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February 24, 2004

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Division of Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Comments to Citizen Petitions filed on behalf of Jones Pharma, Inc., Dated March 28, 2003, Docket No. 2003P-0126 and on behalf of Abbott Laboratories dated August 25, 2003, Docket No. 2003P-0387

Dear Sir or Madam:

We are submitting these comments to respond to the above-referenced pending Citizen Petitions (the "Petitions"). Both Petitions request the Food and Drug Administration ("FDA" or "Agency") to refrain from approving pending applications for levothyroxine sodium tablets for which bioequivalence is established on the basis of standards set forth in FDA's February 2001 Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Dissolution Testing and as announced by the Food and Drug Administration ("FDA") at the March 12-13, 2003 meeting of the Pharmaceutical Sciences Advisory Committee ("the current standard").

Each of these Petitions alleges deficiencies with the current standard which are purported to render it inappropriate to establish the bioequivalence of levothyroxine sodium tablets. In effect, these Petitions contend that (1) it is necessary to measure Thyroid

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Stimulating Hormone (TSH) rather than total T4 as a measure of bioequivalence and (2) levothyroxine sodium products have a narrow therapeutic range which render the determination of bioequivalence within the Agency's standard 80-125% confidence interval clinically inappropriate.

As set forth in further detail below, these arguments are unfounded and simply do not provide a basis for FDA to disregard its current standard which is more than scientifically appropriate to establish the bioequivalence of levothyroxine tablets.

For the following reasons, we urge FDA to deny these Petitions and to continue to review and approve applications for levothyroxine tablets in accordance with the Agency's current standard for bioequivalence.

I. Use of Thyroid Stimulating Hormone (TSH) rather than Total T4 as the Marker for Bioequivalence Is Unnecessary and Unfounded.

The Petitions recommend the use of blood levels of TSH as a marker for determining bioequivalence. TSH was recommended because that is what physicians generally use to assess thyroid function, and to aid in titration. At the March 13, 2003 meeting of the Pharmaceutical Sciences Advisory Committee ("March 13 Meeting"), FDA staff and the Advisory Committee recommended and continued to support the use of total T4 levels – the hormone that is administered in the dosage form as provided in the current standards. As noted by Dr. Steven Johnson of FDA at this meeting: "Regarding the bioequivalence measures that have been discussed this morning, total thyroxine is the preferred measure for demonstrating bioequivalence. It can be accurately measured in vivo and is the drug that is being administered to the subject. T3, on the other hand, is merely an active metabolite, and the Food and Drug Administration does not use active metabolites for conferring bioequivalence, unless the active parent cannot be measured in vivo." See p. 182 of the meeting transcript.

Dr. Johnson went on to say that use of total T4, rather than TSH is consistent with regulatory standards: "According to the Code of Federal Regulations, in descending order of accuracy, sensitivity and reproducibility for determining bioavailability and bioequivalence of a drug product, the best choice for evaluating bioequivalence is the concentration of the active ingredient and that's where T4 fits in. TSH, on the other hand, would be relegated to the third or fourth category." See p. 183 of the meeting transcript.

Further, on April 16, 2003, shortly after the March 13 meeting of the FDA's Pharmaceutical Sciences Advisory Committee, the Expert Advisory Committee of Health Canada also considered the issue whether a baseline corrected total T4 is an appropriate and sensitive measure. Just as the FDA staff and Pharmaceutical Science Advisory Committee concluded, this Expert Advisory Committee also concluded that total T4 is the preferred method and that TSH is a "downstream" bio-marker that is considerably more variable. Accordingly, the Expert Advisory Committee came to the consensus that "T4 is an acceptable marker for rate and extent of absorption" and that "T4 alone should be used as a measure of comparative bioavailability." See the Record of Proceedings of the Expert Advisory Committee on Bioavailability and Bioequivalence attached hereto as Attachment I.

Ignoring the views of FDA staff, the Pharmaceutical Sciences Advisory Committee, and the Canadian Expert Advisory Committee, Petitioners argue against using total T4 as the marker and, in support thereof, provide the results of a study purportedly showing that total T4 measurements could not distinguish products that are 12.5% different in dose, but did differentiate products with 25% or more difference in dose. But, in fact, as discussed in Section 2 below, this result actually confirms the adequacy of the present guidance.

The primary reason for using total T4, rather than TSH to establish bioequivalence is that TSH is a secondary effect of T4 levels. Moreover, TSH is much more variable within an individual patient than total T4. Both of these facts support the use of total T4, rather than TSH, as a measure of bioequivalence. Secondary or pharmacodynamic variables are not used to assess bioequivalence unless blood concentrations of active drug moieties or metabolites cannot be adequately measured. If the actual drug moiety in the dosage form can be measured in the blood with good precision, there is no reason to measure a surrogate marker.

Further, the intra-subject variability of the concentration of the bioequivalence marker measured in the blood is another key factor. In this regard, there is no reason to measure TSH, which is substantially more variable than total T 4, particularly given that TSH is a secondary effect to T4 levels. Subsequent to the March 13 Meeting, Dr. Sanford Bolton analyzed the variability of TSH, as compared to T4, from data in a bioequivalence study which he discussed at the meeting. In this study, TSH was measured in 26 subjects at screening and prior to dosing, an interval of 28 days. T4 was measured in 24 subjects at three intervals up to one-half hour prior to dosing on two occasions, prior to dosing during Period 1 and prior to dosing in Period 2, an interval of 35 days. In his analysis, Dr. Bolton found the coefficient of variation ("CV") for TSH was 25.8% (based on log, transformed

values). The CV of T4 was 10.4% based on the range of six measurements, three prior to each of the two dosing periods. With a log transformation, the CV was 9.5%.[1] These data clearly demonstrate that total T4 blood levels are considerably less variable than blood levels for TSH.

This significant difference in variability, alone, would make the use of TSH as a marker less desirable than total T4 for establishing bioequivalence. When it is also considered that TSH levels are a pharmacodynamic effect resulting from the administration of levothyroxine, the suggestion to use TSH, rather than T4, as a measure of bioequivalence becomes all the more untenable.

Finally, we note that on January 27, 2004, the American Thyroid Association submitted its guidelines for detection of thyroid dysfunction to the docket for Abbott's Citizen Petition, Docket No. 2003P-0387. The stated objective of the guideline is to define the optimal approach to identify patients with thyroid dysfunction and, in this regard, recommends the use of serum TSH measurement to diagnose forms of hypothyroidism and hyperthyroidism. We take no issue with respect to this guideline or the recommendations therein. Any belief, however, that this guideline somehow supports the Petitioners' position that measurement of TSH serum levels is a more appropriate measure of bioequivalence than measurement of total T4 serum levels would be misplaced. It is adequate to use TSH serum levels as a diagnostic tool to determine thyroid dysfunction, but this has little, if anything to do with the best methodology for determining the bioequivalence of different levothyroxine sodium tablets.

II. The FDA bioequivalence standards for levothyroxine sodium tablets are scientifically sound and appropriate.

The current bioequivalence standards are appropriate to establish the bioequivalence of levothyroxine sodium tablets. They include the addition of a baseline correction for the T4 blood levels to improve the analysis. The use of 600 mcg of levothyroxine was applied

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[1] As a confirmation of the CV for T4, one value was selected randomly from each of the three pre-dose concentrations in the two dosing periods. This would make the comparison of T4 and TSH comparable (one reading at each of two occasions, 28-35 days apart). The CV for the log transformed values was 10.0%, in close agreement with the above calculation.

because of the substantial endogenous concentrations of the drug. Again, we refer the Agency to the comments made by Dr. Johnson of the FDA staff at the March 13, 2003 meeting of the Pharmaceutical Sciences Advisory Committee, in which Dr. Johnson cogently articulated the basis for the current standards and why the measurement of T4, rather than TSH, is a more appropriate measure. See pages 180-185 of the Meeting Transcript attached hereto as Attachment II.

Abbott's study showing that a 400 mcg dose cannot be distinguished from 450 mcg dose, but can be distinguished from doses 25% or more different, makes perfect sense, and, if anything, substantiates the relevance of the current standard. The present guidance will accept products that meet the 80-125% confidence interval. Therefore, products that are 12.5% different will pass the current confidence interval guidelines, using an adequate sample size. (In Abbott's study, the actual observed difference was 8.4%.) Based on the low variability of total T4 blood concentrations, a sample size of approximately 24 subjects is adequate to define bioequivalence. Products that are more than 20% different should fail the confidence interval. Not surprisingly, this is exactly what happened in the Abbott study. In fact, using 600 mcg instead of 400 or 450, should make the test more sensitive. Therefore, Abbott's own study shows that the current FDA guidance yields the expected results.

In point of fact, however, Abbott's concern that levothyroxine sodium tablets which differ by as much as 12.5% will pass the standard confidence intervals is a red herring. First, it is extremely unlikely that FDA will be asked to find that two products with labeled dosage strengths that differ by 12.5% are bioequivalent. Further, the likelihood that levothyroxine sodium tablets which are approved and manufactured for identical dosage strengths will actually differ by 12.5% is exceedingly low. The FDA also evaluates other data, in addition to bioequivalence studies, to assure the products will perform comparably to a reference listed drug. For example, FDA considers the dissolution profile and the formula as part of its global evaluation. For levothyroxine, the formulation is simple; there are no complicated ingredients or slow release mechanism. The dissolution is relatively rapid and uncomplicated. For a simple formulation, as is the case for levothyroxine products, if the same amount of active is in each dosage unit, the tablet can be expected to deliver the same amount of drug. The likelihood of differences between products is further minimized by the approval requirement that overages above 100% of label claim are not permitted for levothyroxine sodium tablets. All of this helps to assure that products that meet the current FDA guidelines will behave the same as the reference drug.

III. The Bioequivalence Of Levothyroxine Sodium Tablets Can Be Determined By Use Of The Agency's Standard Confidence Interval.

Petitioners assert that levothyroxine sodium tablets have a narrow therapeutic range which renders the determination of bioequivalence within the Agency's standard 80-125% confidence interval clinically inappropriate. In point of fact, there is no such formal designation by the FDA for so-called narrow therapeutic index drugs.

Further, as a matter of regulating principles, because of FDA's strict manufacturing controls and bioequivalence criteria, the Agency does not regulate drugs with a so-called narrow therapeutic index as being clearly different from other drugs for the purpose of therapeutic substitution. Accordingly, in considering the bioequivalence of drug products, the FDA does not impose specific confidence intervals for specific drugs. The recommended confidence interval applicable for all drugs was chosen based on a reasonable assessment of the difference in doses that could cause problems.

Petitioners' concerns rest on a false assumption that a product that is consistently at 80% of the blood level of the reference listed drug could be shown to be bioequivalent to it. This well-established confidence interval, however, will not result in a consistently subpotent or superpotent drug being found to be bioequivalent to the reference listed drug. Rather, it is a statistical test that includes normal variation in studies comparing two drugs that are, in fact, bioequivalent.

Every drug has its own optimal range, but to evaluate this precisely, and then apply individual confidence intervals for each specific drug would be a Herculean task. Applying a reduced confidence interval to only those products with a NTR would also be a very difficult task. One would need a clear definition, and official listing of such drugs to avoid further confusion. A separate interval for each drug, e.g., 95 to 105%, another 90 to 110% another 85 to 115% might be needed. FDA's experience to date in approving drugs with NTRs on the basis of a 80 to 125% confidence interval shows, however, that applying the same bioequivalence standards to NTR drugs is not a significant clinical concern.

T4 is a labile drug. It would not be surprising to see differences of average potency being close to 10% between production and prolonged storage. In addition, individual tablets vary in their potency and dissolution. Then, of course, there is biologic variability within an individual patient. All products are subject to such unavoidable variability.

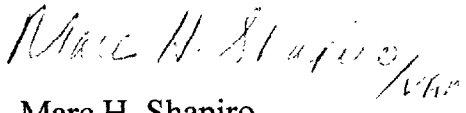
Notwithstanding these inherent variations within the same product, in clinical practice, physicians are able to titrate and treat patients safely and effectively with levothyroxine sodium tablets. This very fact belies the concerns expressed by Petitioners that small differences in potency are of clinical consequence, and that levothyroxine products should not be subject to the Agency's usual confidence interval with respect to bioequivalence testing.

* * * *

CONCLUSION

In summary, the current FDA bioequivalence standards for levothyroxine sodium tablets are scientifically sound and appropriate. In particular, the Petitioners' suggestion to use TSH, rather than T4, as a marker for bioequivalence, is unfounded and unnecessary. Further, the bioequivalence of levothyroxine sodium tablets can be determined by use of the Agency standard confidence interval. Accordingly, these Petitions should be denied.

Very truly yours,



Marc H. Shapiro

MHS/vam

Attachments