CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200655Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 20065
Resubmission
Review Date: 04/19/2016

Drug Name/Dosage Form	Fluorodopa F-18 Injecion
Strength	(b) (4) mCi/mL
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	The Feinstein Institute for Medical Imaging, Nanhasset, NY 11030
Representative	Thomas Chaly, Ph.D.

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505(b)(2)**

2. **RELATED/SUPPORTING DOCUMENTS:**

   A. DMFs:

Table 1 Drug Master Files (DMFs)

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	III	(b) (4)		3	2/24/2009 Adequate	"
	III			3	Adequate, amended on 4/16/2013, new information under review (DARRTS)	"

[1]DMF reviewed
[2]Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3]Reviewed previously and no revision since last review

   B. Other Documents: *IND, RLD, or sister applications*
   IND 78861 ("FDOPA" held by Feinstein Institute.)

3. **CONSULTS: N/A**

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber, Ph.D.	DNAPAPI/NDBII
Drug Product	Martin Haber, Ph.D.	DNAPAPI/NDBII
Process	N/A	N/A
Microbiology	Dupeh Palmer, Ph.D.	OPQ/OPF/DMA/MABIII
Facility	Michael Klapal	OMPT/OPQ/OPF/DIA
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	N/A	N/A
Application Technical Lead	Eldon E. Leutzinger, Ph.D.	ONDP/Branch VII/Division II
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Analysis (EA)	Martin Haber, Ph.D. (exclusion requested and accepted)	DNAPAPI/NDBII
Microbiology	Palmer, Dupeh, Ph.D.[1]	OPQ/OPF/DMA/MABIII
Pharm/Tox	Sally Hargus, Ph.D.	OND/ODEIV/DMIP

(1) Resubmission. Robert Mello, Ph.D. performed review of the complete response.

Table 2 Documents (Resubmission)			
DOCUMENT	**DOCUMENT DATE**	**DESCRIPTION**	**Section/reviewer**
Resubmission	12/15/2015	NDA Resubmission	Martin Haber, Ph.D.
Amendment	02/16/2016		"
Amendment	03/15/2016		"

Table 2 Documents (Previous)			
DOCUMENT	**RECEIPT DATE**	**DESCRIPTION**	**Section/reviewer**
Original NDA	10/22/2010	Resubmission after RTF in 2010	Martin Haber, Ph.D.
CMC Amendment	01/14/2013		"
CMC Amendment	06/07/2013		"
FDA Complete Response Letter	10/22/2013		N/A

Executive Summary

I. Recommendations

Approval

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

At the end of the first CMC review (06/14/20130, the major issues that remained unresolved were (1) the absence of a CGMP supply of the precursor ([redacted]), (2) absence of a test for chirality of drug substance precursor, (3) absence of justification for non-USP conforming product pH, (4) need for finalization of the specifications for the drug product, and (5) absence of validation of the drug product HPLC chiral identity and purity.

Resolution of Precursor Issues – GMP Supply (1):

Currently, [redacted] manufactures the precursor ([redacted]) as a research grade material, and without a DMF. The necessity for production of precursor ([redacted]) under CGMP is based on the fact that the drug substance ([^{18}F]fluorodopa) is [redacted] That causes the level of scrutiny for the precursor to rise to the level of a drug substance. In lieu of finding another manufacturer of the precursor, who can do this under CGMP, arrangement has been made by the sponsor to proceed with [redacted], shifting from research grade to GMP-grade precursor, although implementation will not be able to be effected until after the PDUFA date of June 15, 2016. However, the arrangement includes a Post-Marketing Commitment made by the sponsor, with supporting chemical data (collected by [redacted]) to be provided in a Post-Approval Supplement to the NDA. The decision to allow for the Post-Marketing Commitment, along with the PAS is based on [redacted] experience with successful production of [redacted] (as research grade material), [redacted], where the GMP-grade material is not required. Further support for the PAS approach under the Post-Marketing Commitment is derived from the fact that [redacted] has been inspected by the FDA several times for [redacted] precursor, used in PET production of [redacted], under approved NDA's/ANDA's. **It is agreed by the CMC team that the agreements under the Post-Marketing Commitment should be fulfilled within one year from approval of the NDA.**

A teleconference with Dr. Chaly was held on 04/14/2016 to clarify the timeframe and how the precursor will be provided from [redacted]. **Subsequent to this teleconference, a letter from the sponsor (04/14/2016) confirmed that they are "committed to submit a supplement by the end of July or as soon as we receive the GMP manufactured precursor and the CMC information from [redacted]."** In the letter (04/14/2016), including the CMC documentation supplied by [redacted], the supplement will also contain the information regarding the [redacted] production that [redacted] is using to manufacture the precursor under GMP procedure:

[redacted]

With the PAS and the Post-Marketing Commitment, along with supporting data in the supplement, the precursor GMP supply issue (1) for CMC is resolved. A copy of the commitment made by Dr. Chaly is appended to this executive summary (page 5). **Chirality Test Issue (2)** is resolved with establishment of a suitable chiral test for the precursor.

Resolution of Non-USP pH Issue (3):

The sponsor claimed that the drug product is [redacted]. Supporting data has been provided to support the lower pH, and it is deemed to be acceptable.

Resolution of Issues (4) and (5) for Test Methods and Specifications:

validation data has been provided to address the issue (4) for product HPLC chiral identity and purity, and (5) the finalization of drug product specifications. **In conclusion, the sponsor has adequately addressed all the issues in the CMC sections of the CR letter (10/22/2013). As well, all of the issues pertaining microbiology have been deemed resolved (see Microbiology Review, Dupeh Palmer, 04/13/2016). The facilities are determined to be acceptable to support approval of NDA 200655 (Facilities Review, Michael Klapal, 04/15/2016).**

2. Action letter language, related to critical issues such as expiration date

There will need to be a statement (PMC) in the action letter regards the Post-Marketing Commitment. Wording on the language for the PMC statement is under consideration by the CMC team, and should include the projected time frame of one year to fulfill the agreements under the Post-Marketing Commitment.

3. Benefit/Risk Considerations

From a CMC perspective, the **final Risk Assessment rating is Low**. See the Risk Assessment table at the end of this Executive Summary.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

Fluorodopa F18 (USAN). 6-[^{18}F]fluorodopa. Adequate for Drug Substance (Refer to CMC Review #2 (Resubmission), 04/15/2016) and CMC Review #1 (06/14/2013).

B. Drug Product [Established Name] Quality Summary

Fluorodopa F-18 (Established Name). Refer to CMC Review #2 (Resubmission), 04/15/2016, and CMC Review #1 (06/14/2013).

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Product	Fluorodopa F-18 Injection
Non Proprietary Name of the Drug Substance	Fluorodopa F-18
Proposed Indication(s) including Intended Patient Population	Radioactive diagnostic agent for use with PET to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian disease
Duration of Treatment	Single dose
Maximum Daily Dose	(b) (4) 5.0 mCi
Alternative Methods of Administration	N/A

Biopharmaceutics Considerations

N/A

D. Novel Approaches

N/A

E. Any Special Product Quality Labeling Recommendations: N/A

F. Process/Facility Quality Summary (see Attachment A)

N/A

G. Life Cycle Knowledge Information (see Attachment B)

N/A

(b) (4)

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Risk Assessment - Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA[1]	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation[1,3]**	**Lifecycle Considerations/ Comments****
Radionuclidic Identity/purity	-Target purity -Process parameters (cyclotron)	2 (low)	None necessary	2 (low)	N/A
Radiochemical identity	-Precursor ID/purity -Lack of chirality test & validation; -acceptance criterion	50 (medium)	-Commitment to produce precursor under CGMP -Implementation of chiral test, & validation, and acceptance criterion	2 (low)	Post-marketing commitment to establish CGMP for precursor
Radiochemical purity	-Precursor ID/purity -Lack of chirality test & validation; -acceptance criterion	50 (medium)	"	2 (low)	"
Chemical purity	-Precursor purity -Stability of drug product -Limit for (b) (4)	36 (medium)	"	2 (low)	"
Strength (mCi/mL)	-Process parameters -Scale (RAD input) -RAD yield	2 (low)	None necessary	2 (low)	N/A
Specific activity (SA)	-RAD yield -Radionuclide SA	2 (low)	None necessary	2 (low)	N/A
Osmolality	-Formulation	2 (low)	None necessary	2 (low)	N/A
Appearance	-Stability -Formulation process	2 (low)	None necessary	2 (low)	N/A
pH	-formulation & its stability	5 (low)	Data provided to support non-USP compliant pH limit[2]	2 (low)	N/A

1. Specifications for the drug product are now finalized
2. Sponsor claims that the drug product is (b) (4) The sponsor also states that the USP monograph for the product has been

withdrawn for revision. Supporting data is provided in the responses to support the lower pH, and it is deemed acceptable.

3. Mitigation for Radiochemical Identity, Radiochemical Purity, Chemical Purity and pH was effected. No mitigation was found necessary for Radionuclidic Identity/Purity, since these CQA's were well under control as evidenced in the original submission. Since it the RPN is < 25 for each Attribute/CQA, the **final Risk Assessment rating for this product is Low**.

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E. Leutzinger -A

Digitally signed by Eldon E. Leutzinger -A
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Date: 2016.04.19 14:07:15 -04'00'

NDA 200-655
Resubmission

Fluorodopa F-18 Injection

The Feinstein Institute for Medical Research

Martin Haber, Ph.D.
Office of New Drug Quality
OPQ

For
Division of Medical Imaging Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-655

2. REVIEW #2

3. REVIEW DATE: April 15, 2016

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	10/22/2012 (Resubmission after RTF in 2010)
CMC Amendment	1/14/2013
CMC Amendment	6/7/2013
CMC Review #1	6/13/2013
FDA Complete Response Letter	10/22/2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA Resubmission	12/15/2015
Amendment	2/26/2016
Amendment	3/15/2016

7. NAME & ADDRESS OF APPLICANT:

Name: The Feinstein Institute for Medical Research

Address: 350 Community Dr, Manhasset, NY 11030

Chemistry Assessment Section

Representative: Thomas Chaly, Ph.D.

Telephone: 516-562-1042

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Fluorodopa F-18
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (NME)
- Submission Priority: Standard review

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Positron Emission Tomography (PET) Product - Diagnostic Imaging Agent for Parkinson's disease

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 5-100 mCi per vial

13. ROUTE OF ADMINISTRATION: Intravenous Injection

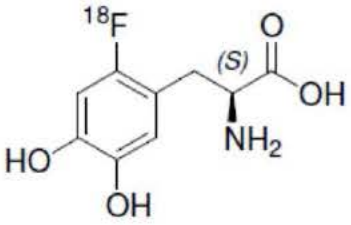
14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: $C_9H_{10}FNO_4$

Charge: 0

Mass: 214.18098

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	2/24/2009	
	III			3	Adequate, amended on 4/16/2013, new information under review (DARRTS)		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78861	This IND is for product name "FDOPA" held by the Feinstein Institute. Note: A DARRTS search did not find this IND under the product name "fluorodopa". (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Manufacturing Facilities	Approval	4/13/2016	Dr. M. Klapal
Pharm/Tox	Approval	6/10/2013	Dr. S. Hargus
Quality Biopharm	NA		
Methods Validation	NA (product is radioactive)		
DMEPA	Pending		
EA	Exclusion requested and accepted	6/13/2013	Dr. M. Haber
Microbiology	Complete Response Approval (Resubmission)	6/4/2013 3/3/2016	Dr. R. Mello Dr. D. Palmer

The Chemistry Review for NDA 200-655

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval, based on resolved chemistry deficiencies and a satisfactory overall facilities cGMP recommendation in Panorama

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

See Review #1.

B. Description of How the Drug Product is Intended to be Used

See Review #1.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended because the sponsor has responded adequately to the CMC sections of the CR letter sent 10/22/2013. Specifically, 1) the specifications for the drug product have been finalized, 2) a test for the chirality of the drug substance precursor has been established, 3) data justifying a non-USP conforming product pH has been provided and 4) validation data for the drug product HPLC chiral identity and purity method has been provided. 5) A Post-Marketing Commitment has been made with the sponsor that the precursor manufacturer ((b) (4)) will apply cGMP controls to the synthesis of the non-radioactive precursor and that supporting chemical data will be supplied in a PA supplement to the NDA.

III. Administrative

A. Reviewer's Signature

Martin Haber, Ph.D.
Chemist/ONDP/OPS/CDER
4/15/16

Martin T. Haber -S

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B. Endorsement Block

Eldon Leutzinger, Ph.D.
CMC Lead- DMIP/ONDP/OPS/CDER
Date

Danae Christodoulou, Ph.D.
Branch Chief –BVI/ONDP/OPS/CDER
Date

Danae D. Christodoulou -S

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Product Quality Microbiology Review

March 3, 2016

NDA: 200655

Drug Product Name
Proprietary: N/A
Non-proprietary: Fluorodopa [F-18] Injection

Review Number: #3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/15/15	12/15/15	N/A	N/A*
12/15/15	12/16/15		

* This review is not assigned in Panorama or DARRTS. The reviewer received an email notification of the assignment.

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
11/22/12	1	6/4/13
8/13/13	2	8/30/13
8/21/13		

Applicant/Sponsor
Name: The Feinstein Institute for Medical Research
Address: 350 Community Drive, Manhasset, NY 11030
Representative: Thomas Chaly Ph.D.
Telephone: 516-562-1042
Fax: 516-562-1041

Name of Reviewer: Dupeh Palmer, Ph.D.

Conclusion: The submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(2)

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product

3. MANUFACTURING SITE:
The Feinstein Institute for Medical Research
Cyclotron/Radiochemistry
350 Community Drive
Manhasset, NY 11030

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile injectable [F-18] PET drug; intravenous administration, 0.42 - 8.33mCi/mL, packaged in a 20mL multidose vial. The vial is packaged in a (b) (4) container for shielding from radiation.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Positron Emission Tomography (PET) radiodiagnostic imaging agent

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Filing Review DARRTS dated 11/7/12
- Microbiology reviews #1 and # 2 dated 6/4/13 and 9/3/13

C. REMARKS: This review covers responses to deficiencies found in the previous 9/3/13 review.

Filename: 200655a3.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

[redacted]

B. Brief Description of Microbiology Deficiencies – None identified.

C. Assessment of Risk Due to Microbiology Deficiencies - No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/ Dupeh Palmer, Ph.D.
Microbiology Branch Chief/ Division of Microbiology Assessment - Branch 3/Stephen Langille, Ph.D.

C. CC Block
cc: Panorama review platform

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Dupeh R. Palmer-ochieng -S

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Date: 2016.04.13 08:52:59 -04'00'

Stephen E. Langille -S

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Memorandum

Date October 15, 2013

From Linda Ng, Ph.D., Compliance Officer
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment

Subject Non-concurrence with New York District Office (NYK-DO) Withhold Recommendation for NDA 200-655, Fluorodopa F18 Injection

Thru Tara Gooen, Acting Branch Chief
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment

To Danae Christodoulou, Acting Branch Chief
Branch VII
Division of New Drug Quality Assessment III

To Kevin Gonzalez, Pre-Approval Manager
ORA/New York District Office

Applicant: The Feinstein Institute for Medical Research
350 Community Dr
Manhasset, NY 11030

Manufacturer: North Shore/Long Island Jewish Health System
The Feinstein Institute for Medical Research
Manhasset, NY, 11030
FEI: 3004971261

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) and GMP inspection conducted by New York District (NYK-DO) and CDER investigators from May 6 to 9, 2013 at the North Shore/Long Island Jewish Health System facility. DGMPA has also reviewed the firm's (May 28, August 13, August 21, and September 16. 2013) written responses to the FDA Form-483 observations. This inspection was initiated by NYK-DO to provide pre-approval coverage multiple applications, including NDA 200-655. According to the NYK-DO, the inspection was initially classified VAI with a withhold recommendation pending the firm's response.

After review of the four responses, DGMPA does not concur with the NYK-DO's initial withhold recommendation for NDA 200-655. NYK-DO recommended withholding approval of this application due to product specific deficiencies. The FDA Form-483 included ten observations with the first two being the most significant, product specific observations

impacting application action. The following discussion highlights the first two observations specific to NDA 200-655, Fluorodopa F18 Injection, 5-100 mCurie per vial.

Observation 1:
You did not reject the batch of a PET drug product that did not conform to specifications.

Specifically,
For the Sodium Fluoride F-18 Injection Drug Product, the radioactive assay acceptance criteria listed in the NDA submission is (b) (4) mCi/ml. However, validation batch numbers 032612-1 and 040312-1 have assay values of (b) (4) mCi/ml and (b) (4) mCi/ml, respectively.

Firm response to observation 1: In the May 28th, 2013 response, the sponsor claimed that all future validation runs will "conform to all specifications". The sponsor explained their misunderstanding of performing a spiking study for validation using amount higher than the proposed acceptance criterion. The data resulted in outside the criterion range. They repeated the studies and submitted the data including analytical method validation to support SOPs V007, NAF003, FDOPAQC002 and QC011 in the August 21, 2013 response.

NYK-DO evaluation of firm's response: NYK-DO supported the withhold recommendation based on the review of the May 28th, 2013 response which outlined proposed corrective actions. NYK-DO may not have a chance to evaluate the later firm responses which captured completed corrective actions.

CDER/OMPQ/DGMPA evaluation of firm's response: The sponsor's updated data confirmed their statement of the high assay values being due to the addition of drug substance outside of the high end of the acceptance criterion. The data and explanation in the August 21, 2013 response was reviewed and appear acceptable.

Conclusion: Response is acceptable

Observation 2:
Your firm lacks adequate production and process controls to ensure the consistent production of a PET drug that meets the applicable standards of identity, strength, quality and purity.

Specifically, for the Fluorodopa F-18 Injection Drug Product:

A) The final volume specification of (b) (4) ml in the NDA submission is inaccurate. Review of actual batch records show variable volumes (FDOPA011312 = 8.3ml and FDOPA011312-2 = 8.5ml).

B) The equipment list in the batch record is incomplete in that there is no reference to the following instruments: (b) (4).

C) Critical process parameters are not documented. For example, batch records do not include (b) (4).

D) (b) (4)

E) Your current microbiological monitoring program [redacted] is inadequate [redacted]

F) You failed to conduct microbiological monitoring [redacted].

G) [redacted].

Firm response to observation 2: To items A, B, and C, the sponsor agrees to add the data to the batch records. To item A, the master batch record was updated and an amendment was submitted on August 21, 2013. To item D, the [redacted] procedure was updated on August 13 and 21, 2013 amendments. [redacted] To items E and F, the sponsor submitted SOPs for microbiological monitoring. To item G, the sponsor will now [redacted].

NYK-DO evaluation of firm's response: NYK-DO supported the withhold recommendation based on the review of the May 28th, 2013 response which outlined proposed corrective actions. NYK-DO may not have had a chance to review the later amendments which captured completed corrective actions.

CDER/OMPQ/DGMPA evaluation of firm's response: The August 21, 2013 response addressed these 483 items. SOP V010 [redacted]) and data [redacted] were submitted. Also submitted were SOPs EC002, EC003, EC004, covering Environmental monitoring of microbial contamination and data for [redacted]. The [redacted] data in the August 13 and 21, 2013 responses were reviewed by Dr. Brenda Uratani as discussed below. Though there were some concerns with [redacted], the data submitted demonstrated adequate sterility assurance (see below for specific concerns). The sponsor claimed that [redacted]. All submitted data and SOPs appear reasonable.

Conclusion: Response is acceptable

General CGMP observations and response evaluation:

Ten observations were listed in the 483. The eight remaining observations covered general PET drug manufacturing operations. These observations included: not establishing adequate specifications for each PET drug product, not establishing appropriate written specifications for the identity, quality, and purity of components, not implementing procedures to ensure that all the equipment is suitable, and laboratory analytical methods are not suitable for their intended use. The firm has provided an adequate response to all remaining 483 items, as briefly discussed below.

The May 28, 2013 response provided explanation and commitments to a) update the master batch record with details, b) submit an amendment to the NDA correcting information as advised by the investigators, and c) validate the HPLC method(s) for radiochemical identity, purity and specific activity. No immediate correction was provided in the May 28, 2013 response.

The August 21, 2013 response indicated that the sponsor has provided supporting documents in the form of SOPs and supporting validation data for [redacted], the HPLC method, stability and expiry of the drug product. Additional information on the stability data of the product between the pH 3-6 was provided and found acceptable. SOPs were provided for

static and dynamic environmental monitoring of microbial contamination [redacted] (b) (4) where the drug product is prepared and appear acceptable.

All items except observation #9 were addressed in the August 21, 2013 response. Observation #9 cited the lack a signature of a qualified individual to release the PET product. In the Master Batch Record, the name/signature was needed for the following entries: Performed by, Releasing Authority and Quality Review performed by. In the appropriate documents, the MBR included the requirement for secondary signatures. This satisfies the concern expressed in observation #9.

The September 16, 2013 response provided the rest of the stability data validation that were not completed at the time of the August 21, 2013 response.

The review of all responses to the Form FDA-483 confirmed that all observations have been satisfactorily addressed and support an approval recommendation. NDMAB requests that NYK-DO communicate the following two points to the applicant, to be covered on the next inspection. These concerns do not support a recommendation to withhold approval at this time.

a. [redacted] (b) (4)

b. [redacted] (b) (4)

If you have any questions, please contact me at (301) 796-1426 or by email at linda.ng@fda.hhs.gov.

cc:
CMS #70040
Eldon Leutzinger, Ph.D., CMC Team Lead, OPS/ONDQA/DNDQAIII
Martin Haber, CMC Reviewer, OPS/ONDQA/DNDQAIII/BRVII

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/s/

LINDA L NG
10/15/2013

TARA R GOOEN
10/15/2013

Product Quality Microbiology Review

30 August 2013

NDA: **200-655**

Drug Product Name
Proprietary: None
Non-proprietary: Fluorodopa [F-18] Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
13 August 2013	14 August 2013	17 August 2013	20 August 2013
21 August 2013	22 August 2013	26 August 2013	26 August 2013

Submission History (for 2nd Reviews or higher):

Submit Date(s)	Microbiology Review #	Review Date(s)
22 October 2012	1	04 June 2013

Applicant/Sponsor
Name: The Feinstein Institute for Medical Research
Address: 350 Community Drive
Manhasset, NY 11030

Representative: Thomas Chaly Ph.D.
Chief, Cyclotron/Radiochemistry
Telephone: 516-562-1041

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(2)

2. SUBMISSION PROVIDES FOR: Marketing Authority

3. MANUFACTURING SITE: The Feinstein Institute for Medical Research
Cyclotron/Radiochemistry
350 Community Drive
Manhasset, NY 11030

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile injectable [F-18] PET drug; intravenous administration, 0.42 - 8.33mCi/mL, packaged in a 20mL multidose vial. The vial is packaged in a (b) (4) container for shielding from radiation.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Positron Emission Tomography (PET) Radiodiagnostic Imaging Agent

`

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Filing Review DARRTS dated 07 November 2012
- Microbiology review #1 dated 04 June 2013

C. REMARKS:

- A Late Cycle Meeting with the Applicant was held on 15 July 2013 and microbiology issues were presented and discussed.
- The 13 August 2013 submission is in response to an ONDQA and OPS Microbiology request (during an August 12, 2013 conference call) for the Applicant to submit their updated (b) (4) protocol prior to the PDUFA Action date of 22 October 2013. The responses are directly related to deficiency #3 of the June 4, 2013 review (the "R1" review)
- The 21 August 2013 submission is in response to the 483 Observations from the 06 May 2013 ORA/CDER DMPQ inspection. Observations #2A, #2E and #2F are directly related to analogous deficiencies in my R1 review and will be discussed here.
- Since the Applicant has not as yet responded (to the NDA file) to other Microbiology items discussed during the Late Cycle Meeting conference call (15 July 2013), this review will re-state those remaining Deficiencies found in the "R1" review plus any other additional deficiencies or comments that have been found in the current submissions.

filename: N200655N001R2

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies -

- (b) (4)
- The bacterial endotoxins assay is not adequately validated to address the low pH ((b) (4)) of the drug product.

C. Assessment of Risk Due to Microbiology Deficiencies – The non-pyrogenicity of the drug product cannot be fully assured due to the deficiencies in the assay validation.

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block_____

David Hussong, Ph.D.
Director, New Drug Microbiology Staff

C. CC Block

NDA 200-655

Product Quality Microbiology Assessment

During the initial review of this application (R1, dated 04 June 2013), the following deficiencies were noted:

1. As submitted in the application, the QC samples used for product sterility and bacterial endotoxins release testing may not be representative of the final drug product (b) (4) The Applicant should amend the submission as well as their internal procedures to clarify the process flow for the final steps of the process. The Applicant should specifically address the following:
   A. (b) (4)
   B. (b) (4)
   C. When and where are the QC samples removed?

(b) (4)

(b) (4)

4. Bacterial Endotoxins Assay: The gel clot assay method does not mention any measurement or recording the pH of the diluted sample or sample plus lysate mixture to determine if it is near the optimum pH (neutrality) for the gel clot assay. Additionally, no enhancement/inhibition data were provided to support the validity of the bacterial endotoxin assay method other than the test results from the three stability batches which simply listed the results as "PASS." For the pH assessment, we recommend that you (b) (4) Reference is made here to USP36 <85> Bacterial Endotoxins Test, "Preparation of Solutions". You should prepare and submit a development report in which such assay pH determinations are conducted for the full range of you pH specification (i.e., (b) (4)). We also recommend that you refer to USP36 <85> for the conduct of the "Test for Interfering Factors".

   You stated that you were qualifying the (b) (4) system for bacterial endotoxins testing. If you intend to use this assay system for product release, you are reminded to submit for review, prior to implementation of the test, the summary reports of the product specific qualification of this assay.

Each was discussed with the Applicant at the July 15, 2013 Late Cycle Meeting (LCM) teleconference. At that meeting the Applicant indicated that corrective actions were being (or had been) implemented and that they were preparing to submit amendments to address these issues as well as issues from the other disciplines.
Another teleconference occurred on August 12, 2013 between the Applicant, the Office of Compliance Inspection team and the CMC chemistry and microbiology reviewers to discuss the May 09, 2013 inspection items (483 citations) as well as the outstanding chemistry and microbiology issues.

The Applicant has submitted two amendments to the NDA 200655 file (submit dates: 13 August and 21 August) which attempted to address the above issues. Several, but not all of the issues have been resolved and these are discussed below. The original deficiency is shown in *italics*. The review of the Applicant's response is in normal type.

Item 1:

As submitted in the application, the QC samples used for product sterility and bacterial endotoxins release testing may not be representative of the final drug product (b) (4)

C. When and where are the QC samples removed?

Review of Applicant's response: In the 21 August 2013 submission the Applicant submitted a complete revision of the CMC portion of the application (a "tracked-changes" version, highlighting the changes, was also submitted). Section 3.2.S.4.1 *Specifications/Sampling Procedures* addressed item #1A-1C by stating that:

' (b) (4) ".

- Adequate -

Reviewer's Comment: The Applicant has clarified the product and process flow. (b) (4)

Item 2:

(b) (4)

Review of Applicant's response: These concerns were communicated to the applicant during the 15 July 2013 LCM. In the 21 August 2013 submission the Applicant submitted (to the NDA file) responses to the 483 inspection observations 2E and 2F which addressed these same issues. (b) (4) . The Table 1 below is an outline of their current program.

Table 1: Environmental Monitoring Program

(b) (4)

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/s/

ROBERT J MELLO
09/03/2013

DAVID HUSSONG
09/03/2013

The review properly notes that there remain outstanding deficiencies that the applicant should address prior to approval of the NDA. Additional advice is also provided.

Memorandum

Date: August 29, 2013

From: Martin Haber, Ph.D., Review Chemist

Subject: NDA 200655 August 21, 2013 Amendment

As a result of the Form 483 issued after the cGMP inspection in May 2013, the NDA sponsor, Dr Chaly, submitted a revised NDA CMC section and batch record on August 21, 2013 containing numerous typographical and editorial changes. This memo will briefly summarize the changes to the NDA relevant to the chemistry review and as impacted by observations or cGMP violations in Form 483.

The Form 483 listed 10 observations. Observation #1 and #6-10 concern cGMP and SOP's. Observation #2 led to a revision of the NDA description of the volume (b) (4). Therefore, the final drug product volume, (b) (4), was revised (b) (4). Observation #3 led to several NDA revisions regarding the specifications. Drug substance specifications are provided instead of the more usual drug product specifications for PET products. The observed pH of the drug product is routinely 3.5-4.0 whereas (b) (4). The NDA proposed specification range for the product pH is (b) (4). Adequate supporting stability data at different pH's is not provided. Also, the NDA was revised to specify the enantiomeric purity (> (b) (4)%) as well as the chemical purity of the drug substance. Regarding testing for a possible (b) (4) impurity, the acceptance limit was lowered to ≤ (b) (4) µg/mL, (b) (4). An additional specification on purity was added such that no single impurity can be > (b) (4)% of the total radioactivity. Finally, the radionuclidic purity specification was revised (b) (4). Observation #4 led to the statement in the cover letter that validation data are provided for the HPLC purity test. No validation data is in fact provided, but there is a validation plan. Observation #5 led to revised acceptance criteria for the precursor such that optical rotation is used to establish > (b) (4)% enantiomeric purity for the drug substance precursor.

The overall Office of Compliance (OC) recommendation is Withhold for this NDA 200655, as reported by the EES system. The chemistry, manufacturing and controls recommendation for this NDA is Complete Response. Major CMC issues are specifications for the chiral precursor, drug product specifications, data for stability at low pH and validation data for the HPLC purity test.

R/D Init by: Dr. D. Christodoulou, Branch Chief

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/s/

MARTIN T HABER
08/29/2013

ELDON E LEUTZINGER
08/29/2013

DANAE D CHRISTODOULOU
08/29/2013

NDA 200-655

Fluorodopa F-18 Injection

The Feinstein Institute for Medical Research

Martin Haber, Ph.D.
Division of New Drug Quality Assessment III

For
Division of Medical Imaging Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-655

2. REVIEW #1

3. REVIEW DATE: June 13, 2013

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10/22/2012 (Resubmission after RTF in 2010)
CMC Amendment	1/14/2013
CMC Amendment	6/7/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	The Feinstein Institute for Medical Research
Address:	350 Community Dr, Manhasset, NY 11030
Representative:	Thomas Chaly, Ph.D.
Telephone:	516-562-1042

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Fluorodopa F-18
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (NME)
- Submission Priority: Standard review

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Positron Emission Tomography (PET) Product - Diagnostic Imaging Agent for Parkinson's disease

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 5-100 mCi per vial

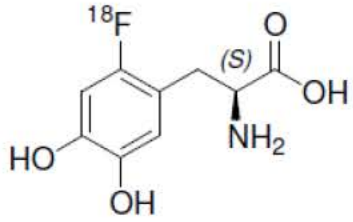
13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: $C_9H_{10}FNO_4$

Charge: 0

Mass: 214.18098

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	2/24/2009	
	III			3	Adequate, amended on 4/16/2013, new information under review (DARRTS)		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78861	IND for product name "FDOPA" held by the Feinstein Institute. Note: A DARRTS search did not find this IND under the product name "fluorodopa". (b) (4)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Approval	6/10/2013	Dr. S. Hargus
Quality Biopharm	NA		
Methods Validation	NA (product is radioactive)		
DMEPA	Pending		
EA	Exclusion requested and accepted	6/13/2013	Dr. M. Haber
Microbiology	Complete Response	6/4/2013	Dr. R. Mello

The Chemistry Review for NDA 200-655

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend complete response, based on unresolved deficiencies and pending overall cGMP recommendation by the Office of Compliance

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Fluorodopa F-18 Injection drug product is a sterile product for intravenous injection containing 5 – 100 mCi (0.185 – 3.7 GBq) of fluorodopa F-18 in (b) (4) mL of sterile water for injection with the following inactive ingredients: 12.7 mg of acetic acid and 108 mg of sodium chloride. The drug product is manufactured at the Feinstein Institute for Medical Research, Manhasset, NY. The drug product specifications follow the USP drug product monograph for fluorodopa F 18 injection. Specifications include tests for appearance, radionuclidic identity, radiochemical identity and purity, chemical identity, radionuclidic purity, assay (amount of radioactivity), specific activity (mCi/mmol), pH, (b) (4) , bacterial endotoxin testing, sterility testing, osmolality and chemical impurity testing for (b) (4) breakthrough. Data was provided for three validation batches (b) (4) mCi/mL) and 48 development batches produced in the last 3 years. The expiry is limited by the short F-18 half-life and is set at 10 hours after synthesis.

The drug substance is 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine or F-18 labeled FDOPA. Carrier added F-18 fluorine is produced in a cyclotron at the Feinstein Institute. (b) (4)

B. Description of How the Drug Product is Intended to be Used

Flurodopa F 18 Injection is a short-lived radiopharmaceutical used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in patients with suspected Parkinsonian syndromes. F-18 is a positron emitting isotope with a short physical half-life of 110 minutes. The positron annihilates with an electron to produce dual 511 keV gamma photons emitted simultaneously in opposite directions. The recommended dose is (b) (4) 5 mCi ((b) (4) 0.185 GBq). The sterile drug product (5-100 mCi at end of synthesis) is supplied in a septum capped 20 mL multi-dose clear glass vial.

C. Basis for Approvability or Not-Approval Recommendation

Complete response is recommended because the sponsor has not responded adequately to CMC information requests sent 12/28/2012 and 5/31/2013. Specifically, the specifications for the drug product and drug substance precursor have not been finalized, data justifying a non-USP conforming pH has not been provided and validation data for the HPLC chiral identity and purity method has not been provided.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

Chemistry Assessment

Comment in 74-day letter:

Please note that [^{18}F]-fluorodopa, the active ingredient, has not been the subject of a previously approved NDA and therefore it is a new molecular entity from the Agency's viewpoint, contrary to what you state in your cover letter.

The applicant acknowledged the comment and agreed. Note that fluorodopa F-18 is not a novel compound and the drug product is the subject of a USP monograph.
Adequate.

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE [fluorodopa, The Feinstein Institute]

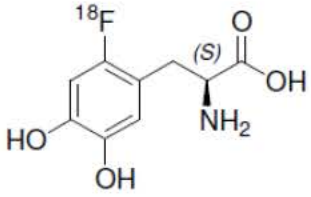
S.1 General Information [fluorodopa, The Feinstein Institute]

S.1.1 Nomenclature

Proprietary Name:	**None**
USAN Name:	**Fluorodopa F18**
Chemical Name(s):	**6-[^{18}F] Fluoro-L-3,4-dihydroxyphenylalanine**
	(S)-2-amino-3-(2-fluoro-4,5-dihydroxyphenyl)propanoic acid
Abbreviated form:	**^{18}FDOPA**
Other:	**6-[^{18}F]fluorodopa**
CAS:	75290-51-6

The drug substance is the 6-Fluorine derivative of L-dopa or levodopa.

S.1.2 Structure



Molecular Formula: $C_9H_{10}FNO_4$

Charge: 0

Mass: 214.18098

S 1.3 General Properties

Fluorodopa is an aromatic, neutral amino acid, a fluorine-substituted analog of L-Dopa with one chiral center in the (S) configuration. It is a colorless solid that is very soluble in water. In the presence of moisture, L-dopa is rapidly oxidized by atmospheric oxygen and darkens.

S.2 Manufacture [fluorodopa, The Feinstein Institute]

S.2.1 Manufacturers

Address: The Feinstein Institute for Medical Research
Department of Cyclotron/ Radiochemistry
North Shore-LIJ Health System
350 Community Drive
Manhasset, NY 11039 **FEI: 3004971261**
Contact: Thomas Chaly, Ph.D., F.A.I.C. **Phone:** (516) 562-1042 **Fax:** (516) 562-1041

The following testing laboratory was used for testing (b) (4) in the drug product.

(b) (4)

S.2.2 Description of Manufacturing Process and Process Controls

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P DRUG PRODUCT [fluorodopa F-18, injection]

P.1 Description and Composition of the Drug Product [fluorodopa F-18, injection]

The NDA states: Fluorodopa F 18 Injection is a radioactive diagnostic imaging agent administered intravenously prior to PET imaging. "It is supplied in a multi-dose glass vial containing 0.0155-0.3082 GBq (sic) (0.42-8.33 mCi/mL) of Fluorodopa F 18 Injection, 12.7 µg (sic) of acetic acid and 108 mg sodium chloride in (b) (4) mL of sterile water for injection."

Note: Slightly different numbers are given elsewhere in the NDA. Also, units for acetic acid should be milligrams, not micrograms.

Comment in the 12/28/2012 74-day letter:

Regarding the drug product composition, provide the calculation used to estimate the amounts of each component, including fluorodopa. Correct the units used for acetic acid from micrograms to milligrams (where necessary) and state the exact final volume, if specified.

The applicant provided a calculation. A slightly corrected and rounded calculation (the applicant does not use the exact final volume) is as follows:

Fluorodopa F-18 Injection drug product is supplied in a multi-dose glass vial containing 5 to 100 mCi (0.185 to 3.7 GBq) of Fluorodopa F-18, 12.7 mg of acetic acid and 108 mg of sodium chloride in (b) (4) mL of sterile water for injection. The radioactivity concentration is (b) (4).

The calculated total mass of (b) (4) fluorodopa, based on a specific activity of > 100 mCi/mmol, ranges from (b) (4) to (b) (4) mg, depending on the yield of from 5 to 100 mCi of product. This corresponds roughly to (b) (4) mg FDOPA/mL of product.
Adequate.

Note: The amount of radioactivity per mL is not 0.0155-0.3082 GBq/mL (0.42 – 8.33 mCi/mL) as stated in the NDA (dividing by 12 mL instead of (b) (4) mL, which is the true final volume). Corrected values are provided above. The applicant did correct the units for acetic acid from micrograms to milligrams. The final volume for the product is stated to be (b) (4) mL. However, see the comment and discussion in Section P.3.3., Manufacturing Description. The FDA facility inspectors noted during their site visit that the actual product volume varied from 7 mL to 13 mL and cited this on the 483.

Note: The specific activity is highly variable, ranging from (b) (4) mCi/mmol (a 30-fold range), based on batch data. Also, the specific activity is relatively low for a PET

product and the resultant mass dose of FDOPA is relatively large. This is not a safety issue because the clinical dose of L-dopa is much larger, up to several grams per day.

Note: Ordinarily, without a preservative, the drug product should be designated as used for single-dose only. However, the microbiology team decided that this is not a critical issue because other similar PET products are also not designated as single-dose use only. The shelf-life is only 10 hours so there is only a limited time for organisms to grow.

(b) (4)

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A	**APPENDICES**	
A.1	**Facilities and Equipment (biotech only)**	**NA**
A.2	**Adventitious Agents Safety Evaluation**	**NA**
A.3	**Novel Excipients NA**	
R	**REGIONAL INFORMATION**	
R1	**Executed Batch Records**	**Provided**
R2	**Comparability Protocols**	**NA**
R3	**Methods Validation Package**	**NA (Radioactive Product)**

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Note: Labeling will be reviewed in next review cycle.

Package Insert:

Description section:

Note: The structure provided does not indicate chirality of the amino acid but the L-form is stated in the text.

The description section also contains a physical characteristics section which includes information on radiation emission and shielding.

Carton and vial labels:

Reviewed in collaboration with the Office of Drug Safety Evaluation, see report in DARRTS. Draft labels were provided:

LABEL FOR CONTAINER CLOSURE SYSTEM

(b) (4)

LABEL FOR LEAD PIG CONTAINER

(b) (4)

B. Environmental Assessment Or Claim Of Categorical Exclusion

Request for categorical exclusion was made and it is acceptable, as F-18 rapidly decays and only very tiny amounts of drug substance are made.

III. List of Comments To Be Communicated in CR letter:

1. You have not sufficiently characterized the chiral identity of the precursor to the drug substance. Regarding chirality of the precursor, circular dichroism (CD) measurements would also establish the enantiomeric excess of the L-isomer. Provide characterization by CD or optical rotation measurements for the precursor to the drug substance.

2. Provide final revised drug product specifications, in tabular format, with all the appropriate changes requested by the Agency previously. Provide a revised NDA document with tracked changes identified.

3. In your drug product specifications, you indicate that all radionuclidic purity testing is completed prior to release of the drug product. However, it is not possible to carry out (b) (4) of decayed samples prior to release of the drug product, as you propose. Please explain. Also, regarding radionuclidic identity, the acceptance criteria should require the measured half-life to be between (b) (4) and (b) (4) minutes, as per USP.

4. Regarding the pH of the product, (b) (4) .

5. Provide validation data for the drug product HPLC purity method establishing the limit of detection and quantitation, accuracy, precision, linearity and robustness.

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/s/

MARTIN T HABER
06/13/2013

ELDON E LEUTZINGER
06/13/2013

DANAE D CHRISTODOULOU
06/14/2013
I concur with the reviewer's conclusions and recommendations

Product Quality Microbiology Review

04 JUNE 2013

NDA: **200-655**

Drug Product Name
Proprietary: None
Non-proprietary: Fluorodopa [F-18] Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
22 October 2012	22 October 2012	24 October 2012	30 October 2012
14 January 2013	14 January 2013	n/a	n/a
05 April 2013	05 April 2013	n/a	n/a

Submission History (for 2nd Reviews or higher): N/A

Applicant/Sponsor
Name: The Feinstein Institute for Medical Research
Address: The Feinstein Institute for Medical Research
350 Community Drive
Manhasset, NY 11030
Representative: Thomas Chaly Ph.D.
Chief, Cyclotron/Radiochemistry
Telephone: 516-562-1042

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(2)

2. SUBMISSION PROVIDES FOR: Marketing Authority

3. MANUFACTURING SITE: The Feinstein Institute for Medical Research
Cyclotron/Radiochemistry
350 Community Drive
Manhasset, NY 11030

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile injectable [F-18] PET drug; intravenous administration, 0.42 - 8.33mCi/mL, packaged in a 20mL multidose vial. The vial is packaged in a (b) (4) container for shielding from radiation.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Positron Emission Tomography (PET) Radiodiagnostic Imaging Agent

`

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Filing Review DARRTS dated 07 November 2012
- DMF (b) (4) (vial manufacturer).

C. REMARKS:

- The NDA was submitted in CTD format and was located in EDR.
- The application was originally submitted on 29 October 2009 and the Applicant was issued a Refuse To File letter on 19 March 2010 due to numerous multi-disciplinary omissions. There was no microbiology consult issued at that time and, therefore, no microbiology filing review was performed. The Applicant resubmitted the application on 22 October 2012.
- The following microbiology information request, as part of the 74-day letter, was sent to the applicant on 28 December 2012 (note, these were listed as items #11 - #14 in the 74-day letter:
    - Clarify the locations where the following operations occur:
        - (b) (4)
        - c. The QC sample removal for the final drug product
    - Provide copies of the following assay procedures:
        - a. Sterility testing (SOP QC009)
        - b. Endotoxin testing (SOP QC010)
        - (b) (4)
    - (b) (4)

- Provide a copy of the Certificate of Analysis (CoA) for the (b) (4) empty vials to be used for the final drug product.

The Applicant provided responses to the above items on 14 January 2013. These will be discussed in the appropriate review sections that follow.

- The following microbiology information request, as part of the mid-cycle review, was sent to the applicant on 25 March 2013:
    1. Endotoxin Testing:
        A. Revise the drug product Specifications section of the submission (Module 3, page 31/90, Section 3.2.S.4.1) to indicate that the drug product shall not be administered to the patient prior to completion of the test for pyrogens.
        B. Revise the "Action if Test Fails" section of SOP QC009 and QC018 to be in conformance with the investigation provisions of 21 CFR 212.70(c), (d) and 212.71(b).
    - Sterility Testing:
        A. In order to comply with the provisions of 21 CFR 212.70(e) concerning the holding of sterility samples, submit for review the results of testing that demonstrates that holding the sterility sample longer than 30 hours does not adversely affect the sample. Alternatively, in lieu of such data, you may modify SOP QC010 to clarify how you comply with the intent of 21 CFR 212.70(e).
        B. Revise the "Action if Test Fails" section of SOP QC010 to be in conformance with the provisions of 21 CFR 212.70(e). The revisions should clearly stipulate the performance of an investigation following the initial test failure. Provide a description of how you will comply with the investigation provisions of 21 CFR 212.70(e).

The Applicant provided responses to the above items on 05 April 2013. These will be discussed in the appropriate review sections that follow.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended as Approvable Pending a Complete Response to Microbiology Deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies -

- The sterility and endotoxins sample may not be representative of the final drug product.
- (b) (4)
- The bacterial endotoxins assay is not adequately validated to address the low pH ((b) (4)) of the drug product.

C. Assessment of Risk Due to Microbiology Deficiencies – The sterility assurance and non-pyrogenicity of the drug product cannot be fully assured due to the deficiencies in sampling, and (b) (4).

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block_____

David Hussong, Ph.D.
Director, New Drug Microbiology Staff

C. CC Block

NDA 200-655

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE: Not Applicable. [redacted].

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –The drug product (Fluorodopa F 18 injection) is a multidose, sterile, non-pyrogenic, non-preserved clear and colorless radio-pharmaceutical used for diagnostic positron emission tomography (PET) imaging. The isotope activity is 0.0155-0.3082 GBq (0.42-8.33 mCi/mL) (OES) and the half-life of the isotope is 110 minutes. The recommended adult dose (per the submitted draft labeling) is [redacted] 5.0 mCi ([redacted] 0.185GBq).

- Drug product composition – Each milliliter of the drug product contains [redacted] mg of the active drug substance (6-[18F] Fluoro-L-3, 4-hydroxyphenylalanine), [redacted] mg of acetic acid, [redacted] mg of sodium chloride and sterile water for injection. The total volume of the vial is approximately [redacted] mL. The drug solution pH is [redacted].

- Description of container closure system – The drug product is packaged in a [redacted], 20mL vial (Manufactured by [redacted]. The vials, as purchased from [redacted]. The container closure system is a 20mL [redacted] glass vial [redacted] sealed with a [redacted] gray rubber stopper and a [redacted] aluminum crimp seal.
  NOTE: The rubber formulation of the stopper was not clearly stated in this submission. However, in Module 3, section 3.2.P.2.4 (submission page 47/90), the applicant states that they are using the same type of [redacted] vial as was used in their previous NDA. Reference to that submission (NDA 22-119) was made in Module 3, section 3.2.S.2.5 (submission page 28/90). The chemist's review of NDA 22-119 identified the stopper as a [redacted] gray rubber stopper.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package Integrity - No formal container closure integrity studies were submitted. The Applicant stated that the product filled

container vial was held inverted for 12 hours during extractables/leachable studies and that there was no evidence of any septum leak. The same vial type has been used for the past 5 years for the Applicant's other PET drug product (having similar needle penetrations). There have been no reports of any incidents related to container-closure integrity.

- Adequate -

Reviewer's Comment: The half-life of the isotope is 110 minutes and the drug product is used within 10 hours of production, therefore, container/closure studies supporting the maintenance of drug product sterility are not required.

- Preservative Effectiveness - Not Applicable. The product is not preserved.

- Adequate -

Reviewer's Comment: –In general, a multiple dose drug product must either be preserved or data must be submitted to support the premise that it is self-preserving. The purpose of such testing is to provide assurance that any low level microbial contamination (resulting from the multiple stopper penetrations) will not proliferate over the "in-use" shelf life of the drug product. For [F-18]-labeled radiopharmaceuticals the half-life of the isotope is approximately 110 minutes. For the current (F-18) Fluorodopa Injection, the expected dosing is 5mCi. Based on the submitted manufacturing description, the volume/vial is approximately (b) (4) + 1.0mL. Based on the submitted stability, the product will be used within 10 hours. Therefore, from a risk perspective, the combination of (b) (4), the high radioactivity, the short isotope half-life and the 10 hour product stability results in a very low probability of any significant microbial proliferation occurring from multiple penetrations of the drug product vial during its "in-use" lifetime.

- Justification for not having a microbial limit specification for a non-sterile drug product - Not Applicable

P.3 Manufacture

P.3.1 Manufacturers

The Feinstein Institute for Medical Research
Cyclotron/Radiochemistry
350 Community Drive
Manhasset, NY 11030
FEI #3004971261

(b) (4)

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(b) (4)

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. PACKAGE INSERT: Draft labeling was submitted. Appropriate handling and storage conditions were recommended for the drug product. The recommended storage conditions stated in the proposed draft labeling are: *"Store the Fluorodopa F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid direct light. Fluorodopa F 18 Injection should be used within 10 hours from the time of the end of synthesis (EOS)."*

- Adequate -

Reviewer's Comment: The storage conditions are appropriate and are consistent with other similar F 18 PET drug products.

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/s/

ROBERT J MELLO
06/04/2013

DAVID HUSSONG
06/04/2013
The review has identified information that should be clarified before approval. Specific defiencies are provided for the applicant to respond to.