MEMORANDUM OF MEETING MINUTES

Meeting Date: February 14, 2000
Time: 12:30 pm
Location: PKLN 14B-56

Application: NDA 21-137

Drug: Levolet (Lovothyroxine Sodium) Tablets

Type of Meeting: Team Meeting -Update on Final Review

Meeting Chair: John K. Jenkins, M.D., Acting Division Director

Meeting Recorder: Steve McCort, Project Manager

FDA Attendees:

John Jenkins, M.D., Acting Division Director
David Orloff, M.D., Deputy Director
Duu-Gong Wu, Ph.D., Chemistry Team Leader
David Lewis, Ph.D., Chemistry Reviewer
Hae Young Ahn, Ph.D., Biopharmaceutics Team Leader
Steven Johnson, Ph.D., Biopharmaceutics Reviewer
Chris Rogers, Regulatory Policy, CDER
Steve McCort, Project Manager

Meeting Objectives:

1. To provide an update on the status of the reviews.

2. To decide whether the action taken on this NDA should be Approval (AP), Approvable (AE) or Not Approval (NA)

Discussion Points;

1. **Chemistry** - Review **completed. Recommendation: AE** (will provide final comments for the letter to Steve McCort, Project Manager)

2. **Biopharm** - Review **completed. Recommendation: AE** (Reviewer will provide comments to Steve McCort, Project Manager) for lack of adequate dissolution data from commercial lots.

3. **Medical** - Review **not completed. Preliminary Recommendation: AP** with labeling recommendations to be conveyed to the Sponsor. Review in draft form with Dr. David Orloff , Deputy Director

4. **Pharmacology** - Review **completed. Recommendation: AE** with labeling recommendations to be conveyed to the Sponsor.

5. **DSI Audit - Completed** February 10, 2000. **Recommendation: Acceptable**

6. **EER: Completed. Recommendation: Acceptable** January 19, 2000.

Decisions (agreements) reached:

1. Review recommendation Approvable (AE). Specific deficiencies by discipline and additional labeling comments will be addressed in the action letter to the firm.

2. The action letter will list deficiencies by discipline as well as preliminary labeling recommendations to the package insert. The action letter will state that additional labeling recommendations will be communicated to the Firm at a later date.

2. The date the package will go to Dr. Jenkins has been extended to February 22, 2000.

3. Additional reviews and "Draft comments to Sponsor" will given to Steve McCort Project Manager to complete the Action letter and Package.

Action Items:

	Item	Responsible Person	Due Date
1.	All reviews and Draft comments completed	Review Team	ASAP
2.	Action Letter to Dr. Jenkins	Steve McCort	February 22, 2000
3.	Action letter signed	Dr. John Jenkins	March 2, 2000

Minutes Preparer: /S/

Chair Concurrence: _____

cc: NDA 21-137
HFD-510/Div. Files
HFD-/CSO/SMcCort
HFD-102/JJenkins
HFD-510/DOrloff/JTemeck/DWu/DLewis/RSteigerwalt
HFD-870/SJohnson/HAhn
HFD-007/CRogers

Drafted by:
Initialed by:
final:

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: February 14, 2000

APPLICATION NUMBER: NDA 21-137; Levolet (Levothyroxine Sodium) Tablets

BETWEEN:

Name: Chris Nascone, Regulatory Affairs
Phone: 704-596-0516
Representing: Vintage Pharmaceuticals

AND

Name: Steve McCort, Project Manager, Regulatory Affairs
Jean Temeck, Medical Officer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Labeling for Package Insert

The Sponsor had requested a t/Con to discuss the labeling for pending NDA 21-137. The Sponsor was called and were told that a telephone conversation at this time was premature. The Agency is still waiting for the firm to send a copy of the firm's version of the labeling to the Information request letter from FDA dated January 21, 2000. Chris Nascone is still waiting on a response from their consultant, Dr. — regarding the Sponsor's response to FDA. It was emphasized in the conversation that all formal responses need to be responded to FDA by Vintage and not by Dr. — However, communications should continue to occur in the meantime between the appropriate staff at FDA and Dr. — as long as the appropriate procedural process is adhered to. The Firm was requested to submit a copy of the revised labeling this week or next week.

/S/

Steve McCort, Project Manager

/S/

cc: Original NDA 21-137; Levolet (Levothyroxine Sodium) Tablets
HFD-510/Div. File
HFD-510/SMcCort
HFD-510/JTemeck/DOrloff

TELECON

12-15-1999

Office of Clinical Pharmacology and Biopharmaceutics

MEMO

To: Stephen McCort

From: Steven B. Johnson

CC: HFD-870 (ChenME, HuangS, AhnH)

Date: 15 December, 1999

Re: Request for information

Steve,

Please relay the following information to the sponsors listed below:

As described in the June, 1999 Guidance for Industry, entitled, "In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets," "... Dissolution studies can be performed using the current USP method or others provided that justification for the choice of the method(s) is given. **For each tablet strength to be marketed, multi-point dissolution studies should be performed on three production-sized batches using 12 tablets per batch.**" **"... Dissolution testing should include lots used in the bioavailability studies."**

Vintage Pharmaceuticals, Inc.
NDA 21-137
RFI: Dissolution data on three lots each of the following strengths: 50 µg, 75 µg, 88 µg, 112 µg, 125 µg, 137µg, 175 µg, and 200 µg tablets.

Lloyd, Inc.
NDA-21-116
RFI: Dissolution data on two additional lots for each of the to-be-marketed strengths.

RFI:

/S/

Steven B. Johnson, B.Pharm, Pharm.D.
Office of Clinical Pharmacology and Biopharmaceutics

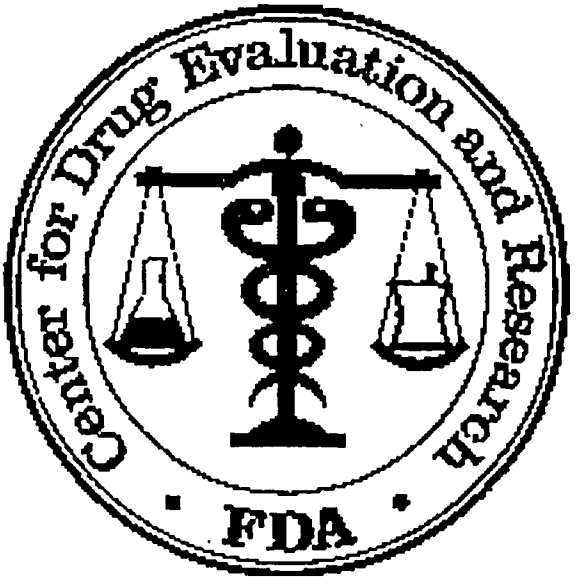
/S/

Hae-Young Ahn, Ph.D., Team Leader
Office of Clinical Pharmacology and Biopharmaceutics

HFD-510/NDA 21-137
HFD-510/DIV FILE
HFD-510/HAHN/SJOHNSON/SMCCORT

FOOD AND DRUG ADMINISTRATION
DIVISIONS OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: **June 23, 1999**



TO:		FROM:	
Name:	**REBECCA CHILDERS**	Name:	**Steve McCort**
Fax No:	704-598-6237	Fax No:	301-443-9282
Phone No:	704-596-0516	Phone No:	301-827-6415
Location:	VINTAGE PHARM	Location:	FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

COMMENT/REQUEST FOR L-THYROXINE NDA 21-137

HFD-510 / NDA 21-137
17FD-540 / Doc File
17FD-510 / SMcCort / JTemple

NDA: 21,137 · Drug: Levolet (Levothyroxine sodium) tablets Date: 6/22/99 ·

From a clinical standpoint, the NDA application is fileable. However, the following review issues should be conveyed to the sponsor:

1. The literature-based assessment by a pediatric thyroidologist of the safety of adding KI to your T4 tablet should address the pediatric population in general, but with special emphasis on the fetus and newborn (particularly premature infants). Also, provide a timeframe for submission of this assessment to the Agency.

2. Based on your assessment of the safety of adding KI to T4 in adult and pediatric patients, are any precautionary statements in the label warranted?

3. Submit additional copies of volumes 1.8, 2.1-2.4.

4. Summarize, by individual bioavailability study, the results of each safety parameter monitored, noting any abnormalities that occurred and if they were clinically significant.

5. Submit the last page which lists references 37-49 for the article entitled "Iodine and the Thyroid: 33 Years of Study" by Lewis Braverman in Thyroid, volume 4, number 3, page 356, 1994, submitted 2/8/99 to your IND.

6. Submit the following references listed in NDA volume 1.9 and which support the product package insert:
   a. American Hospital Formulary Service, 1998
   b. Dallas and Foley, 1990
   c. Peters et al, 1991

7. Provide references to support the following statements in the product package insert:
   a.
   b. References to support the following statements made in the second and third paragraphs of Pediatric Use: Congenital Hypothyroidism (CH):
      -Maintenance of serum T4 level above 103 mmol/L (8 ug/dl) in the first year of age to avoid IQ deficits in infants with TSH levels in excess of 20 uU/ml;
      -Frequency of thyroid function monitoring;
      -The potential for symptoms of hyperthyroidism to appear when attempts are made to normalize an elevated serum TSH with a normal T4 in patients with CH;
   c. Overdosage section:
      -symptoms of hyperthyroidism due to excessive doses of levothyroxine may not reach a maximum until 3 weeks after daily doses are begun.
      -a 1994 reference for Sawin cited in the second paragraph of this section, does not appear in the reference list
   d. Reference(s) to support the statement that measurement of both TSH and FT4 (either directly or indirectly) should be monitored to assess adequacy of the thyroid hormone replacement therapy- in Laboratory Tests to Monitor and Dosage and Administration sections
   e. Dosage and Administration section:
      Hypothyroidism subsection:
      - a starting dose of 50 ug/day T4 in patients with mild hypothyroidism
      - a starting dose of 25 ug T4 in young patients with cardiovascular (CV) disease
      - dose adjustment interval of 6-8 weeks in young patients with CV disease and elderly patients
      - which reference is ASHP, 1978- third paragraph

      Pediatric Dosage section:
      - a T4 starting dose of 25 ug with increases of 25 ug every 2 to 4 weeks in children with severe, long-standing hypothyroidism
      - a daily T4 dose of 8-10 ug/kg/day in infants aged 3-6 months

8. The following points pertain to the package insert and need to be addressed:
   a. the discrepancy in the frequency of thyroid function monitoring of pediatric patients- one schedule is proposed in the Pediatric Use: Congenital Hypothyroidism section and another is proposed in the Pediatric Dosage subsection of the Dosage and Administration section.
   b. the second sentence of the first paragraph in the Pediatric Dosage subsection of the Dosage and Administration section is incomplete

Note to Project Manager, Steve McCort:
Please convey point #4 above to all Levothyroxine sodium sponsors.

/S/

Jean Temeck, M.D.

/S/ 6-23-99

cc. NDA 21,137
HFD-510 Division file
HFD-510: Dr. Sobel, Dr. Orloff and Mr. McCort

APPEARS THIS WAY
ON ORIGINAL

6/8/99

TELEFAX

TO: Rebecca Childers

FAX: 704-598-6237

PHONE: _____

FROM: _____

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

FAX: (301)443-9282

PHONE: (301)827-6430

DATE: 6/8/99

PAGES: 7 (Inclusive)

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane-HFD-510
Rockville, Maryland 20857-1706

MEMORANDUM OF TELECON

DATE: May 28, 1999

APPLICATION NUMBER: NDA 21-137; L-thyroxine Sodium

BETWEEN:

Name: Rebecca Childers
Regulatory Affairs
Phone: 704-596-0516
Representing:Vintage Pharmaceuticals

AND

Names: Steve McCort, Regulatory Project Manager and
Jean Temeck, M.D., Medical Reviewer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Request for information regarding Pediatric information for pending NDA 21-137.

Information regarding pediatric information for pending NDA 21-137 was FAXED to the Sponsor on May 14, 1999. In the FAX, the sponsor was requested to submit several representative articles from the published literature to support the L-thyroxine product in pediatric age patients; efficacy- including dosing guidelines- and safety. In addition, the Agency requested information regarding the proposed addition of KI to the tablets, which would include an assessment of the safety of the product in the pediatric population.

Dr. Temeck in the t/con elaborated further on the May 14, 1999 request. Regarding the requested information on the use of KI for the pediatric population, Dr. Temeck requested the following:

1. A literature search on the safety profile of the KI tablet, particularly in pregnant women and infants (especially premature infants).

2. An assessment by a pediatric thyroidologist evaluating the safety profile of the KI in pregnant women and infants, especially in newborn and premature infants.

While not a filing issue, the addition of KI will be evaluated as a safety issue during the review of the NDA. Depending on the information presented in the NDA by the Sponsor, possible options to address the KI safety issues could include labeling revisions and/or phase 4 safety follow-up.

The Sponsor agreed to provide the Agency the information requested.

/S/ 6/8/99
Steve McCort
Regulatory Project Manager, HFD-510

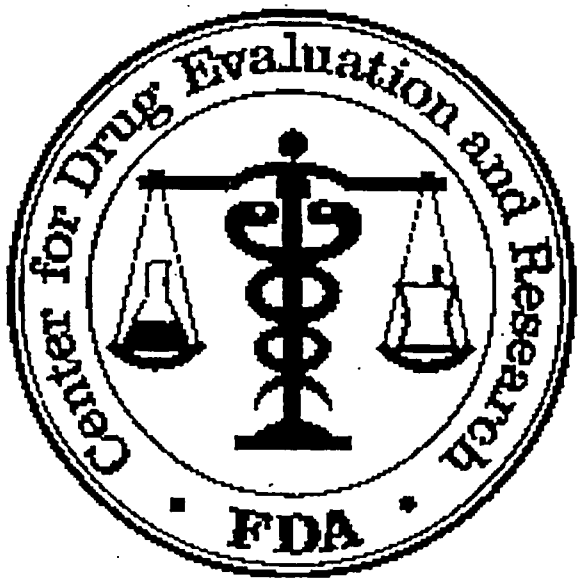
/S/ MD 6/8/99
Jean Temeck, M.D.
Medical Reviewer, HFD-510

cc: Original NDA 21-137
HFD-510/Div. File
HFD-510/Steve McCort
HFD-510/JTemeck

TELECON

FOOD AND DRUG ADMINISTRATION
DIVISIONS OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE:MAY14, 1999



TO:		FROM:	
Name:	REBECCA CHILDERS	Name:	Steve McCort
Fax No:	704-598-6237	Fax No:	301-443-9282
Phone No:	704-596-0516	Phone No:	301-827-6415
Location:	VINTAGE PHARM	Location:	FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

COMMENT/REQUEST FOR L-THYROXINE NDA 21-137

REQUEST FOR L-THYROXINE NDA 21-137

Due to the Pediatric Rule, we are asking that you submit several representative articles from the published literature to support your product in pediatric age patients; efficacy-including dosing guidelines- and safety.

In addition, since you proposing to add KI to the T4 tablets, you should include an assessment of safety of your product in the pediatric population. – by ped thyroidologists, particularly focus on pregnant women + infants : especially premature infants

APPEARS THIS WAY
ON ORIGINAL

1 MCONT

COMMENTS TO THE FEBRUARY 12, 1999, LETTER FROM VINTAGE REGARDING LEVOTHYROXINE

In a reply to a February 12, 1999, letter you requested permission to file the NDA for Levothyroxine Sodium before completion of the additional 50 μgm bioavailability study.

In a March 8, 1999 telephone conversation to Rebecca Childers of Vintage, the firm was informed that the 50 μgm bioavailability study must be completed by the internal filing meeting for the NDA for Levothyroxine Sodium.

After further review by the Agency, the firm will be allowed to complete the 50 μgm bioavailability study by the filing date (60 days from the stamp date for the submission of the NDA) rather than by the filing meeting for the NDA.

If there are any questions, feel free to call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Cleared for FAX:

/S/

Solomon Sobel, M.D.
Division Director
HFD-510

CC:
IND
HFD-510/Div File
HFD-510/SMcCort/SSobel

FOOD AND DRUG ADMINISTRATION
DIVISIONS OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: **April 22, 1999**

TO:		FROM:	
Name:	**REBECCA CHILDERS**	Name:	**Steve McCort**
Fax No:	704-598-6237	Fax No:	301-443-9282
Phone No:	704-596-0516	Phone No:	301-827-6415
Location:	VINTAGE PHARM	Location:	FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

COMMENTS REGARDING [redacted] LEVOTHYROXINE SODIUM
RESPONSE TO FEB 12, 1999 LETTER

MEMORANDUM

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

DATE: April 21, 1999

FROM: Steve McCort
Project Manager
DMEDP, HFD-510

SUBJECT: Follow-up to March 8, 1999 t/con to Sponsor
Timing of submission of completion 50 μgm
bioavailability study

TO: File for IND —

In a reply to an E-Mail message sent March 3, 1999, sent by Steve McCort, Project Manager, it was decided (See Reply to March 3, 1999, memo from Dr. Solomon Sobel) that the 50 μgm study must be completed and the report submitted to the IND prior to the filing meeting of the NDA for Levothyroxine. This decision was conveyed to the firm on March 8, 1999.

After further discussion with Dr. Sobel, it was decided that the firm should be allowed to complete the 50 μgm bioavailability study by the filing date (60 days from the stamp date for the submission of the NDA) rather than by the filing meeting for the NDA. This decision will be conveyed to the firm both t/con and Fax.

/S/ 4-21-99
Steve McCort
Project Manager
DMEDP, HFD-510

/S/ 4-22-99
Solomon Sobel, M.D.
Division Director
DMEDP, HFD-510

cc: IND —
HFD-510/DivFile
HFD-510/SSobel
HFD-510/SMcCort
HFD-510/DOrloff/JTemeck
HFD-510/RSteigerwalt
HFD-510/DLewis/DWu
HFD-870/MFossler/HAhn
HFD-007/CRogers

MEMORANDUM OF TELECON

DATE: March 8, 1999

APPLICATION NUMBER: IND — L-thyroxine

BETWEEN:

Name: Rebecca Childers, Regulatory Affairs
Phone: (704) 596-0516
Representing: Vintage Pharmaceuticals

AND

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

SUBJECT: Need to complete 50 μgm study before submission of NDA?

In a letter dated February 12, 1999, Vintage Pharmaceuticals requested permission to file the NDA for Levothyroxine before completion of the additional 50 μgm bioavailability study.

The firm was told **that the 50 μgm study must be completed and the report submitted to the IND prior to the internal filing meeting of the NDA for Levothyroxine.** The sponsor was told that this communication would be followed with both a FAX as well as a letter to the firm.

/S/ 3-8-99

Steve McCort
Project Manager, HFD-510

cc: IND —
HFD-510/DivFile
HFD-510/SSobel
HFD-510/SMcCort
HFD-510/DOrloff/JTemeck
HFD-510/RSteigerwalt
HFD-510/DLewis/DWu
HFD-870/MFossler/HAhn
HFD-007/CRogers

TELECON

MEMORANDUM

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

DATE: March 8, 1999

FROM: Steve McCort
Project Manager
DMEDP, HFD-510

SUBJECT: Vintage Levothyroxine Bioavailability Study - Needed before completion of NDA?

TO: File for IND —

In a letter dated February 12, 1999, Vintage Pharmaceuticals requested permission to file the NDA for Levothyroxine before completion of the additional 50 μgm bioavailability study. This study was requested by the Division in a FAX dated February 3, 1999, and in the meeting dated October 1, 1998 with the firm.

In a reply to an E-Mail message sent March 3, 1999, sent by Steve McCort, Project Manager, **it was decided (See Reply to March 3, 1999, memo from Dr. Solomon Sobel) that the 50 μgm study must be completed and the report submitted to the IND prior to the filing of the NDA for Levothyroxine.** This decision will be communicated to the firm by telephone communication or by letter.

/S/

Steve McCort
Project Manager
DMEDP, HFD-510

/S/ 3/8/99

Solomon Sobel, M.D.
Division Director
DMEDP, HFD-510

cc: IND —
HFD-510/DivFile
HFD-510/SSobel
HFD-510/SMcCort
HFD-510/DOrloff/JTemeck
HFD-510/RSteigerwalt
HFD-510/DLewis/DWu
HFD-870/MFossler/HAhn
HFD-007/CRogers

pork Blvd.
NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

February 12, 1999

Division of Metabolism and Endocrine Drug products
Center for Drug Evaluation and Research
FDA
Document Control Room
Rm 14B19, HFD 510
5600 Fishers Lane
Rockville, MD 20857

RE IND —
— Levothyroxine Sodium Tablets, USP

Please be advised of Vintage's receipt of notice, February 5, 1999 that Vintage will be required to perform a second bioavailability study comparing the 50 mcg tablet with the 100 mcg levothyroxine tablet. It was our understanding based on earlier communications that this additional bioavailability study would not be necessary. Accordingly, we request permission to file the NDA at this time to start the review process and submit this additional biostudy upon completion. Meanwhile we will start and complete the second biostudy during the next few months so that it will not delay the review process.

Thank you for your consideration.

Sincerely,

Rebecca Childers

APPEARS THIS WAY
ON ORIGINAL

02/13/99 05:12 FAX

FOOD AND DRUG ADMINISTRATION
DIVISIONS OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: **February 3, 1999**

TO:		FROM:	
Name:	**REBECCA CHILDERS**	Name:	**Steve McCort**
Fax No:	704-598-6237	Fax No:	301-443-9282
Phone No:	704-596-0516	Phone No:	301-827-6415
Location:	VINTAGE PHARM	Location:	FDA, Division of Metabolic and Endocrine Drug Products, HFD-510

Comments:

COMMENTS ON 11-2-98 SUBMISSION FOR IND
BIOPHARM COMMENTS

CC: IND

HFD-510/ Div File / mccort / Possley

BIOPHARM COMMENTS:

IND: —

DRUG: Levothyroxine sodium

SUBMISSION: Serial 007

SUBMISSION DATE: 11-2-98

We ask that you perform an additional bioavailability study comparing the 50μg tablet with the 100 μg tablet of the formulation you intend to market. The study should be a randomized crossover study in 24 healthy volunteers, and should follow the suggestions previously conveyed to you.

MEMORANDUM OF A MEETING
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HFD-510)

MEETING DATE: June 22, 1999 TIME: 3:00 am PLACE: Parklawn Rm 14B-56

DRUG: Levolet (levothroxine sodium tablets)

SPONSOR: Vintage Pharmaceutical

NDA: 21-137

TYPE OF MEETING: Filing/Planning Meeting

MEETING CHAIR: Solomon Sobel, M.D., Division Director

MEETING RECORDER: Steve McCort, Regulatory Project Manager

FDA STAFF:

Solomon Sobel, M.D., Division Director (HFD-510)
Jean Temeck, M.D., Medical Reviewer (HFD-510)
David Lewis, Ph.D., Chemistry Reviewer (HFD-510)
Mike Fossler, Ph.D., Biopharmaceutics Reviewer (HFD-870)
Chris Rogers, Policy Management, (HFD-007)
Steve McCort, Regulatory Project Manager (HFD-510)

Meeting Objectives:

1. To discuss whether the application is fileable.
2. To discuss planning dates for the review and action for the application

CONCLUSIONS AND DECISIONS REACHED:

1. IS THE APPLICATION FILEABLE?

Project Manager- Yes. It is fileable.

Medical: Yes. It is fileable. However, the reviewer has the following review issues:
(See attached comments; comments faxed to Sponsor on June 23, 1999)

Biopharmaceutics: Yes. It is fileable. However the Sponsor should be asked to provide The following information:

The Sponsor should be requested to send the study report and data for Study ANA-97-06 in electronic format. The study report should be submitted in word format; the data should be submitted as an Excel file. In addition the draft labeling should be submitted in word format. (Comments faxed to Sponsor on June 23, 1999)

A DSI audit of the analytical laboratories used for the bioavailability studies will be requested.

Chemistry: Not decided at the meeting. A decision regarding fileability will be made at a later date.

APPLICATION FILEABLE AFTER MEETING. Additional review issues will be communicated to the Sponsor at a later date.

Pharmacology: Yes. No fileablity or review issues.
(Ron Steigerwalt, Pharmacology Team Leader not present. Review decision discussed before the filing meeting)

2. PLANNING:

- Application is a Standard Review
- Filing date: July 10, 1999
- Primary Goal Date: March 10, 2000 (10 month goal date)
- Date Reviews Signed Off: February 18, 2000
- Date of Labeling Meeting: February 1, 2000
- Date to Dr. Sobel: March 1, 2000
- Action Performance Goal Date: March 10, 2000

CONCLUSION:

The application is fileable. Requests for information from both the medical officer and the biopharmaceutics reviewer have been communicated the Sponsor. Additional chemistry review issues will be communicated to The Sponsor at a later date.

Signature of Minutes preparer: /S/ 7-14-99

Steve McCort
Project Manager, HFD-510

Signature of Chair: /S/ 7/14/99

Solomon Sobel. M.D.,
Division Director, HFD-510

Concurrence: DLewis 7-13-99/MFossler 7-13-99/JTemeck 7-13-99

cc: NDA 21-137
HFD-510/DivFile
HFD-510/CSO/SMcCort
HFD-510/SSobel/JTemeck/DOrloff/MFossler/HAhn/RSteigerwalt
HFD-870/HAhn/MFossler
HFD-007/CRogers

MCCORT

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 1, 1998
Time: 3:00 pm
Location: PKLN Conference Rm. Q 3rd Flr.

Application: IND

Drug: L-Thyroxine sodium tablets

Type of Meeting: Pre-NDA

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

Meeting Recorder: Steve McCort
Project Manager

FDA Attendees, titles, and Office/Division:

Solomon Sobel, M.D., Division Director, DMEDP
David Orloff, M.D., Medical Team Leader, DMEDP
Jean Temeck, M.D., Medical Reviewer, DMEDP
Christine Rogers, Regulatory Counsel, Regulatory Policy Staff
Hae Young Ahn, Ph.D., Biopharmaceutics Team Leader, OPS
Mike Fossler, Ph.D., Biopharmaceutics Reviewer, OPS
Duu-Gong Wu, Ph.D., Chemistry Team Leader, DNDC 2
David Lewis, Ph.D., Chemistry Reviewer, DNDC 2
Steve McCort, Project Manager

Vintage Pharmaceuticals Attendees and titles:

Pam Troxler, Validation Manager, QC, Chemistry

Bill Propst, Jr., Vice President
John Shultz, Plant Manager
Robecca Childers, Regulatory Affairs

Objective: To review the requirements and package required for an NDA for L-Thyroxine.

Background:

In response to the Federal Register Notice dated August 1996, Vintage Pharmaceuticals submitted an IND November 7, 1996, for L-Thyroxine. In response to the requests for information from the FDA, a telephone conference dated December 18, 1996, was held to discuss the proposed IND protocols (bioavailability studies) and what other requirements would be needed to file the NDA. After review of the IND submission with amendments addressing our concerns,the Agency sent a letter date July 15, 1997, detailing additional comments and recommendations. A meeting request dated July 31 1998, and received August 5, 1998, was sent by the Firm for a pre-NDA meeting.

Discussion Points

1. CMC ISSUES

   a. **Are stability studies adequate?**

      FDA response:

      [

      ]

   b. **Has proper bracketing been conducted to include all the strengths?**

      FDA Response:

      Bracketing for stability lots is general is acceptable depending on how many strengths will be marketed.

2. BIOAVAILABLITY STUDIES

a. **Is the bioavailablity data adequate to support the NDA submission?**

FDA Response:

The lowest dose of 50 μg was not done. (The Sponsor indicated that they were not informed by FDA of such a study). Perhaps a short study may suffice before submission of the NDA.

Need to verify the concentration of KI for each tablet used in the study. It was not clear in the data presented to the Agency.

3. CLINICAL

a. **Is the clinical summary adequate?**

FDA Response:

No. A full summary of information is needed that summarizes the safety and and efficacy of the product.

b. **Is the package insert adequate?**

FDA Response:

It appears adequate. However it will need to be reviewed upon receipt of the NDA and is subject to revision.

c. **Is the information needed relative to the safety of the iodine content in the drug product?**

FDA Response:

The question that concerns the Agency is amount of KI that is to be included in each tablet. The Agency has literature submitted by the firm to support the safety of 30 μgms of KI in a tablet. It was unclear from the submitted information what the amount of KI was in each tablet. The firm will have to submit information regarding the amount of KI. Expanded search of the literature will be needed to support the safety of KI.

d. **Will an "Integrated Summary of Safety and Efficacy" be needed in the NDA package?**

FDA Response:

Yes. The firm can consult with the Division regarding the details of this section.

4. **NDA FORMAT ISSUES**

a. **Is the proposed format of the NDA appropriate according to the proposed "Table of Contents"?**

FDA Response:

The proposed format needs some more revisions. The project manager, Steve McCort, will send the appropriate guidelines relative to the format of submission of an NDA.

Decisions (agreements) reached:

1. The stability information presented at the meeting is inadequate.

2. The firm needs to send information on the amount of KI in their drug product. If amount of the KI is higher than reported to the Agency (greater than 30 μgms per tablet) the firm will have to submit information (literature) that supports the safety of the higher amount of KI for the drug product.

3. The firm needs to submit to the Agency a protocol for a short bioavailability study using 50 μg tablets.

4. The Sponsor needs to reformat their NDA before submission using the guidelines as stated in 20 CFR 314.57 and using guidelines for formatting an NDA that the Project Manager, Steve McCort will send to the Sponsor.

Action Items:

	Item	Responsible Person	Due Date
1.	The Sponsor will send the Information requested at this Meeting to the FDA.	Rebecca Childers Vintage Pharm.	?

/S/
Minutes Preparer: _____ 10-30-98

/S/
Chair Concurrence: _____ 10-30-98

Attachments/Handouts: Meeting materials

Concurrence:DLewis 10-23-98/DWu 10-26-98/MFossler10-27-98/HAhn 10-30-98
CRogers 10-30-98/DOrloff 10-30-98

cc: IND
HFD-/Div. Files
HFD-/CSO/SMcCort
HFD-510/DOrloff/JTemeck/DLewis/DWu
HFD-870/HAhn/MFossler
HFD-510/SSobel
HFD-007/CRogers

Drafted by: smm/October 21, 1998
Initialed by:
final:

MEETING MINUTES

ORIGINAL

JAN 16 1997

MEMORANDUM OF A MEETING/TON
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HAD-510)

MEETING DATE: December 18, 1996 TIME: 3:00 p.m. PLACE: Parklawn Rm 17B43

DRUG: Levothyroxine

IND: —

SPONSOR: Vintage Pharmaceuticals

TYPE OF MEETING: Discussion Internal/TON with Sponsor

MEETING CHAIR: David Orloff, M.D. Medical Team Leader

MEETING RECORDER: Steve McCort, Project Manager

PARTICIPANTS:

FROM FDA:

David Orloff, M..D., Medical Team Leader (HAD-510)
Jean Temeck, M.D., Medical Reviewer (HFD-510)
Mike Fossler, Ph.D., Biopharmaceutics Reviewer (HFD-870)
Steve McCort, Project Manager (HAD-510)

FROM VINTAGE PHARMACEUTICALS:

Mr. Propst, Owner

John Shultz, General Manager
Rebecca Thurman, Regulatory Affairs Manager

MEETING OBJECTIVE:

To discuss with the sponsor their proposed IND protocols and what requirements they will need to file their NDA for L-Thyroxine.

DISCUSSION ITEMS:

1. Bioavailablity requirements
2. Additional clinical data/studies?
3. Discussion of the Vintage IND
4. T/Con to Vintage Pharmaceuticals

CONCLUSIONS:

1. The firm will be required to submit a single bioavailability study of total T_4 AND total T_3 in normal volunteers.

   (Details of this will be FAXED to the sponsor)

2. The firm will not be required to submit a bioequivalence study to support a new NDA.

3. Dr. — will ask Dr. — if Potassium Iodide —— will affect either the efficacy or safety of the product.

4. Published literature on the efficacy and safety of levothyroxine for hypothyroidism will satisfy the clinical requirement for a 505(b)(2) NDA application.

5. The chemistry staff in this Division will communicate to the sponsor in the future regarding dissolution and stability studies required to support an NDA application.

ACTION ITEMS:

Item	Responsible person	Due Date
1. The Division will FAX to firm detailed information regarding the proposed bioequivalence study requirements and additional clinical requirements to support an NDA application.	Steve McCort	January 16, 1997

Signature of Minutes preparer: /S/ 1-16-97

Concurrence Chair: /S/ 1-16-97

cc: IND: —
HFD-510/DivFile
HFD-510/CSO/SMcCort
HFD-510/JTemeck/DOrloff/SSobel/DWu/SMarkofsky
HFD-870/HAhn/MFossler

Pre-IND/Pre-NDA Meeting
Levothyroxine Sodium Tablets
Vintage Pharmaceuticals, Inc.

October 14, 1994

MEMORANDUM OF MEETING

Vintage Representatives:

William Propst, President
Pieter Groenewoud, General Manager
[redacted]

[redacted] (Consultant)

[redacted] (Consultant)

[redacted] Consultant)

[redacted] (Consultant)

FDA Staff:

Dr. Sobel
Dr. Troendle
Dr. Temeck
Dr. Orloff
Dr. Chiu
Dr. Davies
Mr. Short (CSO)
Mr. Fazzari (HFD-313)
Ms. Summy (HFD-325)
Ms. Rogers (HFD-366)
Mr. Hunt (HFD-426)
Dr. Ahn (HFD-426)
Mr. Marticello (HFD-713)

Purpose: Vintage requested the meeting to discuss the requirements necessary for submitting an acceptable NDA. Prior to the meeting, Vintage provided draft protocols for two clinical studies, including bioavailability measurements, in a submission dated October 3, 1994 (attached). A week prior to the meeting they provided (via FAX dated October 7, 1994 -- attached) a revision of the protocol entitled "Evaluation of Clinical Efficacy and Plasma Levels of T_3 and T_4 in a Multiple Dose Comparison of Levothyroxine Sodium with a Currently Marketed Standard Product (Synthroid, Boots)".

Discussion and Conclusions: Dr. — described the 57-day clinical/bioavailability study he intends to perform. He will use 75 to 150 μg levothyroxine sodium tablets supplied by Vintage in 20 previously untreated hypothyroid patients in order to demonstrate the drug's effect on metabolic and biochemical parameters of thyroid function. A standard dose of 1.65 μg/Kg body weight will be used. During the discussion, Dr. — indicated that he probably will limit the age to those patients less than 50 years of age (not included in the protocol). All laboratory tests are to be performed by one laboratory. (See attachments for further details of the study.) Dr. Temeck asked what will be the primary endpoint for this study. Dr. — said there will not be a primary endpoint; the endpoints will be normalization of thyroid function, BMR, and cardiac parameters.

Dr. — presented the details of the other clinical/bioavailability study Vintage intends to perform. The overheads he used for the protocol outline were the same as those FAX'd on 10/7/94. Twenty-four (24) previously-diagnosed hypothyroid patients, who have been stabilized on 100 μg Boots Synthroid, will be randomized to either 100 μg Vintage or Boots levothyroxine sodium tablets. The primary efficacy parameters will be normalization of T_3, T_4, T_7 and TSH. Dr. Temeck asked why only one strength of tablet was chosen. Dr. — said that the 100 μg tablet is the largest seller, and by using only one strength, more uniform bioequivalence data would be generated. But, he said that if we were more concerned about the effect on clinical parameters, they would be willing to consider additional strengths.

Chemistry Comments: Dr. Chiu asked the company to provide comparative in vitro dissolution data for both their product and Synthroid (all strengths). When asked about the stability of Vintage's product, Mr. Groenewoud commented that the product is very stable, but indicated that — is utilized during manufacturing — They intend to release their product at — %. Mr. Groenewoud also said — Dr. Chiu indicated that the only time the — is acceptable (according to cGMP) is to allow for loss during manufacturing, not to compensate for degradation. She said the manufacturing target release should be 100%. Currently, Vintage only has accelerated stability data. Dr. Chiu informed the Vintage representatives that they must have 1 year of real-time stability data (3 batches) at the time of NDA filing in order to get a 2-year expiration date, and that we also require 6-month accelerated data. She said they do not need to do each strength; they can bracket them. Dr. Chiu suggested that Vintage consider — of the drug substance and excipients — manufacturing the drug product — — Mr. Groenewoud agreed, but only gave suggestions relating to protecting the drug product after manufacture, —

Biopharm Comments: As for the dissolution method used, Mr. Hunt said he would like them to use a slower paddle speed than that provided in the USP (100 rpm) and use different media utilizing different pHs. As to whether each strength tablet must be evaluated for its bioavailability, Mr. Hunt said that he would like to see the in vitro dissolution data (as requested by Dr. Chiu) before commenting on the appropriate bioavailability study. It was noted that a bioavailability study for tablet(s) would need to be compared to a reference standard, i.e., oral solution or IV dose. Mr. Hunt suggested a conference call between Vintage representatives and the Biopharm staff. Vintage representatives agreed.

Clinical Comments: Dr. Sobel commented that it will be very important to demonstrate TSH suppression in the bioavailability protocol. As to Dr. Sobel's concern that the tablets being used represent the declared strength, Vintage representatives assured Dr. Sobel that each batch to the used would be assayed and confirmed to be within ±5% of the declared strength. Dr. Sobel asked the Vintage representatives if they included Synthroid in the one protocol because they intend to mimic the Synthroid preparations. Vintage's response was that they were NOT trying to mimic Synthroid but included Synthroid in the protocol so that the medical community could compare the effects of each to make switching easier, once Vintage markets their product.

Dr. Sobel indicated that FDA is planning a Federal Register announcement requiring an NDA for the marketing of thyroid preparations.

Considering that Vintage does not currently market this product, Mr. Short asked if they intend to do their clinical studies under an IND. They responded in the affirmative.

Mr. —— inquired as to whether the first approved liothyronine sodium NDA would be granted exclusivity under the Drug Price Competition and Patent Term Restoration Act of 1984. Dr. Sobel explained that his answer was not a legal response, but he hoped that the first NDA approved would NOT be granted exclusivity and interrupt the supply of this drug in the United States. Dr. Sobel said ——

ACTION ITEMS:

1) Vintage to provide in vitro dissolution data for all tablet strengths.

2) Vintage representatives to be in touch with Mr. Hunt (after he has a chance to review the in vitro dissolution data) to discuss details of the bioavailability protocol.

3) Mr. Short

/S/

John R. Short, CSO

Attachments (3)
Overheads Used by Dr.
Submission dated 10/3/94
FAX dated 10/7/94

cc: HFA-224 (yellow copy)
HFD-510
attendees
HFD-713/ENevius
HFD-510/AJordan, KRaheja, EGalliers, DJenkins
HFD-511/JShort 10/18/94/ft/lp/11/4/94/LVOTHYMM.2JS
Concurrence: JTemeck 10/18, GTroendle, HDavies, YYChiu 10/19, HAhn 10/26, JHunt, DMarticello, SSobel 10/27/94

APPEARS THIS WAY
ON ORIGINAL

Study Objective:

To study the effects of Vintage levothyroxine (l-thyroxine) on metabolic and biochemical parameters of thyroid function in previously untreated hypothyroid patients.

Study Patients:

1. Twenty untreated hypothyroid patients recruited from the outpatient clinics at the —

2. Diagnosis of hypothyroidism will be based on a low free thyroxine index and elevated TSH concentration (>10 uU/ml)

3. Exclusionary criteria - pregnancy, secondary hypothyroidism, medications known to affect thyroid function, underlying heart disease, or other disorders known to affect thyroid function

Thyroxine Preparations

Vintage Pharmaceuticals will supply l-thyroxine tablets in doses ranging from 0.075 to 0.15 mg. Specific l-thyroxine doses will be based on subject's body weight, using a standard dose of 1.65 ug. per kg. body weight.

Study Design:

Day 1

1. Baseline history and physical exam
2. Laboratory studies
    a. T4, T3RU, FTI, T3, TSH
    b. Cholesterol, CPK, SHBG
    c. Basal metabolic rate (BMR)
    d. Echocardiography

Day 29

Repeat Day 1 studies with exception of BMR and echocardiography

Day 57

Repeat Day 1 studies. Patients will then return to the care of their primary M.D.'s.

Laboratory Studies:

1. All serum assays will be performed by a central laboratory facility

2. Basal metabolic rates will be performed by
   using the

3. Cardiac indices of thyroid function will be determined by Doppler Echocardiography

Data Analysis:

Day 1 and Day 57 measurements will be analyzed for statistical significance using the Paired Student's t-test.

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

18-APR-2002

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-137

INFORMATION REQUEST LETTER

Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
Regulatory Affairs
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Mr. Nascone:

Please refer to your pending new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levolet (levothyroxine sodium) tablets, 12 strengths from 25 mcg to 300 mcg.

We also refer to our letter dated March 23, 2001, and to your submission dated December 17, 2001. As stated in our March 23, 2001, letter, we have prepared a template of the package insert labeling to be used for your drug product. The template labeling incorporates special considerations related to the presence of potassium iodide in the drug product.

We request that you revise your package insert and submit it promptly as an amendment to your pending application so we may continue our evaluation of your NDA. It would be very helpful if you could also provide an electronic copy of your revised draft labeling in MS Word 1997.

You also need to submit in duplicate colored mock-ups of the immediate container labels and carton labels for every presentation of the product that you intend to market; e.g., 25 mcg x 100 count and 25 mcg x 1000 count, etc. Please note that the storage conditions should be stated as follows.

Store between 20° and 25°C (68°-77°F) with excursions permitted from 15° to 30°C (59°- 86°F)

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

Sincerely,

/S/

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE

14 pages redacted from this section of the approval package consisted of draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
4/18/02 04:29:41 PM
for Dr. Orloff

APPEARS THIS WAY
ON ORIGINAL

15-FEB-2002

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-137

Vintage Pharmaceuticals, Inc.
Attention: Chris J. Nascone
Director, Regulatory Affairs
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Mr. Nascone:

We acknowledge receipt on December 18, 2001, of your December 17, 2001, resubmission to your new drug application (NDA) for Levolet® (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100 ,112, 125, 137, 150, 175, 200 and 300 mcg.

This resubmission contains additional manufacturing an biopharmaceutics information submitted in response to our March 23, 2001, action letter. Additional information regarding product specific labeling for the drug product will be sent at later date by the Agency.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is June 18, 2002.

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

Sincerely,

/S/

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
2/15/02 03:44:29 PM
for Dr. Orloff

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

23-MAR-2001

NDA 21-137

Vintage Pharmaceuticals
Attention: Chris Nascone
Director, Regulatory Affairs
3241 Wood Park Road
Charlotte, NC 28206

Dear Mr. Nascone:

Please refer to your new drug application (NDA) dated April 30, 1999, received May 10, 1999, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levolet® (levothyroxine sodium tablets, USP) - 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg.

We acknowledge receipt of your submissions dated September 25, October 17, and December 19, 2000. Your submission of September 25, 2000, constituted a complete response to our March 10, 2000, approvable letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

MANUFACTURING FACILITIES:

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. A satisfactory inspection will be required before this application may be approved.

BIOPHARMACEUTICS:

The *in vitro* dissolution data submitted on September 25, 2000, in response to the approvable letter of March 10, 2000, were reviewed and do not support your request for a waiver of the requirement for *in vivo* bioequivalence data for the intermediate tablet strengths that were not evaluated.

The data were complete; however, upon review, it was apparent that the USP 23 dissolution method is not appropriate for this product in that there is essentially no discriminatory power to detect differences (or similarities) among different strengths or different lots of the same strength.

Because the data generated using the USP 23 method are not representative of your product, additional dissolution testing is being requested by the Agency. You should conduct additional dissolution testing such that a more discriminating method specific to your drug product is found. Please submit multipoint dissolution data using a method that is appropriate for your product. We encourage you to consult the Division for guidance on this issue.

LABELING:

Changes in the labeling will be addressed after all outstanding issues have been resolved.

REGULATORY:

As required by 21 CFR 54, submit financial disclosure information for the *in vivo* bioavailability studies, which are considered to be "covered clinical studies." The covered studies include Study 7VN01 - Relative bioavailability and dosage-form and Study 9V-01 - Dosage-form proportionality.

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

Sincerely,

{See appended electronic signature page}

/S/

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

David Orloff
3/23/01 06:01:44 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HE H & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-137

Vintage Pharmaceuticals, Inc.
Attention: Chris Nascone
Regulatory Affairs
3241 Woodpark Bld.
Charlotte, NC. 28206

MAR 10 2000

Dear Mr. Nascone:

Please refer to your new drug application (NDA) dated April 30, 1999, received May 10, 1999, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levolet (levothyroxine sodium) Tablets.

We acknowledge receipt of your submissions dated May 20, June 14, 16, and 24, and July 14, 1999, and January 11 and February 9, 15, and 18, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CHEMISTRY MANUFACTURING AND CONTROLS:

1. In order to formulate an acceptable stability bracket for the drug product Levolet®, we require the following stability studies:

   - Six-month long-term (25°C ± 2°C/60 % RH ± 5 % RH) data and six-month accelerated (40°C ± 2°C/75 % RH ± 5 % RH) data on three lots of 25-mcg tablets.

   - Six-month long-term (25°C ± 2°C/60 % RH ± 5 % RH) data and six-month accelerated (40°C ± 2°C/75 % RH ± 5 % RH) data on three lots of 300-mcg tablets.

   - Six-month long-term (25°C ± 2°C/60 % RH ± 5 % RH) data and six-month accelerated (40°C ± 2°C/75 % RH ± 5 % RH) data on two lots of 100-mcg tablets.

   Your amendment dated February 9, 2000, provided long-term (25°C/60 % RH) stability studies for one lot of 100-mcg tablets, one lot of 50-mcg tablets, and one lot of 300-mcg tablets. The accelerated (40°C/75 % RH) stability studies that you provided in the original NDA (Vol. 1.7, pp. 205-295) cannot be utilized for stability evaluation since those data are not coupled to acceptable long-term data for each provided lot. These data do not satisfy the requirements stated above.

Therefore, we require that the following additional stability studies be performed and submitted:

a. Three lots of 25-mcg tablets studied for 6 months at 25°C ± 2°C/60 % RH ± 5 % RH and for 6 months at 40°C ± 2 °C/75 % RH ± 5 % RH.

b. One lot of 100-mcg tablets studied for 6 months at 25°C ± 2°C/60 % RH ± 5 % RH and for 6 months at 40°C ± 2°C/75 % RH ± 5 % RH.

c. Two lots of 300-mcg tablets studied for 6 months at 25°C ± 2°C/60 % RH ± 5 % RH and for 6 months at 40°C ± 2°C/75 % RH ± 5 % RH.

2. Revise the stability protocol to include monitoring for degradation products. All degradants, that occur at levels greater than or equal to 1.0 % should be identified, and specifications should be established for these levothyroxine-related impurities. In addition, specifications should be set for the sum of total degradants.

3. The quantitative components and composition for each tablet strength provided in the amendment dated February 9, 2000, are incorrect regarding potassium iodide (KI) content. Recalculate the composition and submit the revised information along with a representative calculation.

4. An Environmental Impact Report (EA) was not submitted with this application. All applications, including NDAs, are required to submit an EA or a claim of categorical exclusion for the drug product as required by 21 CFR 25.21 and 40 CFR 1508.4. Submit an EA or a request for a categorical exclusion. A request for a categorical exclusion may cite one of several 21 CFR regulations (21 CFR 25.31(a), (b), or (c)).

BIOPHARMACEUTICS:

5. In your NDA, dissolution data from only one lot each of four tablet strengths were submitted for review. Of these, only one lot of the 100 mcg strength tablets (lot #02036) used in the biostudies was included. The Agency requires that dissolution studies be conducted on three lots each of all to-be-marketed strengths (3 lots x 12 strengths = 36 tests), and your application must include all lots used in the biostudies [50 mcg (lot # 009029B), 100 mcg (Lot # 111039B), and 300 mcg (lot # 044036)]. The dissolution method used in these studies should follow the USP 23 monograph for levothyroxine sodium detailed below:

USP 23 Monograph for Levothyroxine Sodium Tablets

Medium:	0.05 M pH 7.4 phosphate buffer
Volume:	500 mL
Apparatus:	2 (paddles)
Speed:	100 RPM
Time:	80 minutes
Tolerances:	NLT 55% (Q) of the labeled amount of levothyroxine sodium is dissolved in 80 minutes

The Agency will accept the dissolution method and specifications outlined in the USP 23 monograph for levothyroxine sodium on an interim basis.

In addition, we remind you of your Phase 4 commitment specified in your submission dated February 18, 2000, which follows below:

- Within one year of approval, dissolution testing will be conducted, using either USP 24 or another discriminating method specific to your product, for all marketed strengths, and the data will be submitted to the Agency for review.

LABELING:

6. The following are preliminary comments on your proposed labeling for Levolet. Additional comments will follow once we have reviewed your responses to the deficiencies cited in this letter.

   A. **DESCRIPTION** section:

      Add the following sentence:

   B. **INDICATIONS AND USAGE** section:

      Replace this section with the following:

1 pages redacted from this section of the approval package consisted of draft labeling

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 meeting or telephone conference with this Division 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, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely

/S/

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and
Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 21-137

Vintage Pharmaceuticals, Inc.
Attention: Chris Nascone
Regulatory Affairs
3241 Woodpark Bld.
Charlotte, NC., 28206

JAN 21 2000

Dear Mr. Nascone:

Please refer to your new drug application dated April 30, 1999, for Levolet® (levothyroxine sodium) Tablets.

We also refer to the FAXED communication dated June 23, 1999, from FDA requesting additional clinical information for the NDA submission and the amendment dated June 14, 1999, providing additional biopharmaceutics information.

We are reviewing the Clinical and Biopharmaceutics sections of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

CLINICAL

Please refer to our FAXED communication dated June 23, 1999, requesting information regarding the Clinical portion of the NDA. As of this date we have received only a partial response to our request. The following information is still needed and has not been received:

1. We have no acknowledgment in your proposed labeling regarding the content of iodide in Levolet. The iodide content raises potential safety issues. Please propose labeling that addresses these issues. Use in pregnant/lactating women and in patients at risk for iodine-induced thyrotoxicosis should be included in your safety considerations. Please provide support in the form of data and discussion for proposed labeling.

2. Please provide an integrated safety summary from the Levolet bioavailability studies (VS, EKG, physical exam, chemistry profile, hematology, UA, adverse reactions). Please note if any of these abnormalities were clinically significant.

3. Submit the last page of the article entitled *"Iodine and the Thyroid: 33 years of Study" by Lewis Braverman in "Thyroid, volume 4, number 3, Page 356, 1994"*, submitted February 8, 1999, to your IND.

4. Submit the following references listed in NDA volume 1.9, pages 83, 90 & 104.
   a. American Hospital Formulary Service, 1998
   b. Dallas and Foley, 1990
   c. Peter, et al, 1991

5. Provide references to support the following statements in the product package insert:

   a. [redacted] in the **Precautions** section.

   b. **Pediatric Use: Congenital Hypothyroidism (CH):**

   c. **Overdosage:**

   d.

   e. **Dosage and Administration** section:
   Hyporthyroidism subsection:
   - A starting dose of 50 µg/day T4 in patients with mild hypothyroidism.
   - A starting dose of 25 µg T4 in young patients with cardiovascular (CV) disease.
   - A dose adjustment interval of [redacted] weeks in young patients with CV disease and elderly patients.
   - Submit reference " [redacted] ", referenced in the third paragraph

   Pediatric Dosage section:
   - A T4 starting dose of 25 µg with increases of 25 µg every 2 to 4 weeks in children with severe, long-standing hypothyroidism.
   - A daily T4 dose of 8-10 µg/kg/day in infants aged 3-6 months.

6. The following points pertain to the package insert and need to be addressed:

   a. The discrepancy in the frequency of thyroid function monitoring of pediatric patients - one schedule is proposed in the Pediatric Use: Congenital Hypothyroidism section and another is proposed in the Pediatric Dosage subsection of the **Dosage and Administration** section.

   b. The second sentence of the first paragraph in the **Pediatric Dosage** subsection of the **Dosage and Administration** section is incomplete.

   c. A 1994 reference for Sawin cited in the second paragraph of this section, does not appear in the reference list.

BIOPHARMACEUTICS:

The following additional information is requested:

The June, 1999 Guidance for Industry, entitled **"In Vivo Pharmacokinetics and Bioavailability Studies and in Vitro Dissolution Testing for Levothyroxine Sodium Tablets"** includes the following:

> Dissolution studies can be performed using the current USP method or others provided that justification for the choice of the methods [is given]. For each tablet strength to be marketed, multi-point dissolution studies should be performed on three production-sized batches using 12 tablets per batch. [Note that] dissolution testing should include lots used in the bioavailability studies.

Please provide dissolution data on three lots of each of the following strengths: 50 µg, 75 µg, 88 µg, 112 µg, 125 µg, 137 µg, 175 µg, and 200 µg tablets using a single dissolution method.

To provide adequate review time for this NDA submission, please respond no later than January 30, 2000, to both the Clinical and Biopharmaceutics requests for information.

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

Sincerely,

/S/

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Concurrence: J Temeck 1-11-00/S Johnson 1-11-00/E Galliers 1-13-00/D Orloff 1-14-00
cc:
Archival NDA 21-137
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/JTemeck/DOrloff
HFD-870/SJohnson/HAhn
HFD-510/JJenkins
DISTRICT OFFICE

Drafted by:SMcCort //N21137IR.doc/January 10, 2000
Revised by:SMcCort/N21137IM.doc/January 11,2000
final: SMcCort/N21137I2.doc/January 18, 2000

filename: n21137I2.doc

INFORMATION REQUEST (IR)

JAN 18 2000

NDA 21-137

Vintage Pharmaceuticals Inc.
Attention: Chris Nascone
Regulatory Affairs
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Mr. Nascone:

Please refer to your April 30, 1999, new drug application for Levolet (levothyroxine sodium) Tablets, USP.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. The quantitative compositions and contents, as provided in Vol. 1.1, pp. 25-27 are incorrect, regarding the target amounts of microcrystalline cellulose (MCC), and potassium iodide (KI) per tablet. These quantities should be calculated correctly, and a corrected target formulation provided for each strength for the drug product.

2. Provide a Color Additive certificate from the supplier for each of the following pigments:
   a. D & C Red # 27.
   b. FD & C Red # 40
   c. D & C Red # 30.

3. There is some inconsistency in the designation of the coloring principles (dyes) utilized for the drug product. Please clarify whether the following pairs of color additives mentioned at various times in the NDA are identical. Supplier's Certificates of Analysis and your acceptance specifications should be provided for each additive (in cases when the matched pair of color additives are separate entities).
   a. FD & C Yellow # 6 Lake, and FD & C Yellow # 6
   b. D & C Red # 27, D & C Red # 27, and D & C Red # 27
   c. FD & C Red # 40, and FD & C Red # 40 HT.
   d. D & C Yellow # 10, and D & C Yellow # 10

4. Provide Certificates of Analysis (COA) and your acceptance criteria for the [redacted] In addition, provide the manufacturer/supplier's COA for [redacted]

5. Are there specifications for content uniformity or particle size for the intermediate blend [redacted] Provide evidence that the intermediate does not form agglomerates after screening (during storage). Provide a description of the method by which the moisture content is monitored.

6. Are there in-process specifications for moisture content and content uniformity for the levothyroxine sodium [redacted]

7. Provide Letters of Authorization allowing the FDA to refer to DMF [redacted] DMF [redacted] DMF [redacted]

8. As communicated previously by telephone, the long-term stability data (collected at 25°C and ambient humidity) cannot be used for the purpose of evaluating stability and assigning shelf life, since these data were obtained utilizing storage conditions of uncontrolled humidity. These studies must be repeated for all strengths utilized in the stability bracket (25-, 100-, and 300-mcg tablets), stored under ICH storage conditions (25 ± 2 °C and 60 % ± 5 % RH).

9. There are some discrepancies in the manufacturing dates and the initiation dates of stability testing for the lots listed below. Please clarify and provide certificates of analysis for these lots (tested at release).
   a. Lots 036036A and B (Levothyroxine sodium 25-mcg tablets, 100- and 1000-count bottles, Vol. 1.7, pp. 265-268) with a manufacturing date of [redacted], and a stability initiation date of [redacted].
   b. Lots 037036A and B (Levothyroxine sodium 25-mcg tablets, 100- and 1000-count bottles, Vol. 1.7, pp. 269-272) with a manufacturing date of [redacted] and a stability initiation date of [redacted]

10. The testing results for Lots 026036A and B (Levothyroxine sodium 100-mcg tablets, 100- and 1000-count bottles, Vol. 1.7, pp. 274-277) indicates a T_4-assay value of [redacted] This represents a significant [redacted] which is not considered acceptable by the FDA. Data for this lot may not be utilized for the assessment of shelf life.

11. The stability studies for NDA 21-137 should include the following eight batches/lots: Three lots of the lowest strength (25-mcg tablets), three lots of the highest strength (300-mcg tablets), and two lots of one intermediate-strength tablets (e.g., 100-mcg tablets). Stability data consisting of two lots of 25-mcg tablets (036036 and 037036), one lot of 100-mcg tablets (026036), one lot of 150-mcg tablets (041036), and three lots of 300-mcg tablets (042036, 043036, and 044036) is not acceptable for utilization as a bracket for all strengths of the drug product. There are two types of stability data submissions, which will be acceptable for use as a stability bracket:
    a. The inclusion of data on THREE LOTS of the 25-mcg tablets, TWO LOTS of one intermediate strength (e.g., 100-mcg), and THREE LOTS of the 300-mcg tablets.
    b. The inclusion of data on THREE LOTS of the 25-mcg tablets, THREE LOTS of the 300-mcg tablets, and ONE LOT APIECE of each intermediate strength (50, 75, 88, 100, 112, 125, 137, 150, 175, and 200-mcg tablets).

12. There is no mention of stress testing (forced degradation) studies for the drug product. Have these studies been done? If so, provide documentation, including the particular stress conditions utilized for the test, the associated test (assay) method used to separate and quantify any generated degradants, and evidence of the suitability of these methods as a stability-indicating assay.

13. The stability protocol for the drug product does not include specifications for degradation products other than — There should be an attempt to identify all degradants (impurities) which could potentially occur at levels of greater than 0.1 %. The specifications for each identified impurity (degradant) may be established based on data obtained from ongoing stability studies.

14. Are the associated test methods for the stability protocol identical to those which are used for the finished drug product release?

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

Sincerely,

/S/ 1-18-00

Duu-Gong Wu, Ph.D.
Chemistry Team Leader II for the
Division of Metabolic and
Endocrine Drug Products, (HFD-510)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc
Archival NDA 21-137
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/DWu/DLewis
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: /January 11, 2000
Initialed by: LewisD 1.14.00/WuD 1.14.00/Galliers 1.14.00/McCort 1.14.00
Final: ddk/January 14, 2000
filename: N21137IR.DOC

INFORMATION REQUEST (IR)

NDA 21-137

Vintage Pharmaceuticals
Attention: Rebecca Childers
Regulatory Affairs
3241 WoodPark Blvd.
Charlotte, NC 28206

MAY 11 1999

Dear Ms. Childers:

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

Name of Drug Product:	Levolet (Levothyroxine Sodium) Tablets, USP, 12 strengths
Review Priority Classification:	Standard
Date of Application:	April 30, 1999
Date of Receipt:	May 3, 1999
Our Reference Number:	NDA 21-137

Because the appropriate user fee for this application was not paid within five days of our receipt of the application, the application was considered incomplete and not acceptable for filing.

This is to notify you that the Agency has received all fees owed and your application has been accepted as of May 10, 1999.

Unless we notify you within 60 days of the date of receipt of all user fees 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 July 9, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 10, 2000, and the secondary user fee goal date will be May 10, 2000.

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify

you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. 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) 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 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.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

/S/ - 5.11.99

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

cc:
Archival NDA 21-137
HFD-510/Div. Files
HFD-510/S.McCort
HFD-510/DOrloff/JTemeck/DWu/DLewis/RSteigerwalt
DISTRICT OFFICE

Concurrence: E Galliers 11-11-99
Drafted by:SMcCort /May 11, 1999
final: SmcCort/May 11, 1999
filename: N21137.AK2

ACKNOWLEDGEMENT UN/(AC)

MEMORANDUM

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

DATE: 25 February 2000

FROM: Enid Galliers /S/
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II, CDER

SUBJECT: Financial Disclosure Requirement for NDA 21-137 Levolet (levothyroxine sodium) Tablets

TO: File for NDA 21-137

Upon discussion with Linda Carter, Regulatory Policy Advisor, CDER, it was determined that financial disclosure reporting is not required because neither the literature reports or the pharmacokinetics studies that support this application are considered to be "covered clinical studies" under the financial disclosure reporting rule. Therefore, this application is not subject to the requirement for financial disclosure reporting.

Cc: Orig. NDA 21-137
HFD-510/Div. Files
HFD-510/SMcCort
HFD-101/LCarter

14-NOV-2001

MEMORANDUM

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

DATE: November 8 , 2001

TO: Dr. Jenkins
Director, ODE 11

THROUGH: Dr. Orloff
Director, DMEDP

FROM: Steve McCort
Project Manager, DMEDP

SUBJECT: Plan for monitoring phase-down schedule established in the July, 2001, "Guidance for Industry, Levothyroxine Products, Enforcement of August 14, 2001, Compliance Date and Submission of New Applications."

DRUGS: All NDA Applications for levothyroxine sodium tablets pending before the Agency on August 14, 2001.

BACKGROUND:

The Agency announced the availability of a guidance for industry entitled *"Levothyroxine Sodium Products- Enforcement of August 14, 2001 Compliance Date and Submission of New Applications."* in July, 2001. This guidance discussed how FDA plans to exercise its enforcement discretion after August 14, 2001, with regard to levothyroxine sodium products that are marketed without approved applications. In this guidance the Agency established a plan which included the establishment of a phase-out of the marketed product over a two-year period. This guidance is currently under revision to specify a grace period of 10 business days from November 1, 2001, and from the other dates in the phase-down schedule, by which manufacturers must submit amendments to their applications certifying that they have reduced average monthly distribution of levothyroxine in accordance with the phase-down schedule specified in the guidance. This memo proposes an FDA plan for monitoring compliance with this phase-down requirement.

PLAN:

1. All firms that have pending new drug applications for levothyroxine products before the Agency as of August 14, 2001, will be reminded by telephone and/or in writing of the requirements for reporting on distribution of their marketed product as per the *"Guidance for Industry, Levothyroxine Sodium Products- Enforcement of August 14, 2001 Compliance Date and Submission of New Applications."* We will request submission of the first report (and all subsequent reports) within 10 business days of each date in the phase-down schedule.

2. Quarterly reports should be submitted to the NDA and should be clearly identified as amendments to the pending NDA in the heading of the cover letter. The reports should include the information specified in the guidance. (The COMIS code for the amendment will be "BZ".)

3. Tracking of the quarterly reports will be monitored by the Project Management Staff in DMEDP.

4. DMEDP staff will prepare a quarterly summary that includes a table of *"Average monthly distribution per quarter as a % from baseline"* for all pending levothyroxine NDAs. Copies will be sent to the Office of Regulatory Policy; John Jenkins, Office of Drug Evaluation II; and John Loh, DPDCS, Office of Compliance, CDER. (See copy of proposed table, *"Average Monthly Distribution Per Quarter [% of Baseline]."*)

5. If any firm has not met the reduced distribution requirements, the DMEDP project manager will notify the Office of Compliance for appropriate action.

ATTACHMENTS:

TABLE – AVERAGE MONTHLY DISTRIBUTION PER QUARTER
COMIS LIST OF ALL PENDING LEVOTHYROXINE NDAs
GUIDANCE
FEDERAL REGISTER NOTICE

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stephen McCort
11/9/01 01:01:42 PM
CSO

Revised information page to include the NDAs for the memo to the File

David Orloff
11/14/01 02:48:34 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL