CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022494Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-494
Sodium Fluoride F 18 Injection

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: National Institute of Health
Address: 6130 Executive Blvd. MSC 7412 Suite 6000
Bethesda, MD 20892-7412

Indication: Sodium Fluoride F18 Injection is indicated for diagnostic PET imaging of areas of altered osteogenic activity

Establishments Evaluation Report (EER) Status: Acceptable

Consults:		
	EA –	Acceptable (Categorical Exclusion requested)
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharmaceutics–	N/A
	Microbiology –	Acceptable
	Pharm. Toxicology –	N/A

Original Submission:	June 29, 2029
Re-submissions:	July 26, 2010
Post-Approval CMC Agreements:	None at this time.

Presentation:
Sodium Fluoride F 18 injection is supplied in a multiple-dose type I glass vial with elastomeric stopper and aluminum crimp seal containing between 370 and 7400 MBq/mL (10-200 mCi/mL) in aqueous 0.9% sodium chloride solution. Each vial is enclosed in a shielded container of appropriate thickness. The product is available in a 30mL vial configuration with variable fill volume.

Drug Substance:
The active ingredient, sodium ^{18}F-fluoride, has the molecular formula of $Na^{18}F$ and a molecular weight of 40.99.
The CMC information of the drug substance is provided in DMF 21582 (holder is SMI- PETNET). The DMF contains all the CMC aspects of the manufacturing process of Sodium Fluoride F 18 drug substance and drug product. The main steps include the (b) (4)

(b) (4)

The above DMF 21582 was reviewed and found acceptable.

Drug Product:
Sodium Fluoride F18 Injection is a ready-to-use isotonic, sterile, pyrogen-free, clear and colorless solution. Each mL of solution contains between 370 to 7,400 MBq/mL (10 to 200 mCi/mL) of ^{18}F-fluoride, at the EOS (reference time) in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8.0. The solution does not contain preservatives. Sodium Fluoride F18 Injection is presented in a multiple-dose Type 1 glass vial with elastomeric stoppers and aluminum caps. The product does not contain preservatives; its shelf life is 12 hours after End of Bombardment (EOS).
The product is a multiple dose presentation and. (b) (4)

Specifications include: appearance, clarity, particulates, radiochemical identity and purity, radionuclide identity and purity, specific activity, filter integrity, radioactive concentration, pH, bacterial endotoxin and sterility.
All the CMC information for drug substance and drug product was provided in DMF 21582 (holder: SMI-PETNET). The DMF was reviewed and found acceptable.

Overall Conclusion: The NDA is recommended for approval.

Ali Al-Hakim, Ph.D.
Branch Chief, Division III
ONDQA/CDRR/FDA

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/s/

ALI H AL HAKIM
02/01/2011

NDA 22-494

Sodium Fluoride F 18 Injection

National Institutes of Health
National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Imaging Program

Milagros Salazar Driver, Ph.D., Review Chemist
ONDQA-Division of New Drug Quality Assessment III
Branch VII

For
OND-ODE IV
Division of Medical Imaging Products

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Chemistry Review Data Sheet

1. NDA 22-494

2. REVIEW # 2

3. REVIEW DATE: 14-Jan-2011

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
See Review #1	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission (N-011 in DARRTS) –RS Incomplete	12-May-2010
Resubmission (N-016 in DARRTS) – RS/Class2	26-Jul-2010
Amendment (N-013 in DARRTS)-BH	1-Dec-2010
Amendment (N-014 in DARRTS)- BL	6-Dec-2010
Amendment (N-015 in DARRTS)-QR/BL	27-Dec-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Cancer Imaging Program Division of Cancer Treatment and Diagnostics National Cancer Institute
Address:	6130 Executive Blvd. MSC 7412 Suite 6000 Bethesda, MD 20892-7412
Representative:	Paula Jacobs, Ph.D. Regulatory Affairs Director
Telephone:	301-496-9531 Direct line: 301-435-9181 Fax: 301-480-3507 jacobsp@mail nih.gov

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Sodium Fluoride F 18 Injection
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: PET Radiopharmaceutical

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 370 to 7,400 MBq/mL (10 to 200 mCi/mL) @ EOS

13. ROUTE OF ADMINISTRATION: Intravenous

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:

Chemical name: Sodium Fluoride F 18
Structural/ Molecular Formula: Na ^{18}F
MW: 40.99

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	LoA
21582	II	Siemens Molecular Imaging, Inc.	Na [^{18}F]-fluoride Injection	1	Adequate	12-Jan-2011	16-Sep-2008
							(b) (4)

** The reference to this submission was withdrawn in the 27-Dec-2010 amendment.

[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
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Compliance Status: Acceptable	1-Dec-2010	Office of Compliance
Pharm/Tox	N/A (502(b)(2)		
Biopharm	N/A (502(b)(2)		
LNC	Not requested- name as per USP, USAN		Milagros Salazar, Ph.D.
Methods Validation	N/A- Test methods are as per USP monograph		Milagros Salazar, Ph.D.
SEALD	SEALD cannot review	2-Mar-2009	Jeanne Delasko
DDMAC (DMEPA)	Comments	2-Mar-2009	Michelle Safarik, PA-C
EA	Categorical Exclusion claimed and granted under 21CFR 25.31(b).	10-Mar-2009	Milagros Salazar, Ph.D.
Microbiology	See Microbiology Review	Pending	Robert Mello, Ph.D.

N/A = Not Applicable

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

N/A = Not Applicable

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

File name: N 22-494 Na F18 fluoride Inj-Rev2.doc

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is Approvable for the chemistry, manufacturing and controls (CMC) as stated in 21 CFR 314.50, pending acceptable microbiology quality review.

The CMC sections for Sodium Fluoride F 18 Injection final drug product are referenced in one drug master file (DMF) 21582 from by Siemens Molecular Imaging-PETNET Solutions Inc. (SMI-PETNET) which is the manufacturer and distributor for this product. The review of this DMF was acceptable from the CMC perspective, the microbiology review is covered under separate review assessment.

The Office of Compliance has issued acceptable overall recommendation dated 01-Dec-2010) for the SMI-PETNET, Durham, NC manufacturing facility

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

None

II. Summary of Chemistry Assessments

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

Sodium Fluoride F18 Injection is a radioactive agent for diagnostic osteogenic activity using Positron Emission Tomography (PET). It is an aqueous sterile, pyrogen free solution of no-carrier-added sodium fluoride F18 in 0.9% sodium chloride with strength of 370 to 7,400 MBq/mL (10 to 200 mCi/mL) at the end of synthesis, EOS, calibration. It is a multiple dose, preservative free and is presented in 30 mL vials with variable volume and total radioactivity per vial.

The active ingredient, sodium ^{18}F-fluoride, has the molecular formula $Na^{18}F$ with a molecular weight of 40.99 with the following chemical structure: $Na^{+18}F^{-}$. ^{18}F-fluorine decays by positron (β+) emission and has a half-life of 110 (109.7) minutes. Ninety-seven percent of the decay results in emission of a positron with a maximum energy of (b) (4) and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the annihilation interaction of the emitted positron with an electron. Fluorine F18 decays into a stable oxygen O18 atom.

Sodium Fluoride F 18 Injection will be manufactured for NCI by SMI-PETNET via a reference to DMF 21582, Type II and following procedures that conform to the USP General Chapter <823> Radiopharmaceuticals –For PET Compounding and with the USP monograph for Sodium Fluoride F 18 Injection. SMI-PETNET manufactures the

product [redacted] (b) (4)

Sodium Fluoride F18 Injection is a ready-to-use isotonic, sterile, pyrogen-free, clear and colorless solution. Each mL of solution contains between 370 to 7,400 MBq/mL (10 to 200 mCi/mL) of ^{18}F-fluoride, at the EOS (reference time) in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8.0. The solution does not contain preservatives. Sodium Fluoride F18 Injection is presented in a multiple-dose Type 1 glass vial with elastomeric stoppers and aluminum caps. The product does not contain preservatives; its shelf life is 12 hours after EOS.

In the original submission of 12-May-2010, DMFs 21582/SMI-PETNET and [redacted] (b) (4) (the second proposed supplier) were referenced as containing the complete CMC sections in support of drug product for this NDA. A DMF deficiency letter was issued to SMI-PETNET on 17-Jun-2009, the holder responded in the DMF amendment of 25-Mar-2010. After CMC review #2 for this DMF, a second deficiency letter was issued on 10-Sep-2010. The responses from SMI-PETNET were provided in DMF amendment dated 6-Jan-2011. The responses were reviewed and found to be acceptable.

On the other hand, a DMF deficiency letter was also issued to [redacted] (b) (4) on 23-Jun-2009, the holder responded with DMF amendment of 8-Feb-2010. After CMC review #2 for this DMF, a second deficiency letter was also issued on 10-Sep-2010. In a T-con with [redacted] (b) (4) on 20-Dec-2010, the holder stated that they would not be able to have the responses available before the NDA due date and they would inform the NDA applicant about it.
In amendment dated 27-Dec-2010, the applicant decided to withdraw [redacted] (b) (4) as a supplier of drug product because the DMF holder can not respond to the agency's deficiency letter in a timely manner (before PDUFA date) .

SMI-PETNET, the holder of DMF 21582, is the manufacturer, quality control and labeler of the radionuclide, drug substance and drug product as well as the distributor of the Sodium Fluoride F18 Injection. Therefore, the review of the CMC content of this DMF has been treated as it would be the information and data in an NDA application. During the review process of this application, there has been a concern about how the CMC changes will be controlled and incorporated into the NDA application from the DMF holder manufacturer and after approval. The applicant was asked to provide information to address this concern and to include the report of adverse events as a post-marketing controls and surveillance. The applicant has provided an acceptable comprehensive protocol, SOP 22-494-001: "Post-approval coordination between NCI and Drug Master File holders who supply Sodium Fluoride F18 Injection for NCA NDA 22-494."

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

Sodium Fluoride F18 Injection is indicated for diagnostic PET imaging of areas of altered osteogenic activity. The product is a multiple dose presentation and it is preservative free. (b) (4) It is intravenously administered with doses ranging from (b) (4) 740 MBq (0.5 to 20 mCi). The imaging of Sodium Fluoride F18 under a PET camera is recommended to begin 1-2 hours after administration.

Sodium Fluoride F18 Injection is to be used for 12 hours after EOS calibration.

Sodium Fluoride F18 Injection is manufactured for the National Cancer Institute, Division of Cancer Treatment and Diagnosis, Cancer Imaging Program, Bethesda, MD, the sponsor of this NDA, by Siemens Molecular Imaging-PETNET Solutions, Inc., Knoxville, TN 37932 (corporate address). The distribution of Sodium Fluoride F18 Injection is also performed by SMI-PETNET Solutions, Inc. in Durham, NC which is the approved manufacturing site and is the sole supplier of the drug product under this NDA.

C. Basis for Approvability or Not-Approval Recommendation

The application is Approvable, based on the CMC requirements in 21 CFR 214.50, pending an acceptable microbiology review.

III. Administrative

A. Reviewer's Signature: (in DARRTS)

B. Endorsement Block

Chemist, ONDQA Div. III-Branch VII: Milagros Salazar, Ph.D.
CMC Lead ONDQA Div. III-Branch VII: Eldon Leutzinger, Ph.D.
Branch Chief ONDQA Div. III-Branch VII: Ali Al Hakim, Ph.D.
Project Manager, OND/ODEIV/DMIP: James Moore
Project Manager, ON ONDQA Div. III-Branch IX DQA: Youbang Liu

C. CC Block

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/s/

MILAGROS SALAZAR DRIVER
01/14/2011
CMC Recommendation: Approvable pending Microbilogy review.

ALI H AL HAKIM
01/14/2011

NDA 22-494

Sodium Fluoride F 18 Injection

National Institutes of Health
National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Imaging Program

Milagros Salazar Driver, Ph.D., Review Chemist

For the
Division of Medical Imaging and Hematology Products

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I. Overview- Description of Drug Substance and Drug Product 11

II. List of manufacturing sites which manufacture and distribute the drug substance / drug product. 12

III. Drug Substance / Drug Product Specifications. 15

IV. Protocol for Changes and Post-approval Stability Protocol. 20

V. Labeling: Package Insert and Product Labels. 23

VI. Environmental Assessment 33

VII. Responses to CMC deficiencies. 34

VIII. List of Deficiencies to be Communicated, for the CR letter. 42

Chemistry Review Data Sheet

1. NDA 22-494

2. REVIEW #: 1

3. REVIEW DATE: 6-Jun-2009

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NONE	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-Dec-2008
Amendment N-000 BZ	3-Feb-2009 revised SPL; LoA DMF (b) (4)
Amendment N-000 BC	6-Feb-2009 establishments info.
Amendment N-000 BC	19-Feb-2009 removal of (b) (4) as manufacturer
Amendment N-000 BZ (4)	31-Mar-2009 with 3/10/09 label
Amendment N-000 BC (5)	10-Apr-2009 Updated establishments info.
Amendment N-000 BC (6)	24-Apr-2009 Draft change protocol
Amendment N-000 BC (7)	11-May-2209 CMC responses, specs, labels

7. NAME & ADDRESS OF APPLICANT:

Name:	Cancer Imaging Program Division of Cancer Treatment and Diagnostics National Cancer Institute
Address:	6130 Executive Blvd. MSC 7412 Suite 6000 Bethesda, MD 20892-7412
Representative:	Paula Jacobs, Ph.D. Regulatory Affairs Director 301-496-9531
Telephone:	Direct line: 301-435-9181 Fax: 301-480-3507 jacobsp@mail.nih.gov

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Sodium Fluoride F 18 Injection
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: PET Radiopharmaceutical

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 370 to [redacted] (b) (4) MBq/mL
(10 to [redacted] mCi/mL) @ EOS

13. ROUTE OF ADMINISTRATION: Intravenous

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:

Chemical name: Sodium Fluoride F 18
Structural/ Molecular Formula: Na ^{18}F
MW: 40.99

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	LoA
21582	II	Siemens Molecular Imaging, Inc.	Na [^{18}F]-fluoride Injection	1	Deficient	24-May-2009	16-Sep-2008
[redacted] (b) (4)							

[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
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Compliance Status: Pending	9-Mar-2009 2-Jun-2009	Request for Inspection of multiple manufacturing sites to be added to EES database. Compliance Status: Pending All sites had 483, one (b) (4) with a VAI and another (b) (4) with OAI (warning letter)
Pharm/Tox	N/A (502(b)(2)		
Biopharm	N/A (502(b)(2)		
LNC	Not requested- name as per USP, USAN		Milagros Salazar, Ph.D.
Methods Validation	N/A- Test methods are as per USP monograph		Milagros Salazar, Ph.D.
SEALD	SEALD cannot review	2-Mar-2009	Jeanne Delasko
DDMAC	Comments	2-Mar-2009	Michelle Safarik, PA-C
EA	Categorical Exclusion claimed and granted under 21CFR 25.31(b).	10-Mar-2009	Milagros Salazar, Ph.D.
Microbiology	Fileable Deficient DMFs	3-Feb-2009 12-May-2009	Robert Mello, Ph.D.

N/A = Not Applicable

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

N/A = Not Applicable

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

File name: N 22-494 Na F18 fluoride Inj-Rev1.doc

Chemistry Review for NDA 22-494

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for a Not-Approval action based on the chemistry, manufacturing and controls (CMC) deficiencies under 505(b)(2) of the Act. The CMC sections for Sodium Fluoride F 18 Injection for this application were referenced in two drug master files (DMF) one from Siemens-PETNET and the other from (b) (4) which are the manufacturers and distributors of this drug product. After a comprehensive review of the DMFs from each manufacturer, they were found to be deficient from the CMC and the Microbiology perspective. The NDA itself does not provide the means to assure that the CMC changes made by the manufacturers of the drug product will be in the control of the applicant to support the quality and safety use of this product.

The Office of Compliance overall recommendation is pending, as of the date in this review. The six drug product manufacturing facilities proposed in this application were inspected and were issue 483 citations with a recommendation for a warning letter to one of the sites.

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

None

II. Summary of Chemistry Assessments

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

Sodium Fluoride F18 Injection is a radioactive agent for diagnostic osteogenic activity using Positron Emission Tomography (PET). It is an aqueous sterile, pyrogen free solution of no-carrier-added sodium fluoride F18 in 0.9% sodium chloride with strength of 370 to (b) (4) MBq/mL (10 to (b) (4) mCi/mL) at the end of synthesis, EOS, calibration. It is a multiple dose vial and it is preservative free, it is presented in (b) (4) 30 (b) (4) mL with variable volume and total radioactivity per vial.

The active ingredient, sodium ^{18}F-fluoride, has the molecular formula $Na^{18}F$ with a molecular weight of 40.99 with the following chemical structure: $Na^{+}{}^{18}F^{-}$. ^{18}F-fluorine decays by positron (β+) emission and has a half-life of 110 (109.7) minutes. Ninety-seven percent of the decay results in emission of a positron with a maximum energy of (b) (4) and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging

are the 511 keV gamma photons, resulting from the annihilation interaction of the emitted positron with an electron. Fluorine F18 decays into a stable oxygen O18 atom.

The manufacturing of sodium fluoride F18 injection is a continuous process with simultaneous production of the drug substance and drug product. It includes the following: [redacted] (b) (4)

Sodium Fluoride F 18 Injection will be manufactured for NCI by Siemens Molecular Imaging, PETNET Solutions (DMF 21582, Type II) and by [redacted] (b) (4) following procedures that conform to the USP General Chapter <823> Radiopharmaceuticals –For PET Compounding and with the USP monograph for Sodium Fluoride F 18 Injection. PETNET manufactures the product [redacted] (b) (4)

Sodium Fluoride F18 Injection is a ready-to-use isotonic, sterile, pyrogen-free, clear and colorless solution. Each mL of solution contains between 370 to [redacted] (b) (4) MBq/mL (10 to [redacted] (b) (4) mCi/mL) of ^{18}F-fluoride, at the EOS (reference time) in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8.0. The solution does not contain preservatives. Sodium Fluoride F18 Injection is presented in a multiple-dose Type 1 glass vial with elastomeric stoppers and aluminum caps. The shelf life is 12 hours after EOS.

DMFs 21582-Siemens [redacted] (b) (4) were referenced as containing the complete CMC sections in support of drug product for this NDA. The DMF holders received deficiency letters that were responded to with amendments to their respective DMF applications. The review status for both DMFs is deficient, based on lack of information and data regarding the target material [redacted] (b) (4) drug product manufacturing processes, specifications of analytical methods and their validation, container closure system information, drug product compatibility and labeling.

The DMF holders are the manufacturers of the radionuclide, drug substance and drug product and distributors of the drug product. Therefore, there is a concern about how the CMC changes will be controlled and incorporated into the NDA application in the future. The NDA was asked about information and after a deficiency letter and discussions with the applicant, a detailed path and a comprehensive protocol are still missing to assure that the CMC changes in the DMF are captured an incorporated under the control of the NDA application.

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

Sodium Fluoride F18 Injection is indicated for diagnostic PET imaging of areas of altered osteogenic activity. It is intravenously administered with [redacted] (b) (4) to 740 MBq (0.5 to 20 mCi). The imaging of Sodium Fluoride F18 is recommended to begin 1-2 hours after administration.

Sodium Fluoride F18 Injection is to be used for 12 hours after EOS calibration.

FDA approved Sodium Fluoride F 18 Injection, 2 mCi/mL, (NDA 17-042) as a bone imaging agent to define areas of altered osteogenic activity in 1972. The NDA holder, Nycomed Amersham (now GE Healthcare) stopped marketing the drug in 1975. There was a Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons and the product is listed in the FDA Discontinued Drug Products List. Since the strength of the originally approved product is different from the proposed one in this application, the applicant opted for a 505(b)(2) application following the Guidance for Industry: PET Drug Applications. Based on the lack of availability of a PET bone diagnostic agent in the market and the fact that there are sporadic shortages of molybdenum (parent of technetium Tc 99m) required for the preparation of the Tc 99m-diphosphonates (currently the only available bone agents for the diagnostic imaging), the Agency designated this application to have priority review status.

Sodium Fluoride F18 Injection is manufactured for the National Cancer Institute, Division of Cancer Treatment and Diagnosis, Cancer Imaging Program, Bethesda, MD, the sponsor of this NDA, by Siemens Molecular Imaging-PETNET Solutions, Inc., Knoxville, TN 37932 and [redacted] (b) (4). The distribution of Sodium Fluoride F18 Injection is also done by Siemens-PETNET [redacted] (b) (4).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for a Not-Approval action based on the failure to satisfy the chemistry, manufacturing and controls (CMC) under section 505 (b)(2) of the Act. The bases for the recommendation of the Not-Approval action are the following:

- The DMF review status is deficient for both DMF holders Siemens-PETNET and [redacted] (b) (4) which are the manufacturers of the radionuclide, drug substance and drug product and distributors of the drug product.
- The NDA path to assure control over changes made in the CMC by the DMF holders of this drug product is lacking.
- A document identifying labeling and distribution controls for the product approved under NDA regulations is not provided.

- All six drug product inspection sites were inspected and issued 483 citations with five having a VAI status and one OAI – status and withhold recommendation, the office of compliance overall recommendation is pending.

III. Administrative

A. Reviewer's Signature: (in DFS)

B. Endorsement Block

Chemist: Milagros Salazar, Ph.D./Date:
Pharmaceutical Assessment Lead: Eldon Leutzinger, Ph.D./Date:
Branch Chief: Sarah Pope, Ph.D./Date:
Project Manager, OND: Thuy Nguyen, M.P.H./Date:
Project Manager, ONDQA: Deborah Mesmer/Date:

C. CC Block

35 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

Milagros Salazar
6/10/2009 04:19:31 PM
CHEMIST
CMC recommendation: Not Approval.
CMC Review #1.

Eldon Leutzinger
6/10/2009 04:24:48 PM
CHEMIST

Sarah Pope
6/11/2009 09:23:33 AM
CHEMIST