

HOGAN & HARTSON

L.L.P.

DAVID M. FOX
PARTNER
(202) 637-5678
DMFOX@HHLAW.COM

COLUMBIA SQUARE
555 THIRTEENTH STREET, NW
WASHINGTON, DC 20004-1109
TEL (202) 637-5600
FAX (202) 637-5910
WWW.HHLAW.COM

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BY HAND DELIVERY

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

**Re: Docket No. 03P-0387
Supplement to Citizen Petition**

Dear Sir or Madam:

On behalf of Abbott Laboratories ("Abbott"), we submit the following supplement under 21 CFR 10.30(g) to the above-referenced citizen petition (the "Petition"). We are submitting this supplement within the time frame set forth in our Notice of Intent to Respond to Comments, dated April 28, 2004.

In this document, we first respond to comments by Frederic J. Cohen, M.D., submitted to the Food and Drug Administration ("FDA") on April 14, 2004 (the "Comment").¹ Dr. Cohen argues that levothyroxine sodium is not a narrow therapeutic index ("NTI") drug for which precise dosing is essential, and challenges the interpretation of Abbott's simulation study and bioequivalence challenge study. *See infra* section I.

Second, we respond to a March 31, 2004, amendment to a citizen petition submitted by Jerome Stevens Pharmaceuticals ("JSP"). *See* Docket No. 04P-0061. JSP's amendment raises two issues relevant to Abbott's Petition that warrant a response. As part of our response, we also are amending our Petition's request for relief by seeking a determination that sponsors may seek therapeutic equivalence ("TE") ratings *only* through the submission of an abbreviated new drug

¹ These comments were not made available to the public until on or about April 27, 2004.

03P-0387

SUP 7

application (“ANDA”) under section 505(j) of the Food, Drug, and Cosmetic Act (“FDCA”). As discussed below, Abbott believes that FDA lacks the authority to grant such ratings through the submission of applications or supplements under section 505(b)(2) of the FDCA. *See infra* section II.

Finally, we present an analysis of the April 14, 2004, meeting of the Advisory Committee for Pharmaceutical Science (“ACPS”). At this meeting, FDA proposed revising its standard bioequivalence (“BE”) methodology for highly variable drugs. The scheduling of this meeting, and the statistical and clinical issues discussed there, strongly support the arguments raised in the Petition. *See infra* section III.

Abbott again requests that FDA refer the issues raised in the Petition to an advisory committee or similar expert panel. We also urge the agency to refrain from approving any further applications (or supplements) that rely on BE data until a valid methodology has been established. As shown below, a persuasive argument against Abbott’s fundamental position – that FDA lacks in this instance a scientifically valid BE methodology – has yet to be presented.

I. RESPONSE TO THE COHEN COMMENTS

On behalf of an unnamed pharmaceutical company, Dr. Cohen makes three arguments: (1) Levothyroxine is not an NTI drug; (2) small differences in the dose of levothyroxine do not pose serious clinical risks; and (3) Abbott’s simulation and clinical studies cannot be applied to other levothyroxine products. *See* Comment at 3-7. Each of these arguments ignores and, moreover, defies extensive evidence described thus far in this proceeding – much of it developed by FDA itself.

A. FDA and Leading Clinical Experts Have Concluded That Levothyroxine is a Narrow Therapeutic Index Drug

The argument that “there is very little direct evidence” that the dose of levothyroxine must be maintained within a narrow range, Comment at 3, is belied by FDA’s own findings and by the overwhelming opinion of the nation’s leading endocrinologists:

- “This guidance defines *narrow therapeutic range* drug products as containing certain drug substances subject to therapeutic drug

concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation.”²

- “Levothyroxine has a *narrow therapeutic index*. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under-treatment.”³
- “Levothyroxine sodium is a compound with a *narrow therapeutic range*.”⁴
- “In order to allow for fine adjustments of dose, which are necessary due to levothyroxine sodium’s *narrow therapeutic range*, levothyroxine sodium products are marketed in an unusually large number of dosage strengths.”⁵
- “Because of levothyroxine sodium’s *narrow therapeutic index*, it is particularly important that the amount of available active drug be consistent for a given tablet strength.”⁶
- “Synthroid (levothyroxine) . . . require[s] individualized titration of the dose prescribed and *very careful dosing in order to avoid serious and potentially life-threatening side effects*.”⁷

² Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* 20 (Mar. 2003) (emphasis original and footnote omitted).

³ Synthroid® Approved Labeling, *Precautions* (2002) (emphasis added).

⁴ Guidance for Industry: *Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* 2 (Feb. 2001) (emphasis added).

⁵ Citizen Petition Response, Docket No. 97N-0314/CP2 (Apr. 26, 2001), at 8 (emphasis added) (“Knoll Petition Response”).

⁶ 62 FR 43535, 43538 (Aug. 14, 1997) (emphasis added).

⁷ Supplement to Petition (Feb. 9, 2004), Tab E (FDA Press Release, *Recent FDA/U.S. Customs Import Blitz Exams Continue to Reveal Potentially Dangerous Illegally Imported Drug Shipments* (Jan. 27, 2004)) (emphasis added).

- “Because levothyroxine has a *narrow therapeutic range*, small differences in absorption can result in subclinical or clinical hypothyroidism or hyperthyroidism.”⁸
- “Levothyroxine has a *narrow toxic-to-therapeutic ratio*: The body is very sensitive to even small changes in thyroid hormone levels. Thus, optimal titration of thyroid hormone dosage is critical.”⁹

Dr. Cohen presents no evidence that would call into question these categorical statements.¹⁰ In fact, Dr. Cohen appears to have missed the relevant clinical and scientific point; levothyroxine patients must be maintained within the narrow range to which they have been titrated. Generic products approved as interchangeable must be shown to keep patients within this narrow range; otherwise, as FDA has concluded, patients will be exposed to serious side effects.

B. FDA and Leading Clinical Experts Have Concluded That Small Differences in the Dose of Levothyroxine Pose Clinical Risks

Dr. Cohen next argues that there is “no scientific evidence to support the assertion that very small changes in dosing, of the magnitude described by the Petitioners, . . . poses serious health risks, or, in fact, any health risks at all.” Comment at 7. To the contrary, the record in this proceeding includes extensive and unrebutted evidence of the need for precise dosing of levothyroxine, from dose-to-dose and from refill-to-refill, to avoid serious health risks.

Once again, much of this evidence was developed by FDA itself, in support of its decision to regulate levothyroxine products as “new drugs” under the FDCA. For example, in its August 14, 1997, *Federal Register* notice, FDA cited 58

⁸ American Association of Clinical Endocrinologists, *Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism*, 8 Endocrine Practice 457, 464 (2002) (emphasis added) (attached at Tab A).

⁹ Supplement to Petition (Feb. 9, 2004), Tab A (Declaration of Jerome M. Hershman, M.D.), at ¶ 21 (emphasis added). Dr. Hershman is past president of the American Thyroid Association.

¹⁰ Dr. Cohen quotes portions of a Health Canada Expert Advisory Committee on Bioavailability and Bioequivalence meeting for the proposition that levothyroxine is not a narrow therapeutic range drug. He omits, however, the Committee’s conclusion in the same discussion that “levothyroxine is a critical dose drug.” Record of Proceedings (Apr. 16, 2003), at 2 (attached at Tab B).

adverse event reports associated with the potency of levothyroxine products. *See* 62 FR at 43536. Hypothyroid symptoms included severe depression, constipation, and edema. Hyperthyroid symptoms included atrial fibrillation, heart palpitations, and difficulty sleeping. *See id.* Nearly half of these events occurred when patients received refills of products on which they previously had been stable. *See* Petition, Tab 5, at 194.

The agency collected additional evidence of “serious clinical problems.” 62 FR at 43536. In its *Federal Register* notice, FDA stated that several physicians had reported that their patients had developed thyroid toxicity, including atrial fibrillation, after receiving refills of products later determined to possess increased potency. *See id.* Ultimately, the agency concluded:

If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on one product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmias. In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous.

Id.

Several years later, in its response to the citizen petition on the regulatory status of Synthroid®, FDA reiterated the “safety risks” caused by super- or sub-potent levothyroxine products, including angina, tachycardia, arrhythmia, depression, arthralgia, and paresthesias. Knoll Petition Response at 8. The agency also prepared a confidential analysis illustrating why even a nine percent difference between levothyroxine products poses a health risk. *See* Petition at 24-25. According to FDA’s analysis, patients may suffer serious consequences if, with each levothyroxine refill, they receive a different dose than the one to which they have been carefully titrated. *See id.*

Dr. Cohen questions the agency’s conclusion that serious health consequences may result from differences in dose of as little as nine percent, comparing this to missing a single dose during a week of therapy. *See* Comment at 6. This comparison neglects, however, that most patients take levothyroxine on a long-term, chronic basis. *See* Synthroid® Approved Labeling, *Precautions*. A

patient taking a dose different than the one to which he or she has been titrated will be exposed to this difference not once, but as long as the product is taken.¹¹ See 62 FR at 43536; Knoll Petition Response at 8.

In addition to the evidence collected by FDA, Abbott has submitted to the docket the testimony of the numerous clinical experts who testified during the March 13, 2003, ACPS meeting. See Petition at 25-27, Tab 5, at 178-89. These clinicians, including representatives from the American Association of Clinical Endocrinologists, the American Thyroid Association, The Endocrine Society, and the Thyroid Foundation of America, all testified to the sensitivity of patients to fine differences in the dose of levothyroxine products. See *id.*

More recently, Abbott submitted four declarations from several of the nation's leading endocrinologists. See Supplement to Petition (Feb. 9, 2004). Each supports the fact that small differences in the dose of levothyroxine can have clinically significant effects. For example, Dr. Jerome Hershman stated that:

[L]evothyroxine has a narrow therapeutic-to-toxic ratio: Differences in dosages of as little as 12.5% can alter the patient's serum [thyroid stimulating hormone, or "TSH"] levels, which may result in medical consequences for the patient. Indeed, in my clinical experience, even differences in dosages of as little as 9% (*e.g.*, the difference between 137 and 150 mcg of levothyroxine) can have clinically significant effects on a patient's serum TSH levels.

Id., Tab A (Declaration of Dr. Jerome Hershman), at ¶ 25.

The evidence in the record of this proceeding is overwhelming: Levothyroxine patients must be maintained at the dose to which they have been titrated. Just as FDA previously took steps to ensure the consistent potency of levothyroxine products, it must now ensure that "bioequivalent" levothyroxine products are interchangeable, without the need for any retesting or retitration.

¹¹ This problem would be exacerbated by the approval of multiple generic products referencing a single brand name levothyroxine product, where patients could be switched repeatedly among a variety of generic products of varying potency, each time the patients' prescriptions were refilled.

C. Abbott's Simulation and Clinical Studies Conclusively Demonstrate the Inadequacy of FDA's BE Methodology

Finally, Dr. Cohen argues that Abbott has "over-interpreted" the results of the simulation study (performed by Thomas M. Ludden, Ph.D.) and the bioequivalence challenge study (Study M02-417) to reach the conclusion that FDA's BE methodology cannot detect significant differences between levothyroxine products. Comment at 7. As shown below, Abbott's studies were well conducted and can readily be extrapolated to other levothyroxine formulations and products.

1. Abbott's Simulation and Challenge Studies

Dr. Cohen asserts that Abbott cannot generalize the results of its simulation study, because the study relied solely on data from Abbott's bioavailability ("BA") studies. Comment at 7 ("Presumably, then, the conclusions are valid only for theoretical test products that are compared with Abbott's reference product (since the variability characteristics of other test or reference products cannot be assumed to be identical to Abbott's reference product)."¹² Even if Dr. Cohen were correct (and he is not), he has conceded the issue as to sponsors seeking to show equivalence to Synthroid®. That is, according to Dr. Cohen, Abbott's analysis raises significant questions about any test product purported to be equivalent to Synthroid®.

In fact, Abbott's data and analysis have far broader applicability. FDA, for example, recognized the breadth of Abbott's findings when the agency reversed its prior position and began recommending – based on Study M02-417 – the use of baseline correction for *all* levothyroxine BE studies. See Petition at 14, 17, Tab 5, at 198.

Dr. Cohen also states that the "simulation results can't be generalized to an actual BE comparison of two products of different stated molar dose (not different *delivered* dose)." Comment at 11 (emphasis original). The meaning of this statement is unclear, because the relevant consideration in an actual BE study is delivered dose, not stated molar dose.

¹² Dr. Cohen also states that "the Petitioners did not make this study available for general review . . ." Comment at 7. This is incorrect. Abbott made the simulation study publicly available, including the full technical report and all software code and output. See Petition, Tab 13.

In any event, Abbott's simulation study, based on the BA (delivered dose) data from previous clinical studies, was used to develop predictions of how likely it is that two levothyroxine products that deliver different amounts of drug would be declared equivalent. For example, Abbott's simulation predicted that a test product that delivers 15 percent less (or more) levothyroxine than a reference product would have a 26 (or 42) percent chance of being declared equivalent to that reference product. See Petition at 9, Tab 13, at 612. Abbott then confirmed these predictions in Study M02-417, where different stated doses of levothyroxine were used to ensure different delivered doses, as a means of challenging the ability of FDA's methodology to distinguish significantly different products. In all other respects, the study was identical to a traditional BE study.¹³

Taken together, the simulation study (based on data from the most widely prescribed levothyroxine product) and Study M02-417 present an evidence-based challenge to the current levothyroxine BE methodology. Thus far, no one – including Dr. Cohen – has presented any evidence that would call Abbott's analysis into question. If such evidence has been presented to FDA, it should be included in the record of this proceeding and made available for comment.

2. Dr. Cohen's "Other Factors" Argument

Dr. Cohen next states that "FDA always considers factors other than relative BA comparability" to find products equivalent, including *in vitro* potency, stability, and dissolution testing. Comment at 8. In fact, Dr. Cohen states that "FDA relies on [these] key sources of product data . . . regardless of the outcome of a BA study." *Id.* at 11 (emphasis added).

As discussed in Abbott's previous supplement, the additional factors cited by Dr. Cohen *cannot* assure equivalence inside the body. See Supplement to Petition (Apr. 15, 2004), at 5-8. Even when two products are pharmaceutically equivalent, they may release different amounts of drug at different rates, because of differences in particle size, excipients, manufacturing process, equipment, and even

¹³ Dr. Cohen acknowledges that a "qualified expert," Ronald J. Sawchuk, Ph.D., reviewed Abbott's simulation study and found it to be "well-designed." Comment at 7. In fact, Dr. Sawchuk found that the study was "exceptionally well-performed" and "accurately assessed the likelihood that different doses (or products with different bioavailability) of levothyroxine would be bioequivalent . . ." Supplement to Petition (Feb. 25, 2004), Tab A (Declaration of Dr. Ronald Sawchuk), at ¶ 23; see also *id.* at ¶¶ 25, 29. This declaration remains unrebutted in this proceeding.

batch size. *See id.* at 6; *see also* ACPS Transcript (Nov. 16, 2000), at 16, 18 (at www.fda.gov/ohrms/dockets/ac/00/transcripts/3657t2.pdf) (statement of Ajaz S. Hussain, Ph.D., then Acting Director of the Office of Pharmaceutical Science's Office of Testing and Research). Abbott provided in its previous supplement two examples where *in vitro* testing was *not* an accurate predictor of *in vivo* levothyroxine bioavailability. *See* Supplement to Petition (Apr. 15, 2004), at 7.

Since that supplement, FDA has reiterated that *in vitro* testing is insufficient to assure therapeutic equivalence. On April 20, 2004, FDA sent a letter to the New Hampshire Pharmacists Association, objecting to the purchase of prescription drugs from Canada (attached at Tab C). According to the agency:

Chemical laboratory analysis of a drug product is not sufficient to demonstrate interchangeability with a U.S. approved product Although chemical analysis can show whether the active ingredient is present and in what amount, as described above, *even the slightest change in the manufacturing process, or different types or amounts of inactive ingredients, can affect interchangeability*, yet not be apparent through simple chemical analysis.

Id. (emphasis added). Contrary to Dr. Cohen, FDA concluded that only an adequate *in vivo* methodology, in *addition* to a demonstration of pharmaceutical equivalence, "can support a finding that two drugs are therapeutically interchangeable." *Id.*

In short, Dr. Cohen is incorrect when he asserts that FDA can and should make BE determinations "*regardless of the outcome of a BA study.*" Comment at 11 (emphasis added). For levothyroxine products, a BE study is pivotal and, as such, the study must have the sensitivity needed to detect clinically relevant differences between products.

3. FDA's Survey Data

Finally, Dr. Cohen cites in support of his arguments two FDA surveys demonstrating that the mean observed difference between generic and reference products is approximately ± 3.5 percent. *See* Comment at 10; *see also* Petition at 36 n.32, Tab 24. These surveys, however, included all products approved during given time periods, including those with high intra-subject variability. As discussed below, products with high variability must be very closely matched in BA in order to pass FDA's 80 to 125 percent acceptance range. *See infra* section III; *see also*

Petition at 20-21, 36-37; Supplement to Petition (Apr. 15, 2004), Tab C (Declaration of Walter W. Hauck, Ph.D.), at ¶ 23. These survey results, presented in the aggregate, thus do not reflect the differences between specific products with *lower* intra-subject variability, which can pass as equivalent with greater – and clinically significant – differences in BA.

In addition, these surveys are based on comparisons of the mean BE measurements only, rather than on the confidence intervals around those means. As stated by the Director of FDA's Division of Bioequivalence, "you have to really look at [such point estimates] very carefully because . . . *that isn't the true mean of the product*. That is simply an estimate of the center of the data in your small sample of the universe." ACPS Transcript at 141 (Apr. 14, 2004) (at www.fda.gov/ohrms/dockets/ac/04/transcripts/4034T2.pdf) (emphasis added) ("Transcript"). In other words, only the confidence intervals around those mean measurements should be considered in evaluating the true differences between products. See Supplement to Petition (Apr. 15, 2004), Tab C (Declaration of Dr. Walter Hauck), at ¶¶ 17-18.

* * *

Abbott's simulation and clinical studies conclusively demonstrate that FDA's current BE methodology cannot detect clinically significant differences between levothyroxine products. No amount of *in vitro* testing can assure therapeutic equivalence, when the applicable *in vivo* methodology is itself incapable of distinguishing among products known to deliver significantly different amounts of levothyroxine.

II. RESPONSE TO THE PETITION AMENDMENT

On February 10, 2004, JSP submitted to FDA a citizen petition, requesting that FDA: (1) Issue guidance for ANDAs for levothyroxine products; (2) not approve any ANDAs that fail to conform to the standards established for new drug applications ("NDAs"); and (3) withdraw approval of Mylan Pharmaceuticals' ("Mylan's") ANDA 76-187. On March 31, 2004, JSP amended its request that FDA withdraw Mylan's ANDA, "because the approval was based on a pre-NDA sample of [JSP's] Unithroid." Amendment to Petition, Docket No. 04P-0061, at 1 ("JSP Petition Amendment").

Two relevant issues emerge from JSP's amendment. First, JSP discloses that it sought to show that Unithroid is therapeutically equivalent to

Division of Dockets Management

June 4, 2004

Page 11

Synthroid® using pre-NDA reference material. Abbott raised with FDA nearly two years ago the issue of whether sponsors may demonstrate equivalence using pre-NDA levothyroxine. The agency informed Abbott in November 2002 that only post-NDA levothyroxine may be used in BE studies. That decision should control here.

Second, JSP attempted to demonstrate the TE of Unithroid to Synthroid® through a supplement to its NDA. Abbott's view is that FDA does not have the authority to assign TE ratings through applications (or supplements) submitted under section 505(b)(2) of the FDCA. Abbott raised this issue with FDA nearly two years ago, as well; the agency has yet to respond. We therefore must re-raise the issue here (and amend Abbott's request for relief accordingly).

A. FDA May Not Accept Pre-NDA Samples of Synthroid® as the Reference Material in BE Studies

In its amendment, JSP details its attempt to obtain an "AB" rating to Synthroid® through a supplement to its approved NDA. See JSP Petition Amendment, Tab A, at 1-2. The agency refused to file JSP's supplement because the sponsor's BE studies were conducted with pre-NDA Synthroid®. By analogy, JSP now argues that Mylan's ANDA must be withdrawn, because it used a pre-NDA sample of Unithroid in *its* BE studies. See *id.* at 2.

In refusing to file JSP's supplement, FDA stated that its regulations require the reference material in a BE study to be "appropriate." See JSP Petition Amendment at 6, Tab A, at 3; see also 21 CFR 320.25(c). That is, the material "should be taken from a current batch of a drug product that is the *subject of an approved new drug application . . .*" 21 CFR 320.25(e)(3) (emphasis added). In addition, FDA stated that because pre-NDA levothyroxine products were released with overages of varying sizes, test products found to be equivalent to pre-NDA reference products may not be pharmaceutically equivalent to post-NDA products. See JSP Amended Petition at 6, Tab A, at 3.14

¹⁴ JSP also alleges that post-NDA Synthroid® contains a stability overage. See JSP Petition Amendment at 2. This is incorrect. As required by FDA, Synthroid® is targeted for release at 100 percent of its labeled strength. See *id.*, Tab A, at 3 ("The Agency noted that stability overages are not allowed for any of the approved levothyroxine products."); see also Guidance for Industry: *Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications* 6 (July 2001).

HOGAN & HARTSON L.L.P.

Division of Dockets Management

June 4, 2004

Page 12

In July 2002, Abbott wrote to FDA to inquire generally about this issue. In its letter, Abbott presented several reasons why a BE study using pre-NDA Synthroid® could not, as a matter of law, be used to support marketing approval or the assignment of a TE rating. On November 26, 2002, FDA agreed:

The Office of Generic Drugs agrees with your conclusion that it would be inappropriate for FDA to accept any BE study that used the previous, unapproved version of Synthroid® tablets as the reference products in such a study. Therefore, FDA would not expect to assign an "AB" therapeutic equivalence code to an already approved 505(b)(2) application for levothyroxine sodium tablets that used the previous version of Synthroid® tablets in its study. Neither would FDA accept an abbreviated new drug application that contains a BE study that used the previous version of Synthroid® tablets.

Letter from Gary J. Buehler, R.Ph. to David M. Fox, at 2 (attached at Tab D).

Abbott only learned of JSP's dispute with FDA regarding the use of pre-NDA Synthroid® with the submission of the JSP Petition Amendment in March 2004. We therefore are placing FDA's November 26, 2002, letter on this issue into the record, to ensure that only NDA-approved levothyroxine products are used as the reference material in BE studies. *See id.*

Also, now that JSP has submitted a citizen petition, it should release all of the materials from its dispute resolution, just as Abbott did in its Petition. *See* Petition, Tabs 2-4, 15, 16, 19. JSP's BE study, for instance, and its arguments in support of a determination of therapeutic equivalence, should be put into public view. Disclosure of this information would be consistent with the principles behind FDA's May 15, 2003, letter to Abbott, requesting that this issue be considered in a public manner. As explained by FDA:

This approach will allow others the opportunity to comment and participate in the decision-making process, will provide [the petitioner] the opportunity to comment publicly on the views and opinions of others, and will establish an administrative record on which the Agency may base any future decisions.

Petition, Tab 1, at 1.

Such disclosure would allow Abbott and others to refine the conclusions reached in the simulation study and Study M02-417. For example, it would help answer the questions raised by Dr. Cohen regarding the extrapolation of Abbott's analysis to other levothyroxine formulations and products. *See supra* section I. It also would provide information on the intra-subject variability of these formulations, and the extent to which baseline correction affected their ability to pass FDA's standard 80 to 125 percent acceptance range. *See* Petition at 20-21, 36-37, Tab 11, at 479.

Accordingly, we have submitted to FDA a Freedom of Information Act request seeking all records relating to JSP's formal dispute resolution (attached at Tab E). We urge FDA to respond promptly to our request, and we urge JSP to voluntarily disclose this material, in order to advance resolution of the scientific issues that are central to this proceeding.

B. FDA Lacks the Authority to Assign TE Ratings through Applications or Supplements Under Section 505(b)(2)

According to JSP, FDA's refusal to file its supplement seeking an "AB" rating to Synthroid®, together with the approval of Mylan's ANDA (also based on pre-NDA reference material), is "the very definition of illegal 'arbitrary' action by FDA . . ." JSP Petition Amendment at 7. Equally problematic, however, is FDA's failure to reject JSP's supplement on the ground that sponsors may seek TE ratings *only* through the submission of ANDAs, not supplements to approved NDAs.

Abbott previously raised this issue with FDA in comments to the joint citizen petition submitted by Pfizer Inc. and Pharmacia Corp. regarding the scope of section 505(b)(2). *See* Comments of Abbott Laboratories, Docket No. 01P-0323 (July 10, 2002) ("Comments to Joint Petition") (attached at Tab F and fully incorporated herein); *see also* Petition at 19 n.19. FDA did not address this issue when it answered the Joint Petition, and JSP's amendment compels us to re-raise it here. We are therefore also amending our pending request for relief, to seek a determination that FDA currently lacks the authority to assign TE ratings outside the scope of section 505(j).

A TE rating represents FDA's judgment whether two products can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. *See Approved Drug Products with Therapeutic Equivalence Evaluations* (24th ed.), at viii (the "Orange Book").

The agency classifies two products as therapeutically equivalent (and assigns "AB" ratings) only if the products are pharmaceutically equivalent and bioequivalent. *See id.* at 1.2.

FDA has not memorialized through notice-and-comment rulemaking its standards for assigning TE ratings. Rather, the agency views its ratings as "unofficial" acts of no legal significance, despite the fact that these ratings are the decisive factor in many states for determining whether one drug product may be substituted for another. Absent notice-and-comment rulemaking, however, FDA's interpretation is defensible only for ANDAs submitted under section 505(j). *See Comments to Joint Petition at 4-8.*

This is so for several reasons. First, an "AB" rating communicates to the public that a product has been determined by FDA to be a therapeutically equivalent generic, and section 505(j) contains the exclusive statutory standard for the approval of such products. State regulators, acting pursuant to state laws, associate "AB" ratings with the "pharmaceutical equivalence" and "bioequivalence" standards contained in section 505(j) of the FDCA. *See id.* at 7.

Second, FDA's argument that TE ratings are of "no legal significance," and therefore not subject to rulemaking, is plausible only when the ratings are applied to products approved under section 505(j). The ratings communicate the findings that FDA is obligated to make under that section, and are thus coextensive with it. In that sense alone, the ratings are "fairly encompassed" within section 505(j). *See Air Transport Ass'n of America, Inc. v. FAA*, 291 F.3d 49, 55-56 (D.C. Cir. 2002). The same cannot be said for products approved under section 505(b)(2). *See Comments to Joint Petition at 7-8.*

Finally, when Congress amended the FDCA in 1984, it incorporated the *Orange Book* into the statute, to facilitate the approval of generic drugs under section 505(j). *See 21 USC 355(j)(7)*. In fact, Congress essentially incorporated the agency's TE standard into section 505(j) as the standard for the approval of generic drugs. *See id.* at 355(j)(2)(A). No parallel foundation exists under section 505(b)(2). To the extent that Congress adopted the agency's TE ratings, it did so only for products approved under section 505(j). *See Comments to Joint Petition at 8.*

Again, as demonstrated in Abbott's comments, FDA's TE ratings have the force and effect of law, in that they have been incorporated into federal and state laws. *See id.* at 9; *see also Tozzi v. Dep't of Health and Human Services*, 271 F.3d 301 (D.C. Cir. 2001) (holding that the Department's listing of chemicals as carcinogens is subject to Administrative Procedure Act review because it triggers binding obligations under federal and state laws). The agency may not, therefore, apply these ratings outside section 505(j) without first engaging in notice-and-comment rulemaking. For this reason, Abbott hereby amends its formal request for relief, to seek a determination that the agency lacks the authority to assign TE ratings outside the scope of section 505(j) of the FDCA. *See* Petition at 3. As applied here, that determination would ensure that JSP cannot continue to seek an "AB" rating to Synthroid® through its 505(b)(2) application.

III. ANALYSIS OF THE ACPS MEETING

On April 14, 2004, FDA convened a meeting of its Advisory Committee for Pharmaceutical Science, to discuss revising the agency's standard methodology for demonstrating the equivalence of highly variable drugs ("HVDs"). Analytically, the issues raised at this ACPS meeting are the mirror image of the issues on which Abbott has sought, for two years, a public meeting and dialogue.

As shown at the meeting, the increased intra-subject variability of HVDs can make it too difficult for sponsors to develop confidence intervals that fall fully within FDA's standard (80 to 125 percent) acceptance range. *See* Transcript at 9, 132-33, 167. By comparison, the lower variability of drugs such as levothyroxine can make it too easy for sponsors to develop confidence intervals that fall within the standard range. *See* Petition at 20-21, 37; Supplement to Petition (Apr. 15, 2004) (Declaration of Dr. Walter Hauck), at ¶¶ 23-30. Thus, clinically equivalent HVD products may *fail* a BE study for precisely the same reason that clinically inequivalent levothyroxine products may improperly *pass* a BE study.

This relationship between intra-subject variability and the likelihood of products passing as bioequivalent was recognized throughout the ACPS meeting:

[I]t is very obvious today that if you have a narrow therapeutic index drug it is *very easy to pass the bioequivalence criteria*, and that is because narrow therapeutic index drugs, by definition, must have *small intra-subject variability*. If this were not true for narrow therapeutic index drugs, patients would routinely experience cycles of

toxicity and lack of efficacy, and therapeutic monitoring would be useless.

Transcript at 64 (emphases added).

In this light, it is remarkable that the agency convened this ACPS meeting without giving any indication as to its position on Abbott's pending request – and the request of the nation's leading endocrinologists – for a substantively equivalent meeting.¹⁵ While FDA maintains discretion in the scheduling of advisory committee meetings, that discretion is not unlimited. The agency's failure to consider relevant factors, or to engage in reasoned decision making, deprives it of the discretion normally due under the law. See *Motor Vehicle Mfrs. Ass'n of the United States v. State Farm Mut. Ins. Co.*, 463 U.S. 29, 52 (1983); *American Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001); see also Supplement to Petition (Apr. 15, 2004), at 9-11; Supplement to Petition (Dec. 22, 2003), at 3-5.

Finally, we note the concern expressed during the ACPS meeting that sponsors rarely support calls for the revision of FDA's BE methodology with data: "Maybe it is just because the data [are] hard to come by but *it disturbs me to this day that most of these discussions are not supported by any kind of scientific support . . .*" Transcript at 146 (emphasis added) (remarks of FDA's Director of the Division of Bioequivalence).¹⁶ To our knowledge, Abbott has put forth the most comprehensive set of data and analysis yet in support of revising the standard BE methodology for a specific product. Abbott has provided FDA with a stochastic simulation study, a clinical study, six declarations from leading experts (including an expert cited by FDA¹⁷), and peer-reviewed literature. See Petition at 8-13;

¹⁵ On May 26, 2004, the American Thyroid Association, The Endocrine Society, and the American Association of Clinical Endocrinologists submitted to FDA yet another letter, expressing the societies' "continuing and heightened concern that FDA has postponed a thoughtful and complete review of information regarding thyroxine therapeutic equivalence." Letter to Steven Galson, M.D. (attached at Tab G) (at www.thyroid.org/professionals/advocacy/04_05_26_fda.html).

¹⁶ See also Letter from Roger L. Williams, M.D., to Carmen A. Catizone (Apr. 16, 1997) (attached at Tab H) ("No clinical data has been submitted to the Agency in the ten plus years since [FDA's Bioequivalence Task Force] hearing that would warrant the Agency narrowing the present confidence interval of 0.80 to 1.25 on any drug or class of drugs.").

Supplements to Petition (Apr. 15, Feb. 25, and Feb. 9, 2004). Abbott also has entered into the record countless statements by FDA on the risks associated with imprecise levothyroxine dosing.

Yet, despite having received an unprecedented amount of data from Abbott, including the results of a well-designed clinical study (now published in a peer-reviewed journal), FDA continues to remain silent as to the scheduling of an appropriate scientific meeting. In light of the ACPS meeting, the issues Abbott has raised clearly warrant expert consideration in an appropriate public meeting. Nor can FDA legitimately argue that it lacks the time or resources to promptly hold a meeting on such issues.

IV. CONCLUSION

During the April 14, 2004, meeting of the Advisory Committee for Pharmaceutical Science, the Director of the Office of Generic Drugs discussed the importance of good science and of bringing these kinds of "difficult scientific issues" before the relevant experts. Transcript at 167. The agency cannot continue to disregard the extraordinary amount of evidence that Abbott has presented, demonstrating the inability of FDA's current BE methodology to detect significant differences between levothyroxine products.

Nor can this citizen petition proceeding take the place of an informed, in-person dialogue between the relevant scientific experts. A series of adversarial submissions to an administrative record simply cannot substitute for a meaningful exchange between the appropriate clinical and biopharmaceutics experts. Rather, FDA should promptly convene an advisory committee or similar scientific meeting, so that these experts may work together to develop an appropriate methodology for demonstrating the bioequivalence of levothyroxine products.

¹⁷ During the meeting, FDA presented a study by Dr. Walter Hauck, which examined the impact of expanding the agency's acceptance range to 70 to 143 percent. See Transcript at 129. Dr. Hauck prepared a declaration on behalf of Abbott. See Supplement to Petition (Apr. 15, 2004), Tab C.

HOGAN & HARTSON L.L.P.

Division of Dockets Management

June 4, 2004

Page 18

As always, we appreciate your attention to this matter.

Sincerely,



David M. Fox
Brian R. McCormick
Hogan & Hartson L.L.P.

Attachments

cc: John M. Leonard, M.D.
Douglas L. Sporn
Neal B. Parker
Abbott Laboratories

Kevin M. Fain
Office of the Chief Counsel, GCF-1

Docket No. 03P-0126

Docket No. 04P-0061