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July 23, 2004

BY HAND DELIVERY

Division of Dockets Management, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Submission to Docket No. 03P-0126

Dear Sir or Madam:

On behalf of Abbott Laboratories, please include the following petition for reconsideration in Docket No. 03P-0126.

Sincerely,



David M. Fox
Hogan & Hartson L.L.P.

Enclosure

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July 23, 2004

BY HAND DELIVERY

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs
c/o Division of Dockets Management
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Petition for Reconsideration
Docket No. 2003P-0387**

Dear Dr. Crawford:

On behalf of Abbott Laboratories ("Abbott"), we submit this petition under 21 CFR 10.33 for reconsideration of the decision dated June 23, 2004, denying Abbott's request that the Food and Drug Administration ("FDA") establish a valid levothyroxine bioequivalence ("BE") methodology prior to the approval of generic versions of Synthroid® (levothyroxine sodium, USP) Tablets. See FDA Docket No. 2003P-0387/CP1 and PDN1. Among other things, Abbott requested that the agency hold a public meeting to obtain expert clinical and biopharmaceutical advice, prior to adopting a levothyroxine BE methodology. The agency denied this request and, concurrent with the denial, immediately approved the marketing of generic versions of Synthroid® and other brand-name levothyroxine products. 1

FDA's decision is a matter of profound public interest. Literally millions of patients are being impacted. The course of their treatment is now uncertain, as patient advocates and clinicians are calling into question the analysis used by the agency to approve "substitutable" levothyroxine products. Indeed, three leading endocrinology organizations, representing more than 4,600 clinicians

1 The June 23, 2004, denial letter also responded to (and denied) a citizen petition submitted by Jones Pharma Inc. (Docket No. 2003P-0126/CP1). As we have done throughout this proceeding, we will submit a copy of this petition for reconsideration to the docket for the Jones petition.

worldwide, have issued a joint statement expressing their deep concern with the agency's decision. *See* attached Tabs A and B. They have recommended steps to prevent health complications that may result from substituting ongoing brand-name levothyroxine treatment with the newly approved generic products. *See id;* *see also* attached Tabs C and D. Thyroid patients and clinicians are also being alerted to the potential danger of switching treatments without additional testing, re-titration, and/or frequent monitoring. *See* Tabs A-D. These organizations have even recommended that clinicians "[e]ncourage their patients to ask to *remain* on their current levothyroxine preparation." Tabs A-C (emphasis added).

To our knowledge, it is unprecedented that immediately after an FDA decision to approve a series of new products, clinical organizations and patient advocates would recommend *against* their use. Regrettably, this situation could have been avoided had FDA done two things: (1) properly considered all of the relevant evidence presented in Abbott's citizen petition, and (2) openly discussed the scientific and medical issues in a public meeting with the leading experts.

Instead, the agency's June 23, 2004, response failed to address the key evidence and arguments at nearly every turn. The response, for example,

- Incorrectly accused Abbott of misrepresenting a key FDA document showing that a 9 percent difference in levothyroxine dosing can lead to serious risks for patients
- Failed to respond to expert evidence from Dr. Walter Hauck, a renowned biostatistician, showing that FDA would deem as "bioequivalent" a generic levothyroxine product that is *15 percent more (or less) bioavailable* than the approved brand-name product
- Ignored Abbott's assay data, which shows that the hormone levels achieved in Abbott's "challenge study" could be measured with ease and precision
- Failed to acknowledge that the doses used in Abbott's challenge study were consistent with FDA's own recommendation to use "*several times the normal dose*"
- Rejected the 450 and 400 mcg doses used in Abbott's study, because they were below FDA's recommended 600 mcg dose, but nevertheless *accepted a 500 mcg test dose* in a generic drug applicant's study

- Failed to address expert evidence from Dr. Ronald Sawchuk, a leading biopharmaceutics researcher, who confirmed the design of the challenge study
- Relied on *uncorrected data* to assert – incorrectly – that levothyroxine tablets “behave like solutions” and thus are unlikely to raise BE issues
- Relied on *average data* from two outdated surveys to suggest that generic levothyroxine products can be expected to be within 3.5 percent of the brand-name product, when FDA has already approved at least one generic levothyroxine product that showed an *8 percent* difference in bioavailability from the brand
- Failed to explain why the agency had instructed its Advisory Committee for Pharmaceutical Science *not to discuss* Abbott’s data at a March 2003 meeting on endogenous drug products (*see n. 13 infra*), and
- Omitted any mention of the agency’s commitment to the American Thyroid Association (“ATA”) in November 2003 to *plan and hold a public workshop* on BE standards for levothyroxine products.²

In this light, the case for reconsideration of the evidence, and the process used to evaluate the evidence, could not be clearer. FDA failed to consider the relevant evidence, presented in good faith, on a matter of profound interest to patients and clinicians. *See* 21 CFR 10.33(d). As matters stand, the agency has lost the confidence of a core constituency – the many clinicians who prescribe levothyroxine products.

For these reasons, we respectfully request that you reconsider the methodology used to approve generic levothyroxine products; promptly schedule a

² In a letter to ATA, dated November 5, 2003, the agency stated that “we [FDA] are committed to plan and hold a workshop of sufficient depth and duration. At that workshop we plan to address all of the relevant issues raised at our meeting: bioequivalence testing baseline correction, optimal test subjects, and acceptable confidence limits; and TSH as a pharmacodynamic measure.” Tab E, attached. No mention is made of this letter in the FDA Response. Even more puzzling, the agency added this letter to the public docket on July 16, 2004, three weeks after it issued the petition response and approved the generic products. *See id.*

public meeting to examine the evidence; and commit to a process for establishing a levothyroxine BE methodology that can stand up to challenge.

DECISION INVOLVED

On August 25, 2003, Abbott submitted the above-referenced citizen petition requesting that FDA establish a valid methodology for determining the BE of levothyroxine products (the "Petition"). Abbott supplemented the petition on December 22, 2003, January 9, 2004, February 9, 2004, February 25, 2004, April 15, 2004, and June 4, 2004. Among other things, Abbott requested that the agency hold a public meeting to review the evidence and seek the advice of the leading clinical and biopharmaceutical experts, before finalizing a recommended BE methodology.

On June 23, 2004, FDA denied the Petition and approved at least two generic levothyroxine products as therapeutically equivalent to Synthroid®. See FDA Docket No. 2003P-0387/PDN1 (the "FDA Response"). According to the FDA Response, the agency's recommended BE methodology is "scientifically sound" and Abbott's concerns about adverse clinical effects "are unfounded." FDA Response at 26, 36. The agency also denied Abbott's request that an advisory committee be consulted on developing a valid levothyroxine BE methodology. *Id.* at 29-32. Finally, the agency's decision effectively denied the effort by the endocrinology organizations to have the views of the leading experts heard and considered in a public meeting.

ACTIONS REQUESTED

Based on the grounds set forth below, Abbott respectfully requests reconsideration of FDA's denial of the Petition, including reconsideration of the following decisions:

1. The decision to refuse to hold a public meeting to review the evidence and receive expert opinion and advice;
2. The decision to adopt a BE methodology that would "pass" as bioequivalent a generic levothyroxine drug product that differs in bioavailability from an approved brand-name product by 9 percent, 12.5 percent, and even 15 percent; and

3. The decision to approve additional generic levothyroxine products and assign A-level therapeutic equivalence ratings to other products before arriving at a valid BE methodology.

Given the public interests set forth below, we further request that you address this petition for reconsideration with haste. While administrative petitions ordinarily are addressed in 180 days or longer, we ask that you respond "promptly" (*see* 21 CFR 10.33(d)), given the public health issues associated with levothyroxine therapy and the concerns that have been expressed by clinicians.

STATEMENT OF GROUNDS

Under 21 CFR 10.33(d), the agency must grant a petition for reconsideration if all of the following apply: (1) FDA failed to consider or did not adequately consider relevant evidence in the administrative record; (2) reconsideration is requested in good faith; (3) reconsideration is supported by sound public policy; and (4) reconsideration is not outweighed by public health or other public interests. *See* 21 CFR 10.33(d). Further, the agency may grant a petition for reconsideration when a determination is made that it is in the public interest, and the interest of justice, to do so. *Id.* Under either test, the grounds for reconsideration in this instance are abundant and profound.

FDA failed repeatedly to address relevant arguments and evidence. Nor can there be any question that Abbott has raised and continues to raise these arguments in good faith. In fact, Abbott's original petition was submitted *at the agency's request*, based on FDA's own recognition that levothyroxine therapy raises significant public health and public interest issues. *See* Petition at 18, Tab 1. Finally, while the availability of lower cost drugs is a critical "public interest" issue, it is not the only relevant issue. In this case, the paramount public interest issue is in ensuring the validity of the science behind the approval of generic levothyroxine products. The reaction of the clinicians to the agency's decision is a fair indicator of the public interest issues at stake in this matter; by all appearances, the clinicians do not trust the agency's decision and they do not accept the process that led to the decision. Restoring that trust, by reconsidering the agency's decision, is the overwhelming public interest.

I. REGULATORY BACKGROUND

FDA is required by law to determine whether a generic drug is "bioequivalent" to an approved brand-name or "listed" drug. 21 USC 355(j); 21 CFR 314.105(c). A generic drug is bioequivalent if "the rate and extent of absorption of

the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose” 21 USC 355(j)(8)(B); *see also* 21 CFR 320.1(e). A valid BE study must, therefore, be able to detect whether there is “a significant difference” in absorption between the generic and the listed drug.

As FDA describes it, “[t]he purpose of bioequivalence testing is to measure the release of the drug substance from the drug product.” FDA Response at 25. A generic drug may contain the same amount of active ingredient, and have the same *in vitro* dissolution profile as the listed drug, but still may not perform the same way in the body. The intent of most BE testing is, therefore, to determine whether two products that appear to be the same *outside the body* perform the same *inside the body*.

Bioequivalence testing thus can be divided into three parts: (1) defining what would represent a “significant difference” between the test and reference products; (2) establishing a protocol for dosing subjects and measuring blood levels; and (3) analyzing the data using statistical tools to reach a reasonably certain scientific conclusion. In other words, BE testing presents *clinical issues, study design issues, and statistical issues*. Abbott argued that levothyroxine raises challenges with respect to each issue, as follows.

Clinical issues. It is well established that levothyroxine is a narrow therapeutic range drug. ³ As described in the approved labeling, patients must be titrated to and maintained on a precise dose. *See* Petition, Tab 7 at 262. Precise BE testing is, therefore, critical for levothyroxine, where small changes in the amount of drug in the blood may result in therapeutic failure or serious side effects. *See id.* at 4, 23-28; Supp. (Feb. 9, 2004), Tabs A-D (enclosing expert clinical declarations); Supp. (June 4, 2004) at 4-6. This distinguishes levothyroxine from most other drugs; a dosing difference that would be insignificant for other drugs may be very significant for levothyroxine. Thus, when developing a BE method for levothyroxine, it is necessary to define *in advance* what would be considered a “significant difference” in absorption between the generic and the listed drug. *See* Petition at 23.

Study design issues. Levothyroxine (“T4”) is an endogenous hormone. This means that steps must be taken in BE testing to distinguish between levothyroxine released from the drug product and levothyroxine that is

³ *See* Petition at 4, Tab 7 at 262. We listed several examples of the agency’s own findings that levothyroxine is a narrow therapeutic range drug in our June 4, 2004, Supplement at 2-4.

already present in the body. *See id.* at 8, 28-29; Supp. (Apr. 15, 2004) at 2; FDA Response at 13-14. As FDA put it, “[c]omparisons of total T4 concentrations that also include endogenous T4 do not reflect the rate and extent of absorption of the drug solely *from the drug product.*” FDA Response at 13 (emphasis in original). To overcome this problem, FDA originally recommended using high doses of the study drug – well above the normal dose – to dilute the effect of endogenous T4. *See* Petition at 37. Another method is to include some form of “baseline correction,” in which each subject’s endogenous T4 is subtracted from post-dose measurements taken during the study. *See, e.g., id.* at 8-13. Baseline correction is, however, easier stated than done; because the body’s own production of levothyroxine may fluctuate, and may be suppressed during a BE study, baseline correction can itself introduce error into the study.

Statistical issues. The data generated in a BE study must be analyzed to develop a conclusion that can be applied to the general population. Most drugs can be analyzed using a standard statistical model (*i.e.*, a 90 percent confidence interval within an 80 to 125 percent acceptance range), where the theoretical differences allowed by this model between the generic and the listed drugs (up to a 20 percent difference) would not be clinically significant. However, this difference, and even smaller differences, would be clinically significant for levothyroxine therapy. *See id.* at 23-28; Supp. (Feb. 9, 2004) at 2, Tabs A-D; Supp. (June 4, 2004) at 4-6. Thus, Abbott argued that the statistical criteria used in a levothyroxine BE study must be adjusted, to align with the narrow range within which levothyroxine patients must be maintained. *See* Petition at 36-38; Supp. (Apr. 15, 2004) at 3.

II. ARGUMENTS AND EVIDENCE IN THE RECORD WERE NOT CONSIDERED OR ADEQUATELY ADDRESSED

In its response, FDA concluded that there is no need to define what would represent a “significant difference” between generic and brand-name levothyroxine products; that its recommended baseline correction method was sufficient to ensure the equivalence of generic products; that the BE limits used for most other drug products (80-125 percent) are adequate for levothyroxine testing; and that the agency was not required to use a public process to determine the BE standards for levothyroxine products. *See* FDA Response at 12-14, 19-21, 27, 29-34.

As shown below, the agency reached each of these conclusions without considering key arguments and evidence. What is most striking is that FDA never affirmatively demonstrated that it would “fail” a generic levothyroxine product that differs in bioavailability from a brand-name product by 9 percent or more.

A. Clinical Issues

The first issue in developing a valid BE methodology is to assess what would represent a “significant difference” between a test and reference product. *See, e.g.*, 57 FR 17950, 17973 (Apr. 28, 1992) (“The determination of a significant difference requires first a judgment as to what difference in a bioequivalence parameter of interest is medically important . . .”). Abbott argued that a 9 percent or greater difference in bioavailability between a brand-name levothyroxine product and a generic substitute would be a “significant difference” because such a difference would likely have an impact on the care of the patient. *See* Petition at 24-28; Supp. (Dec. 22, 2003) at 8; Supp. (Feb. 9, 2004) at 2, Tabs A-D; Supp. (June 4, 2004) at 5-6. Abbott based this argument on several layers of evidence.

First, most levothyroxine products are approved in 12 different strengths to allow for fine dosing increments (as little as 9 percent). *See* Petition at 4. The approved labeling for these products recommends titrating patients in increments as little as 12.5 mcg. *See id.*, Tab 7. Second, FDA itself argued in a 2001 decision that a 9 percent difference in levothyroxine products, at the time of refill, could result in “serious consequences” for the patient. *Id.*, Tab 9 at 349. Third, Abbott submitted expert declarations from leading endocrinologists, including Jerome M. Hershman, M.D., former president of the American Thyroid Association, showing that differences of 9 percent (*e.g.*, the difference between 137 and 150 mcg of levothyroxine) can have significant effects on serum TSH (thyroid-stimulating hormone) levels. *See* Supp. (Feb. 9, 2004), Tab A at 7-8; *see also id.*, Tab C at 6.

The agency offered three arguments in response.

1. *The Misrepresentation Argument*

The agency argued that Abbott “misrepresented” a 2001 FDA statement to reach the conclusion that 9 percent differences in bioavailability can have clinically significant effects on levothyroxine patients. FDA Response at 26 n.18. The agency claims that its position in the 2001 statement is that *a 19 percent difference*, and not a 9 percent difference, would be clinically significant. *See id.* In fact, the agency has misread its own document. ⁴

⁴ The agency’s 19 percent figure is also inconsistent with other evidence in the record showing that the FDA-approved labeling and dosage strengths (*i.e.*, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg) suggest that much smaller differences, down to 12.5 and 9 percent, are clinically significant. *See, e.g.*, Petition at 4. The agency ignored all such evidence in its response.

The statement at issue is found in a confidential appendix authored by the agency to support FDA's 2001 citizen petition response on the regulatory status of Synthroid®. See FDA Docket No. 97N-0314 (April 26, 2001); see also Petition, Tab 9 at 349. There, the agency describes the potential "serious consequences" that may result if the potency of a levothyroxine product is allowed to vary from refill to refill. *Id.* To illustrate the point, the agency presented a hypothetical situation in which a thyroid patient has been stabilized on 112 mcg of levothyroxine daily. See *id.* The hypothetical discusses what would happen if the patient's prescription were to be filled one month with tablets containing approximately 122 mcg of levothyroxine, and the next month with tablets containing approximately 101 mcg of the drug. See *id.* In such a situation, the agency concluded that "[o]n the first dose, the patient is likely to be mildly hyperthyroid, while on the second dose, the patient is likely to be mildly hypothyroid." *Id.*; see also FDA Response at 26 n.18.

Abbott relied on this passage for the proposition that a 9 percent difference, from refill to refill, is likely to produce clinically significant consequences. See Petition at 24-25; Supp. (June 4, 2004) at 5. Indeed, the passage corroborates the declarations submitted by the clinical experts, as well as the dosing increments found in the approved labeling and strengths of levothyroxine products. See Petition, Tab 7; Supp. (Feb. 9, 2004), Tabs A and C.

The agency, however, now claims that the hypothetical illustrates the impact of a *19 percent difference*, not a 9 percent difference. See FDA Response at 26 n.8. The agency apparently added the percentage differences between each refill amount and the titrated dose (112 mcg); that is, the 9 percent difference (112 mcg up to 122 mcg) was *added* to the 10 percent difference (112 mcg down to 101 mcg). The hypothetical, however, clearly states that with the first dose (122 mcg instead of 112), the patient "is likely to be mildly hyperthyroid," and with the second dose (101 mcg instead of 112 mcg) the patient "is likely to be mildly hypothyroid." See Petition, Tab 9 at 349. Each is approximately a 9 percent difference from the 112 mcg dose to which the patient has been titrated.

In short, the agency's argument that it is on record only as saying that a 19 percent difference is clinically significant is wrong. It is also inconsistent with unrebutted evidence in the record. Finally, the allegation that Abbott misrepresented the agency's position is belied by the facts; it is the agency that misread its own document.

2. *The Demonstration Argument*

The agency's second argument is equally wrong. FDA states that even if a 9 percent difference is significant, the agency has "demonstrated" that it will not allow products that differ in bioavailability by 9 percent to be deemed equivalent. *See* FDA Response at 27. According to the agency, this is shown in Section VII of the FDA Response. *See id.*

The focus of Section VII is on a clinical study conducted by Abbott in which a 450 and 400 mcg dose of levothyroxine were shown to "pass" FDA's recommended BE test. *See id.* at 14-16. FDA rejected the study, for reasons vigorously contested by Abbott (*see* below). The agency, however, never provided its own affirmative demonstration as to the sensitivity of its methodology. FDA certainly did not show how its methodology would recognize and "fail" a generic levothyroxine product that is 9 percent more (or less) bioavailable than a brand-name product. FDA's criticism of Abbott's study notwithstanding, the agency never demonstrated the validity of its own methodology when applied to levothyroxine products.

The only other argument in Section VII is the obvious point that FDA would not approve two different *dosage strengths* – *e.g.*, 100 and 112 mcg products – as equivalent. *See id.* at 16-17. FDA states that it would know that such products differ based on the chemistry, manufacturing, and controls ("CMC") data it ordinarily reviews prior to approving a product. *See, e.g., id.* at 17. This is true but irrelevant: Abbott never argued that the agency might inadvertently approve two products of *different strengths* as if they were the same drug. Rather, the issue is whether two products manufactured to contain the *same* amount of drug (*e.g.*, a 100 mcg product versus a 100 mcg product) might release different amounts of drug *in the body*, and whether FDA would be able to detect that difference. *See* Petition at 2, 11-13. Again, there is no affirmative evidence in Section VII of the FDA Response demonstrating that the agency would "fail" a generic product that differs by 9 percent under its recommended BE methodology.

Finally, in other sections of the response, FDA argues that it is unlikely to be presented with a generic levothyroxine product that releases 9 percent less (or more) drug than the approved reference product. *See* FDA Response at 16-17, 22-24, 26-27. The agency argues that it has dissolution, formulation, and CMC data that suggest that generic levothyroxine products can be expected to perform about the same *in vivo* as the reference drug. *See id.* However, the pivotal evidence in assessing the BE of a solid oral drug product is an *in vivo* BE study. *See* Supp. (Apr. 15, 2004) at 7-8; Supp. (June 4, 2004) at 8-9. The other data cited by

the agency may provide indirect “assurances,” but they do not constitute direct evidence of equivalence in this case. ⁵

3. *The 3.5 Percent Argument*

The agency’s final clinical argument is that quantification of a “significant difference” for levothyroxine products was not necessary because FDA’s standard BE methodology generally ensures no more than a 3.5 percent difference among products. *See* FDA Response at 27. That is, while Abbott showed that a 9 percent difference is clinically significant for levothyroxine, FDA insists that no more than a 3.5 percent difference should be expected. *See id.* at 20. According to the agency:

FDA’s two reviews of passing bioequivalence studies (224 studies reviewed in the 1980s and 127 reviewed for ANDAs approved in 1997) found that the average observed differences in AUC were 3.5 and 3.3 percent, respectively. *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).*

Id. at 27 (emphasis added).

Here, FDA relies on an *average* figure from two retrospective surveys (the “1987 survey” and “1997 survey”) to argue that most approved generics release about the same amount of drug as the brand-name product, to within 3.5 percent. Based on this figure, FDA argues that it can assure patients, *including thyroid cancer patients*, that generic levothyroxine products should be within 3.5 percent of their brand-name counterparts. *Id.*

This is misleading, to say the least. In fact, FDA approved a generic version of Unithroid® in 2002 with an area under the curve (“AUC”) that was shown

⁵ The agency also argues that most approved generics, on average, are within 3.5 percent of the reference drug based on standard bioavailability measures. *See* FDA Response at 20. This point, however, does not demonstrate the sensitivity of the agency’s BE methodology; it is a retrospective finding about the formulation of generic products – on average. In fact, the first generic levothyroxine product approved by the agency in June 2002 was shown in one study to be *8 percent less bioavailable* than the reference product, far outside the historical average. As with other contrary facts, the agency ignored this evidence. *See* discussion *infra*.

in one study to be *8 percent less* than the reference product (based on baseline-corrected data). See Petition, Tab 11 at 479; Supp. (Apr. 15, 2004), at 7. Moreover, the confidence interval for the generic product extended down to 85 percent, meaning that the true difference between the generic and the reference product could considerably be greater than 8 percent. See Petition, Tab 11 at 479. 6

Further, in the 1987 survey relied upon by FDA, the agency approved at least 13 generic drug products that differed in AUC from their reference drugs by 10 percent or more, and one that differed by 19 percent. See Petition, Tab 24. 7 Clearly, a 10 percent and a 19 percent difference would have profound clinical consequences for levothyroxine patients, including thyroid cancer patients.

The surveys also say nothing about the sensitivity of FDA's BE methodology, as applied to a particular product, and its ability to "fail" products deviating from these average results. The surveys are pure retrospective analyses; they provide a profile of what the agency has tended to approve. They do not, however, demonstrate that the agency's methodology would be able to recognize when a generic levothyroxine product releases 9 percent more or less than the approved brand-name product.

* * *

The starting point for designing a valid BE methodology for levothyroxine products is to begin with a clinical determination of the maximum difference that may be allowed for products that will be deemed equivalent. Only then can patients and clinicians be assured that products deemed equivalent may be substituted with no adverse clinical effects. FDA's reasons for not doing so in this instance do not stand up to scrutiny. Even the agency's claim that Abbott misrepresented a key piece of clinical evidence proved to be wrong. FDA's reliance on the 1987 and 1997 surveys is misplaced. The surveys speak only to the ability of generic drug manufacturers, in most cases, to formulate their products to match the bioavailability of brand-name products. The surveys do not show that FDA would be able to recognize or that FDA would "fail" a generic levothyroxine product that deviated from the historical average.

6 Even more remarkable, the generic product had a nearly *5 percent greater potency* than the reference product. See Petition, Tab 11 at 373.

7 To our knowledge, the 1997 survey relied upon by FDA has not been published. FDA did not make its workpapers available as part of the FDA Response.

B. Study Design Issues

A BE study of a solid oral drug product generally consists of a two-arm crossover design, in which test and the reference drugs are administered to healthy subjects, separated by an appropriate washout period. During the study, measurements are taken to determine the rate and extent to which the active ingredient in the test and the reference products becomes available in the body. A "bioavailability" profile is developed for the test and reference drugs, and the two profiles are compared with each other. If the profiles are similar, based on statistical criteria established by FDA, the products are deemed "bioequivalent."

Abbott conducted a clinical study to pressure-test whether this standard BE methodology is appropriate for levothyroxine products. *See* Petition at 11-13, Tab 12. It was designed as a standard challenge study, in which an intentional difference was introduced into the study, to see whether that difference could be detected. *See id.*

Essentially, Abbott provided the same group of subjects a 600 mcg dose of levothyroxine (12 tablets of 50 mcg each), 450 mcg dose of levothyroxine (9 tablets) and a 400 mcg dose of levothyroxine (8 tablets). *See id.*, Tab 12 at 501. The additional 50 mcg tablets in each successive arm of the study served as surrogates for a product that releases comparatively more (or less) drug into the body. This allowed Abbott to evaluate whether FDA's BE methodology could detect a significant difference between bioavailability profiles of two levothyroxine products, and whether the sensitivity of the test could be improved by using some form of baseline correction. In the end, the 600 mcg dose could be distinguished from the 450 and 400 mcg doses with baseline correction. *See id.* at 12-13. However, the 450 and 400 mcg doses (a difference of 12.5 percent) were shown to be bioequivalent, even with baseline correction. *See id.*

The study, known as Study M02-417, has now been published in the peer-reviewed journal *Thyroid*. *See* Supp. (Apr. 15, 2004), Tab A. Based on Study M02-417, Abbott argued that additional thought was needed as to the appropriate design of a BE methodology for levothyroxine products. *See* Petition at 23-38. Abbott urged the agency to convene an expert panel to analyze the issue and advise the agency on additional steps that could be taken to increase the sensitivity of its BE methodology for levothyroxine products. *See id.* at 38-41.

The agency refused to open up the issue for discussion. Instead, the agency has now determined that Study M02-417 was invalid and irrelevant, based on the following two arguments.

1. FDA's Test Dose Argument

FDA argued that Study M02-417 is invalid because Abbott's conclusion – that the 450 mcg dose was “bioequivalent” to the 400 mcg dose – was based on too low a dose of levothyroxine. See FDA Response at 14-16. According to the FDA Response, the doses used were “significantly lower than the 600 mcg dose FDA recommends for bioequivalence testing.” *Id.* at 14. A higher dose, such as 600 mcg, provides “greater assurance that the bioequivalence test measures accurately the rate and extent of absorption of the drug.” *Id.* at 15. That is:

At lower doses, such as the 400 and 450 mcg doses used in Abbott's study, the total amount of measured T4 consists of a greater percentage of endogenous T4 than at a higher dose, such as the 600 mcg dose recommended by FDA. When more of the measured concentration of T4 consists of endogenous T4 (“the noise”), the bioequivalence comparison is less sensitive to the actual differences in T4 concentrations that are present from administering the drug product (“the signal”).

Id. In other words, more is better.

Nowhere, however, did the agency demonstrate that more than 450 or 400 mcg of levothyroxine is *necessary* to ensure accurate measurements and an accurate comparison. The agency insists that “Abbott achieved its study results *only by its choice* of doses that are significantly lower than the 600 mcg dose FDA recommends for bioequivalence testing.” *Id.* at 16 (emphasis added). There is no evidence in the record to support that conclusion; in fact, the bulk of the evidence is to the contrary.

a. The 600 mcg test dose was recommended for use in lieu of baseline correction

Abbott demonstrated that the original basis for requiring a 600 mcg dose was an FDA guidance document entitled *Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* (Feb. 2001). See Petition at 31-33, Tab 10. There, FDA recommended using “several times the normal dose . . . to raise the levels of the drug significantly above baseline to allow measurement.” *Id.*, Tab 10 at 354. A 600 mcg test dose was

convenient because it represents two times the highest available strength levothyroxine tablet. Abbott made this point in its Petition. *See id.* at 32. The agency not only failed to respond, it failed once again to show why it believes 600 mcg represents a critical threshold (rather than just a convenient way, based on the highest approved strength, to achieve a hyperphysiologic dose). 8

Second, FDA originally recommended using a high test dose (several times above normal) *in lieu of baseline correction*. *See id.* at 6-7, Tab 10 at 356. The large dose is intended to raise the level of the drug significantly above baseline to allow for accurate measurement. *See id.* at 31, Tab 10 at 354. However, when baseline correction is used, the need for a high dose, such as 600 mcg, falls away. *See id.* at 33. In an apparent response to this point, FDA states that “it is not inconsistent to use both baseline correction and a 600 mcg dose for bioequivalence.” FDA Response at 15. True, but Abbott never argued that it would be inconsistent; Abbott only argued that the supposed rationale for using a dose as high as 600 mcg is diminished. *See* Petition at 31-34.

b. FDA relied on a 500 mcg BE study to approve a generic levothyroxine product

Abbott showed that the agency accepted a BE study from a generic sponsor, Mylan, that used a 500 mcg test dose (4 tablets x 125 mcg each). *See* Petition at 32, Tab 11. The Mylan generic product, referencing Unithroid®, was approved in June 2002. *See id.*, Tab 11 at 362. If doses below 600 mcg are likely to lead to biased results, why did the agency accept Mylan’s 500 mcg study?

FDA addressed this apparent inconsistency by noting that Mylan did two other studies, both with a 600 mcg dose. *See* FDA Response at 16 n.8. However, nowhere in the review of the Mylan application did the agency take issue with the 500 mcg dose. To the contrary, the agency deemed the 500 mcg study acceptable for purposes of demonstrating bioequivalence:

The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 125 [mcg] . . . comparing it with the reference

8 FDA claims that it chose a 600 mcg dose because it represents “the highest recommended dose for which there was evidence of safety and effectiveness.” FDA Response at 15. The agency, however, offered no references in support of this point. In any event, whether 600 mcg is (or is not) a safe and effective dose of levothyroxine is not determinative of whether it is the only reasonable dose to use in a BE or comparative bioavailability study.

product . . . has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's Levothyroxine Sodium Tablets, 125 µg, is bioequivalent to the reference product . . . under fasting conditions.

Petition, Tab 11 at 420. FDA routinely rejects BE studies; *it did not reject the Mylan 500 mcg study.*

Finally, it is clear that FDA relied on the 500 mcg study in approving the Mylan generic product. In a petition response issued on the same day as the FDA Response to the Abbott Petition, the agency discussed its reliance on the 500 mcg study as follows:

[Jerome Stevens'] challenge to Mylan's approval for its levothyroxine sodium product *is particularly ill-founded* because Mylan actually conducted more bioequivalence studies than the Agency recommended. In addition to comparing two 300-mcg tablets of its product to two 300-mcg tablets of the innovator product, *Mylan also tested its product against the innovator by comparing four 125-mcg tablets and six 100-mcg tablets. Mylan's product demonstrated bioequivalence to the innovator product for all three comparisons.*

Docket No. 2004P-0061/PDN1 at 4 (June 23, 2004) (emphasis added).

Any suggestion by the agency that it did not rely on the 500 mcg Mylan study is belied by the record in support of the Mylan generic and by the agency's June 23, 2004, petition response to Jerome Stevens. More important, the arbitrary nature of the agency's handling of test doses below 600 mcg could not be clearer – Abbott's 450 and 400 mcg doses invalidated Study M02-417, while Mylan's 500 mcg was found to be acceptable.

- c. *A 600 mcg dose has not been shown to be any better than a 450 or 400 mcg dose in a baseline-corrected study with a sensitive assay*

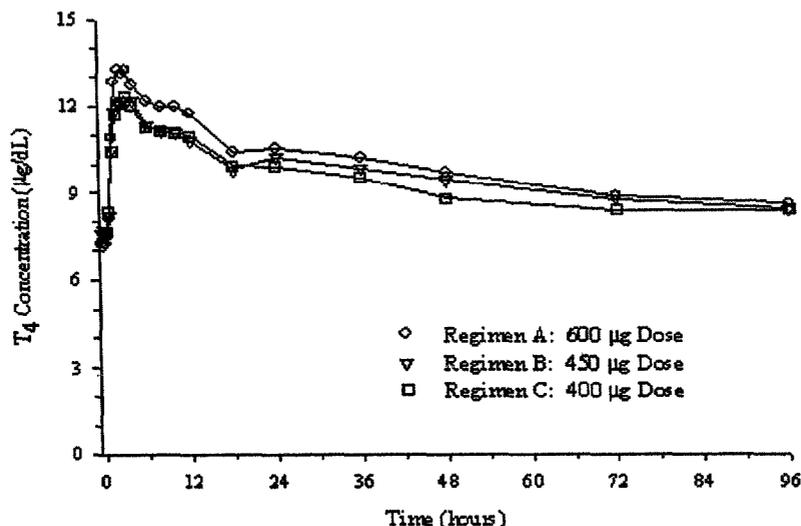
In response to FDA's concerns that lower doses result in an "increase in assay variability," Abbott provided the agency with detailed information about the precision and sensitivity of the assay used in its study, and with the validation

history for the assay. FDA Response at 15 n.6; see Petition at 34-35. At 450 and 400 mcg, the concentration of T4 is so far above the lower limit of quantification (“LLOQ”) of the assay that the agency’s stated concern seems contrived. See Petition at 34-35. Indeed, in response to the data provided by Abbott, the agency could do no better than to assert – without any facts or figures – that “[u]sing a larger dose, such as 600 mcg, makes the bioequivalence comparison more precise because it reduces assay variability.” FDA Response at 15 n.6. Precisely what assay variability FDA is referring to, and why a 600 mcg dose makes a categorical difference in this instance, is left unstated.

FDA also failed to offer any response to the expert declaration of Dr. Ronald Sawchuk. According to Dr. Sawchuk,

All three doses used in Study 417 produced a significant and measurable signal. Moreover, the fact that doses lower than 600 mcg were used, where they remained several times the normal dose of levothyroxine, is not problematic. In the 417 Study, the 600 mcg dose resulted in only a slightly higher [maximum serum concentration] than either the 450 or 400 mcg doses, but this serum concentration quickly declined to near the concentrations associated with the 450 and 400 mcg doses.

Supp. (Feb. 25, 2004), Tab A at 10-11. Dr. Sawchuk illustrated this with the following figure, showing the measurable levels produced by the 400, 450, and 600 mcg doses used in Study M02-417:



Mean Levothyroxine Concentration-Time Profiles on Study Day 1 Following Single Dose Administration of Levothyroxine Sodium – Uncorrected for Endogenous Baseline Concentrations.

Id. at 11.

For all of FDA's stated concerns, it is clear that the measurable levels attained with a 600 mcg dose are not categorically different from those attained with a 450 or 400 mcg dose. Higher may be better, but at levels several times the normal recommended dose (typically 100 mcg), a point of diminishing returns is reached – a 600 foot home run is longer than a 450 home run, but they are both long enough. The agency certainly did not show otherwise. ⁹

⁹ FDA claims that a 600 mcg dose is "more conservative" than a 450 or 400 mcg dose, because with higher levels, the likelihood that endogenous T4 will bias the results is reduced. FDA Response at 15. The higher dose, however, is not without costs. Because of the sensitivity of the thyroid hormone regulatory system to changes in T4 levels, endogenous T4 production and secretion is rapidly suppressed when hyperphysiologic doses are given. *See* Petition at 3-4. The higher the dose, the more complete the suppression. This suppression introduces error into the agency's baseline correction method; with suppression, the pre-dose correction method overstates the amount of endogenous T4 in the system after the test dose is administered. *See id.* at 11-13. The further away from a physiologic dose, the greater the perturbation. In this respect, the use of a 600 mcg dose – in a study that also incorporates baseline correction – actually may add error into the analysis. Once again, the agency is relying on an analysis in favor of 600 mcg that was developed for use *without baseline correction*. With baseline correction, a 600 mcg dose may actually represent a less optimal, *less conservative*, approach. Had the agency paused and held a public meeting of experts, this type of issue could have been properly vetted.

With baseline correction and a precise assay, there is no basis for rejecting Study M02-417 based on the test doses.

2. *FDA's Different Strengths Argument*

FDA also took issue with another aspect of Study M02-417. According to the agency, to conduct a "properly designed" challenge study, Abbott should have used two levothyroxine products "that had been intentionally made to differ in bioavailability, but contained the same labeled amount and content of levothyroxine sodium at a total dose of 600 mcg." FDA Response at 17 n.11.

FDA characterized Abbott's study as testing only whether products with different dosage amounts would be found bioequivalent. *See id.* at 16-17. This allowed FDA to dismiss the results of Study M02-417 by citing other requirements for the approval of generic drug products, and stating that FDA would never approve products that differ by 12.5 percent (*i.e.*, the bioavailability difference tested in M02-417). *See id.* at 22-24, 26-27.

This misstates the intent and design of Study M02-417. The study used products with the same strength and drug content. *See* Petition, Tab 12 at 501. Abbott simply used one additional tablet to simulate what would happen if two products of the same dose actually delivered different amounts of levothyroxine to the body. *See id.* A leading expert, Dr. Ronald Sawchuk, confirmed the design of Abbott's study in his declaration to FDA. *See* Supp. (Feb. 25, 2004), Tab A. Dr. Sawchuk stated that, based on his experience, "the 417 Study was a well-designed study, consistent with the design of a bioequivalence study." *Id.*, Tab A at 9. The agency did not respond to Dr. Sawchuk's declaration, or to the fact that Study M02-417 was recently published in a peer-reviewed journal.

If Abbott had formulated a product that, as FDA suggested, "had been intentionally made to differ in bioavailability," Abbott would have achieved the identical results. In fact, the design of Study M02-417 was likely more rigorous than that proposed by FDA, because Abbott's study controlled for the bioavailability of the tested doses. *See* Petition at 11 n.12. Abbott's study design was optimal because, having controlled all other variables, we knew with certainty that one group of subjects received 50 mcg more (or less) levothyroxine than the other group.

Had we attempted to formulate products that were intentionally made to differ in bioavailability, other variables could have entered into the study. Abbott would not have known with certainty the actual release value of the newly formulated products into the body. Far from providing us a level of certainty as to

the actual release value of the product into the body, creating a new formulation would have corrupted the study. Why the agency believes that a new formulation was needed and why this issue is raised now versus two years ago – when FDA had the opportunity to offer input on Abbott's study – is left unanswered in the FDA Response. ¹⁰ In short, Abbott's challenge study was a conservative design, intended to minimize the number of variables.

* * *

Abbott pressure-tested the agency's levothyroxine BE methodology, and the methodology failed. The 450 and 400 mcg doses of levothyroxine used in Study M02-417 were sufficiently high to evaluate the sensitivity of FDA's BE methodology for levothyroxine products. FDA asserted that a 600 mcg dose is better because it is higher, but provided no data or analysis to indicate why 450 and 400 mcg doses are too low. Study M02-417 effectively simulated a BE study in which the test and reference products release different amounts of drug in the body. There was no need to specially formulate a product that intentionally releases too much or too little drug, as suggested by FDA. Study M02-417 shows that, even with baseline correction, products that release different amounts of levothyroxine into the body (12.5 percent, as tested) are likely to "pass" FDA's BE criteria.

C. Statistical Issues

FDA does not require that a brand-name drug and a generic substitute have an identical bioavailability profile. Instead, FDA has established statistical criteria under which the ratio of the generic and the reference drugs must fall within certain acceptance limits. These limits (generally 80 to 125 percent) theoretically allow the generic to differ from the reference product by upwards of 20 percent. This theoretical limit reflects the general determination that the clinical response to most drugs would not be expected to be significant, or evident, if there were a 20 percent difference in dose.

¹⁰ For example, Abbott submitted the protocol for Study M02-417 to FDA in February 2002. *See* Petition, Tab 2 at 24-25. Three months later, FDA denied Abbott's request for a meeting to discuss the study and provided no written or oral feedback on the study. *See id.*, Tab 2 at 36. In January 2003, FDA wrote to Abbott stating that, based on Study M02-417, it would incorporate into its BE methodology a statistical baseline correction for endogenous T4 levels. *See id.* at 14. Again, no mention was made of this design issue. At a February 2003 meeting with FDA officials and a March 2003 advisory committee meeting in which Abbott's study was discussed, none of the agency participants raised this as an issue. *See id.* at 14-15, 16-17.

In practice, generics must be formulated to be much closer to the reference product to meet the agency's statistical criteria. That is because FDA always requires that a 90 percent confidence interval for the relative bioavailability must fall entirely within the acceptance limits. If any part of the interval falls outside the 80 to 125 percent limits, the generic "fails" bioequivalence. Thus, if the BE data are highly variable, the confidence interval will be wide, and it may be difficult to fit the entire interval within the acceptance limits. If, however, the data developed in the study are less variable, the confidence interval will be narrow and easier to fit within the acceptance limits. The less variable the data, the narrower the interval and, in turn, the more that the generic drug can differ from the reference product and still fit within the acceptance limits. See Supp. (Apr. 15, 2004), Tab C at 8.

1. *Argument and evidence*

Abbott presented this well-established paradigm to FDA in the context of levothyroxine products. Without baseline correction, data developed in a BE study of levothyroxine products tend to show very low variability (compared with most other drugs). See Petition at 8-13. This would allow a generic product that differs significantly from the brand-name product to be considered equivalent. See *id.* at 11-12. With baseline correction, the variability of the data increases, but not enough to adequately protect against a "false positive" declaration of equivalence. See *id.* at 12-13. 11

In support of this argument, Abbott presented the results of a simulation study conducted by Thomas M. Ludden, Ph.D. See *id.* at 8-11, Tab 13. Dr. Ludden showed that, even with baseline correction, a generic product that delivers 12.5 percent more (or less) levothyroxine than a listed drug would have a 62 (or 52) percent chance of being declared bioequivalent. See *id.* at 13.

11 FDA asserts that in challenging the statistical criteria for bioequivalence, Abbott and Jones "implicitly challenge FDA's statistical analysis for their own [new drug applications]." FDA Response at 20. That is, Abbott and King are arguing for standards that the agency believes neither company could meet. This is pure speculation on the part of the agency. How Abbott would have formulated, manufactured, or tested its product – had a different analytical standard been in place at the time – is unknown. The relevant point is that Abbott and, presumably, Jones, followed and met the agency's recommendations for levothyroxine new drug applications as set forth in the agency's final guidance, *Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing*. Once again, the agency is looking in the wrong place; the agency should be concerned about whether its methodology is sound, and whether it ensures equivalence between generic and innovator products. Looking back at approved NDAs, to see how they would stack up now, is an idle and speculative exercise.

In addition, Abbott submitted a declaration from Walter W. Hauck, Ph.D. *See* Supp. (Apr. 15, 2004), Tab C. Dr. Hauck demonstrated, using baseline-corrected data, that a generic levothyroxine product that differs in bioavailability by 15 percent or more from the brand-name product could still be declared bioequivalent. *See id.*, Tab C at 8-9. Dr. Hauck used baseline corrected data, and data on levothyroxine intra-subject variability, to show how – as a mathematical matter – a test product that actually releases 15 percent more (or less) levothyroxine in the body could easily “pass” as bioequivalent under an 80-125 acceptance range. *See id.* While a 15 percent difference may be tolerable for most drugs, it is not tolerable for levothyroxine therapy. *See, e.g.*, Petition at 23-28; Supp. (Feb. 9, 2004), Tabs A-D.

2. *FDA’s response*

FDA recognized in its response that variability is relatively low (and would lead to narrow confidence intervals) when the levothyroxine data are not corrected to account for endogenous T4. *See* FDA Response at 18. However, when the data is corrected, the agency found that “the intrasubject variability of levothyroxine sodium is higher and is similar to that for other approved drug products. Thus, baseline correction *adequately addresses the potential problem of intrasubject variability.*” *Id.* (emphasis added).

This conclusion is unsupported by any evidence or analysis. The idea that levothyroxine data can be made to look similar to that of other approved drugs does not resolve the issue. Levothyroxine requires precise dosing in a way that distinguishes it from most other drugs. *See* Petition at 4-5; *id.*, Tab 7 at 262. As a result, allowable differences between generic and reference drugs for most other products would be clinically significant when applied to levothyroxine. *See, e.g., id.* at 23-28. The assertion that baseline correction “adequately addresses” the issue is, at best, hopeful guesswork on the part of the agency. There certainly were no facts put forth by the agency to support its conclusion.

Moreover, FDA failed to mention or address Dr. Hauck's analysis. Dr. Hauck showed that even with baseline-corrected data, a generic product with a mean bioavailability of *15 percent more (or less)* than the mean bioavailability of the brand-name product could still be deemed bioequivalent by FDA. *See* Supp. (Apr. 15, 2004), Tab C at 8-9. This is purely a function of the statistical criteria, which allows for such differences, and which reflects the general finding that such differences are clinically acceptable for most drug products.

FDA's next argument is the assertion – made repeatedly in the petition response – that “other information” can help ensure that significantly different products will not be approved. *See* FDA Response at 7, 17, 20 n.13, 22-24, 27. For example, FDA argued that it is unlikely that a generic product would differ in bioavailability from a brand-name product by 15 percent because levothyroxine formulations tend to dissolve fully and efficiently. *See id.* at 22-24. In support of this point, FDA compared the bioavailability of approved levothyroxine products to an oral solution. *See id.* at 23. The agency stated that this comparison demonstrated that these products all dissolve rapidly and completely, and thus are unlikely to raise BE issues. *See id.* at 24.

In fact, the formulations of the approved products were shown to be quite different from each other. *See id.* at 23. Some of the approved products were shown to be within 1 percent of a solution (with respect to AUC), while others (including the market leader, Synthroid®) were shown to be within 6 or 7 percent of the solution. *See id.* The formulations also differed widely with respect to the peak levels reached in the body (C_{max}). *See id.* Some were shown to be within 1 percent of a solution, while others attained levels that were 7, 9, and 16 percent less than solution. *See id.*

Even more, FDA's showing is based on *uncorrected data*.¹² This means that the agency is underestimating the true differences among the products. It is remarkable that FDA would rely on such data when, only 9 pages earlier, the agency explained the perils of making judgments based on uncorrected data:

[T]he presence of endogenous T4 biases the results of a bioequivalence comparison in favor of demonstrating equivalence. When baseline levels are included in these comparisons, the difference in T4 that is attributable to the difference between the two drug products is a smaller percentage of the total measured difference in T4. When baseline levels are subtracted from the data, however, the same difference in T4 that is attributable to the difference between the two drug products becomes a much larger percentage of the bioequivalence comparison.

Id. at 13-14 (emphasis added).

¹² *See* Approval Packages for Levothyroxine Sodium Tablets (USP) (*see* Petition, Tab 11), Levoxyl®, Levo-T®, Novothyrox®, Synthroid®, ThyroTabs®, and Levolet®.

FDA gives the impression that most levothyroxine tablet products tend to be equivalent to solution – within "3 percent" on average (FDA Response at 23). Again, this is misleading and flawed, because the agency is relying on data that are "biased" in favor of showing equivalence. *Id.* at 13; *see also id.* at 14 (showing that what appears to be a 1 percent difference among levothyroxine products is, more likely, a 10 percent difference).

With baseline correction, it is apparent that different levothyroxine formulations, made by different manufacturers, do tend to behave differently inside the body. The agency reached the opposite conclusion based on an analysis that, only a few pages earlier in the FDA Response, was shown to be erroneous. 13/

Finally, along this line, FDA argued that it has CMC information, and *in vitro* dissolution data, that helps to ensure that generic products that differ in potency by 9, 12, or 15 percent will not be approved. *See* FDA Response at 17, 20 n.13, 27. This information, however, is not a substitute for a valid *in vivo* BE method. For example, as noted above, Abbott showed that in a BE study comparing the first approved levothyroxine generic product to Unithroid®, the test product was found in one study to be *8 percent less bioavailable* than the reference product. *See* Petition, Tab 11 at 479; Supp. (Apr. 15, 2004) at 7. At the same time, the potency of the Mylan test drug was, according to CMC data, *nearly 5 percent higher* than the potency of the brand-name product. *See* Petition, Tab 11 at 373; Supp. (Apr. 15, 2004) at 7. Clearly, the *in vitro* analysis and specifications did not correlate with the *in vivo* performance. FDA offered no response to this concrete example.

* * *

The threshold for review of a petition for reconsideration is a showing that "relevant information or views contained in the administrative record were not previously or adequately considered." 21 CFR 10.33(d)(1). For each of the above issues, FDA ignored or inadequately responded to decisive evidence.

13 FDA notes, correctly, that there is no right in the citizen petition process to have the evidence discussed in a public meeting, and no person is guaranteed the right to have scientific disputes heard by an advisory committee. FDA Response at 29-32. However, the issue presented in the text is yet another example of why such a meeting should have been held in this instance. On technical scientific issues such as this, the petition process is not a substitute for in-person dialogue. We also note the claim in the FDA Response that Abbott "had the opportunity to discuss the results of its Study M02-417 at the March 13, 2003, advisory committee meeting." FDA Response at 30. With whom? Several days before the meeting, FDA instructed the advisory committee members that Abbott's study "*is not a topic for discussion at this ACPS meeting.*" Petition at 16.

On clinical issues, FDA failed to quantify what would represent a medically "significant difference" between levothyroxine products. Instead, it argued that, on average, most generics do not differ from the brand by more than 3.5 percent. In actuality, many generics, including the first generic levothyroxine product, may differ in bioavailability by 8 percent or more. In addition, the agency's argument is misdirected; it does not in any way show that FDA would "fail" a generic levothyroxine products that differs from the brand by 9 percent or more.

As to study design issues, the agency never responded to Abbott's assay data, to the fact that the doses used in Abbott's challenge study were well above normal therapeutic doses, and that – with baseline correction – the justification for a 600 mcg dose is no longer compelling. The agency also failed to explain why, in light of its apparent concerns about test doses below 600 mcg, it accepted a BE study with a 500 mcg dose from a generic sponsor

With respect to statistical issues, even with baseline corrected data, a generic levothyroxine product that differs in bioavailability from the brand-name product by 9, 12, or 15 percent may still "pass" as bioequivalent, absent a change to a more exacting statistical test. The agency argued that, given the nature of levothyroxine formulations, such a result is unlikely. However, the agency's primary support for this argument is based on *uncorrected* data, which tends to mask differences between products. Finally, FDA did not show how dissolution, formulation, and CMC data would prevent a "false positive" result. *In vivo* BE studies represent the "gold standard." In light of the agency's response, it is difficult to understand the purpose of requiring an *in vivo* study, especially one that could not detect a clinically significant difference.

III. THE PETITION IS SUBMITTED IN GOOD FAITH

This petition for reconsideration is not frivolous and is submitted in good faith. 21 CFR 10.33(d)(2). It is being submitted because, as shown above, the agency failed to consider relevant evidence, misstated key arguments, and incorrectly accused Abbott of having misrepresented the contents of a confidential document. In addition, it is being submitted because of the outcry by clinicians about the process that led to the recent generic drug approvals and the questions that have been raised about the science that supports the approval decisions.

At all times during this process, Abbott has acted in good faith. Abbott cooperated fully with the agency's recommendation to initiate a petition process and Abbott has responded to all comments on the petition in a timely way. *See generally* Petition at 8-14 and related supplements. Abbott is now requesting reconsideration

of the evidence, in good faith, in an effort to obtain a consensus standard for ensuring the substitutability of levothyroxine tablet products.

IV. PUBLIC POLICY SUPPORTS RECONSIDERATION

A petition for reconsideration must also be supported by “sound public policy grounds.” 21 CFR 10.33(d)(3). Ensuring that generic levothyroxine products are substitutable for brand-name products is critical from a public policy standpoint. Levothyroxine is a narrow therapeutic range drug that must be precisely dosed and titrated for each patient. *See* Petition, Tab 7 at 262; *see also* Supp. (June 4, 2004) at 2-4. Small differences among products may result in serious adverse events or therapeutic failures. *See* Petition at 23-28; Supp. (Feb. 9, 2004), Tabs A-D; Supp. (June 4, 2004) at 4-6.

Whether generic levothyroxine products are truly substitutable under FDA’s methodology has been the fundamental concern of the leading endocrinology organizations. *See* Petition, Tab 21; Letter to J. Woodcock from ATA (Oct. 1, 2003) (posted to the docket on Nov. 3, 2003); *see also* Tabs A-D. These organizations requested an FDA workshop and were assured that the agency was “committed to plan and hold a workshop of sufficient depth and duration . . . to address all of the relevant issues . . .” *See* Supp. (Dec. 22, 2003), Tab A. FDA has now approved an array of “therapeutically equivalent” levothyroxine products, without holding a public workshop or otherwise addressing the concerns of these organizations.

In an extraordinary move, the three organizations jointly issued a statement immediately following issuance of the FDA Response. *See* Tabs A and B. A statement from a related patient advocacy group is also raising concerns about the potential for “dangerous health problems” as a result of the FDA’s action. Tab D. Thus, instead of alleviating concerns raised by clinicians and instilling confidence in FDA’s decision, the FDA Response has had the opposite effect.

As a matter of public policy, the agency must grant reconsideration, to address the concerns that have been raised and to restore confidence among clinicians and thyroid patients. As the agency has recognized, if FDA’s “customers” – *i.e.*, clinicians, patients, and pharmacists – are not satisfied with the agency’s approval of generic drugs, “you can’t build confidence and generate trust” in that process. Petition, Tab 5 at 207-208, 210. In this instance, it is evident that confidence and trust in the agency has been compromised.

V. RECONSIDERATION IS NOT OUTWEIGHED BY PUBLIC HEALTH OR OTHER PUBLIC INTERESTS

Finally, reconsideration must not be outweighed by “public health or other public interests.” 21 CFR 10.33(d)(4). We recognize that the Drug Price Competition and Patent Term Restoration Act (the “Hatch-Waxman Act”) was intended to increase the availability of lower cost generic drugs. However, for this system to work, the science supporting the approval of the generic products must be sound and credible. While the availability of lower cost generic drugs is certainly an important public interest, ensuring that those drugs are truly substitutable for brand-name products is likewise paramount.

If clinicians continue to question the credibility of FDA’s levothyroxine BE methodology, and perceive that brand-name levothyroxine products are not truly substitutable, switching to generic levothyroxine will create additional costs beyond the price of the drugs themselves. To ensure that patient health will not be jeopardized, patients may be forced to undergo additional testing and more constant monitoring, as well as possible re-titration of the dose. Patients, who are switched to a generic product may suffer even greater costs if adverse events occur before preventative measures can be taken.

VI. CONCLUSION

For the foregoing reasons, reconsideration under 21 CFR 10.33 must be granted. Major substantive arguments and evidence, presented in good faith, have not adequately been addressed by the agency. As a result, pointed questions are being raised by leading clinicians as to the science and process used to support the approval of generic levothyroxine products.

To address the public’s profound interest in this matter, we ask the agency to reconsider its June 23, 2004, decision, reexamine the evidence, and promptly convene a public meeting to obtain the input of the country’s leading experts on thyroid disease.

Respectfully submitted,



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