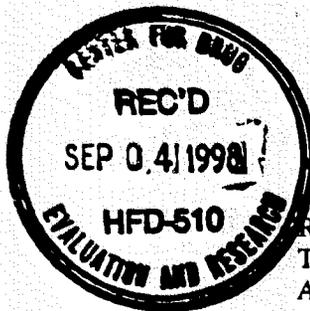


genzyme

September 3, 1998



GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
Amendment 009

Dr. Solomon Sobel  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

**RE: Thyrogen® NDA: Minor Labeling Amendment**

Dear Dr. Sobel:

In accordance with 21 CFR 314.60, the purpose of this correspondence is to provide an updated Package Insert for Thyrogen based upon the discussions of our August 31, 1998 meeting with the Division. We have analyzed the data required using [redacted]. The Package Insert (PI) includes proposed language incorporating the results of this analysis. As requested by Dr. Temeck, we have specifically provided data in the PI on the detection rate of Thyrogen stimulated Tg using the combined reference standard [redacted].

Please find the following documentation in support of this minor labeling amendment:

Attachment 1: Updated Package Insert (PI) incorporating the August 26, 1998 labeling changes as well as changes necessitated by the August 31, 1998, [redacted]

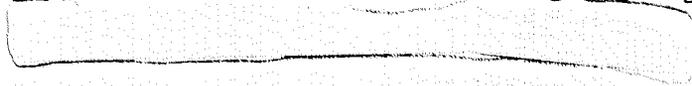
Attachment 2: Table to support patient numbers used in the second footnote of WBS table in PI.

Attachment 3: For your information, a patient data listing for all 170 Tg eligible patients (successfully ablated and Tg antibody negative). This patient data listing replaces Attachment 4 from the August 26, 1998 minor labeling amendment using [redacted]

Attachment 4: Patient data listing for detection rate of THST Tg using the [redacted]

NDA 20-898/Amendment 008  
August 26, 1998  
Page 2

Attachment 5: Patient data listing for detection rate of Thyrogen Tg using



Attachment 6: Patient data listing for detection rate of Thyrogen



As discussed at the August 31, 1998 meeting, I will be following up with Steve McCort to set up a teleconference to discuss the labeling changes proposed in this amendment. In light of the upcoming action date for Thyrogen, we look forward to working closely with you to finalize the Package Insert.

Should you have any questions or need additional clarification concerning this correspondence, please do not hesitate to call me at 617-374-7425.

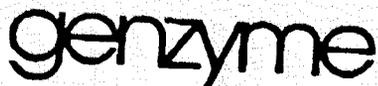
Sincerely,

A handwritten signature in black ink, appearing to read 'Ilze Antons', written over a horizontal line.

Ilze Antons  
Manager, Regulatory Affairs

APPEARS THIS WAY  
ON ORIGINAL

Desk Copies: Dr. Jean Temeck  
Dr. David Orloff  
Dr. James Bilstad  
Dr. Solomon Sobel  
Steve McCort, Regulatory Project Manager



GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

August 26, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
Amendment 008

Dr. Solomon Sobel  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

**RE: Thyrogen® NDA: August 31, 1998 Pre-meeting Package and Minor Labeling Amendment**

Dear Dr. Sobel:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997, the August 13, 1998 Minor Labeling Amendment and the subsequent meeting requested by Genzyme to discuss the proposed changes based upon input from our scientific advisors. As confirmed by Steve McCort on August 20, 1998 by telephone, we will meet with the Agency on August 31, 1998 from 3 p.m. until 4:30 p.m. in Room 14B-56 of the Parklawn Building to discuss the package insert text.

List of Attendees for Genzyme Corporation:

- David Meeker, M.D., Sr. Vice President of Medical Affairs
- Kevin McEllin, Associate Director, Clinical Affairs
- Leonard Wartofsky, M.D., Scientific Advisor for Genzyme
- Alison Lawton, Vice President of Regulatory Affairs
- Ilze Antons, Manager, Regulatory Affairs

Included in the pre-meeting package, are changes requested by Dr. Wu on August 24, 1998 concerning the activity of thyrotropin alfa and, in response to Dr. Martin Yau's

Additionally, please find the following documentation in support of the meeting:

- Attachment 1: Agenda for August 31, 1998 meeting: Intended format comprised of presentation followed by active discussion/resolution point by point.
- Attachment 2: Updated Package Insert (PI) incorporating above-noted changes as well as minor editorial updates. Please note that the rationale for the changes made in the August 13, 1998 amendment based upon input from our advisors was provided in Attachment 3 of that amendment. For your convenience, we have provided each reason for the PI changes in the left-hand margin of the PI text.
- Attachment 3: Table to support patient numbers used in the second footnote of table in PI.

NDA 20-898/Amendment 008  
August 26, 1998  
Page 2

Attachment 4:

For your information, a patient data listing for the 105 Tg eligible patients (successfully ablated and antibody negative) who had a detectable Tg at the  $\geq 2$  ng/ml functional sensitivity level. This patient data listing identifies the 35 metastatic patients (♦) and provides corrected patient values for the 6 Tg antibody negative patients (strikeout with new values to the left of each column). One patient for whom we received corrected values was antibody positive and is therefore not included in the analysis.

Attachment 5:

For your information, a patient data listing for all 170 Tg eligible patients (successfully ablated and Tg antibody negative). As in Attachment 4, this patient data listing also identifies the 35 metastatic patients (♦) and provides corrected patient values for the 6 Tg antibody negative patients (strikeout with new values to the left of each column). One patient for whom we received corrected values was antibody positive and is therefore not included in the analysis.

We look forward to working with you on August 31, 1998 to finalize the Thyrogen PI.

Should you have any questions or need additional clarification concerning this correspondence, please do not hesitate to call me at 617-374-7425.

Sincerely,



Ilze Antons  
Manager, Regulatory Affairs

Desk Copies: Dr. Jean Temeck  
Dr. Steven Orloff  
Dr. DuGong Wu  
Dr. James Bilsted  
Dr. Solomon Sobel  
Steve McCort, Regulatory Project Manager

APPEARS THIS WAY  
ON ORIGINAL

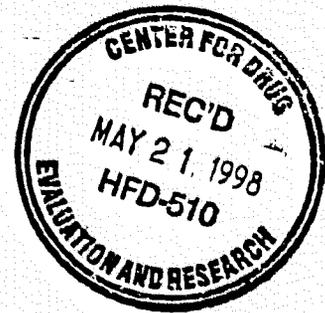
genzyme

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

May 20, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
General Correspondence

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997, the facsimile received by Genzyme May 7, 1998.

Enclosed please find the Microbiology information requested in your facsimile dated May 7, 1998.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "Matthew R. Patterson".

Matthew R. Patterson  
Principal Regulatory Affairs Associate

APPEARS THIS WAY  
ON ORIGINAL

genzyme

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

May 13, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
Amendment 002

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857

RE: Thyrogen® NDA Amendment 002: Safety Update

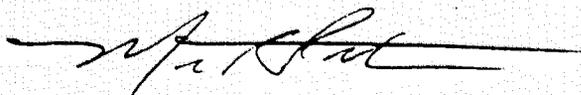
Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and to 21CFR314.50(5)(vi)(b).

Enclosed please find the NDA safety update report for Thyrogen® (20-898).

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,



Matthew R. Patterson  
Principal Regulatory Affairs Associate

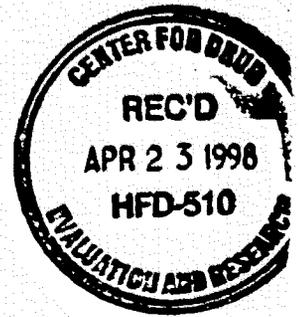
genzyme

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

April 22, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
General Correspondence

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and to the facsimile sent to FDA April 17, 1998.

Enclosed please find an official copy of the fax from Genzyme to FDA dated April 17, 1998 for the NDA file. This communication was from Alison Lawton to David Orloff, M.D. of the reviewing division.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "Matthew R. Patterson".

Matthew R. Patterson  
Principal Regulatory Affairs Associate

genzyme

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

April 7, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
General Correspondence

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and the phone call from Mike Fossler of FDA on April 7, 1998.

Enclosed please find the tables requested by Dr. Fossler. These pages were inadvertently missing from the NDA submission. I apologize for the inconvenience.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "Matthew R. Patterson".

Matthew R. Patterson  
Principal Regulatory Affairs Associate

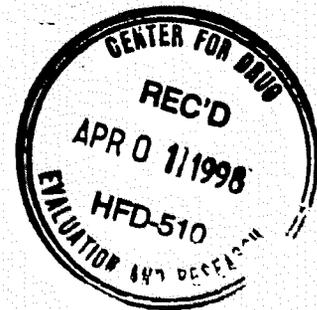
genzyme

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

March 31, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
General Correspondence

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997, the facsimile received by Genzyme March 23, 1998.

Enclosed please find a response to your fax of March 23, which contained an information request from the Thyrogen NDA Biopharmaceutics reviewer.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson  
Principal Regulatory Affairs Associate

genzyme

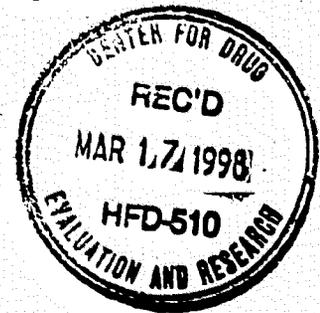
NDA SUPPL AMENDMENT  
ORIGINAL

GENZYME CORPORATION  
P.O. BOX 9322  
ONE MOUNTAIN ROAD  
FRAMINGHAM, MA 01701-9322  
508-872-8400  
FAX 508-872-9080

March 16, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
Amendment 001

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Minor Labeling Amendment

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 in the facsimile received by Genzyme February 19, 1998, and during the teleconference with FDA February 24, 1998.

In response to the Division's concerns about appropriate labeling guidance for Thyrogen considering its comparative performance against current standards, enclosed please find an updated proposed package insert. We have modified the indication, added additional precautionary statements, and expanded the clinical trials section of the labeling. To support these changes, we are including a position paper that provides a thorough review of the current clinical management of thyroid cancer, limitations of the current diagnostic tests, and finally the proposed uses of Thyrogen based on available clinical trial data.

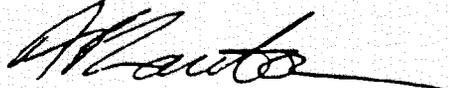
Genzyme believes that Thyrogen is a safe and effective alternative to withdrawal of Thyroid Hormone Suppression Therapy (THST) for Whole Body Scan (WBS) in combination with serum thyroglobulin (Tg) testing. Additionally, Thyrogen can be used as an alternative/supplement to Tg testing on THST alone since it provides added sensitivity.

We strongly believe that an opportunity to discuss the information presented in this position paper would be advantageous to both parties and would like to reiterate our request for a meeting with Dr Sobel, Dr Orloff and Dr Temeck to discuss this submission. We will also call you to arrange a conference call so that we can discuss the division's comments and thoughts on this amendment later this week.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Should you have any question or need additional clarification concerning this amendment, please do not hesitate to call Ilze Antons at (617) 374-7425 during the week of March 16 and Matt Patterson at 617-374-7676 thereafter.

Sincerely,

A handwritten signature in cursive script, appearing to read "Alison Lawton".

Alison Lawton  
Vice President, Regulatory Affairs

APPEARS THIS WAY  
ON ORIGINAL



07011



01003N

ORIGINAL

Genzyme

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

March 10, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
General Correspondence

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997, the facsimile received by Genzyme February 19, 1998, and the NDA General Correspondence submitted by Genzyme March 2, 1998.

Enclosed please find follow-up information as committed to by Genzyme in the NDA General Correspondence dated March 2 1998. In that submission Genzyme responded to second part of point 3b from the February 19 fax from FDA and indicated in several patients narratives that information was still pending from the investigational sites.

Genzyme has now received this information, and the narratives for these patients have been updated accordingly. The new information is clearly identified as such, in order to ease your review.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson  
Principal Regulatory Affairs Associate



ORIG AMENDMENT

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B.M.

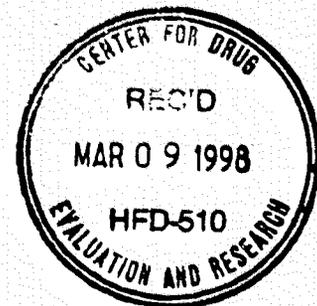
genzyme

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562, U.S.A.  
617-252-7500  
FAX 617-252-7600

March 6, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
General Correspondence

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Requested information

Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and to the facsimile received by Genzyme March 5, 1998.

Enclosed please find information requested in the telephone conversation between Dr. Jean Temeck and myself February 26, 1998 and confirmed in the FDA fax to Genzyme March 5, 1998.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

Matthew R. Patterson  
Principal Regulatory Affairs Associate

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

genzyme

ORIGINAL

GENZYME CORPORATION  
ONE KENDALL SQUARE  
CAMBRIDGE, MA 02139-1562 U.S.A.  
617-252-7500  
FAX 617-252-7600

March 2, 1998

Ref. NDA #20-898  
Thyrogen® (thyrotropin alfa)  
General Correspondence

Mr. Steve McCort  
Division of Metabolism and Endocrine Drug Products  
Food and Drug Administration  
Parklawn Bldg., HFD-510, Rm. 14-B-30  
5600 Fishers Lane  
Rockville, MD 20857



RE: Thyrogen® NDA: Requested information

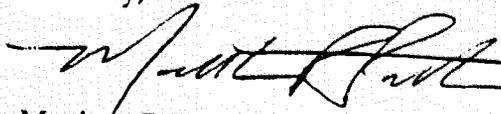
Dear Mr. McCort:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997 and to the facsimile received by Genzyme February 19, 1998.

Enclosed please find information requested in point 3b of the February 19 fax to Genzyme. Genzyme responded to the first part of this question in the submission to FDA dated February 26, 1998. Genzyme committed to responding to the second part of this question by March 2, 1998. The specific patient population for this request was clarified by telephone conversation with Dr. Jean Temeck on February 20, 1998.

Thank you and please do not hesitate to call me at (617) 252-7676 with any questions or concerns.

Sincerely,

  
Matthew R. Patterson  
Principal Regulatory Affairs Associate

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE