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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-137**

# Clinical Pharmacology and Biopharmaceutics Review

10-APR-2002

# Clinical Pharmacology and Biopharmaceutics Review

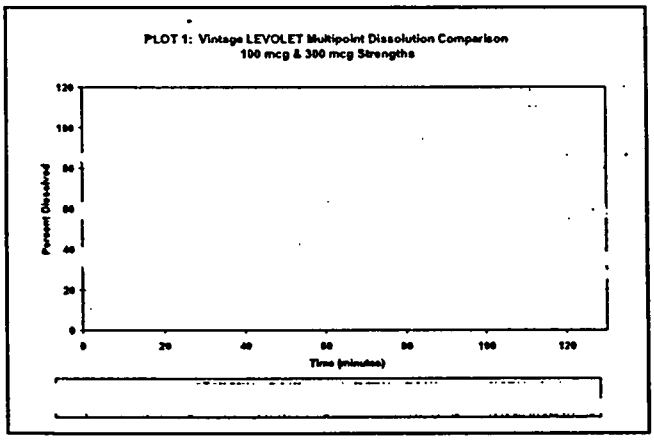
| | | | |
|---|---|---|---|
| **NDA:** | 21-137 N000 BB | **Relevant IND:** | |
| **Brand Name:** | Levolet™ | **Generic Name:** | Levothyroxine Sodium |
| **Strength(s):** | 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets | | |
| **Sponsor:** | Vintage Pharmaceuticals, Inc.<br>3241 Woodpark Blvd, Charlotte, NC 28206 | | |
| **Submission Date:** | 17-DEC-2001<br>03-AUG-2001 | **Submission Type:** | New Drug Application |
| **Reviewer:** | Steven B. Johnson, B.S.Pharm, Pharm.D. | | |

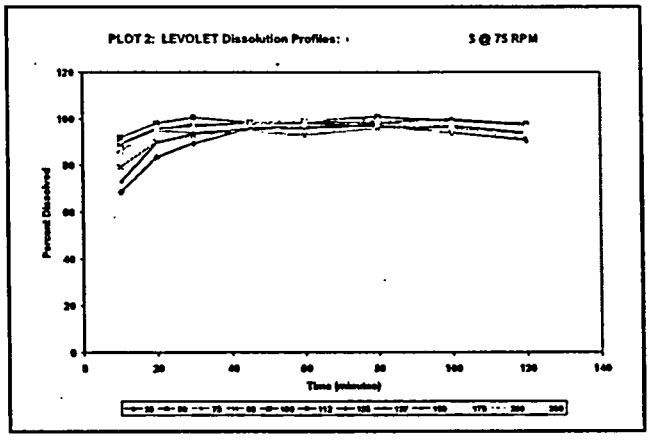
**SYNOPSIS.**

In response to the telephone conference of 18-JUN-2001, the sponsor has submitted multipoint dissolution data on one lot of each of their to-be-marketed strengths of LEVOLET®. The method that was used (see TABLE 1) for this study is a modified version of the USP 24 S1 method. This modified method was chosen from [redacted] methods, including USP 24 S1, and appears to be the most appropriate for LEVOLET tablets (see PLOT 1).

| TABLE 1: Dissolution Method for LEVOLET® Tablets | |
|---|---|
| **Media:** | [redacted] |
| **Apparatus:** | 2 (paddles) |
| **Volume:** | 500 mL @ 37°C |
| **Speed:** | 75 RPM |
| **Units:** | 12 |
| **Tolerance:** | [redacted] (Q) @ 30 minutes |

PLOT 2 is a presentation of the mean data from representative lots from each of the to-be-marketed strengths. These results suggest that the dissolution tolerance specification for LEVOLET tablets, using the method described in TABLE 1, should be [redacted]; (Q) @ 30 minutes.




**RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed NDA 21-137 N000/B2, dated 03-AUG-2001 and 17-DEC-2001, for LEVOLET® tablets and finds the application acceptable.

There are no additional pending issues for this application. Please convey the following comments to the sponsor:

The dissolution method and tolerance specifications for LEVOLET® tablets should be changed to the following:

| | |
|---|---|
| **Media:** | |
| **Apparatus:** | 2 (paddles) |
| **Volume:** | 500 mL @ 37°C |
| **Speed:** | 75 RPM |
| **Units:** | 12 |
| **Tolerance:** | (Q) @ 30 minutes |

Steven B. Johnson, Pharm.D.
CPB Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader

RD Sign Off: _____

FD Sign Off: _____

APPEARS THIS WAY
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/s/

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Steve Johnson
4/5/02 10:13:03 AM
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Hae-Young Ahn
4/10/02 04:15:38 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

# Clinical Pharmacology and Biopharmaceutics Review

| | | | |
|---|---|---|---|
| **NDA:** | 21-137 N000 BB | **Relevant IND:** | |
| **Brand Name:** | Levolet™ | **Generic Name:** | Levothyroxine Sodium |
| **Strength(s):** | 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets | | |
| **Sponsor:** | Vintage Pharmaceuticals, Inc.<br>3241 Woodpark Blvd, Charlotte, NC 28206 | | |
| **Submission Date:** | 28-JUN-2001<br>03-AUG-2001 | **Submission Type:** | New Drug Application |
| **Reviewer:** | Steven B. Johnson, B.S.Pharm, Pharm.D. | | |

**SYNOPSIS.**

Vintage Pharmaceuticals, Inc., submitted two amendments to their NDA 21-137 for LEVOLET® tablets in response to an Agency request for preliminary dissolution data. The Agency requested that dissolution be conducted on two strengths (100 mcg & 300 mcg) under the conditions described in **TABLE 1**, because the USP 23 and USP 24 S1 methods were found to be unacceptable (i.e., USP 23 has been superseded by USP 24 S1, and the sponsor experienced difficulty using USP 24 S1 —

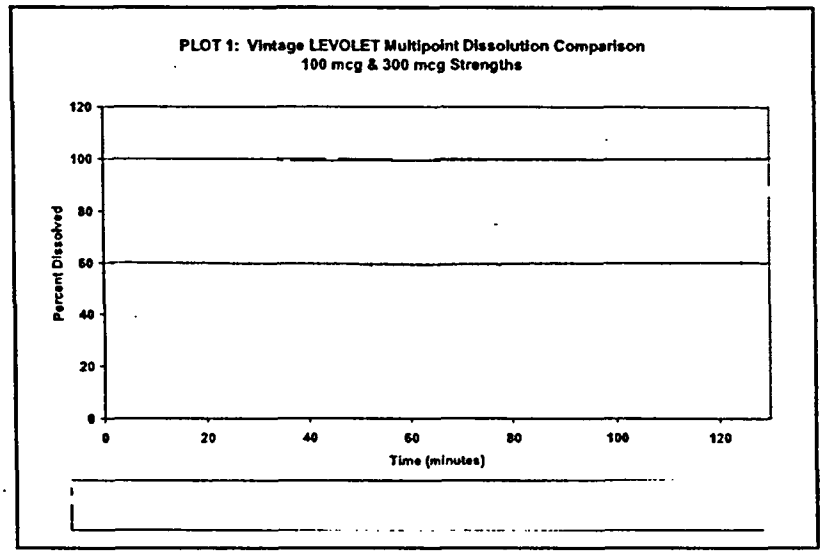
**TABLE 1: Investigational Dissolution Methods for LEVOLET® Tablets**

| **Media:** | — | — | — | — |
|---|---|---|---|---|
| **Apparatus:** | 2 (paddles) | 2 (paddles) | 2 (paddles) | 2 (paddles) |
| **Speed:** | 50 RPM | 75 RPM | 75 RPM | 75 RPM |
| **Units:** | 6 | 6 | 6 | 6 |
| **Time:** | 10, 20, 30, 45, 60, 80, 100, & 120 min | 10, 20, 30, 45, 60, 80, 100, & 120 min | 10, 20, 30, 45, 60, 80, 100, & 120 min | 10, 20, 30, 45, 60, 80, 100, & 120 min |

The submitted data is presented in **TABLE 2** and **PLOT 1**.

**TABLE 2: Investigational Multipoint Dissolution for LEVOLET® Tablets Under Various Conditions**

| | | 10 | 20 | 30 | 45 | 60 | 80 | 100 | 120 |
|---|---|---|---|---|---|---|---|---|---|
| **50 RPM /** | **100 mcg** | | | | | | | | |
| | **300 mcg** | | | | | | | | |
| **75 RPM /** | **100 mcg** | | | | | | | | |
| | **300 mcg** | | | | | | | | |
| **75 RPM /** | **100 mcg** | | | | | | | | |
| | **300 mcg** | | | | | | | | |
| **75 RPM /** | **100 mcg** | | | | | | | | |
| | **300 mcg** | | | | | | | | |




Results of this investigational dissolution study indicate that the sponsor should proceed forward by providing the Agency with multipoint dissolution data on a single lot of each of their to-be-marketed strengths of LEVOLET® using a paddle speed of 75 RPM in the [redacted] media. This method was chosen, because it was the only one that exhibited any semblance of consistency between two strengths that were found to be dosage-strength equivalent.

**COMMENTS TO FIRM**

Please provide multipoint dissolution data on one lot of each to-be-marketed strength of LEVOLET® tablets using a paddle speed of 75 RPM in [redacted] media. When this data is submitted to the Agency, please fully describe the dissolution method (e.g., volume, media, pH, temperature, apparatus, etc.).

---

Steven B. Johnson, Pharm.D.
Senior CPB Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader

RD Sign Off: _____

FD Sign Off: _____

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/s/
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Steve Johnson
10/12/01 06:25:52 PM
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Hae-Young Ahn
10/15/01 12:15:08 PM
BIOPHARMACEUTICS

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08-AUG-2001

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS MEMO

| | | | |
|---|---|---|---|
| **NDA:** | 21-137 | **ISSUE:** | **DISSOLUTION** |
| **BRAND NAME:** | LEVOLET® | **GENERIC NAME:** | Levothyroxine sodium |
| **STRENGTH(S):** | 25 – 300 mcg Tablets | | |
| **SPONSOR:** | Vintage Pharmaceuticals, Inc.<br>3421 Woodpark BLVD., Charlotte, NC 28206 | | |
| **SUBMISSION DATE:** | 28-JUN-2001 | **REVIEW DATE:** | 18-JUL-2001 |
| **CPB REVIEWER:** | Steven B. Johnson, Pharm.D. | | |
| **CPB TEAM LEADER:** | Hae-Young Ahn, Ph.D. | | |

**HISTORY**

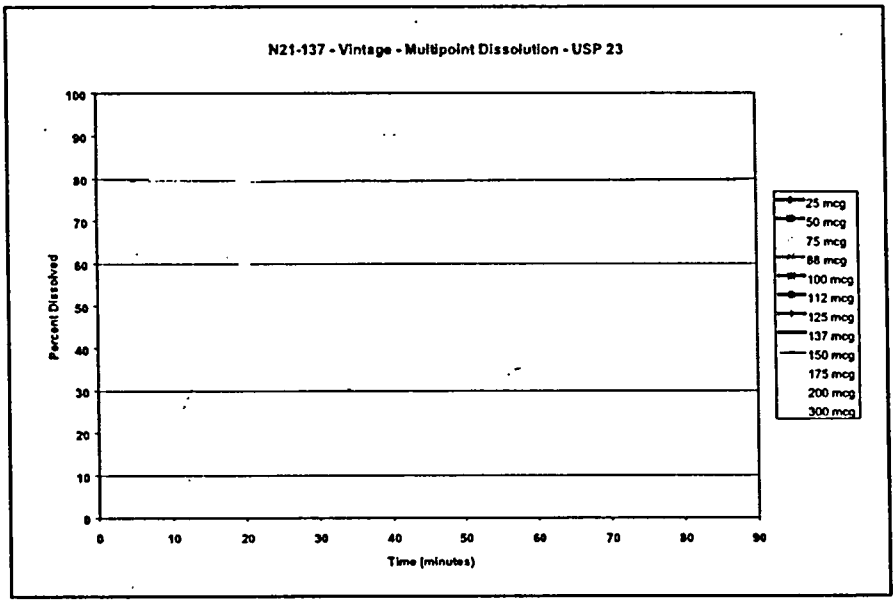
On March 10, 2000 the Agency issued an AE letter to Vintage Pharmaceuticals, Inc. (VPI) for their product LEVOLET®. The reason for the AE letter was based, in part, on the fact that the dissolution information submitted to the application was incomplete. The dissolution comments included in the letter were as follows:

> "In your NDA 21-137 for Levolet™, only dissolution data from one lot each of 4 tablet strengths was submitted for review, which included only one of the two 100 mcg strength tablet lots used in the biostudies (lot #026036). 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 will 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:
>
> **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. (See ***Phase 4 Commitment***).
>
> **Phase 4 Commitment**
>
> Within one year of approval, dissolution testing must be conducted, using either USP 24 or other discriminating method specific to your product, for all marketed strengths, and the data submitted to the Agency for review."

However, since that time, the Agency has gained considerably more experience in dealing with levothyroxine sodium dissolution issues. Therefore, it was clear that when the sponsor submitted the

requested information that utilized the USP 23 dissolution method, that this method was not appropriate for LEVOLET® and the following letter was issued:

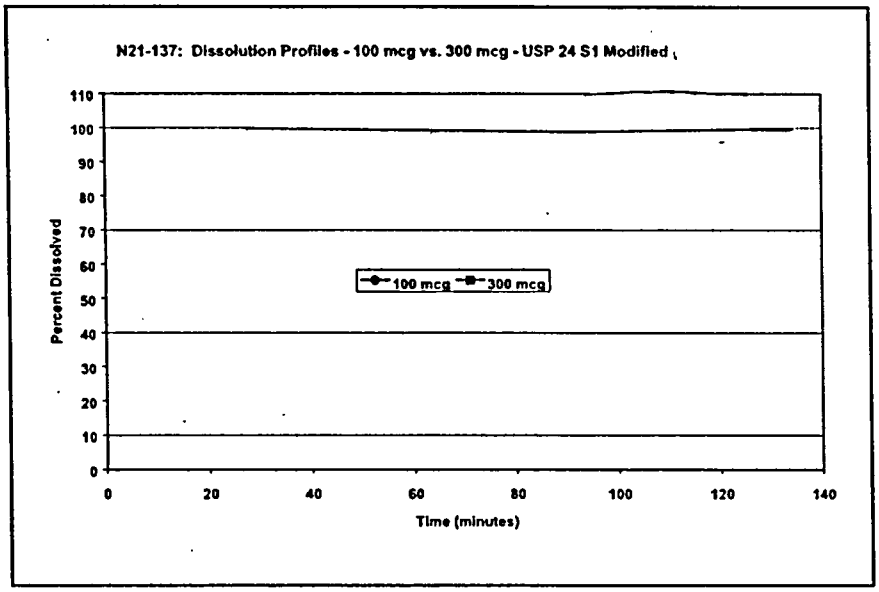
> "... With these criteria in mind, Vintage Pharmaceuticals submitted the requested dissolution information on 3 lots each of their to-be-marketed strengths. Results indicate that the Levolet brand of levothyroxine sodium tablets dissolves very rapidly (on average — % dissolution @ the 10 minutes measurement) under the USP 23 conditions. Therefore, analysis of curve similarity calculations (f2) is a questionable task; especially since the 300 mcg strength tablets were shown to be dosage-form equivalent to the 100 mcg strength tablets, yet their dissolution profiles are considerably different from each other.




> Two problems are readily apparent with the submitted data: 1) the USP 23 dissolution method is not appropriate for this product in that there is essentially no discriminatory power to detect differences (or similarities) between different strengths or different lots of the same strength; and 2) nearly every lot had a peak dissolution of less than —.
>
> In addition, because of the inability of the USP 23 dissolution method to allow for detection of differences within the product line, there is doubt about whether a biowaiver for the intermediate strengths not included in the biostudies can or should be granted."

In order to clarify these issues, on June 28, 2001 the Agency had a teleconference with VPI. Ideas discussed that could help develop LEVOLET's dissolution method were: Follow the general USP 24 method, but alter paddle speed (e.g., 50 to 75 RPM) and amount of surfactant (e.g., — ). The sponsor agreed that they would investigate these alterations and provide the data to the Agency as soon as possible.

As such, the sponsor has submitted a multipoint dissolution comparison between their 100 mcg and 300 mcg strengths in which they used the basic method outlined in USP 24 S1. The only difference is the amount of surfactant used: — (compendial). Results from this comparison are presented in the following plot.




Based on the new dissolution information submitted on 28-JUN-2001 to NDA 21-137, the Agency recommends following:

1. Test two strengths using the USP 24 S1 method with no surfactant;
2. If dissolution is not complete or is very slow by — minutes, then increase the paddle speed to 75 RPM.

From this information, the Agency will be able to instruct the sponsor which method they should proceed with for final dissolution testing of all strengths.

---

Steven B. Johnson, B.S.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 18-JUL-2001

FT initialed by Hae-Young Ahn, Ph.D., Team Leader:

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/s/
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Steve Johnson
7/25/01 04:47:19 PM
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Hae-Young Ahn
8/8/01 10:04:39 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
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01-MAR-2001

# *Clinical Pharmacology and Biopharmaceutics Review*

| | | | |
|---|---|---|---|
| **NDA:** | 21-137 | **Relevant IND:** | |
| **Brand Name:** | Levolet™ | **Generic Name:** | Levothyroxine Sodium |
| **Strength(s):** | 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets | | |
| **Sponsor:** | Vintage Pharmaceuticals, Inc.<br>3241 Woodpark Blvd, Charlotte, NC 28206 | | |
| **Submission Date:** | 25-SEP-01<br>10-MAR-01 | | |
| **Submission Type:** | New Drug Application | | |
| **Reviewer:** | Steven B. Johnson, B.S.Pharm, Pharm.D. | | |

**Synopsis**

Vintage Pharmaceuticals has submitted a response to the Approvable Letter (AE) dated March 10, 2000. In this letter, based on the Office of Clinical Pharmacology and Biopharmaceutics review, stated:

"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 (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 dissolved in 80 minutes |

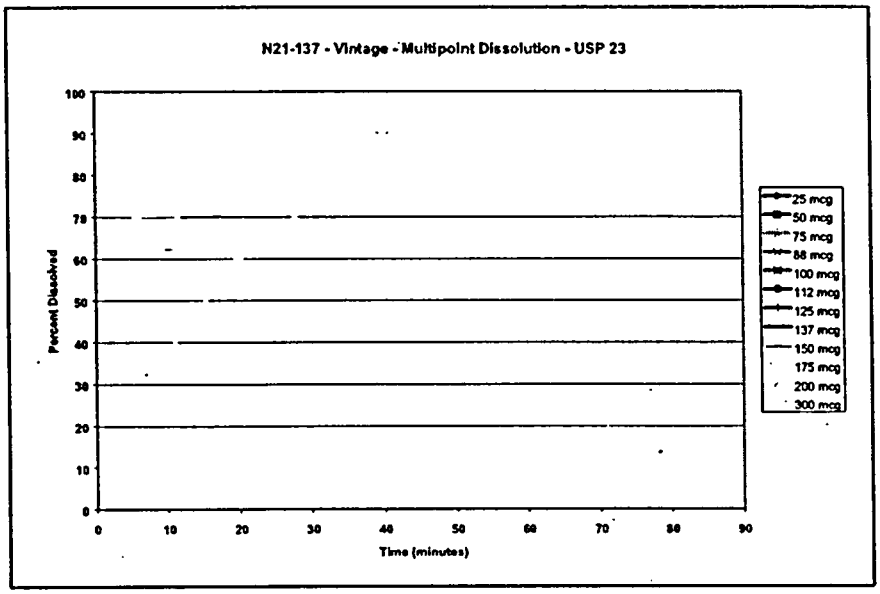
The Agency will accept the dissolution method and specifications outlined in USP 23 monograph for levothyroxine sodium on an interim basis.

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 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."

With these criteria in mind, Vintage Pharmaceuticals submitted the requested dissolution information on 3 lots each of their to-be-marketed strengths. Results indicate that the Levolet brand of levothyroxine sodium tablets dissolves very rapidly (on average ← dissolution @ the 10 minutes measurement) under the USP 23 conditions. Therefore, analysis of curve similarity calculations (f2) is a questionable

task; especially since the 300 mcg strength tablets were shown to be dosage-form equivalent to the 100 mcg strength tablets, yet their dissolution profiles are considerably different from each other.




Two problems are readily apparent with the submitted data: 1) the USP 23 dissolution method is not appropriate for this product in that there is essentially no discriminatory power to detect differences (or similarities) between different strengths or different lots of the same strength; and 2) nearly every lot had a peak dissolution of less than [redacted]%.

In addition, because of the inability of the USP 23 dissolution method to allow for detection of differences within the product line, there is doubt about whether a biowaiver for the intermediate strengths not included in the biostudies can or should be granted.

**Recommendation**
The data submitted in NDA 21-137, 25-SEP-2000, was reviewed and found to be unacceptable to grant a biowaiver for the intermediate strengths not evaluated in the biostudies. The sponsor will be asked to conduct additional dissolution testing such that a more discriminating method specific to their product can be found. Please refer to ***Comments to Sponsor***.

**Comments to Sponsor**
The dissolution results submitted to the Agency in response to the AE letter of March 10, 2000 were complete. However, upon review of these data 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) between different strengths or different lots of the same strength. Therefore, there is doubt about whether a biowaiver for the intermediate strengths not included in the biostudies can or should be granted.

Additional dissolution testing should be conducted using the method described in the USP 24 Supplement 1 monograph for levothyroxine sodium tablets or other appropriate method. Please refer to the Division for guidance on this issue.

Steven B. Johnson, B.S.Pharm, Pharm.D.
Clinical Pharmacology and Biopharmaceutics Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader

RD Sign Off Date: 27-FEB-2001

Final Sign Off Date: 27-FEB-2001

FEB 14 2000

# *Clinical Pharmacology and Biopharmaceutics Review*

| | | | |
|---|---|---|---|
| **NDA:** | 21-137 | **Relevant IND:** | |
| **Brand Name:** | Levolet™ | **Generic Name:** | Levothyroxine Sodium |
| **Strength(s):** | 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets | | |
| **Sponsor:** | Vintage Pharmaceuticals, Inc.<br>3241 Woodpark Blvd, Charlotte, NC 28206 | | |
| **Submission Date:** | 30-APR-99<br>10-JUN-99 | **Review Date:** | 28-JAN-00 |
| **Submission Type:** | New Drug Application | | |
| **Reviewer:** | Steven B. Johnson, B.Pharm, Pharm.D. | | |

## *Terms and Abbreviations*

| | |
|---|---|
| Agency | Food and Drug Administration |
| AUC | Area under the plasma-concentration-time curve |
| BA | Bioavailability |
| BE | Bioequivalence |
| $C_{max}$ | Maximum drug concentration |
| DMEDP | Division of Metabolic and Endocrine Drug Products |
| DSI | Division of Scientific Investigation |
| Industry | Pharmaceutical Industry |
| OCPB | Office of Clinical Pharmacology and Biopharmaceutics |
| NDA | New Drug Application |
| NTR | Narrow therapeutic range |
| $T_{max}$ | Time of maximum drug concentration |
| $T_4$ | Levothyroxine |
| $T_3$ | Triiodothyronine |
| $rT_3$ | Reverse triiodothyronine |
| $t_{1/2}$ | Drug half-life |

## *Synopsis*

Numerous pharmaceutical manufacturers have marketed unapproved levothyroxine sodium in the United States for several decades, in both oral tablet and injectable solution forms. In a Federal Register Notice, August 14, 1997 (Volume 62, Number 157) it was announced, "that orally administered drug products containing levothyroxine sodium are new drugs." This notice was issued because it was apparent that marketed oral levothyroxine sodium products had significant stability and potency problems. These products failed to maintain labeled potency throughout the expiration date and tablets of the same dosage strength from the same manufacturer varied from lot-to-lot in the amount of active ingredient present. This lack of intra-manufacturer product consistency was deemed to have the potential to cause serious public health consequences. Accordingly, all manufacturers wishing to continue marketing oral levothyroxine sodium containing products were given until August 14, 2000 to submit and obtain a new drug application (NDA) approval from the Agency.

Although the Agency deems levothyroxine sodium a "new drug," it has been used clinically for many years. Therefore, traditional clinical trials and PK studies were not required. Rather, a "Draft Guidance for Industry" for levothyroxine sodium was issued which outlined the components necessary for NDA approval. This guidance included information on *in vivo* pharmacokinetics and bioavailability studies and *in vitro* dissolution testing.

More specifically, the guidance suggested that sponsors complete a relative bioavailability study comparing a single strength tablet with an equivalent dose of oral solution. Also, because the Agency felt that dosage form testing of up to 13 tablet strengths was unduly burdensome, a bracketing approach that compared the lowest, middle, and highest strengths was determined to be sufficient to provide a biowaiver for intermediate tablet strengths – assuming linearity between strengths. Finally, a discriminatory *in vitro* dissolution method was to be completed on three production-sized lots of each of the to-be-marketed tablet strengths, including lots used in the BA/BE studies.

Questions that have arisen during the review of this application are as follows:

1) Is the composition of each strength tablet similar?

2) Has the sponsor proposed an appropriate dissolution method and specification?

3) Was sufficient data submitted for evaluation of the dissolution method and specification?

4) Have the analytical methods been sufficiently validated?

5) What is the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference oral solution under fasting conditions?

6) Has the dosage form equivalence been established between the to-be-marketed strengths?

7) Can the biowaiver request be granted for the nine tablet strengths that have not been clinically tested?

Answers are provided in brief within this ***Synopsis*** and are discussed in more detail throughout the remainder of the review.

In addition, DSI was asked by OCPB to conduct a site audit to verify the results of the BA/BE studies. To ensure fairness, DSI site audits will be conducted for each NDA submitted for levothyroxine sodium. Vintage Pharmaceuticals, Inc., was not singled out nor was there any reason to believe that they engaged in any scientifically unsound behavior.

Results of the DSI audit showed several deficiencies, see ***Attachment***. However, these deficiencies do not affect the OCPB recommendation for Levolet™.

The sponsor, Vintage Pharmaceuticals, Inc., submitted NDA 21-137 on May 3, 1999 for Levolet™ (levothyroxine sodium) tablets in twelve strengths ranging from 25 mcg to 300 mcg. In accordance with the "Draft Guidance for Industry," the sponsor has submitted two *in vivo* BA/BE studies and an *in vitro* dissolution study for their levothyroxine sodium product.

The first *in vivo* study, 7VN01, evaluated the bioavailability of two different strength tablets, 100 mcg and 300 mcg, with an equivalent oral solution of levothyroxine sodium. The second *in vivo* study, 9VN01, evaluated the bioequivalence between 50 mcg and 100 mcg tablets following a single oral dose equivalent to 600 mcg levothyroxine sodium. Results of these studies suggest that Levolet™ tablets are 94% to 97% bioavailable relative to an oral solution, and that 50 mcg, 100 mcg, and 300 mcg tablets are dosage form equivalent. Since these three strengths, representing low, middle, and high tablet strengths, are dosage form equivalent, and because the individual tablet strength formulations are proportionally

similar in active and inactive ingredients, sufficient evidence is provided to grant a biowaiver for the intermediate strengths provided that additional dissolution data are submitted.

*In vitro* dissolution studies included data and specifications for three dissolution methods conducted on one lot each of four strengths: 50 mcg, 100 mcg, 150 mcg, and 300 mcg. Based upon the dissolution data submitted in this application, guidelines and requirements were clearly not achieved.

### *Recommendation*

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-137 submitted 30-APR-99 and 14-JUN-99. The overall Human Pharmacokinetic Section is acceptable to OCPB pending an Agency request for additional dissolution data. Presently, only the 100 mcg strength tablets are approved. Approval of the remaining 11 strength tablets is subject to the pending dissolution results. Final recommendations will be made at such time. Currently, this application is ***approvable*** (AE). Please convey ***Comments to Firm*** and ***Labeling Comments*** to the sponsor as appropriate.

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| 9VN01 | Evaluation of the Bioavailability of 50 and 100 mcg Strength Levothyroxine, Sodium Tablets (Vintage Pharmaceuticals) | 34 |
| DSI | Audit Report - Attachment | 51 |

### *Background*

The production of endogenous levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secretes thyroid stimulating hormone-releasing hormone (TSH-RH), which stimulates the anterior pituitary to produce thyroid stimulating-hormone (TSH). TSH then stimulates the thyroid gland to produce

levothyroxine ($T_4$) and triiodothyronine ($T_3$). $T_4$ is subsequently converted to the highly active $T_3$ in the peripheral tissues. High levels of $T_4$ inhibit the production of TSH and to a lesser extent, TSH-RH. This effect in turn decreases the further production of $T_4$.

Because of the negative feedback controlled regulatory system for $T_4$, analysis of *in vivo* levothyroxine sodium pharmacokinetic sample data from healthy volunteers, regarding baseline-corrected vs. uncorrected approaches, is subject to several facts:

*Fact A*: Levothyroxine has a half-life of approximately 6 to 7 days in healthy individuals.

*Fact B*: Since levothyroxine enjoys such a long half-life, $T_4$ levels remain fairly static and are not greatly affected by circadian rhythm.

*Fact C*: When a hyperphysiologic dose of levothyroxine sodium is given to a healthy subject, as in the case of the BA/BE studies in this submission, and because of the exquisite sensitivity of the thyroid hormone regulatory system to subtle changes in $T_4$ levels, endogenous $T_4$ production and secretion approaches zero within 1 hour. Subsequently, as exogenous $T_4$ levels begin to approach normal physiologic values, endogenous production and secretion resumes.

These facts suggest that only baseline-uncorrected data be used for analysis.

Levothyroxine sodium is the synthetic sodium salt of the levo-isomer of the endogenous thyroid hormone, thyroxine ($T_4$). The two, levothyroxine sodium and $T_4$, are identical in form and function and cannot be distinguished from one another. Levothyroxine sodium is considered a narrow therapeutic range (NTR) drug and dosing must be individualized based on $T_4$ and thyroid stimulating hormone (TSH) levels for each patient. Therefore, levothyroxine is supplied in numerous strengths ranging from 25 mcg to 300 mcg. The average daily dose rarely exceeds 180 mcg/day. Levothyroxine sodium products have been used extensively in the clinical setting for the treatment of conditions related to thyroid hormone deficiency, thyroid nodules, and goiters.

There have been multiple manufacturers of multiple levothyroxine products over the years, and while the active ingredient is the same between products, there are numerous product formulations and great debate regarding bioavailability and bioequivalence between products. Although this is not the primary concern of this application or this review, it should be noted that this particular product, Levolet™, might be different than any levothyroxine sodium product currently in clinical use. Namely, Levolet™ tablets contain potassium iodide (KI), [redacted] which may create some safety concerns in certain target-use populations.

# THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

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***Dissolution***

1. Has the sponsor proposed an appropriate dissolution method and specification?
2. Was sufficient data submitted for evaluation of the dissolution method and specification?

The sponsor has conducted three quality control dissolution methods with release specifications of Q (55%) in 75 minutes. Dissolution data on one lot each of the 25 mcg (lot # 036036), 100 mcg (lot # 026036), 150 mcg (lot # 041036), and 300 mcg (lot # 042036) tablets were submitted for review. Dissolution samples were analyzed by a validated HPLC method. Dissolution methods and dissolution data are presented in the following two tables:

| Dissolution Methods | | | |
|---|---|---|---|
| | **Method A** | **Method B** | **Method C** |
| **Apparatus** | 2 (paddles) | 2 (paddles) | 2 (paddles) |
| **Speed** | 100 RPM | 50 RPM | 100 RPM |
| **Medium** | pH 7.4 Phosphate Buffer | pH 7.4 Phosphate Buffer | |
| **Volume** | 500 mL | 500 mL | 500 mL |
| **Units Tested** | 12 | 12 | 12 |
| **Time Points** | 10, 20, 30, & 45 minutes | 10, 20, 30, & 45 minutes | 10, 20, 30, & 45 minutes |

| Dissolution Results | | | |
|---|---|---|---|
| ***25 mcg tablets ( lot # 036036 )*** | | | |
| **Dissolution Method** | Method A | Method B | Method C |
| **Time 10 minutes** | 74.6 ± 4.6 | 47.0 ± 4.4 | 61.9 ± 4.9 |
| **20 minutes** | 99.4 ± 3.8 | 70.1 ± 6.5 | 78.3 ± 5.7 |
| **30 minutes** | 104.6 ± 2.3 | 74.3 ± 6.7 | 83.5 ± 2.2 |
| **45 minutes** | 106.4 ± 3.4 | 79.9 ± 4.2 | 86.2 ± 2.9 |
| ***100 mcg tablets ( lot # 026036 )*** | | | |
| **Dissolution Method** | Method A | Method B | Method C |
| **Time 10 minutes** | 67.0 ± 1.5 | 56.0 ± 13.0 | 52.4 ± 3.4 |
| **20 minutes** | 97.8 ± 3.5 | 94.3 ± 9.2 | 86.2 ± 3.9 |
| **30 minutes** | 100.7 ± 4.6 | 92.2 ± 8.9 | 97.6 ± 3.5 |
| **45 minutes** | 103.8 ± 2.9 | 100.8 ± 6.7 | 103.4 ± 3.9 |
| ***150 mcg tablets ( lot # 041036 )*** | | | |
| **Dissolution Method** | Method A | Method B | Method C |
| **Time 10 minutes** | 63.7 ± 5.7 | 35.6 ± 8.8 | 54.7 ± 6.4 |
| **20 minutes** | 92.9 ± 2.8 | 58.7 ± 12.6 | 79.0 ± 2.5 |
| **30 minutes** | 99.9 ± 2.0 | 70.4 ± 11.1 | 84.3 ± 2.6 |
| **45 minutes** | 100.8 ± 2.9 | 74.3 ± 9.5 | 88.4 ± 2.8 |
| ***300 mcg tablets ( lot #042036 )*** | | | |
| **Dissolution Method** | Method A | Method B | Method C |
| **Time 10 minutes** | 68.8 ± 2.1 | 17.4 ± 28.6 | 43.8 ± 4.8 |
| **20 minutes** | 101.5 ± 2.7 | 28.6 ± 10.9 | 64.9 ± 4.0 |
| **30 minutes** | 103.2 ± 2.3 | 36.2 ± 10.5 | 76.4 ± 3.5 |
| **45 minutes** | 104.5 ± 3.4 | 42.2 ± 12.8 | 84.1 ± 2.4 |
| Mean ± SD | | | |

The dissolution results presented in the above table are incomplete due to the sponsor's bracketing approach and submission of only a single lot for each of four tablet strengths. The Agency requires that all to-be-marketed tablet strengths undergo dissolution testing; hence, a bracketing approach is not acceptable. Additionally, in order to fully evaluate a dissolution method and develop quality control specifications, dissolution data from three lots for each strength tablet should be generated. Also, dissolution data on the 300 mcg tablets (lot # 044036) used in study 7VN01, and the 100 mcg (lot # 111039B) and 50 mcg tablets (lot # 009029B) used in study 9VN01 were not included as per the guidance. (See ***Comments to Firm).***

Regarding the individual dissolution methods: Method A, which closely follows USP 23, is the least discriminating of the three methods, as evidenced by the low variability and rapid tablet dissolution; Method B, while more discriminating, fails to capture data at time points for which — % of the tablet is dissolved – in three of the four tablet strengths presented; and Method C, which appears to be the most discriminatory and somewhat follows the new USP 24, uses a paddle speed of 100 RPM. Method C, however, appears to be the most viable of the three methods and merits further investigation by the sponsor.

At the present time the Agency recommends using Method A, with a specification of Q = 55% in 80 minutes (USP 23 monograph), on an interim basis. However, the Agency will require a phase 4 commitment from the sponsor to conduct dissolution tests using the new USP 24 monograph.

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**USP 24 Monograph for Levothyroxine Sodium Tablets – Effective 01-JAN-00**

| | |
|---|---|
| *Medium*: | 0.01 N HCl containing 0.2% sodium lauryl sulfate |
| *Volume*: | 500 mL |
| *Apparatus*: | 2 (paddles) |
| *Speed*: | 50 RPM |
| *Time*: | 45 minutes |
| *Tolerances*: | NLT 70% (Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes |

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***Analytical Methodology***

Have the analytical methods been sufficiently validated?

Human plasma samples were analyzed for thyroxine ($T_4$) and triiodothyronine ($T_3$) to determine the bioavailability of levothyroxine sodium. Thyroxine samples from study numbers 7VN01 and 9VN01 were analyzed by —, and validated in studies ANA-97-06 and ANA-99-04, respectively. Triiodothyronine samples from study number 7VN01 were analyzed by radioimmunoassay — ) with a validated method. Triiodothyronine sample data was not included in study 9VN01. Assay validations are acceptable.

Results of the quality control analysis are presented in the following table:

| $T_3$ – ANA-97-06 | | $T_4$ – ANA-97-06 | | $T_4$ – ANA-99-04 | |
|---|---|---|---|---|---|
| LOQ (ng/dL): | — | LOQ (mcg/dL): | — | LOQ (mcg/dL): | — |
| Calibration (ng/dL): | | Calibration (mcg/dL): | | Calibration (mcg/dL): | |
| Precision (%RSD) – | | Precision (%RSD) – | | Precision (%RSD) – | |
| 75 ng/dL: | | 4.5 mcg/dL: | | 4.5 mcg/dL: | |
| 175 ng/dL: | | 8.0 mcg/dL: | | 8.0 mcg/dL: | |
| 750 ng/dL: | | 15.0 mcg/dL: | | 15.0 mcg/dL: | |
| Accuracy (%) – | | Accuracy (%) – | | Accuracy (%) – | |
| 75 ng/dL: | | 4.5 mcg/dL: | | 4.5 mcg/dL: | |
| 175 ng/dL: | | 8.0 mcg/dL: | | 8.0 mcg/dL: | |
| 750 ng/dL: | | 15.0 mcg/dL: | | 15.0 mcg/dL: | |

*Human Pharmacokinetics and Bioavailability Studies*

**1. Single-Dose Bioavailability Study**

What is the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference oral solution under fasting conditions?

The relative bioavailability ($F_{rel}$) of levothyroxine sodium was studied in 24 healthy volunteers given either a single dose of six 100 mcg tablets, two 300 mcg tablets, or 600 mcg of an oral solution in a three-way crossover study (7VN01), under fasting conditions. The relative bioavailability of a single dose of six 100 mcg tablets and that of a single dose of two 300 mcg tablets of levothyroxine sodium, compared to an equivalent solution dose, is about 97% and 94%, respectively. Results and 90% confidence intervals are presented in the following two tables:

| Summary of Bioavailability Data – $T_4$ Baseline Uncorrected – Study Number 7VN01 | | | |
|---|---|---|---|
| Parameters | Treatment A<br>6 x 100 mcg tablets | Treatment B<br>2 x 300 mcg tablets | Treatment C<br>600 mcg solution |
| $AUC_{0-48}$ | 504.9 ± 81.0 | 486.6 ± 81.0 | 514.8 ± 73.0 |
| $AUC_{0-inf}$ | 1164.6 ± 260.3 | 1117.1 ± 247.1 | 1201.9 ± 244.5 |
| $C_{max}$ | 14.1 ± 2.07 | 13.5 ± 2.35 | 14.5 ± 2.14 |
| $T_{max}$ | 2.73 ± 1.91 | 2.81 ± 1.31 | 1.67 ± 0.67 |
| $K_e$ | 0.0157 ± 0.0037 | 0.0154 ± 0.004 | 0.014 ± 0.0032 |
| $t_{1/2}$ | 46.9 ± 13.4 | 47.76 ± 11.2 | 49.27 ± 10.33 |
| Mean ± SD | | | |

| Least Squares Mean – 90% Confidence Interval – Study Number 7VN01 | | | | |
|---|---|---|---|---|
| Treatment Comparison | Parameter | Point Estimate | CI (low) | CI (high) |
| A vs. C | ln $C_{max}$<br>ln $AUC_{0-48}$ | 97.27<br>97.83 | 94.51<br>94.99 | 100.11<br>100.75 |
| B vs. C | ln $C_{max}$<br>ln $AUC_{0-48}$ | 93.21<br>94.27 | 90.56<br>91.54 | 95.93<br>97.09 |
| Treatment A = 6 x 100 mcg levothyroxine tablets (%CV: $C_{max}$ = 15.7; $AUC_{0-48}$ = 15.8)<br>Treatment B = 2 x 300 mcg levothyroxine tablets (%CV: $C_{max}$ = 15.8; $AUC_{0-48}$ = 15.7)<br>Treatment C = 600 mcg levothyroxine oral solution (%CV: $C_{max}$ = 15.6; $AUC_{0-48}$ = 15.3)<br>%CV calculated from untransformed data | | | | |

**2. Dosage Form Equivalence Studies**

Has the dosage form equivalence been established between the to-be-marketed strengths?

The sponsor conducted two pharmacokinetic studies to establish dosage form equivalence. Results of study 7VN01 show that 6 x 100 mcg and 2 x 300 mcg tablets are bioequivalent. Percent coefficient of variation were consistent and 90% confidence intervals for $C_{max}$ and $AUC_{0-48}$ parameters.

| Least Squares Mean – 90% Confidence Interval – Study Number 7VN01 | | | | |
|---|---|---|---|---|
| Treatment Comparison | Parameter | Point Estimate | CI (low) | CI (high) |
| B vs. A | ln $C_{max}$<br>ln $AUC_{0-48}$ | 95.82<br>96.37 | 93.10<br>93.57 | 98.62<br>99.25 |
| Treatment A = 6 x 100 mcg levothyroxine tablets (%CV: $C_{max}$ = 15.7; $AUC_{0-48}$ = 15.8)<br>Treatment B = 2 x 300 mcg levothyroxine tablets (%CV: $C_{max}$ = 15.8; $AUC_{0-48}$ = 15.7)<br>%CV calculated from untransformed data | | | | |

A second bioequivalence study, 9VN01, evaluated 50 mcg and 100 mcg levothyroxine tablets in a 600 mcg single-dose, two-way crossover study in 20 healthy subjects. Study results and 90% confidence intervals are presented in the following two tables:

| Summary of Bioavailability Data – $T_4$ Baseline Uncorrected – Study Number 9VN01 | | |
|---|---|---|
| Parameters | Treatment A<br>6 x 100 mcg tablets | Treatment B<br>12 x 50 mcg tablets |
| $AUC_{0-48}$ | 486.33 ± 85.27 | 473.31 ± 84.4 |
| $AUC_{0-inf}$ | 2431.4 ± 1093.5 | 2752.8 ± 1325.9 |
| $C_{max}$ | 13.77 ± 2.38 | 12.9 ± 2.37 |
| $T_{max}$ | 2.55 ± 1.56 | 2.85 ± 1.42 |
| $K_e$ | 0.006 ± 0.002 | 0.005 ± 0.002 |
| $t_{1/2}$ | 147.1 ± 73.74 | 175.06 ± 86.04 |
| Mean ± SD | | |

| Least Squares Mean – 90% Confidence Interval – Study Number 9VN01 | | | | |
|---|---|---|---|---|
| Treatment Comparison | Parameter | Point Estimate | CI (low) | CI (high) |
| B vs. A | ln $C_{max}$ | 92.38 | 89.09 | 95.83 |
| | ln $AUC_{0-48}$ | 96.49 | 92.25 | 100.93 |
| Treatment A = 6 x 100 mcg levothyroxine tablets (%CV: $C_{max}$ = 17.6; $AUC_{0-48}$ = 16.8)<br>Treatment B = 12 x 50 mcg levothyroxine tablets (%CV: $C_{max}$ = 18.1; $AUC_{0-48}$ = 17.7)<br>%CV calculated from untransformed data | | | | |

Results of 9VN01 suggest that the 100 mcg and 50 mcg levothyroxine sodium tablets are bioequivalent based on a single dose of 600 mcg. Evidence obtained from both of these bioequivalence trials, 7VN01 and 9VN01, clearly shows that 50 mcg and 100 mcg, and 100 mcg and 300 mcg tablets are dosage form equivalent.

It should be noted, that $AUC_{0-inf}$ is an unreliable measure of bioequivalence because it uses the values of $K_e$ that cannot be estimated reliably using baseline-uncorrected data because the $T_4$ approached baseline asymptomatically which overestimates the $t_{½}$. Therefore, $AUC_{0-48}$ and $C_{max}$ are the most reliable parameters for determining extent and rate of absorption and the most reliable measures of bioequivalence. For the purposes of this review, only $AUC_{0-48}$ and $C_{max}$ will be used for comparison.

### 3. Biowaivers

Can the biowaiver request be granted for the nine tablet strengths that have not been clinically tested?

- Three strengths of tablets, 50 mcg, 100 mcg, and 300 mcg, representing low, middle, and high strengths of the formulation, have been shown to be dosage form equivalent.
- Each strength tablet is proportionally similar in its active and inactive ingredients.

Therefore, a biowaiver, for the nine intermediate strengths not used in the *in vivo* studies can be granted, provided that additional dissolution information be submitted before the approval of NDA 21-137.

### *Labeling Comments*

(Where applicable, ~~strikeout~~ text should be removed from labeling. Double <u>underlined</u> text should be added to labeling. ✍ Indicates an explanation only and is not intended to included in the labeling)

✍ Because of the number of NDAs submitted for levothyroxine sodium products, DMEDP is using class labeling for all levothyroxine sodium submissions. In the following "class labeling" for pharmacokinetics, content must remain intact with the exception of agent specific information.

**PHARMACOKINETICS – (class content and agent specific – absorption)**

***Absorption*** –

*Comments to Firm*

In your NDA 21-137 for Levolet™, only dissolution data from one lot each of 4 tablet strengths was submitted for review, which included only one of the two 100 mcg strength tablet lots used in the biostudies (lot #026036). 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 will 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:

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**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 |

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The Agency will accept the dissolution method and specifications outlined in the USP 23 monograph for levothyroxine sodium on an interim basis. (See ***Phase 4 Commitment***).

***Phase 4 Commitment***

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

/S/

/S/ 2·14·00

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**CC: NDA 21-137 (orig., 1 copy), HFD-510 (OrloffD, TemeckJ, McCortS), HFD-870 (AhnH, HuangS, JohnsonST), HFD-850 (Lesko, ChenME), CDR**

**Code:** AE

# THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

1 page

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2/27/01 02:42:48 PM
BIOPHARMACEUTICS

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BIOPHARMACEUTICS

APPEARS THIS WAY
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