

Discussion Points

From the September 15, 1998, approvable letter, page 1, the following points were addressed:

1. **Point 1: An acceptable protocol with time-line for establishing an in-house reference standard to be used for product release. The protocol should include procedures for [redacted] and acceptance criteria.**

Firm Proposal: The firm proposed a revised protocol QC-040-20 with acceptance criteria to qualify the reference standard using an array of physical and chemical tests as well as a [redacted] (See Attachment 1 of September 22, 1998 meeting package).

FDA Response: Dr. Wu indicated that the protocol is acceptable except that 1) the acceptance criteria, which were copied from the release specifications, needs to be tightened when more data are obtained. The specific activity of the reference standard will be based on the test results, not on the limit of the release specification sheet. 2) Additional tests that Genzyme committed to develop should be incorporated in the revised protocol, including a final specific activity value for the reference standard.

Firm Response: The firm agreed with FDA's comments and requests as stated above.

2. **Point 2: Release and stability data [redacted] obtained from your current in vivo bio-assay for all batches tested.**

FDA Response: Genzyme was informed that the [redacted] values provided for a number of lots tested under different intervals during stability testing showed a very wide range of variation. Therefore, the [redacted] cannot be used as a [redacted]. The results only demonstrate the existence of [redacted] activity, but did not serve any quantitative purpose. The proposed range on 0.3 -1.1 (ED50) has the specification for this assay is acceptable.

3. **Point 3: An acceptable revised procedure for your current [redacted] to included additional data points for both the sample and the to-be-established reference standard. Additional request by FDA: The firm was also asked to provide a written validation protocol (without data) for the validation of [redacted].** The firm argued that the approvable letter did not specifically request such a written protocol. Dr. Chiu explained to the applicant that in the requested #3, the Agency requested that an acceptable revised protocol procedure for the in [redacted] should be provided, which means an acceptable written validation protocol. This is the standard requirement of an original NDA for any analytical methodology used for [redacted]. It was suggested that the analyst should be qualified to minimize the variation between tests. Genzyme agreed to discuss this with Dr. Wu at a later time (perhaps the following week). The Agency asked that this revised protocol be submitted formally as an amendment to the file for NDA 20-898 for review, followed by a formal or informal discussion of the protocol with the firm.

4. **Point 4: Acceptable upper and lower limits for the release specification based on available data from the [redacted] to replace the current pass/fail specification.**

Firm Proposal: The firm provided justification for what they felt were acceptable upper and lower limits [redacted] (See attachment 4 of the September 22, 1998, meeting package).

FDA response: The firm was told that due to the wide variation of ED50 values observed in the [redacted] should now be used for the release and stability testing in place of the original fail/pass, single point test. This [redacted] needs to validated and data provided within 6 months of approval.

Decisions (agreements) reached:

1. The firm will address the points (both agreement and disagreement) raised in this meeting before submitting their response to the NDA approvable letter. Further discussions (especially with point #4) will be discussed in a later telephone conversation with Dr. Wu.

Action Items:

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
1. Discussion of revised protocol with Dr. Wu, FDA	Genzyme	Week of October 5-10, 1998

Minutes Preparer: JS 10-29-98

Chair Concurrence: JS 10-29-98

Attachments/Handouts: September 22, 1998, meeting materials

cc: NDA 20-898
HFD-510/Div. Files
HFD-510/CSO/SMcCort
HFD-510/DWu
HFD-820/JGibbs/SKoepeke
HFD-800/YChiu

APPEARS THIS WAY
ON ORIGINAL

Concurrence: DWu 10-20-98/JGibbs 10-21-98/SKoepeke 10-23-98/YChiu 10-23-98
Drafted by: smm/October 19, 1998
Revised by: smm/October 29, 1998
final: smm/October 29, 1998

MEETING MINUTES

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

September 22, 1998

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

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: Background Package for Requested Discussion

Dear Dr. Sobel:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997, the September 15, 1998 Approvable Letter and the September 17, 1998 Request for Discussions submission. We are requesting discussion of Points 1, 3 and 4 of the items for submission and clarification of Point 2 of the commitments. Attached please find the following background documentation for discussion:

Attachment 1: Point 1 A proposed protocol for establishing an in-house working reference standard to be used for product release (*Note: the current procedure is located in Volume 7, pg 128 of NDA 20-898*). We have expanded the current protocol, QC-040-20, to include additional physico-chemical tests and included the acceptance criteria as discussed in Section 8.0 of the proposed protocol. Please note that some tests were deleted from the original protocol because they are now either covered by another more specific assay or have become a [redacted]. The timeline for establishing a new reference standard is provided in the commitment section as 6 months from date of approval. Please note that in Section 8.3 we are providing test methods that we have committed to investigate. Timelines for completing these investigations are provided in the June 2, 1998 amendment although the test we are committing to incorporating into routine testing within 6 months of NDA approval.

Attachment 2: Point 3 A revised procedure for our current [redacted] (*Note: the current procedure is QC-049-02 located in Volume 13, pg 34 of NDA 20-898*). Please note that we have [redacted] for both the reference sample and the test sample. Due to the number of test points, assay replicates and the inherent complexity of the test, we are proposing that in support of our stability program to perform this test on an annual basis. (Reference Point 2 in the Commitments section of the Approvable letter).

Attachment 3: Point 4 The justification for acceptable upper and lower limits: [redacted] is provided for the [redacted]

NDA 20-898/General Correspondence
September 22, 1998
Page 2

We look forward to discussing the above documentation with you as soon as expeditiously as possible. 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

APPEARS THIS WAY
ON ORIGINAL

Desk Copies: Dr. DuGong Wu
Dr. James Bilstad
Dr. Solomon Sobel
Steve McCort, Regulatory Project Manager (sent by facsimile)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF A TELEPHONE CONFERENCE

Meeting Date: February 24, 1998
Time: 1:00 pm.
Location: 14B-56

Application: NDA 20-898

Drug: Thyrogen

Firm: Genzyme Corporation

Type of Meeting: Advice and Clarification Clinical Issues

Meeting Chair: Solomon Sobel, M.D.
Division Director

Meeting Recorder: Stephen McCort
Project Manager

FDA Attendees:

Solomon Sobel, M.D., Division Director, DMEDP (HFD-510)
David Orloff, M.D., Medical Team Leader, DMEDP (HFD-510)
Jean Temeck, M.D., Medical Reviewer, DMEDP (HFD-510)
Sonia Castillo, Ph.D., Statistics Reviewer (HFD-715)
Stephen McCort, Project Manager

Genzyme

Loan Tran, Director, Regulatory Affairs
Matt Patterson, Senior Associate, Regulatory Affairs
Kevin McEllin, Associate Director, Clinical Affairs
Mohammed Al-Adhami, Statistician
David Meeker, Vice President, Medical Affairs

Meeting Objective:

To discuss with the firm how they envision the clinical use of Thyrogen vs 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).

Discussion Points:

1. There are problems with interpretation of Tg levels with patients treated with Thyrogen. There are problems with interpretation of Tg levels in patients treated with Thyrogen because there appears to be no correlation between Thyrogen Tg and withdrawal (WD) Tg. A WD Tg of 10 ng/ml does not correspond to a Thyrogen Tg level of 3 ng/ml; a 5 ng/ml Tg on WD does not correspond to a 2 ng/ml Thyrogen Tg; nor does a 2 ng/ml on WD correspond to a 1 ng/ml on Thyrogen. The ROCs (receiver operator curves) only provided the best fit of the Thyrogen Tg data in this study, to WD. This post-hoc best fit was done because the 1:1 comparison of Thyrogen and WD Tg failed to show equivalence (i.e. using the same cut-offs for Thyrogen as for WD).

The firm admitted the above was true but attempted to counter this argument by stating that there is no consensus regarding the clinical management of a thyroid cancer patient based on a given WD Tg level; it depends rather on the cut-off level an individual physician chooses to use.

We countered their argument by pointing out that:

- (1) the rich historical experience with WD has demonstrated it to be a consistent stimulator of thyroid tissue and, hence, of Tg. Being a new product, Thyrogen lacks such an experience and
- (2) A given Thyrogen Tg level is interpreted in relation to withdrawal because that's the reference standard. Since there is no correlation, we cannot clinically interpret it. Therefore, it is immaterial at what Tg cut-off an individual physician will choose to intervene therapeutically.

The firm admitted that what we said was true. The firm stated that there was no consensus among their investigators/experts regarding the clinical use of this product but that they would readdress this issue again with their experts and submit this information to us for review.

Dr. Sobel inquired if the firm has any plans to study a more prolonged period of Thyrogen administration because that is where its clinical utility may lie. The firm stated they had no such plans.

2. The draft labeling does not provide guidance for the physician as to how to use the product. The draft labeling for Thyrogen should be rewritten to provide guidance to physicians as to how to use this product. In addition, the label should focus on presenting scan data information also in a manner that is clinically useful to physicians- e.g. frequency with which the Thyrogen scan missed disease seen on the WD scan, rather than in terms of 95% confidence intervals.
3. The draft product label can only support the use of the product in pituitary disease, or where the patient may be at risk for withdrawal of THST.

Decisions (agreements) reached:

1. The firm will address the issue of how their product can be used clinically with their experts and submit this information for review.
2. The draft labeling for Thyrogen should be rewritten to provide guidance to physicians as to how to use this product. In addition, the label should focus on presenting scan data information also in a manner that is clinically useful to physicians- e.g. frequency with which the Thyrogen scan missed disease seen on the WD scan, rather than in terms of 95% confidence intervals.
2. Additional requests will be met by the firm:
 - a. From the time lines outlined in the February 19, 1998 FAX, request 3a and request 5 may be deleted. Request 3b should be provided by February 27, 1998 as outlined in the February 19, 1998 FAX.
 - b. Need information on the 48 hr analysis for Tg for Thyrogen vs Withdrawal FAXed to the Division by Friday February 27, 1997. This analysis should be presented in a similar fashion as that submitted for the 72 hour data.
 - c. Need to have FAXED to the Division information on patient #1315 Arm 1, and patient # 1210 Arm 2 in tabular form as provided in tab 1 of the January 16 and January 28, 1998 submissions. The comparison table should be similar to the table FAXED by Genzyme on February 9, 1998 which contained data from all patients.

Unresolved issues or issues requiring further discussion:

Firm needs to send a plan of how the firm intends to use Thyrogen vs a vis Withdrawal and Tg on THST and how they intend to label their product to give guidance to the physician regarding the use of the product in therapy.

Action Items:

	<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
1.	Revised plan for use of Thyrogen and revised Labeling for guidance of product with physicians.	Matt Patterson, Genzyme	TBA
2.	Item 3b from 2-19-98 FAX	Matt Patterson, Genzyme	2-27-98
3.	48 hour diagnostic utility Analysis for Thyrogen vs Withdrawal	Matt Patterson, Genzyme	2-27-98
4.	Patient 1315 Arm 1, Patient 1210, Arm 2 information requested Analysis	Matt Patterson, Genzyme	TBA

Minutes Preparer:

[Redacted] /S/ 3-10-98

Chair Concurrence:

[Redacted] /S/

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

FEB 17 1998

DATE: February 17, 1998

APPLICATION NUMBER: NDA 20-898; Thyrogen

BETWEEN:-

Name: Matt Patterson, Regulatory Affairs
Phone: 617-252-7676
Representing: Genzyme

AND

Name: Steve McCort, Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Microbiology Information requested in February 11, 1998, FAX

Matt Patterson of Genzyme responded back to the request for information as follows:

MICROBIOLOGICAL: Please address the following issues within the next two weeks:

1. *Need Part IIB Volume 3, Page 58-121, Viral Safety Information/Viral Clearance Validation.*

FIRM RESPONSE: The reviewer should already have that volume that contains the information. If they do not the firm will be glad to send the information.

2. *Need Stability Data, Volume 3, pages 122-166.*

FIRM RESPONSE: The reviewer should already have that volume that contains the information. If they do not the firm will be glad to send the information.

3. *Need the Appendices which are related to viral clearance (Appendices 11B/8-3 through 8-23).*

FIRM RESPONSE: No problem. The firm will provide the information as soon as possible.

4. Thyrogen is packaged as 2 components: 1 vial containing the active drug product, and another vial containing sterile WFI. The sterilization information for the WPI is missing. It does not appear for instance in the index provided for the CMC submission. Since the WFI is part of the component of the final drug product, please provide this information.

FIRM RESPONSE: the firm has cross-referenced the information in the submission. The firm will be glad to provide the references where the information can be cross-referenced or provide the information directly in a separate submission.

Page 2

The firm was told that Dr. Uratani the microbiology reviewer will be informed of the firm's response and will provide answers to the firm's questions as soon as possible.

/S/

Steve McCort, Project Manger
Project Manager, HFD-510

cc: Original NDA 20-898
HFD-510/Div. File
HFD-510/Steve McCort, Project Manager
HFD-805/BUratani

TELECON

APPEARS THIS WAY
ON ORIGINAL

M-CORT

JAN 16 1998

MEMORANDUM OF TELECON

DATE: January 16, 1998

APPLICATION NUMBER: NDA 20-898; Thyrogen

BETWEEN: -

Name: Matt Patterson
Phone: 617-252-7676
Representing: Genzyme

AND

Name: Steve McCort
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: FAX of Biopharm Comments

The firm was called to inform them a FAX of comments sent to the Firm. These comments concerned the need for PK data not included with the submission. The firm commits to submitting the requested information ASAP but no later than the 60 file date for this NDA.

APPEARS THIS WAY
ON ORIGINAL

/S/

Steve McCort
Project Manager, HFD-510

cc: Original NDA 20-898
HFD-510/Div. File
HFD-510/Steve Mc
HFD-510/MFossler/HAhn/JTemeck/DOrloff

APPEARS THIS WAY
ON ORIGINAL

TELECON

McCort

NDA 20-898

OCT 23 1998

Genzyme Corporation
Attention: Ms. Allison Lawton
Vice President Regulatory Affairs
One Kendall Square
CAMBRIDGE, MA 02139-1562

Dear Ms. Lawton:

We acknowledge receipt on October 8, 1998, of your October 7, 1998, resubmission to your new drug application (NDA) for Thyrogen® (thyrotropin alfa for injection).

This resubmission contains additional information submitted in response to our September 15, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is April 8, 1999.

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

Sincerely,

[Signature]
10-23-98 ✓

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-898

Food and Drug Administration
Rockville MD 20857

Genzyme Corporation
Attention: Ms. Allison Lawton
Vice President, Regulatory Affairs
One Kendall Square
CAMBRIDGE, MA 02139-1562

SEP 15 1998

Dear Ms. Lawton:

Please refer to your new drug application dated December 12, 1997, received December 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Thyrogen® (thyrotropin alfa for injection).

We acknowledge receipt of your submissions dated January 16, and 30, February 10, 13, 23, and 26, March 6, 10, and 16, April 22, May 7, 13, 18, 20, 21, 22, and 27, June 1, 2(2), 8, 18, and 23, July 10, and 27, and August 13 and 26. We also acknowledge receipt of your submission dated September 3, 1998. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies, cited in this letter. The original user fee goal date for this application was June 15, 1998. Your submission dated June 2, 1998, extended the goal date to September 15, 1998.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information regarding the TSH [redacted]

1. An acceptable protocol with time-line for establishing an in-house working reference standard to be used for product release. The protocol should include procedures for [redacted] physico-chemical tests, and acceptance criteria.
2. Release and stability data [redacted] obtained from your current [redacted] for all batches tested.
3. An acceptable revised procedure for your current [redacted] to include additional data points for both the sample and the to-be-established reference standard.
4. Acceptable upper and lower limits for the release specification based on available data from the [redacted] to replace the current pass/fail specification.

In addition, please provide in writing the following commitments:

1. The WHO reference standard, with the [redacted] and [redacted] will be used for the release of the two current lots of drug product any future lots until a valid, [redacted] standard is established.
2. The current stability protocol will be revised to include all changes in tests and specifications.
3. Validation data for the [redacted] used to qualify a [redacted] will be provided no later than 6 months after NDA approval.

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 versus now will facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. 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 not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

NDA 20-898

Page 3

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 the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

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

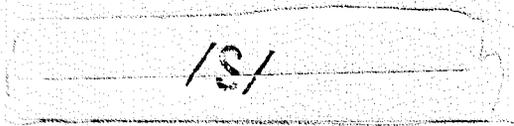
Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond 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.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Metabolic and Endocrine Drug Products to discuss what further steps need to be taken before the application may be approved.

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 Steve McCort, Project Manager, at (301) 827-6415.

Sincerely,



James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

- McCort

NDA 20-898

JUN 10 1998

Genzyme Corporation
Attention: Ms. Allison Lawton
Vice President, Regulatory Affairs
One Kendall Square
CAMBRIDGE, MA 02139-1562

Dear Ms. Lawton:

We acknowledge receipt on June 3, 1998, of your June 2, 1998, amendment to your new drug application for Thyrogen® (thyrotropin alpha) for Injection.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is September 15, 1998.

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

Sincerely yours,

[Signature] 6/10/98

Solomon Sobel, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ORIGINAL

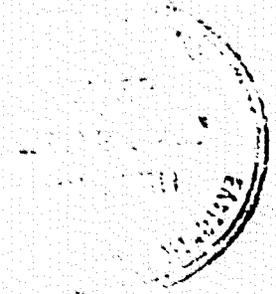
cc:
Original NDA 20-898
HFD-510/Div. Files
HFD-510/S. McCort
HFD-510/SSobel/DOrloff/JTemeck/RSteigerwalt/DWu
HFD-805/BUratani/PCooney
HFD-870/MFossler/HAhn
DISTRICT OFFICE

[Signature] 6.9.98

APPEARS THIS WAY
ORIGINAL

Drafted by: smm/June 9, 1998/n20898
final: smm/June 9, 1998/n20898

REVIEW EXTENSION



M E M O R A N D U M

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

DATE: June 9, 1998
FROM: Solomon Sobel
NDA: 20-898; Thyrogen
SUBJECT: Extension of User Fee Due Date
TO: James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

The User Fee Due Date has been extended for three months. The new due date is September 15, 1998. A major amendment submitted June 2, 1998, in response to the chemistry deficiencies was received within three months of the user fee due date of June 15, 1998 (received June 3, 1998). The User Fee Due Date has been extended for three months. The new due date is September 15, 1998. See the accompanying memo from Dr. Duu-Gong Wu, Chemistry Team Leader regarding the reasons for the extension of the review time.


Solomon Sobel
Division Director
Division of Metabolic
and Endocrine Drug Products, HFD-510

APPEARS THIS WAY
ON ORIGINAL

cc: Lee Ripper

MARKETING APPLICATION

GENZYME
December 1997

THYROGEN®
(thyrotropin alfa)

USER FEE EXEMPTION STATEMENT

In accordance with the FDA Modernization Act of 1997, Genzyme is exempt from paying user fees for review of NDA # 20-898 for Thyrogen® (thyrotropin alfa) due to Orphan Drug status. Thyrogen® is an Orphan Drug Product, Orphan Drug designation [redacted] approved February 24, 1992.

APPEARS THIS WAY
ON ORIGINAL