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September 23, 2004

BY FACSIMILE

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration (HF-1)
5600 Fishers Lane, Room 1471
Rockville, Maryland 20857

Re: *Levothyroxine Sodium, Supplement to Petition for
Reconsideration (Docket No. 2003P-0387)*

Dear Dr. Crawford:

On July 23, 2004, we petitioned the Food and Drug Administration ("FDA") on behalf of Abbott Laboratories ("Abbott") to reconsider the approval of levothyroxine sodium drug products that purport to be "therapeutically equivalent" to brand-name products such as Synthroid® (levothyroxine sodium tablets, USP). We are now writing to supplement our petition with information that is directly at odds with the approval decisions and with key statements made by the agency in support those decisions.

This information, which was recently disclosed by a sponsor of one of the "therapeutically equivalent" products, shows an alarming difference in the mean bioavailability of the product relative to Synthroid® (see Tab 1, attached). Even more, it confirms to the letter the arguments made by Abbott over the last two years regarding the need for a carefully-calibrated levothyroxine bioequivalence test. We respectfully request that you use this information to ask anew whether FDA has fully and fairly responded to the concerns that have been raised about these products by Abbott and the leading endocrinologists.

I. THE SANDOZ DATA

On June 23, 2004, FDA issued a petition response that rejected Abbott's original Citizen Petition, see Docket No. 2003P-0387/CP1 (Aug. 25, 2003)

2003P-0387

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(the "Petition"), challenging FDA's levothyroxine sodium bioequivalence testing methodology. See FDA Docket No. 2003P-0387/PDN1 (the "Petition Response"). In particular, FDA found Abbott's concerns about the clinical consequences of generic substitution to be "unfounded" because "FDA's standards for levothyroxine sodium products will *not* allow products that differ by 9 percent or more in potency or bioavailability to be rated therapeutically equivalent." *Id.* at 26- 27 (emphasis added). The agency also deemed "invalid" Abbott's argument "that FDA would approve as equivalent two levothyroxine sodium products that differ by 12.5 percent in the delivery of levothyroxine sodium." *Id.* at 14. According to the agency, Abbott's clinical study utterly failed to support such a finding. *Id.* at 14-17.

In our July 23, 2004, petition for reconsideration, we showed that neither the evidence in the record nor basic principles of science supported the agency's position. We did not, however, have the benefit of the bioequivalence data that was before FDA when it issued the Petition Response. Now, as a result of a recent release of information by Sandoz Inc. (see Tab 1), we have a summary of the bioequivalence data supporting one of the approvals. These data are starkly at odds with the agency's own argument. They also confirm spot-on Abbott's analysis, the declarations of Drs. Walter Hauck and Ronald Sawchuk, and Abbott's clinical study.

According to the Sandoz materials, the mean bioavailability of the Sandoz product is, on average, 12.5 percent greater than that of Synthroid® after baseline correction based on the AUC₀₋₄₈ parameter. More specifically:

**Sandoz Levothyroxine (A) vs. Synthroid® (B)
 Ratios of LSM (A/B)% (90% Confidence Intervals) (ANOVA)**

Parameter	Total T ₄ - Baseline Adjusted
AUC 0-24	111.3% (103.5 - 119.6%)
AUC 0-48	112.5% (103.3 - 122.5%)
AUC 0-72	109.7% (100.8 - 119.4%)
Cmax	107.9% (100.9 - 115.4%)



See Tab 1.¹

¹ For levothyroxine products, AUC₀₋₄₈ is the most reliable measure of the extent of absorption of the drug, and for comparing one product with another. See Clinical Pharm. and Biopharmaceutics Review for Unithroid® at 9 (approved Aug. 21, 2000); Bioequivalence Review for Mylan Pharmaceuticals generic levothyroxine (approved June 5, 2002) (using AUC₀₋₄₈ data to derive

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Simply put: On the same day the agency insisted that its standards would not permit more than a 9 percent difference in bioavailability between a brand-name levothyroxine product and a generic substitute, the agency approved a product that was shown to differ in bioavailability by an average of 12.5 percent. Compare Petition Response at 27 with Tab 1.

The Sandoz data are also precisely in line with the evidence presented by Abbott. For example, Study M02-417 – which the agency deemed “invalid” – demonstrated that FDA would likely pass as bioequivalent two products that differ by 12.5 percent in bioavailability. See Petition at 11-13; Petition Response at 14. FDA rejected the findings of the study, yet it failed to disclose that it was about to approve at least one generic product that – as predicted by Study M02-417 – had a mean difference in bioavailability of precisely 12.5 percent.²

Similarly, Abbott submitted declarations and testimony on the clinical significance of 12.5 percent differences in bioavailability or dose, including evidence regarding the approved dosing increments for levothyroxine products, the approved labeling for levothyroxine products, and expert declarations. See Petition at 4-5; Supplement to Petition (Feb. 9, 2004). The agency sidestepped the evidence, insisting that Abbott’s concerns are unfounded because FDA would not approve products that differed in bioavailability to this extent. See Petition Response at 27.

confidence interval needed to establish bioequivalence); Clinical Pharmacology Review for Levo-T® at 8 (approved Mar. 1, 2002) and Clinical Pharmacology Review for Synthroid® at 6 (approved Jul. 24, 2002) (relying on AUC₀₋₄₈ as parameter for comparing levothyroxine formulations), available on “Drugs@FDA” at www.fda.gov. FDA based its own comparison of the bioavailability of approved levothyroxine tablets relative to oral solution on the AUC₀₋₄₈ parameter. Petition Response at 23.

² FDA also rejected Abbott’s simulation studies (see Petition at 10, 29). It did so on the basis that the studies assumed a generic levothyroxine product that delivers 15 percent less (or more) drug than the comparable reference product. Petition Response at 20 n.13. According to the agency, historical data show that there is a “less than 1 percent” probability that FDA would approve such a product. Given this “exceedingly unlikely” possibility, FDA deemed the studies invalid. *Id.* Here, again, the Sandoz data undermines the agency’s reasoning. Sandoz achieved a result that falls three standard deviations from the historical mean. Based on FDA’s analysis, there was no better than about a 1 percent chance that the Sandoz product would be found bioequivalent. Remarkably, FDA deemed the Sandoz product bioequivalent to Synthroid® and, simultaneously, rejected Abbott’s studies as “exceedingly unlikely.” Abbott even analyzed a proposed generic product that delivers 12.5 percent more drug than the reference product. See Petition at 29. Again, FDA rejected Abbott’s analysis, even though the argument for doing so was at odds with the data that were before the agency.

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For example, the agency suggested that patients should expect no more than a 3, 3.3, or 3.5 percent mean difference in bioavailability when switched from a brand-name levothyroxine product to a "therapeutically equivalent" product. See Petition Response at 20 and 23; *id.* at 27 (FDA stating: "There is no evidence to suggest that a difference in bioavailability of 3.3 or 3.5 percent would have any clinical consequences, *even for the patients most in need of precise dosing (e.g., thyroid cancer patients).*" (emphasis added)). We are at a loss to understand why the agency would focus on the implications of a 3.5 percent difference in mean bioavailability – *when the actual data before the agency showed a 12.5 percent mean difference.* Had there been a plausible explanation, one would have expected to see it in the Petition Response.

In short, the Sandoz data show – without qualification – that FDA's bottom line conclusion was wrong; the agency's standards for levothyroxine sodium products *absolutely* will allow products that differ in bioavailability by 9 percent, 10 percent, 12 percent, and probably even 15 percent to be marketed as "therapeutically equivalent" to Synthroid[®]. They confirm what Abbott has argued for more than two years: FDA has not taken the steps needed to assure the therapeutic equivalence of levothyroxine products made by different sponsors.

II. DOSE, POTENCY, AND BIOAVAILABILITY

Several times in the Petition Response, the agency switched from the concepts of "bioavailability" and "bioequivalence" to the concepts of "dose" and "potency" to explain away Abbott's evidence. See, e.g., Petition Response at 14, 17, 26, 27. Supposed differences among these terms cannot justify or explain FDA's decision to approve as therapeutically equivalent products that differ in bioavailability by 12.5 percent.

"Dose" or strength is the total quantity or concentration of drug administered to a subject at a given time, expressed as an absolute measure (e.g., micrograms/tablet) or as a relative amount (e.g., micrograms/kg). Potency is that amount of the dose that is required to produce a specific therapeutic effect.³ Finally, bioavailability represents the amount or percentage of the dose that actually enters the systemic circulation. See 21 CFR 320.1(a). It is a measure of the performance

³ See, e.g., 21 CFR 210.3(16) (defining "strength" and "potency" under the agency's good manufacturing practice standards).

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of the formulation and whether the formulation can deliver a potent amount of the dose to the body and, ultimately, to the site of action.

For levothyroxine products, dose, potency, and bioavailability move in step with one another. These products are approved with 11 or 12 different dosage strengths, with differences in dosing increments of as little as 9, 10, and 12 percent.⁴ Each successive dosage strength is expected to yield a proportional increase in systemic exposure which, in turn, results in more drug being delivered to the site of action. FDA reaffirmed this principle when the agency explained in a response to a petition submitted by Jerome Stevens Pharmaceuticals, Inc. ("JSP"), why all sponsors of levothyroxine products must demonstrate the "dosage form proportionality" of each successive dosage strength of levothyroxine. According to FDA, "[d]osage form proportionality means that the bioavailability of each tablet strength is proportional to its labeled content [footnote omitted]." FDA Response to JSP Petition (Docket No. 2004P-0061, June 23, 2004) at 3. Thus, each successive strength levothyroxine tablet yields a proportionately identical increase in systemic exposure or bioavailability.

Keeping this principle in mind, the clinical evidence presented by Abbott – including FDA's stated basis for requiring "new drug" approval of all levothyroxine products – establishes that differences in levothyroxine dose, potency, or bioavailability each cause the same clinical effects. As FDA has often stated, in one form or another:

Levothyroxine sodium is a compound with a narrow therapeutic range. If a drug product of lesser *potency or bioavailability* is substituted in the regimen of a patient who has been controlled on another product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of *greater potency or bioavailability* could result in toxic manifestation of hyperthyroidism such as cardiac

⁴ Levothyroxine patients are titrated in increments as little as 9 percent. This table shows the percent change when the dose is decreased (below 100 mcg) and increased (above 100 mcg):

	25	50	75	88	100	112	125	137	150	175	200	300
	mcg											
Dose % Change:	-50	-33	-15	-12	+12	+12	+10	+9	+17	+14	+50	

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pain, palpitation, or cardiac arrhythmia. In patients with coronary heart disease, even a small increase in the *dose* of levothyroxine sodium may be hazardous.

Petition at Tab 10 at 354 (FDA levothyroxine pharmacokinetic and bioavailability guidance (emphasis added)).⁵ That is, dose, potency, and bioavailability are interchangeable with respect to the clinical concerns associated with levothyroxine's narrow therapeutic range.

In this light, an average difference of 12.5 percent in bioavailability between the Sandoz product and Synthroid® is stunning. It *exceeds* the difference in circulating thyroxine that would result from the 9 percent difference in potency described in FDA's 2001 "new drug" decision involving Synthroid®. See Petition at Tab 9. For example, a patient who is titrated to 100 mcg Synthroid® tablets may, without notice to the physician (in most states), receive 100 mcg Sandoz Levothyroxine tablets from the pharmacist. Based on the data released by Sandoz, the 100 mcg Sandoz Levothyroxine product will behave inside the body like a 112 mcg dose of Synthroid®. It would be as if the patient had been switched – without the physician's knowledge – from a 100 mcg levothyroxine regimen to a 112 mcg regimen. The uncontradicted evidence in the record is that this type of change, made at the pharmacy, puts thyroid patients at risk of hyperthyroidism.

Whether the difference at issue is a difference in strength or in bioavailability, the clinical concern is the same; the delivery of 9 or 12.5 percent more (or less) drug to a patient who has already been titrated to a specific dose of levothyroxine exposes that patient to serious adverse health consequences.

III. CONCLUSION

The Sandoz data support the urgent need for reconsideration and reversal of the agency's June 23, 2004, decision denying Abbott's petition and approving "therapeutically equivalent" versions of Synthroid®.

The data also support the need for immediate disclosure of the bioequivalence data for each of the recently approved levothyroxine products. In

⁵ See also Petition at Tab 9 at 342 (discussing clinical consequences of fine differences in levothyroxine dosing); 62 FR 43535, 43536 (Aug. 14, 1997) (finding that a small change in dose for levothyroxine patients with myxedema or cardiovascular disease may cause manifestations of angina, myocardial infarction, or stroke).

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June 2004, the agency assured the public that "therapeutically equivalent" levothyroxine products will not differ in bioavailability from their brand-name counterparts by more than 9 percent; the agency even suggested that patients should expect no more than a 3.5 percent difference in bioavailability when switching to a generic. Those assurances proved to be wrong; the information discussed above shows that at least one "therapeutically equivalent" product is, on average, 12.5 percent more bioavailable than Synthroid®. In this respect, the agency has *increased* the level of confusion and provoked still more concerns from the clinical community.

The appropriate first step is to make the bioequivalence data from the recent therapeutic equivalence decisions public. Thereafter, as we have requested time and again, we ask that you convene a public meeting to discuss the issues and hear from the relevant experts.

Respectfully submitted,



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cc:

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FDA Docket No. 03P-0387
FDA Docket No. 03P-0126
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Tab 1

Your Patients Now Have A Bioequivalent Alternative To Synthroid® And Levoxyl®.

The Summary Results of the Levothyroxine Biostudy are Below:

Study Synopsis

- Title:** Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Synthroid® as well as Sandoz Levothyroxine and Levoxyl® 300 mcg Levothyroxine Sodium Tablets in Healthy Adult Volunteers Under Fasting Conditions Following Administration of a 600 mcg Dose.
- Objective:** The objective of this study was to compare the single-dose relative bioavailability of Synthroid® as well as Sandoz Levothyroxine and Levoxyl® 300mcg levothyroxine sodium tablets under fasting conditions following a 600 mcg dose.
- Study Design:** Open-label, randomized, single-dose, 2-way crossover bioavailability study performed in 24 healthy adult volunteers and 4 alternates (19 males and 9 females). A total of 26 subjects (17 males and 9 females) completed the crossover for the study comparing Synthroid® and Sandoz Levothyroxine. A total of 27 subjects (19 females and 8 males) completed the crossover for the study comparing Sandoz Levothyroxine and Levoxyl®. Each dose was separated by a washout period of 35 days.
- Methods:** The AUC 0-72, AUC 0-48, AUC 0-24, Cmax and Tmax pharmacokinetic parameters were calculated for baseline-adjusted and levothyroxine (Total T₄). Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were performed on the ln-transformed baseline-adjusted pharmacokinetic parameters AUC 0-24, AUC 0-48, AUC 0-72 and Cmax.
- Results:** The pharmacokinetic results are listed below for Total T₄ in serum:

Sandoz Levothyroxine (A) vs Synthroid® (B)
Ratios of LSM (A/B)% (90% Confidence Intervals) (ANOVA)

Parameter	Total T ₄ - Baseline Adjusted
AUC 0-24	111.2% (103.5 - 119.6%)
AUC 0-48	112.5% (103.3 - 122.5%)
AUC 0-72	106.7% (100.8 - 112.6%)
Cmax	107.9% (100.9 - 115.4%)

Sandoz Levothyroxine (A) vs Levoxyl® (B)
Ratios of LSM (A/B)% (90% Confidence Intervals) (ANOVA)

Parameter	Total T ₄ - Baseline Adjusted
AUC 0-24	99.8% (90.5 - 109.6%)
AUC 0-48	97.7% (87.8 - 108.8%)
AUC 0-72	97.0% (85.3 - 108.4%)
Cmax	101.4% (95.0 - 108.7%)

Sandoz Levothyroxine (A) vs Synthroid® (B)
Ratios of LSM (A/B)% (90% Confidence Intervals) (ANCOVA)

Parameter	Total T ₄ - Baseline Adjusted
AUC 0-24	110.8% (103.6 - 118.1%)
AUC 0-48	111.1% (102.8 - 120.7%)
AUC 0-72	108.2% (100.4 - 116.7%)
Cmax	108.2% (101.0 - 116.0%)

Sandoz Levothyroxine (A) vs Levoxyl® (B)
Ratios of LSM (A/B)% (90% Confidence Intervals) (ANCOVA)

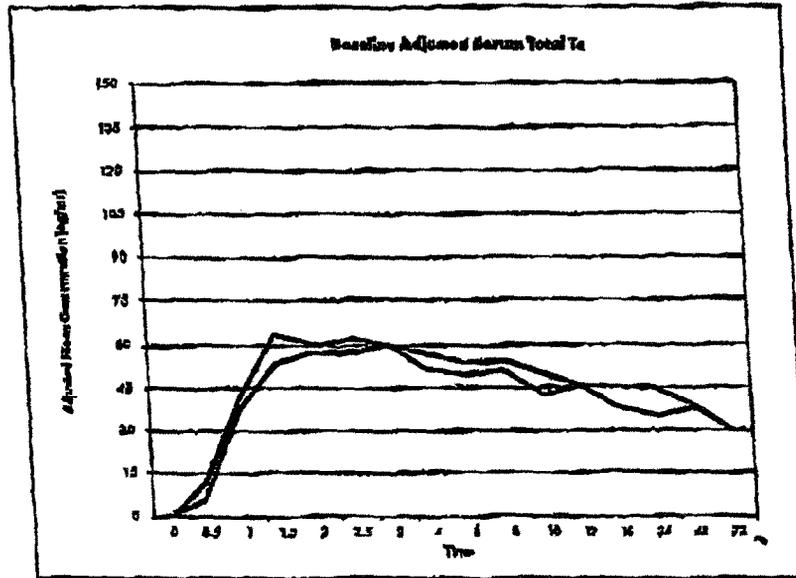
Parameter	Total T ₄ - Baseline Adjusted
AUC 0-24	98.3% (90.1 - 107.0%)
AUC 0-48	96.4% (87.3 - 106.4%)
AUC 0-72	95.1% (85.1 - 106.5%)
Cmax	101.1% (94.6 - 108.0%)

- Conclusions:** From the ANOVA and the ANCOVA, the ratios of least-squares means and 90% confidence intervals derived from the analysis of the ln-transformed baseline-adjusted pharmacokinetic parameters AUC 0-24, AUC 0-48, AUC 0-72 and Cmax for Total T₄ were within the 80-125% FDA acceptance range.
- Results showed that the ratios of least-square means and 90% confidence intervals were also within the 80-125% FDA usual acceptance range. Based on these results, the Synthroid® and Sandoz Levothyroxine, and the Sandoz Levothyroxine and Levoxyl® 300 mcg levothyroxine sodium tablets are bioequivalent under fasting conditions, following a 600 mcg oral dose.

REFERENCES

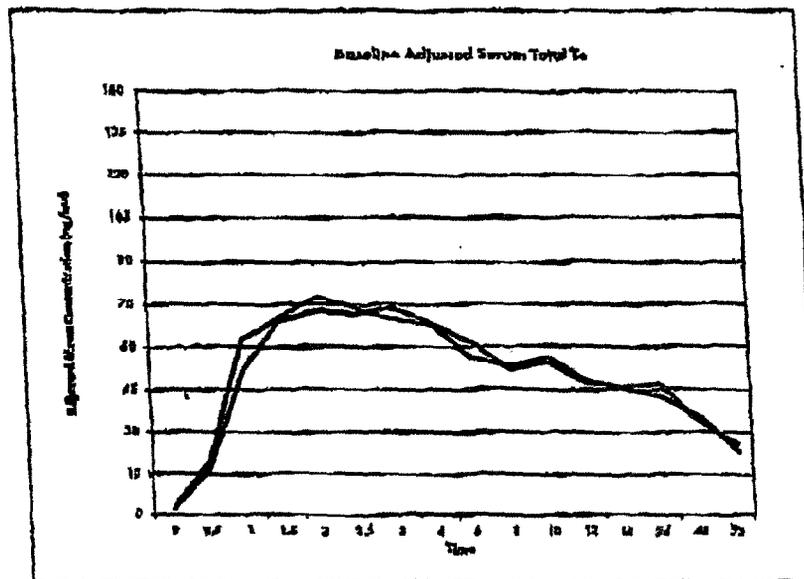
Studies conducted by MDS Pharma Services
Synthroid® Study AA03790
Levoxyl® Study AA01091

COMPARING SANDOZ LEVOTHYROXINE TO SYNTHROID



— Sandoz (A)
 — Synthroid® (B)

COMPARING SANDOZ LEVOTHYROXINE TO LEVOKYL



— Sandoz (A)
 — Levokyl® (B)

Sandoz Levothyroxine has been evaluated by the Food and Drug Administration and has been approved for marketing. FDA is satisfied that it is safe, effective and therapeutically equivalent to Synthroid® and Levokyl®.

Please see full prescribing information in packet.