MCCORT

NDA 20-898

DEC 19 1997

Genzyne Corporation
Attn: Loan T. Tran, Pharm.D.
One Kendall Square
CAMBRIDGE, MA. 02139-1562

Dear Ms. Tran:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Thyrogen® (thyrotropin alpha)

Date of Application: December 12, 1997

APPEARS THIS WAY

Date of Receipt: December 15, 1997

Our Reference Number: 20-898

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 13, 1998, in accordance with 21 CFR 314.101(a). In additon, the decision of whether this drug application will be classified as a standard or priority review will be decided at our filing meeting.

If you have questions concerning this NDA, please contact:

Steve McCort
Consumer Safety Officer
Telephone: (301) 827-6415

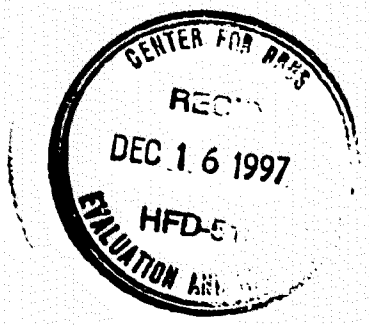
Sincerely yours,

/S/ 12/19/97

APPEARS THIS WAY

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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



December 12, 1997

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products
HFD-510
Document Room, 14-B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Thyrogen® (thyrotropin alfa)
New Drug Application #20-898

Dear Dr. Sobel:

In accordance with the Federal Food, Drug, and Cosmetic Act and the regulations contained in Section 314.50 of Title 21 of the Code of Federal Regulations, Genzyme hereby submits a New Drug Application for Thyrogen® (thyrotropin alfa). This product has been studied under IND [redacted]

Thyrogen® is proposed for use as an adjunct to radioiodine imaging and/or serum thyroglobulin testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer [redacted] For this use, Thyrogen has been granted orphan drug status under Orphan Drug Designation [redacted] approved February 14, 1992.

Genzyme hereby requests consideration for accelerated review of this New Drug Application, as provided for in Title 21CFR 314, subpart H. In clinical trials, Thyrogen has been shown to be safe and effective for the diagnosis of thyroid cancer, a serious life-threatening condition; and results indicate that the use of Thyrogen confers meaningful benefit over current procedure which causes debilitating hypothyroid signs and symptoms.

Reference is made to the pre-NDA meeting between Genzyme and the Division of Metabolic and Endocrine Drug Products on June 16, 1997. During the meeting, the format for this NDA was discussed and agreed upon. This included the modified application format and the electronic submission of the SAS data sets, case report forms (CRFs) and patient data listings (in place of CRF tabulations). Additionally, Genzyme agreed to provide an independent expert opinion on the risks and benefits of Thyrogen®, especially as it relates to the possible risk of missing cancer patients. This report is provided with the company's integrated summary of benefits/risks.

Please contact me directly at 617-761-8924 or Matthew R. Patterson, Senior Regulatory Affairs Associate at 617-252-7676 with any questions regarding this submission.

We look forward to your review and comments on this New Drug Application.

Sincerely,

Loan T. Tran, Pharm.D.
Director, Regulatory Affairs

Enclosure: Thyrogen NDA, Volumes 1-68

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: May 19, 1998

APPLICATION NUMBER: NDA 20-898; Thyrogen

BETWEEN:

Name: Allison Lawton, Vice President Regulatory Affairs (See attached list of other attendees)
Phone: 617-252-7757
Representing: Genzyme Corp.

AND

Name: Steve McCort, Project Manager and
Duu Gong Wu, Ph.D. Chemistry Team Leader
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Discussion of Chemistry Deficiencies Faxed to Sponsor on May 13, 1998

The comments and deficiencies from the May 13, 1998, were discussed. No conclusions were arrived at regarding these deficiencies. A follow-up phone call will be made later in the week by Dr. Duu-Gong Wu, Chemistry Team Leader, later in the week to Genzyme Corporation.

/S/

Steve McCort
Project Manager, HFD-510

cc: Original NDA 20-898
HFD-510/Div. File
HFD-510/SMcCort/DWu

TELECON

NDA: 20,898
Drug: Thyrogen
Date: 3/4/98

Steve,

Please fax the following request to Genzyme and follow with a letter. I have not yet received a reply from them on this important issue, although on Thursday, 2/26/98, when I spoke to Matt Patterson, Regulatory Affairs at Genzyme, about this issue he said he would get back with me on Monday, 3/2/98.

On Thursday, 2/26/98, I spoke with Matt Patterson, Regulatory Affairs at Genzyme, and brought to his attention that in study TSH92-0101, there were 11 scan pairs with different disease stage ratings, yet they were considered "concordant". Review of the individual scan data listings, 11.5.0, description of uptake, did indeed confirm the disease stage assigned to each scan in a given pair for these 11 patients. Why then were these 11 scan pairs considered concordant when the stages were different?

/S/
Jean Temeck, M.D.

cc. NDA Arch 20898
HFD-510 Div file
HFD-510/Dr. Orloff/Mr. McCort
HFD-720/Dr. Castillo
thyrogen.nd9

NDA: 20,898
Drug: Thyrogen
Sponsor: Genzyme
Date: 2/23/98

The main purpose of the T-con tomorrow is to discuss with the firm how they envision the clinical use of Thyrogen vis a vis withdrawal and Tg on THST and to provide in their product label, guidance to physicians regarding the use of this product (i.e. a treatment algorithm).

/S/

Jean Temeck, M.D.

/S/

2-23-98

cc. NDA Arch 20898
HFD-510 Div file
HFD-510: Dr. Orloff and Mr. McCort
Thyrogen.nd8

mcCort.

NDA 20-898

FEB 17 1998

Genzyme Corporation
Attention: Matthew Patterson
Senior Regulatory Affairs Associate
One Kendall Square
Cambridge, MA 02139-1562

Dear Mr. Patterson:

Please refer to your December 12, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thyrogen (thyrotropin alpha).

We also refer to our acknowledgment letter dated December 19, 1997, which stated that the decision regarding the drug review priority classification for this application would be delayed until after our filing meeting.

Upon further consideration of your application, we have concluded that this application should receive a priority review. Our policy regarding determination of priority or standard review status is based on the proposed indications and alternate treatment(s) marketed for the proposed indication.

If you have any questions, please contact Steve McCort, Project Manager, at (301) 827-6415.

Sincerely yours,

/S/ 2/17/98

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MCCORT

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

M.O. Jean Temecht verified that the proposed indication in the labeling falls within that of the Orphan Designation
/S/
12/19/97

DATE: December 17, 1997

FROM: Steve McCort
Project Management

SUBJECT: User Fees For A New NDA

NDA : 20-678; Thyrogen

TO: Enid Galliers
Chief, Project Management

Genzyme has submitted a new drug application, NDA 20-898, Thyrogen (recombinant TSH) [dated December 12, 1997 received December 15, 1997] and has requested a waiver for paying User fees claiming that: (1) the product qualifies as a designated Orphan Drug Product (Orphan Drug Designation 91-631) and that (2) a fee waiver can be granted for such products per the "Food and Drug Administration Modernization Act of 1997."

QUESTION: CAN THE SPONSOR QUALIFY FOR AN EXEMPTION FROM USER FEES AS AN ORPHAN DRUG?

To answer that question I contacted Tom Hassall (see E-Mail from Hassall) and Orphan Drug Products. On the second page of Tom's E-Mail stated that "*The reauthorized PDUFA includes an exemption from application fees for an application for a drug product under section 527 (Orphan Drug Act) for the disease or condition in the NDA. The exemption is not valid in the NDA for other conditions NOT designated fro the drug under section 527.*" *.....Bottom line is that if the company applies only for the designated orphan indication they are not subject to an application fee.*"

The Orphan Indication (See E-Mail from Orphan Drug Products) for file [redacted] As an adjunct in the diagnosis of thyroid cancer."

The firm in their cover letter indicated that their proposed indication in the NDA is the same as the Orphan Drug Indication. Therefore it would seem to qualify for an exemption of user fees. Let's discuss.

Thanks

/S/
Steve McCort

cc: Orig. NDA 20-678 w/ UF Validation

genzyme

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

November 30, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
Amendment 014

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 to provide the final labeling for Thyrogen (thyrotropin alfa for injection) as agreed upon between Genzyme and the Division on November 30, 1998.

Please find the following documentation to support this amendment:

Attachment 1: Final Thyrogen Package Insert text in manuscript format. Please note that the Billewicz Scale will be split in two on the Final Printed Labeling (FPL) due to column size. This format was submitted to Dr. Wu on November 16, 1998. Additionally, we have standardized the cross-referencing to other sections of the package insert (PI) to reflect the type appropriately, i.e. caps for main headings, changing Clinical Studies to Clinical Trials to be consistent with heading used in the PI section.

Attachment 2: Color layout of Thyrogen carton and vial labeling.

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, M.S.
Manager, Regulatory Affairs

Desk Copies: Steve McCort, Project Manager
Division of Metabolism and Endocrine Drug Products

genzyme

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

November 24, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
Amendment 013

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 the final labeling for Thyrogen (thyrotropin alfa for injection) as agreed upon between Genzyme and the Division.

Please find the following documentation to support this amendment:

Attachment 1: Final Thyrogen Package Insert text in manuscript format.

Attachment 2: Color layout of Thyrogen carton and vial labeling.

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 Ahtons, M.S.
Manager, Regulatory Affairs

Desk Copies: Steve McCort, Project Manager
Division of Metabolism and Endocrine Drug Products

genzyme

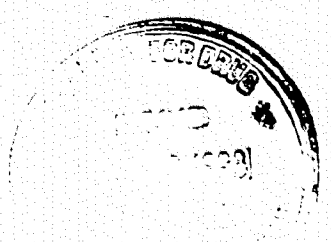
COPY

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

November 18, 1998

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
Amendment 012

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 Amendment

Dear Dr. Sobel:

In accordance with 21 CFR 314.60, the purpose of this correspondence is to provide revisions to the documentation provided in Amendment 010 dated October 7, 1998 to NDA 20-898 as requested by Dr. Duu Gong Wu via telephone on November 9. The enclosed changes were first provided by facsimile on November 13, 1998 and agreed upon by telephone on November 17, 1998. The changes requested by Dr. Wu include revisions to the [redacted], the incorporation of an outlier [redacted] to reduce final result variability associated with the [redacted] activity assay and the development of criteria for required assay replicates to maintain the accuracy of the assigned specific activity value for rhTSH reference standards.

Please find the following documentation in support of the requested changes:

Attachment 1: SOP entitled [redacted] with the additional detail for sample handling and dilution preparation identified by revision bars.

Attachment 2: An outlier testing strategy for [redacted] to be incorporated in the SOP entitled [redacted] provided in Attachment 3 of Amendment 010 dated October 7, 1998.

Attachment 3: [redacted] criteria to maintain the accuracy of the assigned specific activity value for [redacted] to be incorporated in SOP entitled [redacted] provided in Attachment 3 of Amendment 010 and [redacted] provided in Attachment 1 of Amendment 010 dated October 7, 1998.

As agreed upon with Dr. Wu on November 17, 1998, we have committed to providing the above noted documents after final review and sign-off for these documents has been completed. They will be submitted as General Correspondence to NDA 20-898.

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. Duu Gong Wu

genzyme

October 28, 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 011

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 (PI) for Thyrogen based upon the Division's comments provided October 20, 1998 and the teleconference discussions on October 23, 1998 held between Genzyme and the Division. Based upon verbal confirmation of PI text changes following the October 23, 1998 teleconference, it is our understanding that we have come to final agreement on the PI text. Additionally, Dr. Wu has reviewed the chemistry sections of the PI as well as the noninsert labeling and we have reached mutual agreement with these portions of the labeling. As part of this amendment, we are providing color copy of the noninsert labeling that is intended for use initially until a final specific activity is agreed upon with the Agency.

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

Attachment 1:	Updated Package Insert (PI) incorporating the October 20 and 23, 1998 labeling changes. This version of the PI is in REVISION mode so that you can clearly identify changes that were discussed October 23 and finalized with the reviewers on October 27 and 28, 1998.
Attachment 2:	Updated Package Insert (PI) incorporating the October 20 and 23, 1998 labeling changes. This version of the PI is in manuscript format and appears with all revisions incorporated. The text is identical to that in Attachment 1.
Attachment 3:	Color copy of the noninsert labeling.

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. David Orloff, Dr. DuGong Wu, Jayne Peterson, DDMAC (*sent under separate cover*), Steve McCort, Regulatory Project Manager

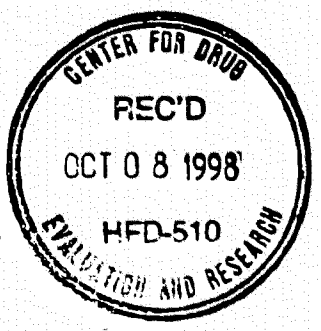
genzyme

October 7, 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 010

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: Complete Response to Approvable Letter

Dear Dr. Sobel:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997, the September 15, 1998 FDA Approvable Letter and the subsequent September 16, 1998 Intent to Amend general correspondence to NDA 20-898.

In accordance with 21 CFR 314.110(a)(1), the purpose of this correspondence is to provide a complete response to the September 15, 1998 approvable letter to NDA 20-898.

As recognized in the September 15, 1998 approvable letter, please incorporate the September 3, 1998 Minor Labeling Amendment as part of the review of this approvable letter response.

Please find the following documentation included in this complete response:

Requested documentation regarding TSH Bio-assay

Attachment 1: **Addresses Point 1 of Approvable Letter:** A proposed protocol for establishing an in-house working reference standard to be used for product release. This protocol was submitted for initial review on September 22, 1998 and found acceptable at the October 2, 1998 teleconference. (Please refer to Commitment 3 for timeline).

Attachment 2: **Addresses Point 2 of Approvable Letter:** Release and stability data [redacted] for all batches tested.

Attachment 3: **Addresses Point 3 of Approvable Letter:** A revised procedure including an SOP for routine testing and validation protocol for the [redacted] The proposed test procedure was submitted for initial review on September 22, 1998 and found acceptable at the October 2, 1998 teleconference.

Attachment 4: **Addresses Point 4 of Approvable Letter:** A proposed upper and lower limit for the /including the justification for upper and lower limits of is provided for the This justification was submitted for initial review on September 22, 1998 and found acceptable at the October 2, 1998 teleconference.

Written commitments to NDA 20-898:

1. We commit to use the WHO reference standard, with revised and an for testing of the two current lots of drug product and any future lots until a valid, in-house working reference standard is established following the protocol provided in Attachment 1.

2. We commit to revising the current stability protocol to include all changes in tests and specifications. We are providing in **Attachment 5** a draft stability protocol which includes the expected changes to the As discussed in the October 2, 1998 teleconference, we commit to run the at 0, 6, 12, 18, and 24 months followed by annual testing thereafter.

3. We commit to provide the validation data for the used to qualify a Genzyme reference standard no later than 6 months after NDA approval.

Updated Safety Information:

Attachment 6: Updated Safety Report to NDA 20-898. This updated report integrates all safety information through August 31, 1998. All new safety information comes from the Compassionate Use program and therefore we have updated Section 4.0 of the ISS.

Introductory Promotional Materials:

One copy of the introductory promotional materials for Thyrogen. This promotional material is based upon the labeling submitted in our September 3, 1998 Labeling Amendment. Two copies of this promotional material are being provided directly to the Division of Drug Marketing, Advertising and Communications (*See enclosed binder of DDMAC submission.*).

It is our intention and understanding based upon the October 2, 1998 teleconference that the information provided in this amendment constitutes a complete response to the September 15, 1998 approvable letter to Thyrogen. We are looking forward to an expeditious review and final approval of NDA 20-898.

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, M.S.
Manager, Regulatory Affairs

Desk Copies: Steve McCort, Regulatory Project Manager (4 Review Copies)