

# KING & SPALDING

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June 12, 1998

2206 '98 JUN 16 P1:43

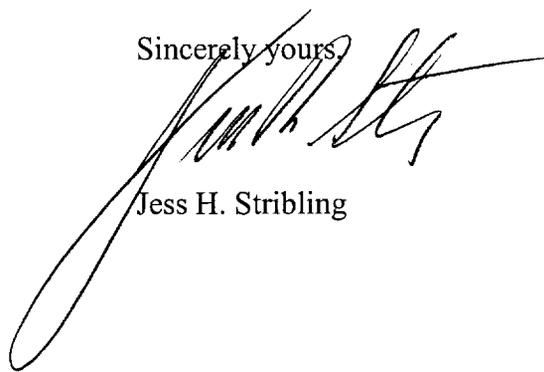
Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parkland Drive, Room 1-23  
Rockville, MD 10857

Re: Docket No. 97N-0314

Dear Sir or Madam:

On behalf of Jones Medical Industries, I am submitting to Docket No. 97N-0314 these letters which were previously submitted to the Center for Drug Evaluation and Research.

Sincerely yours,



Jess H. Stribling

Enclosures

cc. Mr. Stephen M. McCort

97N-0314

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LET 3

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April 17, 1998

Dr. Solomon Sobel, Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane, Room 14B-04  
Rockville, MD 20857



Re: Levothyroxine

Dear Dr. Sobel:

I am writing on behalf of Jones Medical Industries (JMI) with regard to levothyroxine.

On February 25, Dr. Christopher Rhodes, JMI's consultant, and I met with you and other members of the Center for Drug Evaluation and Research (CDER) responsible for handling issues pertaining to levothyroxine. JMI's Andrew Franz, Senior Vice President of Operations, and Nancy Cafmeyer, Vice President of Regulatory Affairs, were on speakerphone. At that meeting CDER provided us with answers to various questions JMI had submitted regarding the requirements for approval of a new drug application for levothyroxine.

One of JMI's questions pertained to use of an overage. An overage is the term applied when an amount in excess of the label claim quantity of drug is added to components which will be fabricated into the finished dosage form (in the case of levothyroxine, a compressed tablet). As we discussed, there are two kinds of overages. A manufacturing overage is excess drug added at the start of the manufacturing process in order to compensate for loss of drug during the manufacturing process. Thus, when the manufacturing process is complete, the average (for n production lots) potency should be 100.0% of label claim. A stability overage, in contrast, is an excess of the active pharmaceutical constituent that will be present at the completion of the manufacturing process. Stability overages, in effect, give the drug product a jump start against the process of degradation and allow a product to remain in the market with an acceptable potency (usually above 90% of label claim) for a longer period than would otherwise be the case.

At that meeting CDER advised that it is permissible for a manufacturer to use a manufacturing overage but under no circumstances would a stability overage be permitted. JMI asked whether CDER would have a different view if it were impossible for *any* manufacturer to

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Dr. Solomon Sobel, Director

April 17, 1998

Page 2

formulate a product that would remain at 90% claimed potency through the expiration period. CDER advised its view would remain the same and suggested manufacturers could deal with this situation by shortening the expiry period.

It has long been JMI's understanding that most if not all manufacturers use *both* a manufacturing overage *and* a stability overage. JMI does. Accordingly, JMI investigated the levothyroxine products on the market manufactured by Mova, Knoll, Forest, Vintage, and Glaxo to ascertain whether they have an excess of label claim potency, thus indicating a stability overage. As the information in Attachment 1 shows, all of them do.<sup>1</sup> JMI also contacted over twenty wholesale distributors to ascertain the expiration period they require on levothyroxine products they distribute. As the information in attachment 2 shows, most wholesalers will not accept a levothyroxine product with less than a 12 month expiry period. JMI is submitting this information to you for your review and consideration, and for your determination about whether to permit a stability overage in levothyroxine products for which NDA's are being sought.

Tables I through VI contain potency data for marketed levothyroxine tablets for five different manufacturers. The information given in these tables comes from three different sources: first, there is data from the public domain, e.g., the September 27, 1983 Schmitz-Michels correspondence at Exhibit 20 to the December 15, 1997 Knoll Citizen Petition (Docket No. 97N-0314/CP) and the Virginia and Massachusetts Formulary Commissions; second, assays performed by JMI laboratories of the potency of levothyroxine tablets obtained from the marketplace; and third, data published by Garnick<sup>2</sup> in order to make an approximate estimate of the potency at the time the various products were released.

JMI understands the concern of CDER, stated at our February 25th meeting, that a stability overage for NDAed levothyroxine products could result in patients receiving products with potencies that vary by 16% (10% from 100% to 90% and 6% from 106% to 100%, which is the stability overage). While levothyroxine is not a narrow therapeutic index drug, there is concern that it be titrated carefully to patients. However, levothyroxine products have been used for over forty years. These products have been manufactured with a stability overage. Patients titrated on a particular dose have been receiving potencies that vary by 16% without reported adverse experience. These facts should be taken into consideration whether it is now necessary, after forty years of use, to narrow the range from 16% to 10% by prohibiting use of a stability overage.

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<sup>1</sup> The Jerome Stevens product was not included in this data base. Stevens' Certificate of Analysis states that the potency is around 100%. However, subsequent internal testing by JMI shows the product does not maintain stability through the expiry period recorded on the label.

<sup>2</sup> Garnick, R.L. et al., "Stability Indicating HPLC Method for QC of Sodium Liothyronine and Sodium Levothyroxine in Tablet Formulations.

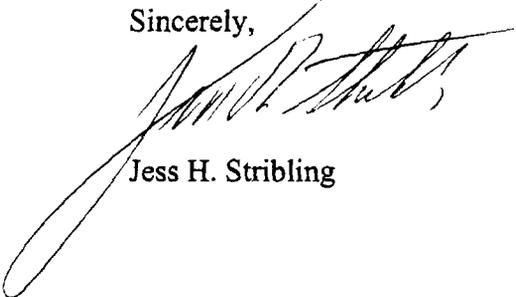
Dr. Solomon Sobel, Director  
April 17, 1998  
Page 3

CDER has acknowledged that studies show that levothyroxine exhibits a biphasic first order degradation profile, with an initial fast degradation rate followed by a slower rate. JMI's records indicate this initial degradation is approximately 3% in the first 30-45 days. Perhaps it is only necessary to permit a 3% stability overage to cover this first portion of the degradation.

Dr. Sobel, it may be that CDER was unaware that currently marketed levothyroxine products use a stability overage, in which case these data should be significant. Or it may be that CDER is aware that one or more companies will submit new drug applications for levothyroxine formulations that do not require a stability overage. If the former, then the agency should reconsider its absolute prohibition of a stability overage in these products. On behalf of JMI, we again ask whether a stability overage may be used in soon-to-be approved levothyroxine products.

I will be calling Mr. McCort next week to see if I can set a time for Dr. Rhodes and me (and Mr. Franz and Ms. Cafmeyer by speakerphone) to meet with him to go over these data, answer any questions, and make arrangements to provide you with any back-up documentation that you wish to examine.

Sincerely,



Jess H. Stribling

Attachments

cc. Mr. Stephen M. McCort, Room 18B08  
Dr. Christopher Rhodes  
Mr. Andrew Franz

**ATTACHMENT 1**

## Tables I-VI

Tables I through VI contain potency data for marketed levothyroxine tablets for five different manufacturers. The information given in these tables comes from three different sources: first, there is data from the public domain, e.g., the September 27, 1983 Schmitz-Michels correspondence at Exhibit 20 to the December 15, 1997 Knoll Citizen Petition (Docket No. 97N-0314/CP) and the Virginia and Massachusetts Formulary Commissions; second, assays performed by JMI laboratories of the potency of levothyroxine tablets obtained from the marketplace; and third, data published by Garnick in order to make an approximate estimate of the potency at the time the various products were released. The key to the tables follows.

Testing Date is *either* the testing date derived from public information *or* from JMI internal testing.

*For example*, in Chart 1 pertaining to Mova's levothyroxine: (2\*) on page 1 shows that data for entries tested on 1/13/98 derives from testing performed by JMI on product purchased from local wholesalers or pharmacies; testing dates for all other entries are from Mova certificates of analysis.

In Chart 1 pertaining to Knoll's levothyroxine, (1\*) on page 3 shows that the data for entries tested on 2/26/98 derives from testing performed by JMI. Other testing dates and data obtained from testing on those dates were obtained from the September 27, 1983 Schmitz-Michels correspondence at Exhibit 20 to the December 15, 1997 Knoll Citizen Petition (Docket No. 97N-0314/CP) (hereinafter referred to as the Knoll Petition).

Manufacturer is the company making the levothyroxine.

Lot Number is *either* from the label *or* from public information.

*For example*, in Chart 1 pertaining to Mova's levothyroxine: (1\*) on page 1 shows that the data on the lot whose number is shown directly under the (1\*) is from information submitted by Mova to the Virginia Formulary.

In Chart 1 pertaining to Knoll's levothyroxine: (1\*) on page 3 shows that the data for entries tested on 2/26/98 derives from testing performed by JMI; thus, those lot numbers are from the product label. Data, including lot numbers, obtained from testing on other dates were obtained from the Knoll Petition.

Strength is *either* from the label *or* from public information.

*For example*, in Chart 1 pertaining to Mova's levothyroxine: (1\*) on page 1 shows that the data, including strength, on the lot whose number is shown directly under the (1\*) is from information submitted by Mova to the Virginia Formulary.

In Chart 1 pertaining to Knoll's levothyroxine: (1\*) on page 3 shows that the data for entries tested on 2/26/98 derives from testing performed by JMI; thus, the strength of those lots is from the product label. Data, including strength, obtained from testing on other dates were obtained from the Knoll Petition.

Release Assay % is from public information, e.g. the Virginia (Mova) or Massachusetts (Glaxo) Formulary or the Knoll Petition (Knoll).

Testing Date Assay % is determined by JMI from its own testing

Expiration Date is *either* recorded directly from the label of products tested by JMI *or* from public information, e.g., the Virginia (Mova) or Massachusetts (Glaxo) Formulary or the Knoll Petition (Knoll).

Expiry Period is calculated *either* from public information, e.g., the Virginia (Mova) or Massachusetts (Glaxo) Formulary or the Knoll Petition (Knoll) *or* by JMI from the lot number coding system (Forest and Vintage).

Expiry Time Lapse is the number of months that have lapsed on the expiry period. It is calculated by JMI by starting with the expiration date; subtracting the number of months of the expiry period; and then adding the number of months from the testing date.

*For example*: in Chart 1 pertaining to Mova's levothyroxine: (1\*) on page 1 the expiration date is 5/98; subtract 10 months (the expiry period), which goes to 8/97; then add the number of months from the testing date (1/98) (e.g., when the testing was done, five months had elapsed out of the ten month expiry period.

Theoretical % Decline of potency for Mova is calculated by JMI by subtracting the average testing date assay % from the average release assay %. The data used for averages is in a separate column.

Theoretical Initial Assay of potency for all other manufacturers is calculated using Garnick's reference of a theoretical loss of 5% per year, which is added to the Testing Date Assay % prorating loss based on the Expiry Time Lapse.

*For example*: In Chart 1 pertaining to Knoll's levothyroxine: Take 10 months that has elapsed on expiry time; divide it by 12 x 5; add that to the testing date assay percentage.

Table I

## Testing of Commercially Available Levothyroxine Sodium Tablets, USP

DATA USED

## Recent Data

FOR AVERAGE

Testing Date (2*)	Manufacturer	Lot number	Strength	Release Assay % (IF KNOWN)	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Theoretical % decline (3*)
	MOVA	1*	25 mcg	105.9			10 months		
1/13/98	MOVA	MPT2911	25 mcg		99.1	May-98	10 months	5 months	6.77
	MOVA	1*	50 mcg	105.4			18 months		
1/13/98	MOVA	MPT2001	50 mcg		99.3	May-99	18 months	2 months	6.1
	MOVA	1*	75 mcg	105.8			18 months		
1/13/98	MOVA	MPT1651	75 mcg		97.7	Dec-98	18 months	7 months	8.1
	MOVA	1*	88 mcg	106.1			18 months		
1/13/98	MOVA	MPT2792	88 mcg		101.7	Jan-99	18 months	6 months	4.4
	MOVA	1*	100 mcg	105.1			24 months		
1/13/98	MOVA	MPT1401	100 mcg		99.3	May-99	24 months	8 months	5.8
1/13/98	MOVA	MPT1582	112 mcg		103	Aug-99	24 months	5 months	2.7
3/23/97	MOVA	MPT1141	125 mcg	109		Mar-99	24 months		
1/13/98	MOVA	MPT1142	125 mcg		102.5	Mar-99	24 months	10 months	3.2
3/15/97	MOVA	MPT0675	150 mcg	106		Mar-99	24 months		
1/13/98	MOVA	MPT1941	150 mcg		98.2	May-99	24 months	7 months	7.5
1/13/98	MOVA	MPT1501	175 mcg		98.6	Jul-99	24 months	6 months	7.1
4/26/97	MOVA	MPT1542	200 mcg	104.8		Mar-99	24 months		
1/13/98	MOVA	MPT1523	200 mcg		102.6	Apr-99	24 months	9 months	3.1
3/22/97	MOVA	MPT0121	300 mcg	106.1		Jun-99	24 months		
1/13/98	MOVA	MPT1551	300 mcg		100	Jun-99	24 months	7 months	5.7

1\* THIS DATA IS DERIVED FROM INFORMATION SUBMITTED BY MOVA  
TO THE VIRGINIA FORMULARY

2\* DATA FROM 1/13/98 WAS FROM TESTING PERFORMED BY JMI-DANIELS. OTHER TESTING DATES  
ARE FROM MOVA CERTIFICATES OF ANALYSIS.

3\* THEORETICAL DECLINE IS BASED ON AN AVERAGE OF 105.7% AS THE INITIAL ASSAY RELEASE VALUE

SUM 3275.8  
AVERAGE 105.671  
N= 31

Table I

Testing of Commercially Available Levothyroxine Sodium Tablets, USP  
Previous Data

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period
(1*)							
11/9/96	MOVA	MNT3531	25 mcg	106.9		Mar-98	16 months
7/3/96	MOVA	MNT235	88 mcg	104.7		Jan-98	18 months
7/2/96	MOVA	MNT236	112 mcg	101.9		Jul-98	24 months
7/1/96	MOVA	MNT234	175 mcg	103.3		Jul-98	24 months

1\* THIS DATA IS DERIVED FROM INFORMATION SUBMITTED TO THE VIRGINIA FORMULARY

Table II

Testing of Commercially Available Levothyroxine Sodium Tablets, USP  
Recent Data

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Theoretical Initial Assay
(1*)			(IF KNOWN)						(2*)
2/26/98	KNOLL	500447	50 mcg		101.7	Apr-99	24 months	10 months	105.9
2/26/98	KNOLL	1000977	100 mcg		102.3	Aug-99	24 months	6 months	104.8
2/26/98	KNOLL	1250207	125 mcg		100	Apr-99	24 months	10 months	104.2

1\* DATA WAS FROM TESTING PERFORMED BY JMI-DANIELS.

2\* DATA WAS CALCULATED USING AN AVERAGE LOSS OF (4-6%) PER YEAR (REF: GARNICK, R.L. ET AL., "STABILITY INDICATING HPLC METHOD FOR QC OF SODIUM LIOTHYRONIINE AND SODIUM LEVOTHYROXINE IN TABLET FORMULATIONS"

Table II

Testing of Commercially Available Levothyroxine Sodium Tablets, USP  
Previous Testing

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Theoretical Initial Assay
(1*)									(2*)
12/17/81	KNOLL	9ZK301A	25 mcg	104		Dec-83	24 months		
3/19/82	KNOLL	8JB062	25 mcg	109.2		Mar-84	24 months		
4/5/82	KNOLL	5JC322	50 mcg	108		Apr-84	24 months		
5/10/82	KNOLL	0JD022	50 mcg	110		May-84	24 months		
4/2/82	KNOLL	7JC302	100 mcg	113		Apr-84	24 months		
5/5/82	KNOLL	9JD292	100 mcg	108		May-84	24 months		
4/7/82	KNOLL	8JC132	150 mcg	108		Apr-84	24 months		
4/8/82	KNOLL	7JC142	150 mcg	108		Apr-84	24 months		
3/11/82	KNOLL	0JB122	200 mcg	106		Mar-84	24 months		
3/11/82	KNOLL	2JC012	200 mcg	108		Mar-84	24 months		
3/23/82	KNOLL	8JC212	300 mcg	112		Mar-84	24 months		
2/18/82	KNOLL	0JB042	300 mcg	110.7		Feb-84	24 months		
5/2/95	KNOLL	11335	50 mcg		105.6	Sep-95	24 months	20 months	113.9
5/2/95	KNOLL	11449	100 mcg		107	Aug-95	24 months	21 months	115.8
5/2/95	KNOLL	10631	150 mcg		104.3	May-95	24 months	24 months	114.3
4/27/95	KNOLL	39523	125 mcg		106.9	Apr-96	24 months	12 months	115.7
8/3/95	KNOLL	13509	50 mcg		103.3	Nov-96	24 months	10 months	108.3
8/3/95	KNOLL	11905	100mcg		102.8	Aug-96	24 months	12 months	107.8
8/3/95	KNOLL	13405	125 mcg		102.4	Aug-96	24 months	12 months	111.2
8/3/95	KNOLL	13403	150 mcg		103.9	Oct-96	24 months	10 months	108.1
8/3/95	KNOLL	13143	200 mcg		103.6	Aug-96	24 months	12 months	108.6

- 1\* DATA WAS OBTAINED FROM CITIZENS PETITION SUBMITTED BY KNOLL IN DEC-97  
IN ADDITION IN THE CITIZENS PETITION KNOLL STATES THAT THERE HAS NOT BEEN A FORMULA CHANGE SINCE 1982  
THEY ALSO STATE THAT A 10% OVERAGE IS ADDED TO ACCOUNT FOR LOSS DURING PROCESSING
- 2\* DATA WAS CALCULATED USING AN AVERAGE LOSS OF (4-6%) PER YEAR (REF: GARNICK, R.L. ET AL., "STABILITY  
INDICATING HPLC METHOD FOR QC OF SODIUM LIOTHYRONINE AND SODIUM LEVOXYROXINE IN  
TABLET FORMULATIONS"

Table III

Testing of Commercially Available Levothyroxine Sodium Tablets, USP

Recent Data

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Theoretical Initial Assay
(1*)	(IF KNOWN)								(2*)
2/26/98	FOREST	7972	50		103	Aug-99	24 months	6 months	105.5
2/26/98	FOREST	109729	100		105.5	Nov-99	24 months	3 months	106.8
2/26/98	FOREST	10978	125		105.3	Oct-99	24 months	4 months	107.0

1\* DATA WAS FROM TESTING PERFORMED BY JMI-DANIELS.

2\* DATA WAS CALCULATED USING AN AVERAGE LOSS OF (4-6%) PER YEAR (REF: GARNICK, R.L. ET AL., "STABILITY INDICATING HPLC METHOD FOR QC OF SODIUM LIOTHYRONINE AND SODIUM LEVOTHYROXINE IN TABLET FORMULATIONS"

Table III

## Testing of Commercially Available Levothyroxine Sodium Tablets, USP

Previous data

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Theoretical Initial Assay
(1*)									(2*)
3/16/95	FOREST	19513	88 mcg		107.7	Aug-96	24 months	7 months	110.6
3/16/95	FOREST	19515	137 mcg		106.5	Aug-96	24 months	7 months	109.4
3/16/95	FOREST	19518	200 mcg		108.9	Aug-96	24 months	7 months	111.8
1/10/95	FOREST	9944	25 mcg		106.4	Apr-96	24 months	9 months	110.2
3/23/96	FOREST	8958	25 mcg		104.1	Feb-97	24 months	14 months	109.9
1/10/95	FOREST	89419	75 mcg		103	Mar-96	24 months	10 months	107.2
1/12/94	FOREST	FP0371	88 mcg		108	Nov-95	24 months	2 months	108.8
1/12/94	FOREST	FP0372	112 mcg		104	Aug-95	24 months	5 months	106.1
4/27/95	FOREST	9945	25 mcg		105.5	Apr-96	24 months	13 months	110.9
4/27/95	FOREST	12949	50 mcg		105.6	Jul-96	24 months	10 months	109.8
4/27/95	FOREST	1955	100 mcg		106.4	Aug-96	24 months	9 months	110.2
4/27/95	FOREST	19514	112 mcg		109.8	Aug-96	24 months	9 months	113.6
4/27/95	FOREST	FP0486	125 mcg		98	Dec-95	24 months	17 months	105.1
4/27/95	FOREST	19516	137 mcg		104.5	Aug-96	24 months	9 months	108.3
4/27/95	FOREST	29422	150 mcg		105.4	Jul-96	24 months	10 months	109.6
4/27/95	FOREST	3951	175 mcg		107.5	Sep-96	24 months	8 months	110.8
4/27/95	FOREST	19518	200 mcg		109.2	Aug-96	24 months	9 months	113.0
4/27/95	FOREST	FP0463	300 mcg		100	May-96	24 months	12 months	105.0

1\* DATA WAS FROM TESTING PERFORMED BY JMI-DANIELS.

2\* DATA WAS CALCULATED USING AN AVERAGE LOSS OF (4-6%) PER YEAR (REF: GARNICK, R.L. ET AL., "STABILITY INDICATING HPLC METHOD FOR QC OF SODIUM LIOTHYRONINE AND SODIUM LEVOTHYROXINE IN TABLET FORMULATIONS"

Table IV

Testing of Commercially Available Levothyroxine Sodium Tablets, USP

Previous Data

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Theoretical Initial Assay
(1*)	(IF KNOWN)				(2*)				
9/8/97	VINTAGE	046077A	50 mcg		96.2	Dec-98	18 months	2 months	97.0
9/8/97	VINTAGE	0362126A	100 mcg		101.1	Jan-99	24 months	9 months	104.9
9/8/97	VINTAGE	033087C	200 mcg		100.1	Jul-99	24 months	2 months	100.9
9/8/97	VINTAGE	054016A	300 mcg		93.9	Jan-98	24 months	20 months	102.2

1\* DATA WAS FROM TESTING BY JMI-DANIELS.

2\* DATA WAS CALCULATED USING AN AVERAGE LOSS OF (4-6%) PER YEAR (REF: GARNICK, R.L. ET AL., "STABILITY INDICATING HPLC METHOD FOR QC OF SODIUM LIOTHYRONINE AND SODIUM LEVOTHYROXINE IN TABLET FORMULATIONS"

Table V

Testing of Commercially Available Levothyroxine Sodium Tablets, USP

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Theoretical % decline
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CHELSEA

DATA WAS NOT INCLUDED DUE TO LOTS IN STUDY WERE SUBSEQUENTLY RECALLED BY THE MANUFACTURER BECAUSE OF POTENCY NOT BEING ASSURED THROUGH THE EXPIRATION PERIOD

Table VI

Testing of Commercially Available Levothyroxine Sodium Tablets, USP  
DATA FROM THE MANUFACTURER

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period
(1*)				(IF KNOWN)			
5/3/94	GLAXO	4E418	100 mcg	106		May-97	36 months
5/3/94	GLAXO	4E419	100 mcg	106.9		May-97	36 months
5/3/94	GLAXO	4E420	100 mcg	105.6		May-97	36 months
5/4/94	GLAXO	4E421	100 mcg	104.8		May-97	36 months
5/4/94	GLAXO	4E422	100 mcg	104.1		May-97	36 months
5/12/94	GLAXO	4E426	200 mcg	99.25		May-97	36 months
5/12/94	GLAXO	4E427	200 mcg	99.95		May-97	36 months
5/14/94	GLAXO	4E417	50 mcg	101		May-97	36 months
5/18/94	GLAXO	4E423	150mcg	103.7		May-97	36 months
5/19/94	GLAXO	4E424	150 mcg	102.3		May-97	36 months
5/19/94	GLAXO	4E425	150 mcg	100		May-97	36 months
5/25/94	GLAXO	4E428	300 mcg	99		May-97	36 months
12/18/95	GLAXO	5M512	25 mcg	101		Dec-97	24 months
1/10/96	GLAXO	5M516	88 mcg	104.5		Jan-98	24 months
1/15/96	GLAXO	5M517	112 mcg	105.2		Jan-98	24 months
1/16/96	GLAXO	5M519	137 mcg	102.4		Jan-98	24 months
1/18/96	GLAXO	5M520	175 mcg	103.4		Jan-98	24 months

1\* THIS DATA IS DERIVED FROM INFORMATION SUBMITTED BY ROBERTS/GLAXO  
TO THE MASSACHUSETTS FORMULARY

Table VI

Testing of Commercially Available Levothyroxine Sodium Tablets, USP  
Previous Data

Testing Date	Manufacturer	Lot number	Strength	Release Assay %	Testing date Assay %	Expiration Date	Expiry Period	Expiry Time Lapse	Actual % decline
(1*)				(IF KNOWN)					
11/30/94	GLAXO	4E418	100 mcg	106	101.9	May-97	36 months	6 months	4.1
11/30/94	GLAXO	4E416	50 mcg		97.7	May-97	36 months	6 months	
11/30/94	GLAXO	4E426	200 mcg	99.25	96.2	May-97	36 months	6 months	3.05
11/30/94	GLAXO	4E423	150mcg	103.7	103.2	May-97	36 months	6 months	0.5
11/30/94	GLAXO	4E428	300 mcg	99	95.2	May-97	36 months	6 months	3.8
5/24/96	GLAXO	5M512	25 mcg	101	98	Dec-97	24 months	5 months	3
5/24/96	GLAXO	5M516	88 mcg	104.5	103	Jan-98	24 months	4 months	1.5
5/24/96	GLAXO	5M517	112 mcg	105.2	103.8	Jan-98	24 months	4 months	1.4
5/24/96	GLAXO	5M519	137 mcg	102.4	103.4	Jan-98	24 months	4 months	-1
5/24/96	GLAXO	5M520	175 mcg	103.4	104.3	Jan-98	24 months	4 months	-0.9

1\* DATA WAS FROM TESTING PERFORMED BY JMI-DANIELS.

## ATTACHMENT 2



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**JONES MEDICAL INDUSTRIES, INC.**

1945 Craig Rd. P.O. Box 46903  
St. Louis, MO 63146

314 576-6100  
Fax 314 469-5749

**TO: DREW FRANZ**

**FROM: BILL LEINHOS**

**SUBJECT: WHOLESALER DATING**

**DATE: MARCH 6, 1998**

The following are wholesalers that were contacted regarding the dating that will be accepted into their facility.

AmeriSource (Paducah) – nothing less than 12 mo.  
- pull product every 6 mo.

AmeriSource (Columbus) – nothing less than 12 mo.  
- believes this is for all dc's

AmeriSource (Johnson City) – nothing less than 12 mo.

Bellco Drug – request 12 mo. dating

Bergen (Corona) – nothing less than 9 mo.  
- special authorizations for shorter dated merchandise

Bergen (Phoenix) – nothing less than 12 mo.  
- will accept 9 mo. (item by item)  
- pull at 6 mo. (Arizona law requires merchandise to be pulled by 3 mo.)

Bindley Western (Corporate) – request 24 mo. dating  
- but will accept shorter dating depending on product & how fast customer needs product

Cardinal (Corporate) – request between 12 & 18 month dating (prefer 18 mo.)  
- anything under 12 mo. must be approved by Inventory Manager  
- start pulling at 6 mo.

Cardinal (Union City) – request 12 mo. dating  
- need to be notified of anything less than 12 mo.  
- start pulling at 6 mo.

Cardinal (Waco) – request 12 mo. dating

- believe 12 mo. is corporate policy
- will refuse product with less than 8 mo. dating
- pull product at 6 mo.

CD Smith – request 18 mo. on every purchase order

- minimum 6-8 mo. (depends on demand)

D&K Wholesale – request 12 mo.

- but will accept 10-11
- anything less than 10 mo, they must be notified

F. Dohmen Co. (Corporate) – request 12-18 mo. dating

Frank W. Kerr – request 12-18 mo.

- must be notified of short dated merchandise

Kinray (Corporate) – prefer 18 mo.

- will accept less depending on item

M. Sobel – requires 13 mo.

- will accept less dating but must be notified prior to shipping

McKesson (Corporate) – will not accept less than 6 mo.

- prefer at least 12 mo.
- for short dated product (6-9 mo.) – like to be notified prior to us shipping

North Carolina Mutual – will not accept less than 12 mo. (in most cases)

- can accept 10-12 mo. dating – but they have to be notified

Morris & Dickson – request at least 15 mo.

- must be notified of short dated merchandise

Neuman Drug – request 12 mo. dating

- prior notification for less than 12 mo.
- start pulling at 6 mo.

Smith Drug – request 12 mo. dating

- will accept short dating but must be notified in advance
- start pulling at 3 mo.

Walsh Dist. – request at least 12 mo.

- must be notified for short dated merchandise
  - pull 4-5 months
-

# KING & SPALDING

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TELEPHONE: 202/737-0500  
FACSIMILE: 202/626-3737

DIRECT DIAL:  
(202) 626-2910

May 18, 1998

By Messenger

Dr. Solomon Sobel, Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Food and Drug Administration 5600 Fishers Lane  
5600 Fishers Lane, Room 14B-04  
Rockville, MD 10857

Re: Levothyroxine

Dear Dr. Sobel:

This is a follow-up to my letter to you dated April 17, 1998 submitting, on behalf of Jones Medical Industries (JMI), results of JMI's investigation and testing of marketed levothyroxine products that show that all manufacturers are using a stability overage, whether it is called by that name or not.

Subsequent to submission of the letter, I had a very helpful telephone conversation with Mr. McCort and Dr. Christopher Rhodes, JMI's consultant, had an equally helpful telephone conversation with Dr. Wu. It is our understanding from Dr. Rhodes that --

- Dr. Wu clearly understood the significance of the information;
- He explained that the decision to require submission of NDA's for levothyroxine was to prevent the use of stability overages;
- In light of the JMI information, CDER will be very careful to assure that sponsors are not using a stability overage (and perhaps mischaracterizing it as a manufacturing overage) by paying close attention to the sponsor's assay at the time of release, which must be around 100%; and
- CDER may even do some assays on its own to double-check the assay-at-release information received from sponsors.

191 PEACHTREE STREET  
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HOUSTON, TX 77002-5219  
TELEPHONE: 713/751-3200  
FACSIMILE: 713/751-0290

Dr. Solomon Sobel, Director  
May 18, 1998  
Page 2

We assume that Dr. Wu is speaking for CDER and the Food and Drug Administration and that this is the policy and practice that CDER will follow.

We also assume, based on the discussions that Dr. Rhodes and I had with you and your staff at our meeting on February 15 (with Andrew Franz and Nancy Cafmeyer of JMI on speakerphone), that the reiteration of CDER's position in light of the JMI information will be conveyed in writing by the Division to all manufacturers of levothyroxine known to FDA (including JMI). To this end, JMI has asked me to advise you that it is quite willing for you to share with the other manufacturers the information it submitted to you. Indeed, Dr. Rhodes believes the information is so important that it should be published, but JMI has not made a decision about that yet.

JMI understands that CDER will refuse to accept §505(b)(2) applications *after* approval of the first §505(b)(2) application. As a result of this policy, manufacturers of levothyroxine are in a race, and JMI does not want to find itself unable to submit a §505(b)(2) application because CDER approved another company's application for a product using a stability overage. It was comforting to hear from Dr. Wu through Dr. Rhodes that CDER will apply the rules consistently and fairly.

There is an issue in my April 17, 1998 letter to you that I discussed by telephone with Mr. McCort, but without receiving an answer. It may be helpful to repeat it here.

JMI understands the concern of CDER, stated at our February 25th meeting, that a stability overage for NDAed levothyroxine products could result in patients receiving products with potencies that vary by 16% (10% from 100% to 90% and 6% from 106% to 100%, which is the stability overage). While levothyroxine is not a narrow therapeutic index drug, there is concern that it be titrated carefully to patients. However, levothyroxine products have been used for over forty years. These products have been manufactured with a stability overage. Patients titrated on a particular dose have been receiving potencies that vary by 16% without reported adverse experience. These facts should be taken into consideration [in determining] whether it is now necessary, after forty years of use, to narrow the range from 16% to 10% by prohibiting use of a stability overage.

To be sure, the August 14, 1997 Federal Register notice (62 Fed. Reg. 43535) discussed fifty eight adverse drug experiences in the last ten years. The significance of that number depends on the number of patients taking levothyroxine during that time, the number of tablets ingested during that time, and the severity of the adverse reactions. Even conceding that not all adverse drug experience is reported, fifty eight experiences in the last ten years, during which time there appears to have been a stability overage used by manufacturers, may -- or may not --

Dr. Solomon Sobel, Director

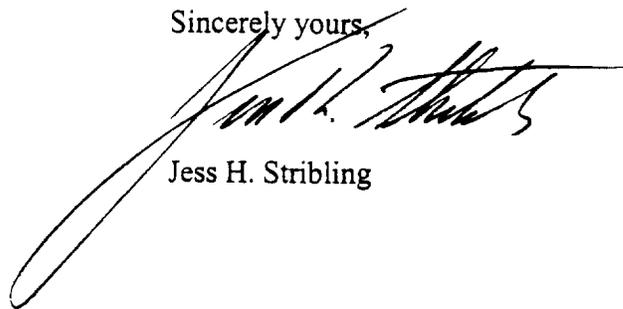
May 18, 1998

Page 3

be significant. That, of course, is a decision for the agency, but a decision that should be considered in the context of the real life situation.

Dr. Sobel, if you or your staff have any question about the interpretation of the charts or would like to see the back-up documentation, please let either me or Mr. Franz know. JMI will be happy to respond. Thank you very much.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Jess H. Stribling", written over a horizontal line. The signature is fluid and cursive, with a long, sweeping underline that extends to the left.

Jess H. Stribling

cc. Mr. Stephen M. McCort  
Dr. Christopher Rhodes  
Mr. Andrew Franz



**KING & SPALDING**

1730 PENNSYLVANIA AVENUE, N.W.  
WASHINGTON, DC  
20006-1706

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Dockets Management Branch (HFA-305)  
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