

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number: 021012**

**Trade Name: NEOTECT 50 $\mu$ g PEPTIDE**

**Generic Name: KIT FOR THE PREPARATION OF  
TECHNETIUM Tc 99m DEPREOTIDE INJECTION**

**Sponsor: DIATIDE INC.**

**Approval Date: 08/03/99**

**INDICATION(s): PROVIDES FOR THE USE OF  
NEOTECT, A SCINTOGRAPHIC IMAGING AGENT  
THAT IDENTIFIES SOMATOSTATIN RECEPTOR-  
BEARING PULMONARY MASSES IN PATIENTS  
PRESENTING WITH PULMONARY LESIONS ON  
COMPUTED TOMOGRAPHY AND/OR CHEST X-RAY  
WHO HAVE KNOWN MALIGNANCY OR WHO ARE  
HIGHLY SUSPECT FOR MALIGNANCY.**

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 021012

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	Included	Pending Completion	Not Prepared	Not Required
<u>Approval Letter</u>	X			
<u>Tentative Approval Letter</u>				X
<u>Approvable Letter</u>	X			
<u>Printed Labeling</u>	X			
<u>Medical Review(s)</u>	X			
<u>Chemistry Review(s)</u>	X			
<u>EA/FONSI</u>				X
<u>Pharmacology Review(s)</u>	X			
<u>Statistical Review(s)</u>	X			
<u>Microbiology Review(s)</u>	X			
<u>Clinical Pharmacology</u>	X			
<u>Biopharmaceutics Review(s)</u>				
<u>Bioequivalence Review(s)</u>				X
<u>Administrative/ Correspondence Document(s)</u>	X			

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: 021012**

**APPROVAL LETTER**



Food and Drug Administration  
Rockville MD 20857

NDA 21-012

Diatide, Inc.  
Attention: J.Kris Piper  
Vice President Clinical and Regulatory Affairs  
9 Delta Drive  
Londonderry, New Hampshire 03053

AUG 3 1999

Dear Mr. Piper:

Please refer to your new drug application (NDA) dated June 15, 1998, received June 16, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NeoTect (Kit for the Preparation of Technetium Tc 99m Depreotide Injection) 50  $\mu$ g peptide.

We acknowledge receipt of your submissions dated July 9, 10, 17, 21, 22, 23, 24, 28, 29, and 30; August 7, 13, 14, 26, and 28; September 22, and 23; October 9, 14, and 22; November 4; December 18, 1998; January 21, and 28; February 5, and 12; April 21; May 13, 14, and 21; June 4, 8, 17 and 25; and July 15, 22, and 30, 1999.

This new drug application provides for the use of NeoTect™ (kit for the preparation of Technetium Tc 99m Depreotide Injection) a scintigraphic imaging agent that identifies somatostatin receptor-bearing pulmonary masses in patients presenting with pulmonary lesions on computed tomography and /or chest x-ray who have known malignancy or who are highly suspect for malignancy.

We have completed the review of this application, as amended, including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling agreed to by Diatide, Inc. on July 30, 1999. Accordingly, the application is approved effective on the date of this letter. The revised labeling is attached to this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, and immediate container and carton labels as submitted and agreed to on July 22, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-012." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase IV commitments specified in your submission dated June 25, 1999. These commitments, along with any completion date agreed upon, are listed below.

1.

2.

3. To submit the following data to the NDA by December 31, 2000:
- a) Fully characterize the pharmacokinetic parameters and metabolism for Depreotide peptide
  - b) Fully characterize the pharmacokinetic parameters and metabolism for Technetium Tc 99m Depreotide Injection in geriatric, renally impaired and hepatically impaired patient populations
  - c) Fully characterize the route of elimination for Technetium Tc 99m Depreotide Injection

Protocols, data, and final reports for these Phase 4 commitments should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time it is the policy of the Center for Drug Evaluation and Research not to withhold the approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that on July 30, 1999 you have requested a waiver. We are deferring a decision on your request until the submission of information to support the waiver. This information should include the occurrence of both malignant and nonmalignant somatostatin receptor-bearing pulmonary masses in pediatric populations.

If you believe that this drug still qualifies for a waiver of the pediatric study requirement, within 60 days from the date of this letter you should submit the supporting information and documentation in accordance with the provisions of 21 CFR 314.55. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact James Moore, R.Ph., M.A., Project Manager, at (301) 827-7510.

Sincerely,

[Redacted Signature]

Florence Houn, M.D., M.P.H., F.A.C.P.  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER : 021012**

**APPROVABLE LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-012

DEC 16 1998

Diatide, Inc.  
9 Delta Drive  
Londonderry, NH 03053

Attention: J. Kris Piper  
Senior Director Regulatory Affairs

Dear Mr. Piper:

Please refer to your new drug application (NDA) dated June 15, 1998, received June 16, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NeoTect™ (Kit for the Preparation of Technetium Tc 99m Depreotide Injection).

We acknowledge receipt of your submissions dated July 9, 10, 17, 21, 22, 23, 24, 28, 29, and 30, August 7, 13, 14, 26, and 28, September 22, and 23, October 9, 14, and 22, and November 4, 1998.

We have completed the review of this application, as amended, and it is approvable "as a scintigraphic imaging agent indicated to identify somatostatin receptor bearing pulmonary masses in patients who are highly suspect for malignancy and have pulmonary lesions on computed tomography." Before this application may be approved, however, it will be necessary for you to address the following:

**I. CLINICAL AND STATISTICAL**

- A. The application lacks sufficient detail to fully characterize the safety database to be used in labeling.

The safety database should be reanalyzed by the subsets of patients who received each formulation.

- B. The application lacks sufficient clarity and consistency to determine which patients should be included in the final evaluable database.

Within the efficacy database there are inconsistencies in the narrative and line listings on a) the number of patients with protocol violations of biopsies before NeoTect™ (24 in the narrative; 33 patients in the line listings); b) the number of patients with actual solitary pulmonary nodules (65 in the narrative; 42 based upon computed tomography

data in the line listings); and c) the number of patients reported as false positive for NeoTect™ (7 in the narrative; 17 in the line listings). Also, an additional 4 patients who were reported as not having biopsy data, had data in the line listings.

Please clarify and reconcile the database. A reanalysis of the sensitivity, specificity and accuracy should include these patients.

Also, the analysis of solitary pulmonary nodules was reported for all patients and for the subgroups of patients with lesions of >0 and <3, and those with <6 cm. Please submit an analysis of the subset of patients with lesions of ≥3 and <6 cm.

- C. The application lacks sufficient clarity to determine the labeled recommendations for the imaging section.

Please clarify in detail which medical imaging procedure was primarily used for the final NeoTect™ image interpretation; (planar, SPECT or both).

## II. PHARMACOLOGY/TOXICOLOGY

Dosing Solutions in several studies were not analyzed as required by GLPs. However, formulation records may adequately document the content of the dosing solutions used. Please provide copies of formulation records for the dosing solutions in the pivotal GLP nonclinical toxicology studies with reconstituted technetium Tc 99m P829. These data are requested for study numbers R4.50, R4.52, R4.53, R4.54, R4.56, and R4.57.

## III. HUMAN BIOPHARMACEUTICS

The application did not provide dosimetry information obtained from Study 829-10 in the current NDA. This information was submitted in the IND (Submission date 10/31/95). Please submit this information to the NDA.

## IV. MICROBIOLOGY

In your NDA, [redacted] were not validated at or near the manufacturer's [redacted] specification. Please submit information on the supporting [redacted] that includes [redacted] this specification. If this cannot be accomplished, then [redacted]

[redacted]

[redacted]

**V. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)**

**A. DRUG SUBSTANCE (Including the Final Intermediate):**

1. Your application lacks sufficient information on the [redacted] to adequately assess the [redacted]. In order to resolve this, provide the following information:

(a)

(b)

2. The application lacks sufficient detail and clarity in the Reference Standard section for [redacted]

(a)

(b)

(c)

(d)

3. The application

[Redacted]

(a) [Redacted]

(b) [Redacted]

(c) [Redacted]

[Redacted]

(d) The application

[Redacted]

Revise the specifications for the final intermediate for the following:

(i) [Redacted]

(ii) [Redacted]

(iii) [Redacted]

4.

5.

**B. DRUG PRODUCT:**

1. The application \_\_\_\_\_ in the manufacturing process for the Kit for the preparation of Technetium Tc 99m depreotide.

(a) The application \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ Provide this information.

(b) The \_\_\_\_\_ of the manufacturing process including \_\_\_\_\_  
\_\_\_\_\_ were not provided. \_\_\_\_\_ / may have  
\_\_\_\_\_ as it relates to the formation of

[Redacted]  
Provide this information.

(c)

[Redacted]  
information regarding the final volume.

Please clarify this

(d)

[Redacted]  
information and the results of the test.

Provide this

(e)

[Redacted]

2. The application [Redacted] on the Regulatory Specifications and Analytical Methods.

(a) The [Redacted] described.  
The application indicates that the [Redacted] Please state [Redacted] that will be analyzed [Redacted] Also, provide [Redacted] description [Redacted] ensuring that the [Redacted] sampling [Redacted]

(b) The regulatory specifications for the drug product specify that [Redacted] This is [Redacted]

This

(c) The specification [Redacted] This represents [Redacted] The [Redacted] as stated in your NDA is [Redacted] Therefore, either adjust the specification or explain how you account for the remaining [Redacted]

(d)

(e)

A large rectangular area is redacted with a solid black line. The labels (d) and (e) are positioned to the left of the redaction.

(i)

(ii)

A large rectangular area is redacted with a solid black line. The labels (i) and (ii) are positioned to the left of the redaction.

(f)

A large rectangular area is redacted with a solid black line. The label (f) is positioned to the left of the redaction.

(g)

(h)

(i)

(j)

A large rectangular area with a hand-drawn border and horizontal lines, divided into sections labeled (g), (h), (i), and (j). The lines are slightly irregular, suggesting a hand-drawn or scanned document. The sections are stacked vertically, with (g) at the top, followed by (h), (i), and (j) at the bottom. Each section is roughly rectangular and contains no text or other markings.

(k)

(l)

3. The submission  of the drug product.

(a)

(b)

(c)

Explain this discrepancy.

(d)

4. The application [redacted]  
[redacted]  
(a) [redacted] Provide documented evidence that the [redacted] was [redacted]

(b) In addition to the above, please provide the following information:

- (1) The manufacturer of the [redacted] including reference to the DMF if any,
- (2) The [redacted],
- (3) A copy of the COA from [redacted] used in [redacted]
- (4) Information on the manufacturer, and the DMF reference, if any, for the [redacted]
- (5) Clarify if the same [redacted] will be used for the [redacted]

5. The application lacks sufficient clarity and information on the drug product stability.

(a) The pre-NDA specification for [redacted] was set at [redacted]. In the NDA, this specification was [redacted]. It appears that the following observations do not support a [redacted] of the specification.

The [redacted] detector was changed from [redacted] to [redacted] radioactivity over a wider range. This led to [redacted] in the [redacted] of [redacted]

The data in [redacted] indicates that the [redacted] for the product [redacted] has been [redacted] months storage. Also [redacted] describes the [redacted] for the [redacted]

Data on [redacted] suggests that the [redacted] resulted in [redacted] as well as the [redacted] with [redacted]. Specifically, the [redacted]

[REDACTED]

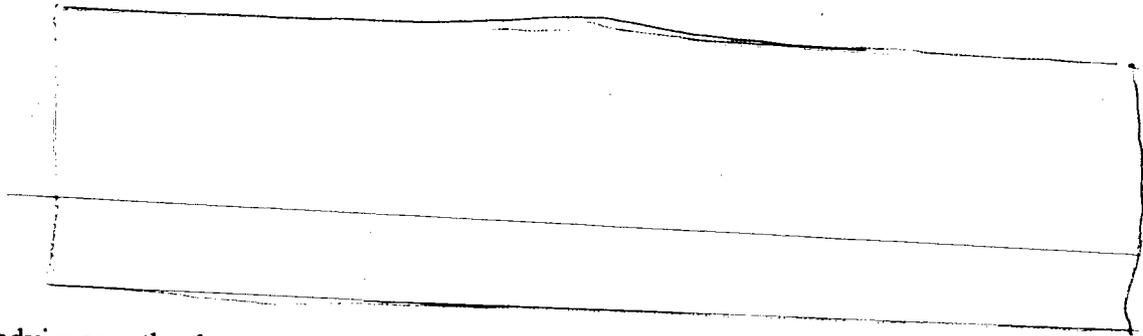
Therefore, reestablish the [REDACTED] at [REDACTED] and, if necessary, [REDACTED] the [REDACTED]

(b) The data indicated that an [REDACTED] produces a [REDACTED] that meets specifications [REDACTED]. The [REDACTED] appears to [REDACTED] of incubation during [REDACTED]. Changing the [REDACTED] rather than the proposed [REDACTED] may not be sufficient to achieve the required [REDACTED]. Provide an explanation for the [REDACTED] with supporting data.

(c) The application lacks sufficient clarity to demonstrate that the [REDACTED] of determining [REDACTED] seem to indicate that the [REDACTED] is sufficiently [REDACTED] to detect all [REDACTED].

A comparison of [REDACTED] reveals that the [REDACTED] remained [REDACTED] over time after [REDACTED]. However, the [REDACTED] data show a [REDACTED] with time after [REDACTED]. In addition, [REDACTED] indicates that the [REDACTED] with time [REDACTED]. However, the [REDACTED] data indicate an [REDACTED] with after [REDACTED].

Additionally, while [REDACTED] methods [REDACTED] for the [REDACTED] samples of [REDACTED], they did [REDACTED] as seen from the [REDACTED] and [REDACTED]. Also, although the [REDACTED] results seem to indicate that the [REDACTED] indicates that the [REDACTED]. Therefore, an [REDACTED] may or may not [REDACTED] with an [REDACTED] for the samples not stored at the [REDACTED].

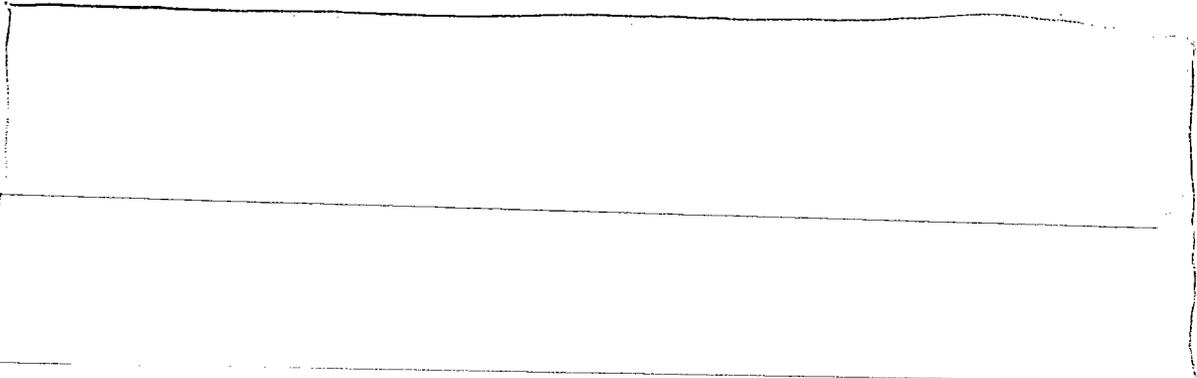


Also, we advise you that based upon the issues discussed under the phase 4 commitments item 10, the data are sufficient to support an expiration date of 12 months, only.

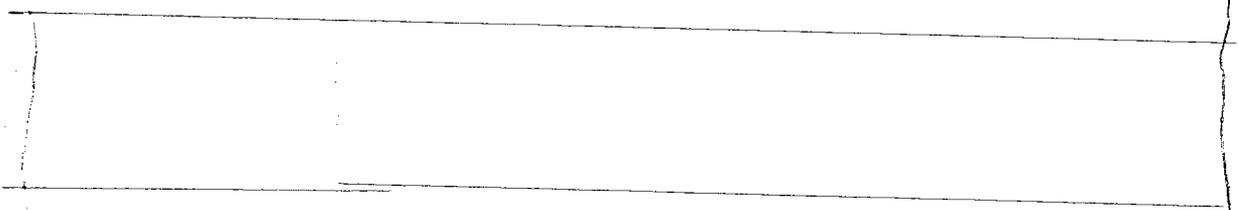
In addition, we request that you commit to the following Phase 4 commitments.

**I. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)**

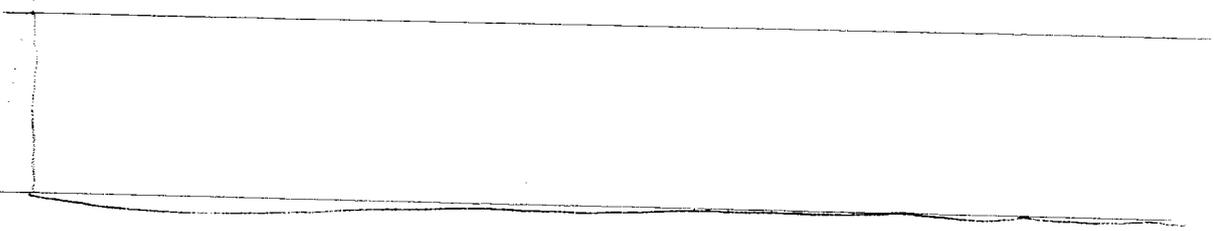
1.



2.



3.



4.

5.

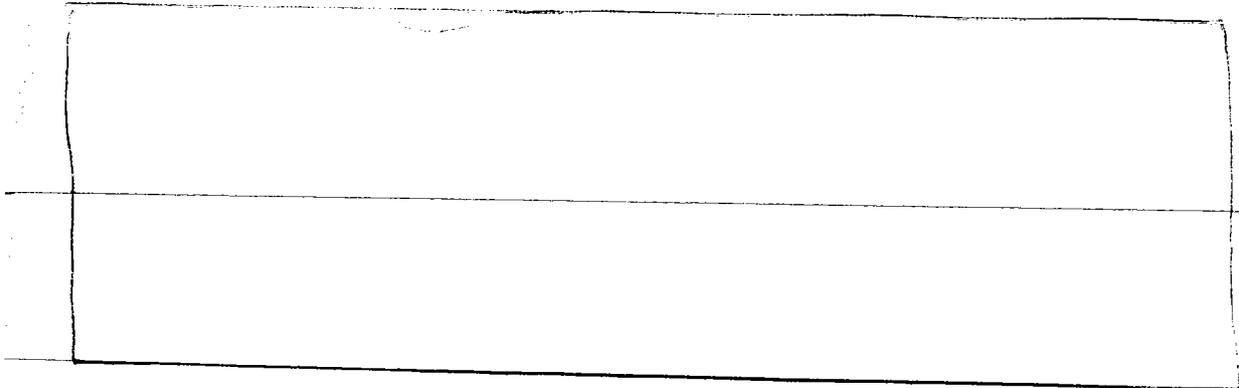
6.

7.

8.

9.

10.



In addition, although not required for approval, we have the following comments and requests for information.

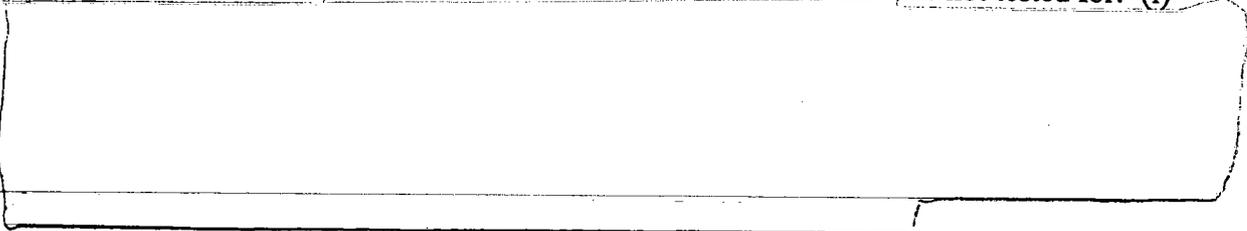
**I. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)**

The NDA requires clearly defined SOPs for controlling the entire manufacturing process from [redacted] to the [redacted] of drug product. For example, the responsibility for lots of the [redacted] received by [redacted] meeting all specifications rests with Diatide. Please submit a detailed SOP(s) that describes how depreotide will be controlled throughout the entire manufacturing process.

1. Although the [redacted] is used for [redacted] some data such as [redacted] to support the suitability of the method to your drug product and under your operating conditions should be included in the NDA. Submit the applicable SOP and validation data on the assay of particulate matter.

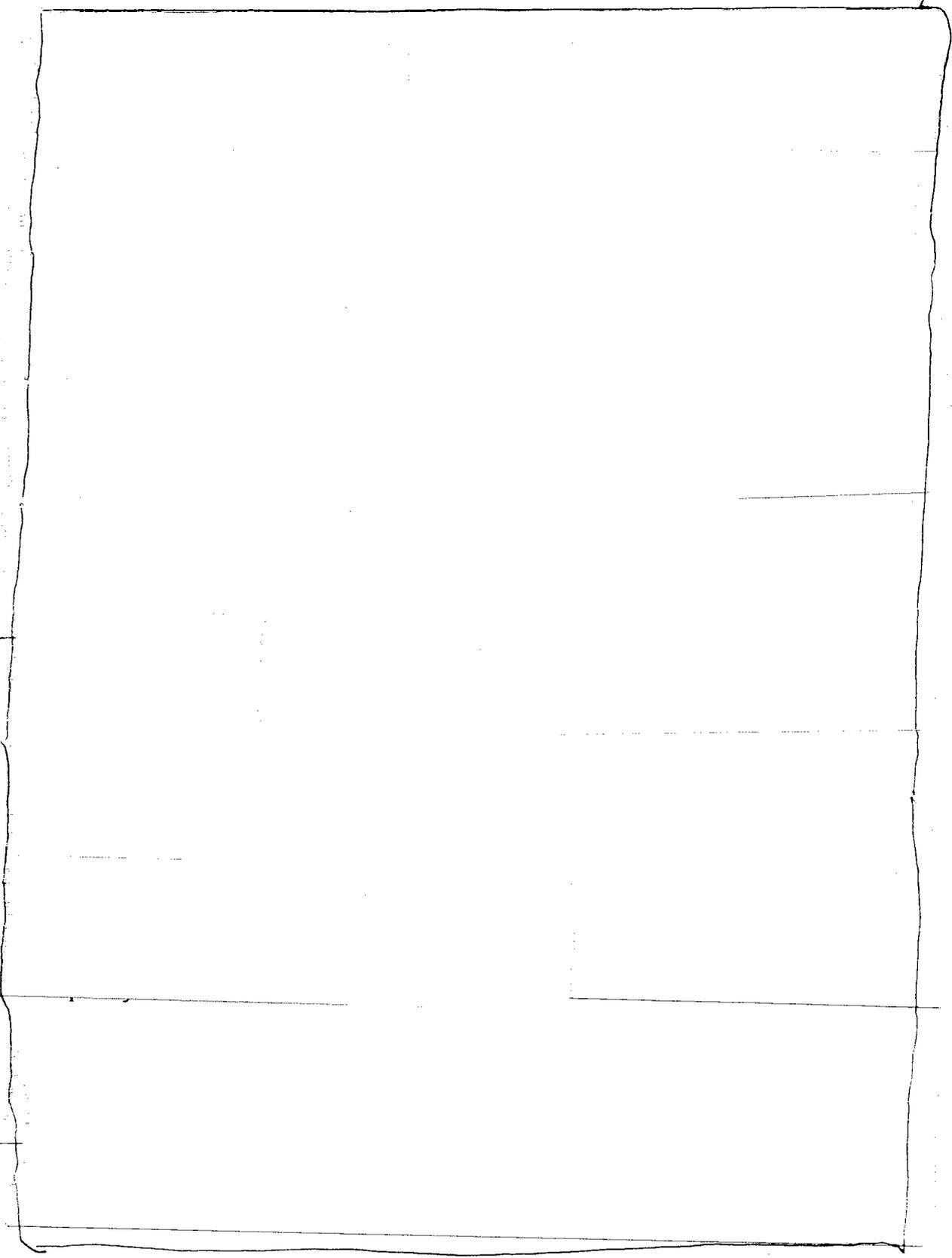
2. Please explain why [redacted] were preferred by Diatide over [redacted] used by [redacted]. Although it appears that it was a minor change in the [redacted] please explain if it would have influenced [redacted].

3. The NDA states that the [redacted] was not tested for: (i)



4. Please refer [redacted]. The [redacted] at [redacted] interacts with the [redacted] (but the assignment in the figure seems to indicate that the [redacted]). Please resolve this discrepancy.

- 5.
- 6.
- 7.
- 8.
- 9.
- 10.
- 11.
- 12.



13.

14.

15.

16.

17.

18.

19.

20.

## II. MICROBIOLOGY

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. As appropriate, these [redacted] should be discussed.
3. Details of any significant changes or findings.
4. A summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling.
7. Information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, immediate container and carton labels).

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

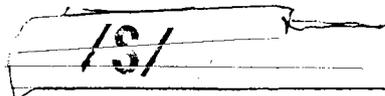
Division of Drug Marketing, Advertising, and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, contact Catalina Ferre-Hockensmith, Consumer Safety Officer, at (301) 827-7510.

Sincerely,



FOR PB 12/16/98

Paula Bostein, M.D.  
Acting Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**