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BY HAND DELIVERY

Dockets Management Branch, HFA-305
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, filed on August 25, 2003 (the "Petition"). The purpose of this filing is to place into the record recent communications between the Food and Drug Administration ("FDA") and the American Thyroid Association ("ATA"). As discussed below, we believe that these communications strongly support Abbott's primary request for relief, as set forth in the Petition. Abbott is also taking this opportunity to respond to the technical comment filed by Sanford Bolton, Ph.D., to the related Docket No. 03P-0126 (citizen petition of Jones Pharma, Inc.).

As demonstrated in the Petition, FDA lacks a scientifically valid method for evaluating the bioequivalence ("BE") of oral levothyroxine sodium drug products. Abbott has presented clinical data showing that FDA's current methodology cannot distinguish among levothyroxine products that differ by 12.5% or more. As shown in the Petition, substitution of two manufacturers' levothyroxine products that differ by 12.5% or more can lead to therapeutic failures. In patients with coronary heart disease, in cancer patients, and in pediatric patients, a small and unexpected difference in dose presents a serious health hazard. Abbott therefore requested in the Petition that the agency refer the issue of levothyroxine

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BE testing to an appropriate advisory committee, and halt the review of generic levothyroxine products until the outstanding BE issues have been resolved.

The communications between FDA and the ATA show that the agency has acknowledged the importance of this matter, and has committed to holding a "workshop" with clinicians on the same analytical and clinical issues that are raised in Abbott's Petition. Tab A (available at www.thyroid.org/professionals/advocacy/03_11_05_fda.html). Abbott's primary request for relief, throughout this entire proceeding,[1] has been for FDA to refer these issues to an appropriate advisory committee, for reasoned consideration before the agency makes any future decisions regarding the bioequivalence of levothyroxine products. Based on the FDA-ATA communications, Abbott's request for a public meeting – as a necessary step in the process of developing a sound levothyroxine BE methodology – becomes even more compelling. The agency would be hard-pressed to justify a denial of Abbott's request when it has already acknowledged to the country's leading endocrinologists that such a meeting is needed.

I. BACKGROUND

As noted in Abbott's Petition, on April 4, 2003, the ATA first wrote to Commissioner McClellan on the issue of levothyroxine bioequivalence. *See* Petition at 27, Tab 21 at 677. In that letter, the ATA expressed its belief that small differences between levothyroxine doses – well within the range of differences that might be undetected with FDA's current BE methodology – can have major clinical implications for thyroid patients. *See id.*

Subsequent to the filing of Abbott's Petition, FDA met with interested clinicians on or about September 16, 2003, to discuss the equivalence of levothyroxine products. According to a letter from the ATA to the Director of the Center for Drug Evaluation and Research ("CDER"), filed in Docket No. 03P-0387 on October 28, 2003, agency officials met with representatives from the ATA, the

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[1] Abbott first requested a meeting on levothyroxine BE testing on May 8, 2002. FDA denied Abbott's request, and stated that it would reconsider after Abbott submitted its clinical data. That data was submitted to FDA on October 10, 2002, along with a renewed request for a meeting. On January 14, 2003, FDA again denied Abbott's request. One month later, on February 12, 2003, Abbott sought formal dispute resolution, and requested an appropriate advisory committee meeting. This request was denied on March 7, 2003. Abbott again sought relief, and it was this appeal that prompted FDA to request that Abbott submit its Petition. *See* Petition at 14-18.

Endocrine Society, and the American Association of Clinical Endocrinologists. *See* Tab B. At this meeting, these organizations presented to FDA their views on the importance of dose precision and strict BE standards for levothyroxine products. According to the October 28 letter, FDA agreed to hold a workshop regarding levothyroxine BE testing. The letter also acknowledges that, per the agency's request, these medical organizations are preparing a draft agenda and a list of potential contributors to the workshop. *See id.*

Abbott has since learned that FDA, in a reply letter dated November 5, 2003, from the Acting Director of CDER to the ATA, has confirmed the agency's commitment to hold a public workshop. *See* Tab A. As stated in the letter,

> [FDA is] 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: [B]ioequivalence testing baseline correction, optimal test subjects, and acceptable confidence limits; and TSH [thyroid-stimulating hormone] as a pharmacodynamic measure.

Id. With regard to pending applications containing BE data, the letter states that FDA will take into consideration the organization's concerns regarding dose precision and limitations in the current BE standard.

II. THE BASIS FOR AN APPROPRIATE PUBLIC MEETING

As noted above, before being requested by FDA to submit a Citizen Petition in this matter, Abbott tried to resolve its concerns regarding the appropriate levothyroxine BE methodology through informal communications with FDA and, later, through formal dispute resolution. In those informal communications, and twice during the course of formal dispute resolution, Abbott requested review of this scientific controversy before an appropriate advisory committee, with joint representation from the Advisory Committee for Pharmaceutical Science ("ACPS") and the Endocrinologic and Metabolic Drugs Advisory Committee ("EMDAC"). *See* Petition, Tab 2 at 4, Tab 3 at 55. Abbott requested such a meeting again in its Petition. *See id.* at 3. In support of such a meeting, Abbott has repeatedly pointed out that the Food and Drug Administration Modernization Act ("FDAMA") provides a right to request review of scientific controversies by an advisory committee or an appropriate scientific advisory panel. *See* FDAMA 404 (codified at 21 USC 360bbb-1); Petition at 38-41.

FDA's obligation to consider such requests and to convene advisory committee meetings to resolve significant scientific disputes is borne out by the legislative history of FDAMA. The legislative history emphasizes that prior to FDAMA, FDA's informal mechanisms for resolving disputed matters were insufficient where important scientific controversies were concerned. The statute's dispute resolution provision was added in recognition that scientific controversies are more properly subject to the formal review of an appropriate scientific body:

> Where there is a scientific controversy between the FDA and a person or company, and it cannot be resolved internally, the Secretary shall establish a process by which a person or company may request review of the matter by an appropriate scientific advisory committee. Any review by an advisory committee should take place in a timely manner. This process may provide that important scientific issues will receive appropriate attention from independent scientists who can bring a fresh perspective to assure that the regulated industry receives a fair and impartial hearing and that the FDA receives sound recommendations and advice.

H. Rep. 105-310, at 73 (Oct. 7, 1997) (discussing the provision that became FDAMA 404); *see* 21 CFR 10.75(b)(2); Guidance for Industry: *Formal Dispute Resolution: Appeals Above the Division Level* 7 (Feb. 2000).

Implicit in the statutory right to ask for a meeting comes a corresponding right that legitimate requests will not unreasonably be denied. Without such an expectation, FDAMA's provisions on the right to ask for an advisory committee meeting would be "bereft of meaning." *City of Roseville v. Norton*, 348 F.3d 1020, 1028 (D.C. Cir. 2003). In fact, FDA itself has stated that it will not unreasonably deny a request for advisory committee review: "It is expected that [the] Centers will fully evaluate each request for section 404 review, and will not unreasonably deny a sponsor, applicant, or manufacturer such review." 63 FR 63978, 63979 (Nov. 18, 1998) (issuing final rule 21 CFR 10.75).

Moreover, the standard for convening such a meeting is surely met in this case. FDA has recognized the scientific importance of each issue presented in the Citizen Petition, as evidenced by its commitment to the ATA to hold a workshop that addresses "bioequivalence testing baseline correction, optimal test subjects, and acceptable confidence limits; and TSH as a pharmacodynamic measure." Tab A. Furthermore, it is undisputed that FDA has been unable to resolve internally the

present scientific controversy. The agency publicly acknowledged this fact in correspondence regarding the related citizen petition of Jones Pharma. On September 23, 2003, FDA informed the company that the agency "has been unable to reach a decision" on its petition "because it raises significant issues requiring extensive review and analysis by Agency officials." Letter from Jane Axelrad, Docket No. 03P-0126. In light of the fact that FDA has been unable to resolve these important scientific issues through internal processes, the agency is obligated under FDAMA to convene an advisory committee or similar scientific meeting.

III. THE ATA WORKSHOP MAY SERVE AS THE MEETING ABBOTT HAS REQUESTED

Abbott is encouraged by the correspondence between FDA and the ATA, which indicates an agency commitment to work with the clinical community on "this important public heath issue," and on the specific issues raised in Abbott's Petition. *See* Tabs A and B. Abbott believes that the agency's planned public workshop may satisfy Abbott's request for scientific review of this controversy, provided the meeting is appropriately structured, as follows:

- It should provide for meaningful discussion of, and input on, the optimal levothyroxine BE methodology, rather than merely provide FDA with an opportunity to present a previously-developed methodology.

- It should provide a meaningful basis upon which future regulatory decisions regarding the BE of levothyroxine products may be based. All views expressed at the workshop must be given serious scientific consideration.

- It should be held as soon as possible, preferably early in 2004, although it must be preceded by enough notice to allow all interested persons time to prepare.

- It should be transcribed, and should be of sufficient duration to provide for a full discussion of the issues.

- It should include independent experts, such as those who sit on the ACPS (*i.e.*, biopharmaceutics experts) and the EMDAC (*i.e.*, clinical experts who routinely work with patients suffering from thyroid

disease), to allow for discussion of both the technical biopharmaceutics and clinical issues.

- It should include discussion of the scientific issues raised by Abbott's Petition, including: Quantification of the clinically acceptable difference that may be allowed between substitutable (*i.e.*, "AB" rated) levothyroxine products, baseline correction, modification of the statistical acceptance criteria, size of the test dose used, study population, washout period, and additional markers.

In sum, the "workshop" should serve as a fair and impartial forum for providing FDA sound scientific advice, or further recommendations for a process designed to reach sound conclusions, regarding an appropriate and scientifically valid methodology for determining the bioequivalence of levothyroxine products. Abbott can facilitate in any way FDA thinks appropriate in the preparation and planning of this workshop, in order to resolve the outstanding levothyroxine BE issues.

IV. RESPONSE TO THE TECHNICAL COMMENT FILED BY DR. SANFORD BOLTON TO THE RELATED DOCKET NO. 03P-0126

On September 8, 2003, Dr. Sanford Bolton submitted a comment to Docket No. 03P-0126.[2] Dr. Bolton recommends that the Jones Pharma petition be denied, and reiterates several of the points he raised at the ACPS meeting, where he presented on behalf of Geneva Pharmaceuticals, Inc. *See* Petition, Tab 5 at 186. Although each of Dr. Bolton's arguments is fully addressed in the Petition, for the convenience of the agency we will respond briefly.

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[2] In addition, a number of electronic comments have been filed to Docket No. 03P-0387 from leading clinical experts, including a past president of the ATA, the chief executive and medical director of the Thyroid Foundation of America, and the chief of the Section of Endocrinology, Diabetes & Nutrition at Boston Medical Center. These comments have been uniform in their message that even small changes in the dose of levothyroxine can have adverse effects on patients. As stated by Jerome Hershman, M.D., past president of the ATA, "[a]s a specialist in management of patients with thyroid disease, I wish to emphasize that differences of [12.5%] can result in over-treatment or under-treatment of patients with significant clinical consequences." In this regard, these comments echo the numerous clinicians who testified before the ACPS on March 13, 2003. *See* Petition at 25-27, Tab 5 at 178-89.

Dr. Bolton states in his comment that during the ACPS meeting, there were approximately 10 presentations by Abbott representatives, and that "[n]otwithstanding those presentations by Abbott, the agency appropriately determined that its existing guidelines and recommendations were more than adequate to show equivalence among levothyroxine products." To the contrary, only two representatives from Abbott presented at the meeting. The presentations to which Dr. Bolton refers were public comments by clinical experts, including representatives from the ATA, the Thyroid Foundation of America, and the Endocrine Society. Although these experts were unanimous in their concern over FDA's BE methodology, none spoke on behalf of Abbott. *See id.* at 25-27, Tab 5 at 178-89. FDA also has not determined that its existing guidelines are adequate to ensure the equivalence of levothyroxine products. As demonstrated by its recent letter to the ATA, this issue is under active consideration within the agency. *See* Tab A.

Dr. Bolton states that an Abbott representative "argued that identical blood levels over time for two products do not necessarily demonstrate equivalence." Neither of Abbott's representatives ever made such a statement at the meeting. Rather, the issue raised in Abbott's Petition is whether FDA's BE methodology is sufficiently sensitive to distinguish between products that deliver different amounts of levothyroxine. As demonstrated in Study M02-417, two doses of levothyroxine that differ by 12.5% were declared BE under FDA's methodology even with the baseline correction method presented at the ACPS meeting. *See id.* at 11-13. Dr. Bolton also says that "[t]he agency correctly understood that Abbott's arguments were not good science and were contrary to the presently accepted, and scientifically valid, bases underlying bioequivalence." To the contrary, the agency never characterized Study M02-417 as "bad science." Rather, FDA stated at the meeting that the study was "very useful when the FDA decided to adopt a baseline correction method." *Id.* at 17, Tab 5 at 198.

Dr. Bolton continues, as he did during the ACPS meeting, by describing the results of several BE studies conducted according to FDA's current methodology. Once again, these statements miss the significance of Abbott's clinical data. Dr. Bolton attempts to demonstrate the adequacy of the recommended methodology by applying it to equivalent doses of two levothyroxine products. During the ACPS meeting, FDA similarly attempted to bolster its methodology by applying it to dosage form proportionality data. *See id.* at 30-31, Tab 5 at 199. Abbott does not dispute that FDA's methodology may declare equivalent identical

doses of levothyroxine; rather, Abbott's clinical data demonstrate that this methodology will also declare equivalent two products that differ by a clinically significant 12.5% or more.

Dr. Bolton's comment also misstates the role that variability plays in BE determinations. Dr. Bolton correctly states that levothyroxine exhibits low intra-subject variability, and that the variability of the data increases as the dose decreases. However, he then states that Abbott "shows the products dosed at 400 and 450 mcg [micrograms] fail the confidence interval. This is not due to the deficiencies of the method, but it is due to the high variability and the bias in the measurements." Thus, Dr. Bolton believes that the 400 and 450 mcg doses in Study M02-417 were declared BE under FDA's methodology because of the higher variability at those doses.

Dr. Bolton is wrong. As discussed in detail in Abbott's Petition, greater variability in BE data widens the resulting confidence intervals, making it less likely that two products will be declared equivalent. *See id.* at 20-21, 32-33, 37-38. At low doses, subjects' measurements are expected to be less tightly grouped, widening the range of values and making it less likely that the entire confidence interval will fall within FDA's 80 to 125% acceptance criteria. *See id.* at 20-21. In Abbott's study, the variability observed with the 400 and 450 mcg doses was somewhat greater than that observed with the 600 mcg dose. Thus, the finding of bioequivalence between the 400 and 450 mcg doses is remarkable for the precise reason (higher variability at lower doses) identified by Dr. Bolton.

Finally, Dr. Bolton argues that a 9% difference in the potency of levothyroxine products will not have significant effects on thyroid patients. Dr. Bolton also states that "tablet variability and biological variability would result in differences of greater than 9% for individual patients taking the same product." The agency itself has specifically stated that patients who have been titrated to a specific levothyroxine strength may suffer serious consequences if those patients actually receive a slightly different dose. According to the agency's analysis, a 9% percent difference (too low or too high) would be sufficient to cause adverse health consequences. *See id.* at 24-25, 40. Also, the meaning of Dr. Bolton's term "biological variability" is unclear. However, tablet variability, in terms of content uniformity within a lot, typically has a coefficient of variation of less than 2%.

V. CONCLUSION

For the reasons stated in Abbott's original Petition and in this supplement, the scientific issues surrounding the equivalence of levothyroxine products must be vetted before an appropriate advisory committee or other scientific body. FDA recently recognized this by committing to hold a workshop, where the agency will work with the clinical community to develop a new BE methodology. This workshop may satisfy Abbott's request for advisory committee review, provided it is carefully constructed to provide meaningful consideration of the scientific issues raised in the Petition. Finally, as discussed in the Petition, it is vital that FDA not approve any applications on the basis of BE data until this process has concluded, and the agency has in place a scientifically valid and clinically sensitive BE methodology.

Sincerely,

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