CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200655Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200-655

MEETING MINUTES

The Feinstein Institute for Medical Research
Thomas Chaly, Ph.D; FAIC
Chief, Radiochemistry/Cyclotron
Associate Professor, NYU Medical College
North Shore/LIJ Health System
350 Community Drive
Manhasset, New York 11030

Dear Dr. Chaly:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluorodopa F18 Injection.

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2010. The purpose of the meeting was to discuss concerns expressed in FDA's March 19, 2010 refuse to file letter for NDA 200-655.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 19, 2010
Meeting Location: CDER White Oak Bldg 22 Room 1419

Application Number: NDA 200-655
Product Name: Fluorodopa F18 Injection
Indication: A radioactive diagnostic imaging agent for Positron Emission Tomography (PET) indicated to (b) (4)

Sponsor/Applicant Name: Feinstein Institute for Medical Research

Meeting Chair: Rafel Dwaine Rieves
Meeting Recorder: Frank Lutterodt

FDA ATTENDEES
Rafel Rieves, M.D., Division Director, DMIP
Libero Marzella, M.D., Medical Team Leader, DMIP
Sally Hargus, Ph.D., Pharm/Tox Reviewer DMIP
Brenda Ye, M.D., Medical Officer, DMIP
Lucie Yang M.D., Ph.D., Medical Officer, DMIP
Ira Krefting M.D., Deputy Director for Safety, DMIP
Shaw Chen M.D., Deputy Director, ODEIV
Ross Filice M.D., Medical Officer, DMIP
Satish Misra, Ph.D., Statistics Reviewer, DBV
Jyoti Zalkikar, Ph.D., Statistics Team Leader, DBV
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, DCP5
Eldon Leutzinger, Ph.D., CMC Lead, DNDQA
Milagros Salazar Driver, Ph.D., CMC Reviewer, DNDQA
Frank Lutterodt, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES
Thomas Chaly, Ph.D; FAIC, Chief, Radiochemistry/Cyclotron Chief, Radiochemistry/Cyclotron. The Feinstein Institute for Medical Research

Matthew Hellman RPH, BCNP, Radiopharmacist, the Feinstein Institute for Medical Research

1.0 BACKGROUND

Dr. Thomas Chaly of Feinstein Institute for Medical Research submitted a meeting request dated April 14, 2010, received April 15, 2010, requesting a Type B face to face meeting, with the Division of Medical Imaging Products (DMIP) to discuss FDA Refusal-To-File Letter dated March 19, 2010, and to discuss the resubmission of the NDA for Fluorodopa [F-18] Injection (FDOPA).

Reference is also made to the meeting background package dated June 16, 2010. This submission and a PowerPoint slide served as the basis for discussions during the July 19, 2010, 12:00PM-1:30PM face to face meeting.

2. DISCUSSION

Following introductions between sponsor representatives and the FDA, the meeting began with a PowerPoint presentation by the sponsor. The discussions centered on the truth standard, sensitivity/specificity assessment, and data needed to assess the safety and efficacy of Fluorodopa [F-18] Injection.

2.1. Discussions on Submitted Data

- The sponsor cited the new CGMP rule and stated that not approving this NDA will result in the disappearance of ^{18}FDOPA from the market after December 2011 and as a result, patients would have to go to foreign countries to decide on their medical condition at the onset of Parkinson's syndromes.

- The FDA pointed out that there will still be mechanisms in place to make the product available after December 2011 even if the product is not approved for marketing. FDA highlighted the need for clinical data that allow the agency to verify the safety and efficacy of drugs proposed for marketing, including ^{18}FDOPA.

- The sponsor stated that they imaged 185 Parkinsonian syndrome patients, and found 158 patients to be ^{18}FDOPA PET positive and 27 patients to be ^{18}FDOPA PET negative. The sponsor concluded that the 27 scan negative patients had SWEDDS (subjects without evidence of dopaminergic deficit) and that the ^{18}FDOPA PET has 100% sensitivity and specificity (b) (4) The FDA pointed out that an independent test needs to be used (b) (4) and the ^{18}FDOPA cannot be both the test drug and the truth standard. The FDA encouraged the sponsor to re-examine the math as the sensitivity should be 85% and not 100%, based upon traditional methods for calculating sensitivity (scan reported as "positive" among 158/185 patients with disease).

- It was further explained by FDA that the study design can not be used to calculate specificity since all patients had disease.

- The FDA advised the sponsor that, the key piece of information is verification of the current clinical diagnosis of the 185 patients (i.e, the clinical diagnosis "truth standard" may be incorrect).

- The sponsor stated that since there has not been any follow-up, the current clinical diagnosis is unknown. The sponsor also said that there have not been any prior studies at the Feinstein Institute.

- The FDA stated that one of the major difficulties with the cited study was the apparent lack of a reliable truth standard; the FDA noted that FDOPA images should not be used in establishment of the truth standard. One option for a truth standard would be the use of an alternate method that provides a reliable diagnosis of Parkinson's syndrome.

- The FDA discussed the potential role of an independent assessor and the types of information supplied to this assessor. The FDA suggested that perhaps a video of the patient could be incorporated into the diagnostic assessment of a patient by an independent assessor.

The FDA concluded that the information provided in the submission did not appear sufficient to support the safety and efficacy of ^{18}FDOPA if only this clinical information was supplied in an NDA. The sponsor was advised to review prior FDA communications and to respond to any highlighted deficiencies as he prepares for an NDA submission. The FDA encouraged the sponsor to work with his site clinicians in an effort to more cogently obtain, organize and present clinical data.

The sponsor asked if they could re-submit the NDA if requested information is provided. The FDA responded in the affirmative and stated that the outcome of the NDA review was contingent upon the quality of the supplied data and the ability to verify the drug's safety and efficacy. The meeting then came to a close.

2.0 ATTACHMENTS AND HANDOUTS

The sponsor's Power point slide presentation

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200655	GI-1	FEINSTEIN INSTITUTE MEDICAL RESEARCH	FLUORODOPA F 18 INJECTION

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/s/

FRANK A LUTTERODT
08/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200655

REFUSAL TO FILE

The Feinstein Institute for Medical Research
Cyclotron/Radiochemistry
Northshore/LIJ Health System
Attention: Thomas Chaly, Ph.D., FAIC
350 Community Drive
Manhasset, NY 11030

Dear Dr. Chaly:

Please refer to your October 29, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluorodopa [F-18] Injection (FDOPA).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

ADMINISTRATIVE

1. As cited by the deficiencies listed below, multiple required sections and content were not supplied within your application. These requisite sections are cited in 21 CFR 314.50; we reiterate portions of the text below. We encourage you to review the full content of 21 CFR 314.50 as you redevelop your application. These regulations are available on the FDA internet web site (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm). We also encourage you to request a meeting to discuss your proposals to address the regulatory expectations.

2. The application lacks a functional index, see 21 CFR 314.50(b). The application lacks consistent pagination; each section of the application is separately paginated. We recommend redevelopment of the index based upon consistent, sequential pagination of the application.

CLINICAL

3. The application does not contain an integrated summary of efficacy (ISE) that maintains consistency with the regulatory expectations.

   a. As described in 21 CFR 314.50 (d)(5)(v), an NDA must contain, "an integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also shall be presented."

   b. Volume III Supporting Data for the Clinical Indication contains individual summaries of 22 publications. As described above, the ISE must contain certain analyses. The brief efficacy summary at the end of Volume III does not contain any efficacy data analyses. In addition, copies of some of the more recent publications cited in the summary (e.g. Thomas Eckert *et al* 2007) are not submitted in Volume III as supporting clinical data.

4. The application does not appear to contain supporting evidence for the proposed dosing as required by 21 CFR 314.50 (d)(5)(v). The proposed dosing for Fluorodopa F-18 Injection is (b) (4) 5 mCi ((b) (4) 185 MBq), and the doses used in various clinical studies described within the submitted articles ranged 74 – 370 MBq. The application lacks dosing assessment or analysis to back the proposed dosing recommendations. In addition, most clinical studies described by the submitted publications administered carbidopa (a peripheral decarboxylase inhibitor) to patients before the [^{18}F]-FDOPA PET to inhibit peripheral decarboxylation. The clinical studies varied in doses and timing of the carbidopa premedication. The proposed dosing recommendation is 150 mg carbidopa given one hour prior to administration of Fluorodopa F-18 Injection for patient preparation; however, the application lacks analysis or discussion to support this recommendation.

5. The application contains limited safety data, and lacks safety data analyses and an integrated summary of safety (ISS). As described in 21 CFR 314.50(d)(5)(vi)(a), "the applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups." This regulatory citation contains other expectations for the ISS. We encourage you to review these expectations as you redevelop your application.

6. The application lacks other summaries of required subjects, see 21 CFR 314.50(c). These summaries are typically supplied in Module 2 of the Common Technical Document (CTD) format. The summaries consist of the "Quality Overall Summary , Nonclinical Overview, Clinical Overview, Nonclinical Written and Tabulated Summaries, and Clinical Summary." The application does not contain any of these summaries.

7. The application lacks a benefit-risk analysis for the product. This expectation is described in 21 CFR 314.50(d)(5)(viii).

8. The application lacked a description of the potential for abuse, as required within 21 CFR 314.50(d)(5)(vii).

PHARMACOLOGY\TOXICOLOGY

9. The application lacks the required nonclinical pharmacology and toxicology section, see 21 CFR 314.50(d)(2). Additionally, no portion of the NDA contained nonclinical information. In developing your revised application, we recommend that you make reference to the Public Meeting held on July 28, 2000, between FDA and the Clinical Institute for PET, during which Fluorodopa F18 Injection was discussed. Supply all additional nonclinical information that you regard as important to support the safety and efficacy of your product.

CLINICAL PHARMACOLOGY

10. The application lacks the required human pharmacokinetics and bioavailability section, see 21CFR 314.50(d)(3). Specifically, the application did not include supportive literature reports for clinical pharmacology-related statements in the proposed label. (b) (4) However, no information is supplied to justify this label description. When revising your application, collate and submit all publications supporting the clinical pharmacology information in the label.

Although not specifically a basis for our refusal to file your application, we have the following comments:

1. The cited clinical efficacy data appears tenuous in its ability to support your proposed labeling. The application contains summaries of multiple publications as the confirmatory data for the clinical efficacy claims. However, this information does not appear to represent data from adequate and well-controlled studies. Only one study (published in two articles) appears to represent a multicenter, confirmatory trial. However, this trial (Alan Whone *et al*, Ann Neurol, 2003) does not appear to be designed for evaluating the efficacy of Fluorodopa F-18 Injection in PET imaging. Instead, the study appears to have been designed for evaluating the response of patients to treatment with ropinirole or levodopa. Therefore, the efficacy endpoint of this study does not match the proposed labeling indication for Fluorodopa F-18 Injection. Other study reports appear even more deficient in study design or relevance to the proposed claim of efficacy.

2. We understand that many patients have been exposed to Fluorodopa F-18 Injection at your clinical site. When redeveloping your application, we encourage you to summarize the safety and nominal diagnostic efficacy data from this experience.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. See FDA meeting guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes (whether you file over protest or not), and you must either remit the appropriate fee or contact Michael Jones in CDER Regulatory Office of Policy for information on waivers: (301) 796-3602.

If you have any questions, contact Ms. Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager at (301) 796-2050 or Thuy.Nguyen@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200655	ORIG-1	FEINSTEIN INSTITUTE MEDICAL RESEARCH	FLUORODOPA F 18 INJECTION

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/s/

THUY M NGUYEN
03/19/2010

LIBERO L MARZELLA
03/19/2010
signing for Dr. Rieves

***CONFIDENTIAL**

FDA - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY DRUG PRODUCTS (DMIHP)

PRE-NDA INDUSTRY MEETING MINUTES

PRE-IND: **78861**

DRUG NAME: **[F-18] Fluorodopa Injection**

SPONSOR: **Thomas Chaly, Ph.D. for Feinstein Institute**

DATE: **Monday, August 10, 2009, at 12:00 pm**

LOCATION: **WO #22 – Conf Room 1421**

SPONSOR PARTICIPANTS
Thomas Chaly, Ph.D., Chief, Radiochemistry
Matthew Hellman, R.Ph., BCNP, Supervising Radiopharmacist

FDA PARTICIPANTS
Phillip Davis, M.D., Clinical Reviewer
Qi Feng, M.D., Clinical Reviewer
Alex Gorovets, Clinical Team Leader
Sally Hargus, Ph.D., Pharm\Tox Reviewer
Christy John, Ph.D., Clinical Pharmacology Reviewer
Joseph Kaminski, M.D., Clinical Reviewer
Ira Krefting, M.D., Safety Team Leader
Eldon Leutzinger, Ph.D., Chemistry Pharmaceutical Assessment Lead
Mark Levenson, Ph.D., Statistical Reviewer
Lou Marzella, M.D. Acting Deputy Division Director/Primary Clinical Team Leader
John Metcalfe, Ph.D., Microbiology Reviewer
Thuy Nguyen, M.P.H., Primary Regulatory Health Project Manager
Rafel Dwaine Rieves, M.D., Division Director
Trinh Scott, Regulatory Health Project Manager
Lucie Yang, M.D., Ph.D., Clinical Reviewer
Brenda Ye, M.D., Primary Clinical Reviewer
Jyoti Zalkikar, Ph.D., Statistical Team Leader

AGENDA: PRE-NDA meeting to discuss the FDA Preliminary Meeting Response, of August 7, to the Sponsor Meeting Request of June 5 and Meeting Package of June 30, 2009 (See Attachment #1).

Following the Sponsor's presentation, the Sponsor provided a Meeting Supplement dated August 10, 2009, with preliminary responses to the FDA preliminary meeting responses of August 7, 2009.

The FDA requested that the Sponsor submit the Meeting Supplement as a formal submission and explained that the FDA may not be able to address the Supplement completely during the meeting since the FDA has not had adequate review time.

In the Meeting Supplement, 08\10\09, the Sponsor stated he has provided preliminary responses to the FDA chemistry response and comments, 08\07\09, and will address the rest of the FDA chemistry comments in the NDA submission.

Upon receiving the FDA preliminary meeting responses, 08\07\09, the Sponsor stated he has revised the proposed indication originally submitted in the Meeting Request dated 06\05\09, FROM:

(b) (4)

TO: (see Sponsor's Meeting Supplement, 08\10\09)

(b) (4)

The FDA stated that, even with the revised proposed indication, as mentioned in the FDA Meeting Response, 08\07\09, at least one adequately powered prospective study is recommended, to be successful for the above proposed claim. The FDA referred the Sponsor to the complete FDA Meeting Response #1 – Clinical. The Sponsor stated that he did not have the resources available to conduct clinical studies. He also referred to an inability to obtain medical/investigator support from his institution.

The FDA asked if the Sponsor has asked other government agencies (ie, NIH), institutions (ie, Feinstein Transfer Office), professional scientific organizations (ie, SNM, Parkinsonian Society), or pharmaceutical companies to assist with the drug development – clinical studies, to which the Sponsor explained that he has asked all of the above for assistance, but to no avail.

Due to the lack of funding and support from others as mentioned above, the Sponsor stated he does not have the resources to conduct a thorough review of the literature nor a clinical study and he would not be able to facilitate an Advisory Committee (AC) meeting.

The Sponsor requested that the FDA assist with the approval of [F-18] Fluorodopa Injection as the FDA has done so in the past for his other NDAs – FDG and Ammonia.

The FDA reminded the Sponsor of the Peripheral and Central Nervous System (PCNS) Advisory Committee on August 11, 2009, which may be beneficial to his drug development. The Sponsor stated he will attend the PCNS AC.

ACTION ITEM:

1. The Sponsor will submit a Meeting Request for a follow-up teleconference and will submit the Meeting Supplement (dated 08\10\09), as a formal submission.

2. The Sponsor will address the FDA chemistry response and comments in the NDA submission.

TCON Minutes Recorded By: T.Nguyen, DMIHP

ATTACHMENT #1

FOOD AND DRUG ADMINISTRATION (FDA)

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS (DMIHP)

PRE-IND 78861: [F-18] Fluorodopa

SPONSOR: Feinstein Institute for Medical Research

Type B Pre-NDA Face-To-Face Meeting: August 10, 2009

Regarding the Meeting Request dated June 5, 2009, and Meeting Package dated June 30, 2009, below are the FDA preliminary responses\comments, August 7, 2009, in preparation for the face-to-face meeting on August 10, 2009, and may not be fully vetted internally and should not be considered as an official position of the FDA. It is shared with the Sponsor solely to promote a collaborative and successful discussion during the meeting. The FDA meeting minutes will reflect agreements and discussion and might not be consistent with these preliminary responses\comments.

SPONSOR MEETING QUESTION #1 - Clinical

Based on new literature support and the approval of Fluorodopa F 18 injection in France and other European Union countries, can the FDA give some priority consideration to help the PET community for the approval of this PET drug?

FDA REPONSE #1

We have reviewed the publications you have submitted so far and have found the supporting evidence to be inadequate for an approval, (b) (4)

FDA REPONSE #1 (cont.)
We encourage you to consider alternative indication proposals. For example, you may wish to consider an indication similar to that undergoing discussion at the Peripheral and Central Nervous System Advisory Committee on August 11, 2009. Clinical data expectations vary, depending upon the proposed indication. We understand you and the Feinstein Institute may have limited resources for the clinical study of F-18 Fluorodopa. At the face-to-face meeting, 08\10\09, we would like to work with you to explore potential resources that could help promote the clinical development of this PET imaging agent.

If your "priority consideration" refers to a "priority review timeline" for your NDA, we do not provide this designation and timeline until an application has been received. We work to promptly report the designation and timeline for the review following our initial examination of the application.

SPONSOR MEETING QUESTION #2 - Chemistry
Since Fluorodopa F 18 Injection is routinely used as a clinical diagnostic imaging agent and not for research studies, why the labeling has to have "Research Only" caution? More over, with all the other labeling materials, the Label is already crowded and including one more item, the letter size has to be reduced further, which will not be readable easily.

FDA RESPONSE #2
A drug that is not approved and is used under an IND must display a label consistent with that for an investigational label and carry a caution statement in accordance to 21 CFR 312.6(a). Fluorodopa F 18 injection is not an approved drug. Hence, under an IND, Fluorodopa F 18 Injection is considered a New Drug and must be labeled accordingly. Also, the phrase, "Research Only," is not consistent with 21 CFR 312.6(a). Rather, the actual caution statement required by the regulation is "Caution: New Drug – Limited by Federal (or United States) law to investigational use."

We also have the following CMC comments on VIII (Attachment 2):

A. A certificate of analysis for the [redacted] (b) (4) precursor from the supplier [redacted] (b) (4) should be included in the forthcoming IND.

B. [redacted] (b) (4)

FDA RESPONSE #2 (cont.)

C. There is absence of information on the Fluorodopa reference standard. As you know, determination that the "correct" drug molecule is present in final drug product is critically dependent on the authenticity of this standard, as well as the specificity of the procedure used in determination of congruence of retention times. Where is the standard obtained, and how do you know that it is suitable for the intended purpose? This information should be included in the IND.

D. A clear statement of the composition of the final drug product was not found in the meeting package. This should be in the IND, and include a list of all components present, along with their amounts.

E. In the description of the analytical procedure for radiochemical identity (page 48), the suitability test of the methodology is indicated to be performance of (b) (4) HPLC runs with standard. Ideally, the retention times will not vary from run to run (but may somewhat). (1) We recommend that you implement an acceptance criterion for (b) (4) suitability runs. (2) Also, is there an expected retention time for the standard under those conditions? This 'expected' retention time should be included in the acceptance criterion of suitability.

F. Although limits are included in narratives of the analytical procedures (pages 43 – 48), it would be helpful to include tests and limits in tabular form. This table could include the test, acceptance criteria (limits), identification of the analytical procedure (e.g., HPLC) and testing frequency (e.g., each batch, prior to release). Then, follow the table with a narrative describing each analytical procedure.

G. (b) (4)

H. Your labels (page 62) are not consistent with 21 CFR 312.6(a). Investigational labels must carry a caution statement, as required by the regulations. That statement reads, Caution: New Drug – Limited by Federal (or United States) law to investigational use."

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 78861	GI 1	FEINSTEIN	F 18 FDOPA
IND 78861	GI 1	FEINSTEIN	F 18 FDOPA

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/s/

THUY M NGUYEN
08/14/2009