# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022494Orig1s000

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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| **Date** | January 26, 2011 |
| **From** | Dwaine Rieves, MD<br>Director, Division of Medical Products |
| **Subject** | Division Director Review |
| **NDA/BLA #** | 22-494 (a 505b2 application) |
| **Applicant Name** | National Cancer Institute (NCI) |
| **Date of Submission** | December 30, 2008 for first cycle<br>July 26, 2010 for second (current) cycle |
| **PDUFA Goal Date** | January 26, 2011 |
| **Proprietary Name / Established (USAN) Name** | (no proprietary name) Sodium Fluoride F-18 Injection |
| **Dosage Forms / Strength** | 30 mL Multiple dose vial presentation containing 10 to 200 mCi/mL of sodium fluoride in 0.9% saline |
| **Proposed Indication(s)** | "indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity." |
| **Action/Recommended Action for NME:** | Approval |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Project Manager | Thuy Nguyen, M.P.H. for first cycle<br>James Moore, PharmD for second cycle |
| Medical Officer Review | Michele Fedowitz, MD for first cycle<br>Ross Filice, MD for second cycle |
| Statistical Review | Not Applicable (relies solely on prior determination of safety and efficacy for previously approved product) |
| Pharmacology Toxicology Review | Adebayo Laniyonu, PhD |
| CMC Review/OBP Review | Milagros Salazar, PhD/Eldon Leutzinger, PhD |
| Microbiology Review | Robert Mello, PhD/Bryan Riley, PhD |
| Clinical Pharmacology Review | Christy John, PhD |
| DDMAC | Michelle Safarik, PA-C |
| DSI | No assignment (not applicable) |
| CDTL Review | Louis, Marzella, MD, PhD |
| OSE/DMEPA | Not applicable (505b2) |
| OSE/DDRE | Not applicable (505b2) |
| Pediatric and Maternal Health | Not applicable (505b2) |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations

DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader

## 1. Introduction:

This 505b2 New Drug Application (NDA) is currently completing a second cycle review. The first cycle was initiated in 2008 and was closed with issuance of a Complete Response, due to deficiencies in a drug master file (DMF). The current (second) cycle was initiated in July, 2010. This review has been somewhat complicated because most of the important information (CMC/microbiology) was contained within DMFs which are held by non-NCI sponsors and the referencing has changed during the review process.

This NDA was submitted by the NCI to support the use of Sodium Fluoride F18 Injection for the indication cited above. The applicant's clinical, preclinical, pharmacology and toxicology data predominantly relate to citation to FDA's March 10, 2000 Federal Register notice that stated FDA has approved F18 Sodium Fluoride injection (NDA 17042) in 1972 for use in defining areas of altered osteogenic activity and that the drug was withdrawn from marketing in 1975 for reasons other than safety or efficacy. The applicant did provide 41 published reports pertaining to the use of F18 sodium fluoride injection. Hence, the bulk of the review contents for this application pertained to manufacturing information.

The original manufacturing information supplied by the applicant was particularly challenging because the applicant's entire information was contained within referenced Drug Master Files (one held by Siemens Molecular Imaging and the other by (b) (4) ). The final approval pertains to information held within the Siemens Molecular Imaging DMF).

Together, the review disciplines found the overall risk-benefit profile favorable. Of note, the clinical review team determined that the published data were sufficient to support labeling of the product for use in children and dosing information has been incorporated into the label.

## 2. Background:

Positron emission tomography (PET) products have a complicated regulatory history that has involved federal register notices, public workshops and certain user fee agreements. However, F18 sodium fluoride regulatory history is relatively straightforward as follows:

-1972 FDA approved sodium fluoride F18 injection (Nycomed Amersham) for use as a bone imaging agent to define areas of altered osteogenic activity

-1975 Marketing of sodium fluoride F18 injection suspended for commercial reasons (not safety concerns)

The NCI notes in the current application that they are relying upon FDA's prior findings of safety and efficacy (the Federal Register notice from 2000) for the previously product. The NCI also notes that they regard approval of their product as important because of periodic shortages of technetium 99m, a major component of the product currently used in bone scans. Hence, approval of sodium flouride F18 injection would, in the applicant's opinion, help provide an alternate diagnostic modality when conventional bone scans can not be performed due to drug shortages.

**3. Chemistry, Manufacturing and Controls:**

I concur with the conclusions reached by the chemistry reviewer (Dr. Salazar) regarding the acceptability of the manufacturing of the product. Multiple manufacturing deficiencies were identified during the first cycle and these issues were resolved, particularly by narrowing the number of proposed production facilities (withdrawal of reference to the (b) (4) DMF). No facility inspectional issues have been identified.

**4. Nonclinical Pharmacology/Toxicology:**

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. No post-marketing commitments/requirements were requested.

**5. Clinical Pharmacology/Biopharmaceutics:**

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. No outstanding issues were identified and no post-marketing commitments were requested.

**6. Clinical Microbiology:**

Multiple microbiology deficiencies were evident in the drug master files and I concur with the reviewer (Dr. Mello) regarding the insufficiency of the available information.

**7. Clinical/Statistical-Efficacy:**

Dr. Michele Fedowitz provided the clinical review for this initial cycle and Dr. Louis Marzella provided the secondary review. Dr. Ross Filice conducted the second cycle review. I concur with these major findings and recommendations. Importantly, 41 publications were reviewed, including a few that cited use of the product in children. No non-publication data were submitted.

**8. Safety:**

As noted above, the applicant has relied upon FDA's prior finding of safety and efficacy for F18 sodium fluoride injection (1972 approval). The review of the 41 submitted publications found no information that altered the risk-benefit assessment that supported the 1972 approval.

***Post-marketing Requirements (PMR):***

No PMR or PMC are anticipated.

**9. Advisory Committee Meeting:**

This application was not presented to an Advisory Committee because the product relies upon FDA's prior finding of safety and efficacy for a very similar product. This application is not for a new molecular entity.

**10. Pediatrics:**

The supplied pediatric plan was a request for waiver of all pediatric studies. However, the review team regards the published data as sufficient to support the use of the product in pediatric patients and dosage information has been incorporated into the label.

**11. Other Relevant Regulatory Issues:**

Overall, the review team found the application acceptable and I concur with the plans for approval. In a telephone conversation with the sponsor (January 25, 2011), the sponsor noted that they did not wish for us to comment upon any plans for marketing of the drug within an action letter.

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RAFEL D RIEVES
01/26/2011