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RESEARCH**

*APPLICATION NUMBER:*

**022494Orig1s000**

**OTHER ACTION LETTERS**



**NDA 22-494**

**COMPLETE RESPONSE**

National Cancer Institute/DCTD/Cancer Imaging Program  
Attention: Paula M. Jacobs, Ph.D.  
6130 Executive Blvd  
EPN – Suite #6000  
Bethesda, MD 20892-7412

Dear Dr. Jacobs:

Please refer to your new drug application (NDA) dated December 30, 2008, received December 31, 2008, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sodium Fluoride [F-18] Injection.

We acknowledge receipt of your amendments of February 3, 6, and 19, March 10 and 31, April 10 and 24, and May 11, 2009.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

**CHEMISTRY**

1. Drug Master File (DMF) 21528-Siemens Molecular Imaging-PETNET and DMF (b) (4) were reviewed and were found to be deficient in support of this NDA. The DMF holders have been informed of the specific nature of these deficiencies.
2. Provide revisions to the Drug Substance section of your application to:
  - a. correct the nuclear reaction, which should be (b) (4)
  - b. include additional information on the radioactive characteristics of F 18, such as decay mode, energy of emissions, CAS number, etc.
3. Revise the application to include the radiochemical identity (RCId) acceptance criteria for the Siemens product. The Siemens product does not comply with the USP monograph for RCId criteria since it does not use an HPLC chromatographic system.

**CHEMISTRY (cont.)**

4. Regarding the chemistry amendment submission dated April 24, 2009: Include revisions to the draft protocol for control of changes, as specifically outlined below.
  - a. (Section 1): No revision necessary; see deficiency #5 below.  
(Section 2): Confirm that any additional DMF holder will be added to the Appendix A list via a post-approval supplement. Also confirm that any such supplements will contain full CMC sections, either inclusively or via cross-reference to a DMF, validation data for three lots tested at release and expiry, and a statement of readiness for FDA inspection.
  - b. (Section 3): List the purpose statement as an independent "Purpose:" paragraph after the "Scope:" paragraph.
  - c. (Section 4):
    - Section 4a: Insert "Chemistry, Manufacturing and Controls" in place of "Manufacturing Process and Quality Control"*
    - Section 4b. Insert "Quality Control Specifications (acceptance criteria and analytical methods)" for the drug product in place of "Quality Control Specification." Add a statement to also include the report of any changes in the quality control specifications or suppliers of the target material, (b) (4)*
    - (b) (4) Clarify the meaning of the following text, "– see number 0 below."*
    - Section 4c: No revision necessary*
    - Section 4d: No revision necessary*
    - Section 4e: Revise to separate addition and removal of sites. State the reason for the removal of approved sites.*
    - Section 4f: Confirm that new sites will be added to the NDA only after a pre-approval supplement is filed and approved by FDA.*
  - e. (Section 5): No revision necessary
  - f. (section 6): Revise the headings as follows:
    - Section 6a. Summary of significant changes*
    - Section 6b. Current chemistry, manufacturing and control specifications*
    - Section 6c. List of sites qualified under the NDA*
    - Section 6d. Full information for manufacturer for each site*
    - Section 6e. Distribution data*
    - Section 6f. Stability data, e.g., annual stability data for each manufacturing site*
    - Section 6g. Out of specifications log book entries*
    - Section 6h. Current package insert and product labels*
5. Regarding Appendix A in the protocol for the control of changes, include additional column(s) for sites already inspected, and insert the current cGMP status of each facility and date of last inspection. (b) (4)  
(b) (4) Also include an additional statement regarding the commitment to report the stability data annually for each site approved under the NDA.

**CHEMISTRY (cont.)**

6. Provide a protocol identifying the labeling and distribution practices that distinguish between the commercial NDA Sodium Fluoride F 18 Injection product from any other products manufactured and distributed without FDA approval under a New Drug Application.
7. Revise the immediate container labels to consistently state the same name for the drug product (Sodium Fluoride F 18 Injection), the statement of composition in the vial, the "Prescription only" statement (for the (b) (4) label) and a statement of Total volume (for the PETNET label).
8. Provide the National Drug Code (NDC) numbers for the package insert and all product labels.

**MICROBIOLOGY**

9. DMF # (b) (4) and DMF #21582 (Siemens Molecular Imaging) were reviewed and found to be deficient in microbiology product quality aspects. The DMF holders have been advised of the deficiencies.
10. The use of a (b) (4) mL vial for a multiple-dose drug product is in conflict with the provisions of the "Packaging and Storage" section of USP<1> *Injections* which states "*Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.*" The current USP 32 monograph for Sodium Fluoride F 18 Injection does not currently contain such a provision. Contact the U.S. Pharmacopeia, directly, to request a revision to the "Packaging and Storage" section of the monograph for Sodium Fluoride F 18 Injection to provide for packaging in a (b) (4) mL Type I glass vial. In the absence of such a revision or clear indication that USP is willing to adopt such a revision, the (b) (4) mL vial presentation of the drug product can not be approved.

**LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Submit draft carton and container labeling revised as mentioned in the Chemistry section above.

**FACILITY INSPECTIONS**

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

**PEDIATRIC PLAN**

We have the following additional comments for you to address in your response to this letter. These comments are not a basis for our inability to approve your application. However, we request a response to facilitate our review of the proposed labeling and the need for any post-marketing expectations.

**PEDIATRIC PLAN (cont.)**

1. You have requested a waiver from the performance of any clinical studies in pediatric patients and your proposed product labeling does not include pediatric dosing information. As you emphasized in your cover letter, you regard this product as particularly important for the assessment of patients with cancer. However, you have indicated that you find no compelling indication/disease state in children that would justify radiation exposure. You have also indicated that you regard your product as unlikely to be used in a substantial number of pediatric patients and that clinical studies in pediatric patients would be impossible or highly impractical because the number of patients is so small or geographically dispersed.
2. We are concerned that, despite your proposals, certain pediatric patients with cancer may importantly benefit from the diagnostic use of your product. You have submitted publications which describe the use of sodium fluoride F18 (using weight-based dosing) among approximately 100 pediatric patients. The product was administered in these studies predominantly for the evaluation of back pain, a condition in which the risk and diagnostic benefits of the product may be even more concerning that its use among pediatric patients with cancer. We believe that the safety of sodium fluoride F18 in children can be extrapolated from the published reports and from dosimetry data obtained from patient simulators (as described by the International Commission on Radiologic Protection, ICRP reports 53 and 80). The dosimetry data estimate effective doses of radioactivity ranging from 0.034 to 0.170 mSv/MBq in children ranging in weight from 55 to 9.8 kg; we consider these levels of exposure to be acceptable.
3. Submit revised labeling that addresses the use of your product among pediatric patients with cancer. You may wish to propose labeling applicable to only a subset of pediatric patients (e.g., patients two years of age or older). Alternatively, provide additional justifications to support your contentions regarding the lack of utility as well as the unacceptable safety of your product when used among any pediatric patients with cancer. You may wish to modify your pediatric plan to request a waiver or deferral for the conduct of post-marketing studies among pediatric patients less than two years of age. If so, please include justifications applicable to this age range. We anticipate that your justifications may more reasonably address a limited deferral or waiver request.
4. We anticipate the need for the performance of a dosimetry study among pediatric patients in the post-marketing period. Provide an outline of a protocol to study the radiation dosimetry of the product in at least six pediatric patients in the following, equally represented cohorts:  
2-5 year old, 6-10 year old, and 11-16 year old.
  - a. Include an outline of the major design features of the study, including eligibility, dosing regimens and imaging procedures, clinical assessments to be performed and their timing, and a summary of the dosimetry methodology.
  - b. Supply a time line (month/year) for: the final clinical protocol submission date; the clinical trial completion date; and the final trial report submission date.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings Between the FDA and Sponsors or Applicants* - May 2009:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Rafel Rieves

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