PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20898	**Trade Name:**	THYROGEN (THYROTROPIN ALFA) 0.9MG INJ
Supplement Number:		**Generic Name:**	THYROTROPIN ALFA
Supplement Type:		**Dosage Form:**	Injectable; Intramuscular
Regulatory Action:	AP	**Proposed Indication:**	An adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with thyroid cancer.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)

____Infants (1-24 Months)

____Children (25 Months-12 years)

____Adolescents (13-16 Years)

_X_ Other Age Groups (listed): Adults above 16 years

Label Status	INADEQUATE Labeling for ALL PEDIATRIC ages
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Protocols are submitted and approved

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

Thyroid cancer is uncommon in the pediatric population. Therefore, pediatric studies are not required for this population (November 24,, 1998)

No pediatric plan submitted.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEPHEN MCCORT

/S/

Signature

11-24-98

Date

MEMORANDUM

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

DATE: May 20, 1998

FROM: Jean Temeck, M.D.

NDA: 20-898

SUBJECT: Pediatric Labeling

TO: File for NDA 20-898; Thyrogen

Thyroid cancer is uncommon in pediatric age patients, Therefore pediatric studies are not required for this population.

/S/

Jean Temeck, Medical Officer
HFD-510

September 13, 1998
Memorandum
To: the File NDA 20-898, Thyrogen (thyrotropin alpha)
From: Solomon Sobel M.D. Director, Division Metabolic and Endocrine Drug Products
Subject: Approvable letter

/S/ 9/13/98

There are several issues which must be resolved before a final approval letter is sent.

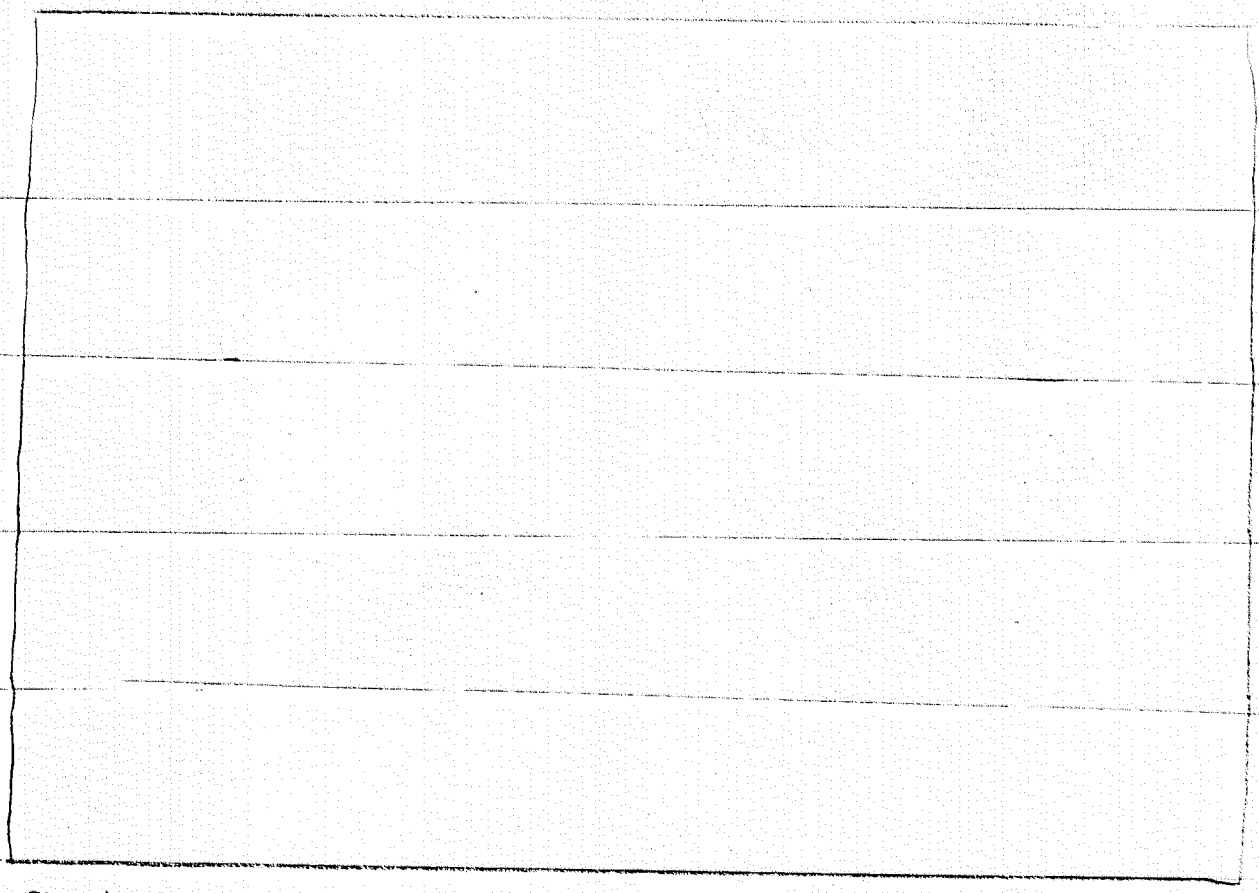
1. Final labeling: There will be refinements in the DESCRIPTION section of the labeling in respect to the designated potency. At present the assigned potency of may have to be modified

2. Submission of protocol for the determination of a reference house standard.

3. Clear delineation of what will constitute the release specification in respect to potency

There are several other issues which have arisen during our review in the areas of pharmacokinetics and statistics which I believe do not have to be addressed before final approval is granted.

Pharmacokinetic reviewer:



Statistical review:
The statistical reviewer believes there may have been significant bias introduced by the fact that the scans were read as a couplet. (that is the Thyrogen scan was read paired with the withdrawal scan in the same patient).
Either this was a direct side by side comparison or the scans were read sequentially with the reader maintainining a sufficient memory of the previous reading.
The bias may be one of wanting to establish equivalence of reading since this might be viewed as the "desirable" outcome.

There is merit to this criticism. However, this possible bias appears to be a remote determinant in these studies. The films were read by three independent reviewers and there was a procedure for discordance arbitration. It is also difficult to determine the direction of the bias; one might argue that the bias would work to establish concordance. However, there is also a possibility that the availability of comparison scans might induce a greater tendency to note discordancies in such issues as extent of disease.
In any event these ideas were presented to our Advisory Committee and they discounted them.

Conclusion: The Division recommends an approvable letter at the present time.

/S/

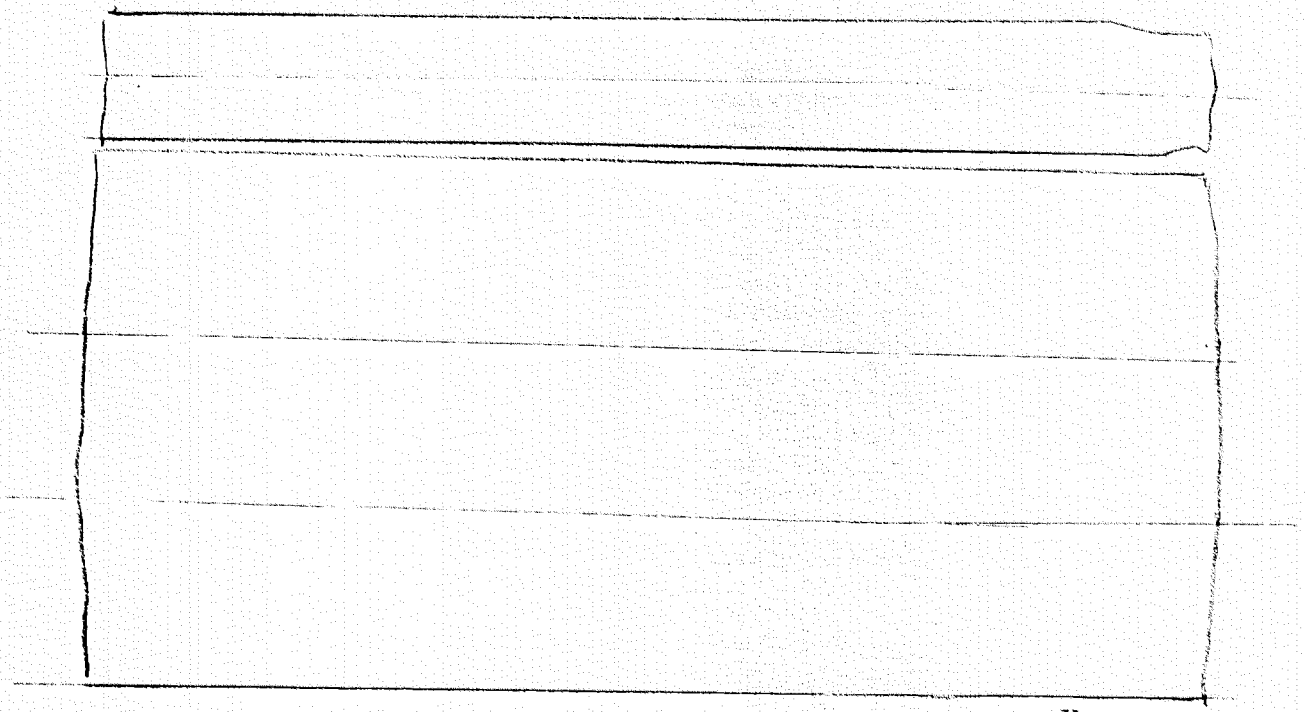
NDA 20-898
Thyrogen (thyrotropin alfa)
Genzyme Corportation
Date of submission: December 12, 1997

Addendum to Medical Team Leader's comments on NDA: June 12, 1998

In the original NDA submission, the sponsor maintained that Thyrogen testing, utilizing whole body radioiodine scanning and thyroglobulin (Tg) testing was comparable, with regard to diagnostic accuracy, to testing after thyroid hormone withdrawal. As such, proposed was to label the drug such that Thyrogen stimulation testing would be recommended as a substitute for withdrawal that had nearly equivalent diagnostic accuracy while sparing the morbidity associated with hypothyroidism after withdrawal.

Review of the data submitted in the NDA revealed that, indeed, Thyrogen whole body scanning tended to underdetect disease relative to withdrawal scanning. The study series included a number of patients with metastatic disease in whom the Thyrogen scan showed minimal or no disease. Furthermore, thyroglobulin levels after Thyrogen stimulation tended to be significantly lower than those after withdrawal, and, importantly, there was no clear correlation between the two. These findings suggested that 1) Thyrogen stimulation using the protocol recommended in labeling was inconsistent and 2) therefore could not be relied upon to assess accurately the location and extent of residual or recurrent local or metastatic well-differentiated thyroid cancer. In short, Thyrogen stimulation testing yielded data that were quantitatively different from those after withdrawal and therefore could not be used in place of withdrawal data to guide clinical decision making in patients with well-differentiated thyroid cancer.

Because of the above, this reviewer's initial recommendation was non-approval of the drug for the proposed use.



Assuming that final agreement can be reached on labeling as described above, this reviewer recommends approval of Thyrogen for use as an adjunct to withdrawal in the follow up of patients with well-differentitated thyroid cancer.

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

6-12-98

Recommendation Code: AP

cc:
HFD-510
NDA Arch 20-898
HFD-510: Sobel/Temeck/McCort

APPEARS THIS WAY
ON ORIGINAL

memo To f. le: NDA 20-898

NDA: 20898 Drug: Thyrogen Sponsor: Genzyme Date: 5/22/98
Proposed changes to Thyrogen labeling:

Clinical Pharmacology

Pharmacodynamics

DRAFT LABELING

Clinical trials
replace entire section with:

DRAFT LABELING

APPEARS THIS WAY
ON ORIGINAL

ADDENDUM TO REVIEW

NDA: 20,898 Drug: Thyrogen Sponsor: Genzyme Date: 4/24/98

Corrections/Clarifications to Dr. Temeck's Clinical Review:
1. Page 8: footnote "C" also applies to the patient in whom the withdrawal scan stage was 2 and the Thyrogen scan was stage 1.
Therefore, on page 9, footnote "C" should read: "These 3 patients..." rather than "Both patients..."

2. Pages 22-24, tables 1-6 are a comparison of the withdrawal and Thyrogen scans.
Page 22, table 1, the 9 discordant scans in arm I and the 8 discordant scans in arm II, refer to the scans favoring withdrawal.

/S/
Jean Temeck, M.D.

/S/
4-24-98

cc. NDA 20,898 Arch
HFD-510. Div. file
HFD-510: Dr. Orloff/ Mr. McCort

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

genzyme

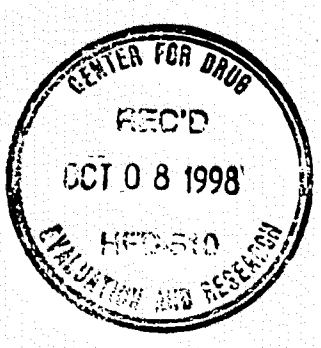
October 7, 1998

NEW CORRESP

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 (ED_{50} values) obtained from our current [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.

Review: No new safety information

/S/
11/30/98

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Attachment 4: **Addresses Point 4 of Approvable Letter:** A proposed upper and lower limit for the release specification including the justification for upper and lower limits of [redacted] 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 *in vitro* specific activity assay (21 data points) and an acceptance criteria of ≥ 4 IU/mg 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 [redacted] As discussed in the October 2, 1998 teleconference, we commit to run the [redacted] at 0, 6, 12, 18, and 24 months followed by annual testing thereafter.

3. We commit to provide the validation data for the [redacted] 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)

APPEARS THIS WAY
ON ORIGINAL

(967)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: **Division of** Metabolism and Endocrine products. **HFD-** 510

Attention: Duu-Gong Wu **Phone:** 301-827-6387

Date: 3/3/98

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark: Thyrogen **NDA/~~ANDA~~#** 20-898

Established name, including dosage form:

Thyrotropin alfa, injection
(Thyroid stimulating hormone)

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy):

for the detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients on hormone suppression therapy

Initial Comments from the submitter (concerns, observations, etc.):

APPEARS THIS WAY
ON ORIGINAL

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	967	HFD#	510	PROPOSED PROPRIETARY NAME:
ENTION:	DUU-GONG WU			THYROGEN

A. Look-alike/Sound-alike

	Potential for confusion:
TRILAFON	XXX Low ___ Medium ___ High
THYROXINE	XXX Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High

B. Misleading Aspects

C. Other Concerns

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations: XXX ACCEPTABLE ___ UNACCEPTABLE

F. Signature of Chair/Date /S/ 4/14/98

MEMORANDUM OF TELEPHONE CONFERENCE MINUTES

Meeting Date: October 23, 1998
Time: 11:00 am
Location: 14B-56

Application: Thyrogen

NDA: 20-898

Type of Meeting: Labeling

Meeting Chair: David Orloff, M.D,, Medical Team Leader

Meeting Recorder: Steve McCort, Project Manager

FDA Attendees, titles, and Office/Division:

David Orloff, M.D., Medical Team Leader, DMEDP, HFD-510
Jean Temeck, M.D., Medical Reviewer, DMEDP, HFD-510
Jayne Peterson, Reviewer, DDMAC, HFY-12
Sonia Castillo, Ph.D., Statistics Reviewer, HFD-720
Steve McCort, Project Manager, DMEDP, HFD-510

External Constituent Attendees and titles:

Allison Lawton, Vice President, Regulatory Affairs
Ilze Antons, Senior Regulatory Manager, Regulatory Affairs
Kevin McEllin, M.D., Director, Clinical Affairs
David Meeker, M.D., Vice President, Medical Affairs
P.K. Tandon, Ph.D., Senior Director, Biometrics

Background:

This meeting was called at the request of FDA to discuss the September 3, 1998, labeling submitted to the file for NDA 20-898. The Division submitted by FAX comments/revisions to the labeling. The firm faxed a revised copy of the labeling on October 21, 1998, incorporating the requested revisions from the Division's October 20, 1998 FAXED comments. In their request the firm asked for clarification regarding patient numbers in the first paragraph of the **Thyrogen Tg results: Overall Sensitivity section.** Their question for the reviewer (either Dr. Jean Temeck or Dr. Sonia Castillo) was to identify the patient numbers of the two patients that were dropped (one in the 2 dose and one in the 3 dose regimen).

Meeting Objectives:

1. Review and Discuss the September 21, 1998 revised draft labeling FAXED to FDA.
2. Discuss the reasons why the response to the Not Approvable letter was determined to be a class 2 submission requiring a 6 month action from FDA, rather than a class 1 response requiring a 2 month action.

Discussion:

APPEARS THIS WAY
ON ORIGINAL

Regulatory:

1. Allison Lawton asked the Division why the firm's October 8, 1998, resubmission to the September 15, 1998, Approvable letter, for NDA 20-898 was classified as a class 2 response requiring a 6 month review rather than a class 1 response requiring only a 2 month review and response from FDA? Ms. Lawton stated that Dr. Bilstad had been contacted and could not comment at the time, but would look into the issue. Dr. Orloff will follow-up on this issue and get back to Genzyme.

Labeling:

The following agreements were made by FDA and Genzyme to the October 21, 1998, labeling FAXED to the Division (see FAXED copy of the package insert):

1. Under **Thyroglobulin Results: Overall sensitivity of Thyrogen Tg Testing Alone and in Combination with Radioiodine Imaging,** paragraph 1:

   * line 5, firm has a question regarding the numbers. Firm asked if the numbers were really 54/122? rather than 54/121). Jean Temeck will get back to Kevin McEllin on Monday October 26, 1998.

   * line 2, [redacted]

   * line 4 - [redacted]

2. Under **Sensitivity of Thyrogen Tg Testing Alone and in combination with Radioiodine Imaging in Patients With Confirmed Metastatic Disease** page 5:

* Paragraph 1, line 6, the last two sentence that read [redacted]

Should now read,

[redacted]

3. Under **Considerations for Use of Thyrogen**, page 7:

* Paragraph 3, line 6 which reads [redacted]

should now read,

[redacted]

4. Under **PRECAUTIONS, General**

APPEARS THIS WAY
ON ORIGINAL

* Paragraph 2, line 3, which reads,

[redacted]

should now read,

[redacted]

* Paragraph 6, line 3, the last two sentences which read,

[redacted]

should be deleted.

* Paragraph 6, line 3, add [redacted] to the end of the second sentence.

5. **Under ADVERSE REACTIONS section,**

   * **Paragraph 6, which reads,**

[redacted]

needs to be revised with a stronger statement which includes more details about the patient and that the MI event was clearly related to the hyperthyroid condition with the 4 Thyrogen injections.

6. The firm wishes to submit a supplement regarding the sensitivity of the Tg assay used in the trials compared to the to the [redacted]

Decisions (agreements) reached:

1. The Firm and FDA agreed with the revised draft labeling dated September 20, 1998 FAXED to FDA (which included revised comments from FDA) except for the following:

   a. Under **Thyroglobulin Results: Overall sensitivity of Thyrogen Tg Testing Alone and in Combination with Radioiodine Imaging,** paragraph 1, line 5, the firm has a question regarding the numbers. Is it really 54/122? (rather than 55/124). Two patients which had unresolved scan ratings were left out by FDA in the final numbers. Dr. McEllin will check on these patients and give Dr. Jean Temeck of this Division an update on these patients on Monday October 26, 1998.

   b. Under **ADVERSE REACTIONS** section, paragraph 6 will be rewritten to include a stronger statement regarding the relationship of the MI adverse event in the 77 year old man to hyperthyroidism occurring after 4 injections of Thyrogen over 6 days.

   c. Under **ADVERSE REACTIONS** section the Table " Summary of Adverse Events During Controlled Studies (≥1%), Number of patients with Adverse Events, the numbers and % of patients in the table should be reversed with the % of patients first followed by the number of patients. (This was communicated in a separate telephone communication on October 23, 1998)

APPEARS THIS WAY
ON ORIGINAL

Action Items:

	Item	Responsible Person	Due Date
1.	Dr. McEllin will communicate with Jean Temeck regarding the two patients in the Thyrogen Tg results in the Clinical Pharmacology section of the PI .	Dr. McEllin, Genzyme	October 26, 1998
2.	The firm will communicate with FDA on the remaining labeling issues before Submitting their labeling amendment to the NDA.	Ilze Antons. Genzyme	?

Minutes Preparer: /S/ 10-29-98

Chair Concurrence: /S/ 10-30-98

Attachments/Handouts:

Concurrence: JTemeck 10-27-98/DOrloff 10-28-98/SCastillo 10-28-98
cc: Original
HFD-510/Div. Files
HFD-510/CSO/SMcCort
HFD-510/SSobel/DOrloff/JTemeck
HFD-720/SCastillo
HFY-12/JPeterson

Drafted by: smm/n20898.t12
final: smm/n20898.t12

MEETING MINUTES

MEMORANDUM OF TELEPHONE CONFERENCE

Meeting Date: October 2, 1998
Time: 10:00 am
Location: PKLN 14B-56

Application: NDA 20-898; Thyrogen

Type of Meeting: Chemistry Issues

Meeting Chair: Duu-Gong Wu, Ph.D.
Chemistry Team Leader

Meeting Recorder: Steve McCort
Project Manager

FDA Attendees, titles, and Office/Division:

Duu-Gong Wu, Ph.D., Chemistry Team Leader, DNDC 2
Steve Koepke, Ph.D., Deputy Director, DNDC 2
John Gibbs, Ph.D., Chemistry Director, DNDC 2
Yuan Yuan Chiu, Ph.D., Deputy Director, ONDC
Steve McCort, Project Manager

Genzyme Attendees and titles:

Alison Lawton, Vice President, Regulatory Affairs
John McPherson, Ph.D., Senior Vice President, Cell and Protein Therapeutics
Edward Cole, Ph.D., Protein Therapeutic Development
Robert Mattaliano, Ph.D., Director, Bioanalytical Development
Kim Raynor, Associate, Regulatory Affairs
Ken Edmonds, Regulatory Affairs
Ilzi Antons, Manager, Regulatory Affairs

Background:
This meeting was called as a result of the approvable letter dated September 15, 1998. The telephone conference was requested in a September 22, 1998 letter to the Agency to discuss the chemistry deficiencies addressed in that letter. Specifically the firm requested clarification of points 1, 3, and 4 and clarification of point 2 regarding the commitments.