

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

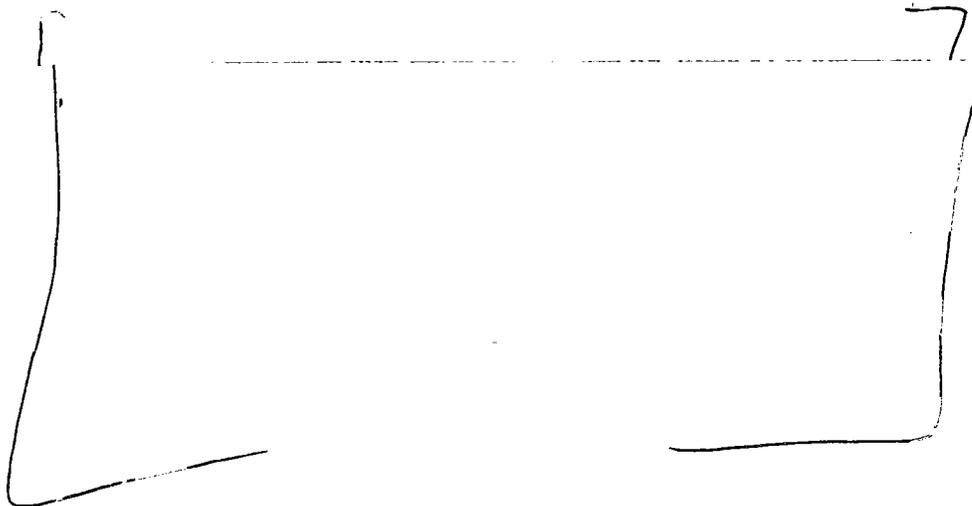
22-119

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 22-119 Ammonia N 13 Injection
Date: July 30, 2007

Introduction

Ammonia N 13 Injection is a sterile pyrogen free saline solution of $^{13}\text{NH}_3$. This is a radiopharmaceutical drug product with a positron emitting N-13 radionuclide which decays to stable C-13 with a half life of 9.96 minutes. When the emitted positron collides with and annihilates with an electron, 511 keV photons are produced.



Administrative

The original submission of this new molecular entity (NME), 505(b)(2) NDA was 16-OCT-2006. Amendments which were also reviewed were received 13-MAR-2007, 12-JUN-2007, and 19-JUN-2007. All referenced DMFs for container closure components are acceptable. These were the only DMFs cited in the application.

Consults were found to be acceptable from EES (30-APR-2007) and Microbiology (23-MAR-2007). No proprietary name was proposed by the applicant.

Summary of Findings

There are no outstanding CMC issues; ONDQA recommends approval (AP) from the CMC perspective.

Rik Lostritto, Director, ONDQA Division III

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Lostritto
7/30/2007 04:33:57 PM
CHEMIST



NDA 22-119

Ammonia N 13 Injection

**The Feinstein Institute for Medical Research
Cyclotron / Radiochemistry
North Shore / LIJ Health System
350 Community Drive
Manhasset, NY 11030**

**Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Division of Pre-marketing Assessment and
Manufacturing Science,
Branch V, ONDQA
CDER, FDA**

For the Division of Medical Imaging and Hematology Products (FHD-160)

Table of Contents

Table of Contents	2
CMC Review Data Sheet	3
The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	6
II. Summary of CMC Assessments	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used	6
C. Basis for Approvability or Not-Approval Recommendation	7
III. Administrative	7
A. Reviewer's Signature	7
B. Endorsement Block	7
C. CC Block	7
CMC Assessment.....	8
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	8
S. DRUG SUBSTANCE [Name, Manufacturer].....	8
P. DRUG PRODUCT [Name, Dosage form].....	10
A. APPENDICES	23
R. REGIONAL INFORMATION	23
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	23
A. Labeling & Package Insert	24
B. Environmental Assessment Or Claim Of Categorical Exclusion	27
III. List Of Deficiencies To Be Communicated.....	27

CMC Review Data Sheet

1. **NDA 22-119**
2. REVIEW # 1
3. REVIEW DATE: 19-Jun-2007 (Revised 25-Jun-2007)
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	16-Oct-2006
Amendment	13-Mar-2007
Amendment	12-Jun-2007
Amendment	19-Jun-2007

7. NAME & ADDRESS OF APPLICANT:

Name: The Feinstein Institute for Medical Research
Cyclotron / Radiochemistry
Address: North Shore / LIJ Health system
350 Community Drive
Manhasset, NY 11030
Representative: Dr. Thomas Chaly, Chief of Radiochemistry
Telephone: (516) 562-1042
Fax: (516) 562-1041
E-Mail: tchaly@nshs.edu

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Ammonia N 13
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1

CMC Review Data Sheet

- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Positron Emission Radiopharmaceutical for Imaging

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 3.75 mCi/mL to 37.5 mCi/mL

13. ROUTE OF ADMINISTRATION: Intravenous

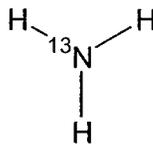
14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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



Mol. Wt.: 16.03

H, 18.86; N, 81.14

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	III	—	—	4	N/A	N/A	S J

CMC Review Data Sheet

	III		1	Adequate	18-Jun-2007	None.
--	-----	--	---	----------	-------------	-------

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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	30-Apr-2007	Office of Compliance
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A (conventional dosage form)		
Methods Validation	Not Needed	N/A	
ODS / DMETS	The product does not have a trademark. Review only provides labeling comments.	5-Mar-2007	Walter L Fava, R.Ph.
EA	No consult. Categorical exclusion claim is acceptable	Same as this review.	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	23-Mar-2007	Anastasia G. Lolas

Executive Summary Section

The CMC Review for NDA 22-119

The Executive Summary

I. Recommendation

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action from CMC perspective.

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

There are no CMC phase 4 commitments, agreements, or CMC related risk management issues with this drug product.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Ammonia N 13 Injection is a sterile, pyrogen free solution of $^{13}\text{NH}_3$ dissolved in saline. $^{13}\text{NH}_3$ is a radioactive drug that contains a positron emitting N-13 radionuclide. Nitrogen N 13 decays by emitting positron to Carbon C 13 (stable) and has a physical half-life of 9.96 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons, produced when emitted positron collides (annihilates) with electron.



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

Ammonia N 13 Injection is indicated for PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease. Following intravenous injection, Ammonia N 13 enters the myocardium through the coronary arteries. It is extracted from the blood in the coronary capillaries into the myocardial cells where it is rapidly metabolized to glutamine N 13 and retained in the cells. The presence of ammonia N 13 and glutamine N 13 in the myocardium allows for PET imaging of the myocardium.

A dose of 10-20 mCi is aseptically withdrawn as a unit dose (not to exceed in a total volume of 7 mL), assayed immediately prior to use and injected through a catheter inserted into a large vein. After 3 minutes from the initial injection, resting data are acquired for 15-20 minutes. Subsequent to this, after 40 minutes from the initial injection

Executive Summary Section

(to allow for isotope decay), a pharmacologic stress-inducing drug may be administered in accordance with its approved labeling. After 8 minutes from the injection of the pharmacologic stress inducing drug, a second dose of Ammonia N 13 Injection 10-20 mCi may be injected, and images acquired for 15-20 minutes. The recommended dose of radioactivity (10-20 mCi) is associated with a mass dose (theoretical) of ~ 0.05-0.1 pM (8.47-16.94 picograms) of ammonia N 13.

The human body already contains ammonia. Blood ammonia concentration in adults ranges from 15–45 µg/dL (deciliter) or 1.4 – 4.5 µg/mL, in children from 40–80 µg/dL, and in newborns from 90–150 µg/dL. The mass amount of ammonia administered in this drug product is negligible compared to the amount of ammonia already present in a human subject.

C. Basis for Approvability or Not-Approval Recommendation

The approval recommendation is based on that, (1) the CMC have been satisfactorily addressed, (2) acceptable cGMP recommendation on manufacturing facility has been received from the CDER Office of Compliance, (3) labeling issues have been addressed, (4) there are no trademark issues as there is no proposed trademark (the drug product will be marketed under “Ammonia N 13 injection”, an established name that has been accepted by USP (drug product) and USAN (drug substance), and (5) the product quality microbiology has recommended an approval action.

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D. (signed in DFS)

B. Endorsement Block

CMC Reviewer's Name/Date: Kasliwal /See DFS for date
CMC Branch Chief Name/Date: Harapanhalli /see DFS for date
Project Manager Name/Date: Nguyen / See DFS for date

C. CC Block

-See DFS.

21 Page(s) Withheld

X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry- 1

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ravi Kasliwal
6/26/2007 08:16:44 AM
CHEMIST

Ravi Harapanhalli
6/27/2007 11:01:06 AM
CHEMIST

Initial Quality Assessment (IQA)
Branch V

Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division: Division of Medical Imaging and Hematology Products
NDA: 22-119
Applicant: Thomas Chaly, Ph.D., Feinstein Institute for Medical
Research, Manhasset, NY 11030
Stamp Date: October 16, 2006
PDUFA Date: August 24, 2007
Trademark: None
Established Name: Ammonia N 13 Injection
Dosage Form: Injection
Route of Administration: Intravenous
Indication: PET imaging of the myocardium under rest or
pharmacologic stress conditions to evaluate myocardial
perfusion in patients with suspected or existing coronary
artery disease.

Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D.

YES NO

ONDQA Fileability: X
Comments for 74-Day Letter X

Summary and Critical Issues:

A. Summary

This is an NDA for Ammonia N 13 Injection, and will be considered Type 1 (NME). Ammonia N 13 Injection is provided as a ready to use sterile, pyrogen-free, clear and colorless solution. Each mL of this solution will contain between 0.138 GBq and 1.387 GBq (3.75 mCi and 37.5 mCi) of ¹³N-Ammonia (at EOS) in 0.9% Sodium Chloride, pH 4.5-7.5. The specific activity is indicated to be NLT ~ Ci/mole. Ammonia N 13 Injection will be packaged in a 20 mL sterile and pyrogen-free glass vial.



B. Critical Issues for Review

This initial quality assessment has not uncovered any especial critical issues with regard to the production of Ammonia N 13 Injection, including _____, target material and other materials used in the manufacture. Aside from ¹³N-Ammonia, the only other component in Ammonia N 13 Injection is sodium chloride, and the latter is USP grade. Reference Standards are accepted as suitable by Certificate of Analysis from the suppliers. All critical tests in the controls of Ammonia N 13 Injection are performed prior to release, and nothing is found in this cursory review that presents an obvious risk to the purity and quality of drug product. Analytical procedures used in the controls for release of Ammonia N 13 Injection are typical for PET drugs, and there is nothing immediately evident that would impact their capability of producing accurate and reliable test results. However, their identity determination of _____ by HPLC uses an _____

_____ They provide some validation data for this procedure. While the use of _____ in HPLC have become well-known in other kinds of analytical applications, _____ has not had wide use in the radiopharmaceutical field. Hence, the review of this NDA will need to include a careful examination of the validation procedures and data in view of how well the _____ HPLC procedure can be expected to perform under real circumstances when applied to Ammonia N 13 Injection.

Finally, it appears that all of the parts critical to filing are present in the NDA. It is, therefore, the opinion in this initial quality assessment that NDA 22-119 is fileable. A Fileability Summary is attached to this IQA.

C. Comments for 74-Day Letter

The initial quality assessment has not identified any comments that need to go to the applicant at this time, and awaits a more thorough review for issues for a 74-day letter.

Fileability Summary

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		Vol. 1, page 3
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?	X		Form FDA 356h, Establishment Information
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		Vol.1, page 40
7.	Does the section contain controls for drug substance?	X		Vol. 1, page 8
8.	Does the section contain controls for drug product?	X		Vol. 1, page 8
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		Vol. 1, page 41
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	N/A		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	N/A		
13.	Has the applicant provided a method validation package?	N/A		
14.	Is a separate microbiological section included?	X		Vol. 1, page 11

Drug Master Files Referenced					
DMF Number	Holder	Item Referenced	LOA Included		Comments
			Yes	No	
			X		Attachment 4

Consults To Be Initiated	
Item	Consult To
1. Microbiology section	Microbiology Staff

Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D. Date: 11/17/2006

Branch Chief: Ravi Harapanhalli, Ph.D. Date:

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Eldon Leutzinger
11/17/2006 08:16:03 AM
CHEMIST

Ravi Harapanhalli
11/17/2006 06:49:58 PM
CHEMIST