg/mL is as follows:

FLT < 0.61 µg/mL

SAMPLE

Checklist for Approval of Manufacturing Site for [F-18]FES

Checklist for Approval of Manufacturing Site Not Previously Approved by NCI CIP to Manufacture a Specific PET agent.

This Checklist can be used to submit updates or corrections.

Documents to be submitted by the trial PI through CTEP PIO to the CIP/NCI	**Included**	**Comment[1]**
1. Site has successfully filed PET NDA or ANDA for clinical use or has ≥ 3 active PET INDs (not RDRC). Cover sheet for the most recent Annual Reports submitted for each one. If none yet, FDA acknowledgement letter provided to CIP.	□ Yes □ No	Pages 3-6, 11, 17, 27, 35, 47, 83, 87
2. Site has submitted latest FDA inspection report (Establishment Inspection Reports (EIR) and/or Form FDA-483) for their INDs, NDA or ANDA to CIP if any have been conducted.	□ Yes □ No	N/A
3. Site has an active DMF or IND for this PET agent. Copy of last Annual Report submitted to CIP. If none yet, FDA acknowledgement letter provided to CIP.	□ Yes □ No	Pages 27 & 35
4. Site can meet the same specifications in the NCI IND including expiration dating. Specification Sheet submitted to CIP with a comparison of the specifications	□ Yes □ No	Page 9
5. Site makes consistent product. Analytical Test Results submitted for last 12 months batch analyses, passed or failed. At least three lots must pass and no more than 10% fail for other than equipment failure.	□ Yes □ No	Page 27
6. Site commits to PET manufacturing stipulations (NCTN Group/Consortium/ ETCTN Study PI/CIP Pre-qualification Steps) for lifecycle of IND trial(s). Statement of Commitment on official letterhead provided to CIP.	□ Yes □ No	TBD
7. Site provides CIP through trial PI with Letter of Authorization to Cross Reference to Site's DMF or IND, in order to include reference to this new/additional manufacturing information in CIP's IND. Site files letter with their application. CIP files letter with their IND for the Clinical Trial.	□ Yes □ No	Page 31
8. NCTN group/Consortium/ETCTN Study PI notifies CIP that they are satisfied with Site's manufacturing qualifications and commitment to compliance responsibilities and submits all of this documentation through CTEP PIO. *(**Stipulation list to be created by Group/CIP* See Points to Consider, on following page.**)*	□ Yes □ No	
9. CIP notifies site that the site is approved to supply PET agent for IND clinical trial.	□ Yes □ No	

*Key Points of Reference for Stipulation List:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM266640.pdf
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm
http://www.gpo.gov/fdsys/granule/CFR-2010-title21-vol4/CFR-2010-title21-vol4-part212/content-detail.html
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM277416.pdf
http://www.gpo.gov/fdsys/pkg/CFR-2010-title21-vol4/pdf/CFR-2010-title21-vol4-part212.pdf

[1]See respective pages of this NCI CIP Qualification Information Package.

SAMPLE

Product Specifications for [F-18]FES

[^{18}F]FES FOR INJECTION- [^{18}F]FES, 16 alpha-[^{18}F]-fluoro-17-beta-estradiol in Phosphate Buffered Saline, for injection, containing 10% Ethanol, 0.075M Phosphate and 0.075M Saline.

NOTE: University of Wisconsin-Madison maximum injection volume (or total dose) for FES is ≤ 10 mL.

Product Specifications for [F-18]FES

Test	Specification	Proposed site specifications	Comments
Radiochemical Purity (TLC):	Rf > 0.5 Purity ≥ 95%	N/A	See footnote[1]
Residual Solvent Levels:	Acetone < 5000 ppm Acetonitrile < 400 ppm	N/A < 400 ppm	See footnote[2] Identical
Radionuclidic Purity:	Measure half-life 100 – 120 minutes	Measure half-life 100 – 120 minutes	Identical
Bacterial Endotoxin Levels:	< 175 EU per dose	< 175 EU per dose	Identical
pH:	6 – 8	6 – 8	Identical
Sterility:	No growth observed in 14 days, also must pass filter integrity test	No growth observed in 14 days, also must pass filter integrity test	Identical
Residual Kryptofix® [2.2.2]:	< 50 µg/ mL Kryptofix®	< 50 µg/ mL Kryptofix®	Identical
Radiochemical Purity (HPLC):	> 95%	≥ 99% of counts must be in 511, 1022 keV photopeaks and the compton scatter peak	UW has a more stringent specification
Chemical Purity (HPLC):	FES < 5 µg per injected dose, other UV absorbing impurities beyond HPLC void volume (280 nm) ≤ 5 µg per injected dose	FES < 5 µg/dose Other UV (280 nm) peaks < 5 µg/dose	Identical
Chemical Purity (particulates)	Clear and Colorless	Clear, colorless and particulate free	Identical
Store at room temperature in a septum sealed, sterile, pyrogen-free glass vial with an expiration time of 8 hours		Store at room temperature in a septum sealed, sterile, pyrogen-free glass vial; expiry time of 4 hours	UW has adopted a more stringent expiration period

[1] UW relies on HPLC method to determine radiochemical purity.

[2] This solvent is not used in the UW production process for FES and therefore no specification is established and this residual solvent is not tested for in the final product.

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ATTACHMENTS

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