

DECLARATION OF RONALD J. SAWCHUK, PH.D.

In Support of the Citizen Petition of Abbott Laboratories Docket No. 2003P-0387/CP1

Ronald J. Sawchuk, Ph.D., under penalty of perjury, declares as follows:

1. Abbott Laboratories ("Abbott") has requested that I evaluate the design, execution, and analysis of the simulation and clinical studies it conducted to investigate a reliable bioequivalence methodology for levothyroxine sodium ("levothyroxine") drug products. Abbott also has requested that I comment on the conclusions that may be drawn from these studies regarding the levothyroxine bioequivalence methodology currently being recommended by the Food and Drug Administration ("FDA").

2. For this evaluation, I have reviewed Abbott's Citizen Petition (including select attachments, such as the technical report of the simulation study), the full report of the clinical study (on file with FDA), and FDA's guidance documents on levothyroxine bioavailability testing, general bioavailability/bioequivalence testing, and statistical approaches to establishing bioequivalence.

Qualifications

3. I am a Professor of Pharmaceutics and the Director of Bioanalytical and Pharmacokinetic Services at the College of Pharmacy at the University of Minnesota (the "University") in Minneapolis. My curriculum vitae is attached at Tab 1.

4. Currently, I teach courses in introductory and advanced pharmacokinetics, as well as pharmacokinetic data analysis and simulation. I have held a number of positions at the University, including head of the Department of Pharmaceutics and Director of Graduate Studies in Pharmaceutics. During my tenure at the University, I have taken a number of leaves of

absence to consult with pharmaceutical companies on a variety of issues involving pharmaceuticals and pharmacokinetics. I hold a Ph.D. in Pharmaceutical Chemistry (with an emphasis in pharmacokinetics) from the University of California, San Francisco, and Masters and Bachelors of Science degrees from the University of Toronto. I sit on the Editorial Boards of two journals, including the *Journal of Pharmaceutical Sciences*. I am a fellow of both the American Association of Pharmaceutical Scientists and the American Association for the Advancement of Sciences. I have given hundreds of invited lectures, and have written hundreds of articles, books, and abstracts, most of which concerned pharmacokinetic or bioanalytic issues.

5. During the course of my career, I have given presentations, conducted studies, and published articles on the pharmacokinetics of numerous drugs, including carbamazepine, cyclosporine, diltiazem, phenytoin, propranolol, theophylline, and valproic acid.

6. My expertise is in the field of pharmacokinetics. Generally, pharmacokinetics is the quantitative study of how the body affects a drug. Pharmacokinetics is studied through the application of mathematical concepts to the absorption, distribution, metabolism, and excretion of drugs in the body. Absorption describes the rate and extent of drug entry into the body; distribution refers to how the drug is distributed to the tissues; metabolism deals with how the drug is chemically transformed in the body; and excretion describes how the drug is eliminated from the body, unchanged.

7. Bioavailability is a pharmacokinetic term that describes the rate and extent to which the active drug ingredient in a drug product is absorbed and becomes available at the body's site of action. Bioequivalence is a determination that the bioavailability of two drug

products, when administered in the same amounts under the same experimental conditions, do not differ by a significant amount.

8. Thus, it is my opinion that any methodology used to determine bioequivalence must be sensitive, accurate, and precise enough to detect a significant difference (if one exists) between tested products. A methodology that cannot detect such differences cannot be used to establish bioequivalence.

Abbott's Simulation Study

9. On behalf of Abbott, Thomas Ludden, Ph.D., initiated a stochastic simulation study entitled "Simulation Study to Assess Alternative Bioavailability Calculations, Study Designs and Acceptance Criteria for Determining the Bioequivalence of Levothyroxine Sodium Tablets" (the "Simulation Study"). I have reviewed the methodology and results of this study.

10. The Simulation Study used data generated from two studies submitted to FDA in support of Abbott's New Drug Application for Synthroid®. One was a single dose, two-way crossover study designed to compare the bioavailability of 2 x 300 mcg tablets to that of a 600 mcg dose administered in an oral solution. The second was a single dose, three-way crossover study designed to assess the dosage form proportionality of 50, 100, and 300 mcg tablets.

11. The Simulation Study was designed to explore two factors: (1) The accuracy of levothyroxine bioequivalence studies with and without correction for endogenous

hormone levels; and (2) the accuracy of alternative methodologies when using a narrower bioequivalence acceptance range (*i.e.*, 90 to 110 percent *versus* 80 to 125 percent).

12. On the ingestion of levothyroxine, the endogenous production of thyroid hormone in healthy subjects is suppressed to some extent, causing a downstream change in baseline levels. This gradual, downward adjustment in the baseline (endogenous) levels may reduce the total levels of levothyroxine observed after a second dose in a crossover study several weeks later. The extent and time-course of this suppression is unknown.

13. Dr. Ludden therefore tested two different assumptions. First, Dr. Ludden prepared an analysis based on the assumption that exogenous levothyroxine has no suppressive effect on the body's natural production of thyroid hormone. Under this assumption, baseline (endogenous) levels measured prior to dosing are assumed to be the same as baseline levels present after dosing. Operating under this assumption, the post-dose simulation data were corrected for baseline levels by subtracting out the average of three pre-dose measurements of endogenous hormone.

14. Second, Dr. Ludden prepared an analysis based on the assumption that exogenous levothyroxine would have a complete suppressive effect on the body's natural production of thyroid hormone, and that any endogenous hormone that is present prior to dosing declines according to its elimination half-life. Operating under this assumption, Dr. Ludden corrected the post-dose simulation data by subtracting out the contribution of endogenous hormone, as it would be expected to disappear exponentially according to its half-life.

15. These two methods conservatively represent the extremes of endogenous thyroid hormone suppression, while the "true" effect of exogenous levothyroxine on endogenous hormone production is likely somewhere in between.

16. These simulations are technically demanding, requiring expertise in advanced pharmacokinetics, mixed-effect modeling, and power analysis, as it is used to design and interpret equivalence tests. Simulation studies are becoming more common in drug development and clinical trial design, where the primary objective is to compare predicted outcomes. One example of such use is in survival analysis, where different doses of a drug, or different frequencies of dosing, are simulated to investigate the drug's effect in prolonging life or reducing the rate of progression of disease.

17. The methodology prepared by Dr. Ludden was well-designed to test both the accuracy of bioequivalence studies with and without correction for endogenous levels of thyroid hormone, and the accuracy of alternative methodologies when using a narrower bioequivalence acceptance range.

Simulation Study Results

18. *For Baseline Uncorrected Data:* The results of the Simulation Study indicate that if FDA's usual acceptance range of 80 to 125 percent is applied to baseline uncorrected peak plasma concentration (" C_{max} ") and area under the plasma concentration-time curve ("AUC") values, a levothyroxine test product whose bioavailability is 35 percent lower than that of the levothyroxine reference product is likely to be declared bioequivalent to the reference product.

19. *Under Assumption One:* After correcting the data under the first assumption (*i.e.*, that endogenous levels measured prior to dosing are the same as baseline levels present after dosing), Dr. Ludden demonstrated 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 bioequivalent to the reference product in a 36-subject study, based on the 80 to 125 percent acceptance range.

20. *Under Assumption Two:* After correcting the data under the second assumption (*i.e.*, that exogenous levothyroxine would have a complete suppressive effect on the body's natural production of thyroid hormone), Dr. Ludden demonstrated that a test product that delivers 15 percent less (or more) levothyroxine than a reference product would have a 33 (or 57) percent chance of being declared bioequivalent to the reference product in a 36-subject study, based on the 80 to 125 percent acceptance range.

21. *Using a Narrower Acceptance Range:* When applying the narrower acceptance range of 90 to 110 percent to uncorrected AUC data, the probability of declaring two products bioequivalent when they differ by 20 to 25 percent is still very high, ranging up to 92 percent, depending on the sample size and whether the test product has a higher or lower bioavailability. Use of the narrower acceptance range for uncorrected C_{\max} values provides similar sensitivity to using an 80 to 125 percent acceptance range for corrected C_{\max} values under assumption one. This suggests that neither this baseline correction method nor a narrower acceptance range alone is sufficient to detect differences of this magnitude.

22. Dr. Ludden's Simulation Study indicates that regardless of the correction method employed, use of FDA's standard bioequivalence methodology, including an 80 to 125

percent acceptance range, will result in a high probability that two products will be declared bioequivalent when they actually differ in bioavailability by 15 percent or more. Based on my understanding of the clinical issues, this is a significant difference.

23. This Simulation Study was exceptionally well-performed. Moreover, I consider Dr. Ludden to be a leader in the field of mixed-effect modeling and in the use of the NONMEM software package that generated the results of the study. In my opinion, the study accurately assessed the likelihood that different doses (or products with different bioavailability) of levothyroxine would be declared bioequivalent, assuming that the extent of the differences were known, and that the variances in the parameters were known for previous studies in a similar population of subjects.

Abbott's Pharmacokinetic Study

24. After the Simulation Study, Abbott designed and conducted a bioequivalence study (the "417 Study") to test the predictions from the Simulation Study in a clinical setting. The 417 Study tested whether levothyroxine products that differ by clinically relevant amounts would indeed pass as bioequivalent if the investigators failed to account for baseline levels of thyroid hormone, or if the investigators applied each of three different methods of baseline correction, in an effort to account for the endogenous hormone.

25. I have reviewed the methodology of the 417 Study, its execution, and its results. The 417 Study was appropriately designed in accordance with FDA's guidance documents on levothyroxine bioavailability testing and general bioavailability/bioequivalence testing. The study's design was consistent with that of a standard bioequivalence study with one

noteworthy exception: Abbott intentionally used different test and reference doses as a means of challenging FDA's standard bioequivalence methodology.

26. As per FDA's guidance, the 417 Study was a single dose, crossover study. A total of 36 subjects (18 men, 18 women) participated in the study. All subjects were euthyroid (exhibiting normal thyroid stimulating hormone levels) and in general good health, based on a thorough physical examination. Each subject was randomized to one of six treatment sequences, with at least a 44 day washout period between doses. Blood samples were collected for 24 hours prior to, and out to 96 hours after, dosing. The relevant pharmacokinetic measures, C_{max} , AUC, and the time to peak concentration (" T_{max} "), were calculated. A variety of statistical tests, including analysis of the interactions between fixed effects, such as sex, sequence, and treatment, also were conducted. Each of these elements met or exceeded those recommended in FDA's guidance documents.

27. Each volunteer was administered a single dose of 400, 450, and 600 mcg of levothyroxine. The study provided three comparisons: The 400 mcg dose was compared to the 600 mcg dose (a difference of 33 percent); the 450 mcg dose was compared to the 600 mcg dose (a difference of 25 percent); and the 450 mcg dose was compared to the 400 mcg dose (a difference of 12.5 percent, or of 11 percent if the 450 mcg dose is used as the reference dose).

28. Abbott took numerous steps to control for all possible study variables. For example, all doses of the study drug came from the same production lot, and were aged to the same date. Serum analytes also were assayed in batches, so that all samples from any one test subject were measured in a single batch, reducing the possibility that any individual's measurements were the result of inter-batch assay variability.

29. Based on my experience, the 417 Study was a well-designed study, consistent with the design of a bioequivalence study. However, as noted above, instead of evaluating test and reference products known to be pharmaceutically equivalent (containing identical amounts of the same active ingredient), Abbott evaluated doses known to differ by clinically significant amounts. Thus, the 417 Study was designed to assess the sensitivity of the particular bioequivalence methodology used, including each of three different methods of correcting for the contribution of endogenous hormone to the total serum levels of levothyroxine.

Pharmacokinetic Study Results

30. The results of the 417 Study – when analyzed without baseline correction – were consistent with the results of the Simulation Study. Each pharmacokinetic measure in the 417 Study, when analyzed without baseline correction, was consistent with a finding of bioequivalence. The 450 mcg dose was found to be bioequivalent to the 400 mcg dose. The 450 mcg dose was found to be bioequivalent to the 600 mcg dose. And, the 400 mcg dose was found to be bioequivalent to the 600 mcg dose.

31. Abbott next used three different baseline correction methods to analyze the data. For example, under one correction method, the pre-dose baseline value on the day of dosing was subtracted from each post-dose concentration. The pre-dose baseline value was calculated as the average of three samples taken prior to dosing in each period. This method assumes no suppression of endogenous thyroid hormone production, and is the same as assumption one in the Simulation Study. It also is the method now recommended by FDA.

32. For two of the dose comparisons – the 600 *versus* 450 mcg comparison and the 600 *versus* 400 mcg comparison – each of the correction methods tested was successful in reducing the likelihood that the doses would be found bioequivalent. However, for the third dose comparison – the 400 *versus* 450 mcg comparison – none of the three methods could distinguish between the doses. Under FDA's recommended methodology, even with the baseline correction methods, these different doses were declared bioequivalent. Based on my understanding of the clinical issues, these results indicate that the current method for assessing the bioequivalence of levothyroxine products is inadequate; clinically important differences in the systemic absorption of levothyroxine products cannot reliably be detected under this method.

33. Based on the documents I have reviewed, Abbott's study was well-designed and well-executed. The three doses used by Abbott were sufficiently high to allow for an accurate evaluation of the true differences between them. For example, FDA has recommended that the doses used in levothyroxine bioavailability testing be "several times the normal dose" of levothyroxine. The labeling for Synthroid® and the other levothyroxine products state that the average dose for total thyroid hormone replacement is approximately 1.7 mcg/kg, or 100 to 125 mcg for a 70 kg adult. Thus, 600, 450, and 400 mcg are all "several times the normal dose."

34. 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 C_{max} 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. This is because the initial distribution half-life of levothyroxine, reflecting the rate at which the drug is distributed from the serum throughout the body, is much shorter than the elimination half-life.

35. This phenomenon is illustrated in the following figure, taken from the 417 Study report, which demonstrates that the 600, 450, and 400 mcg doses used in the 417 Study produce comparable serum levels over the study period if the endogenous levothyroxine levels are not subtracted:

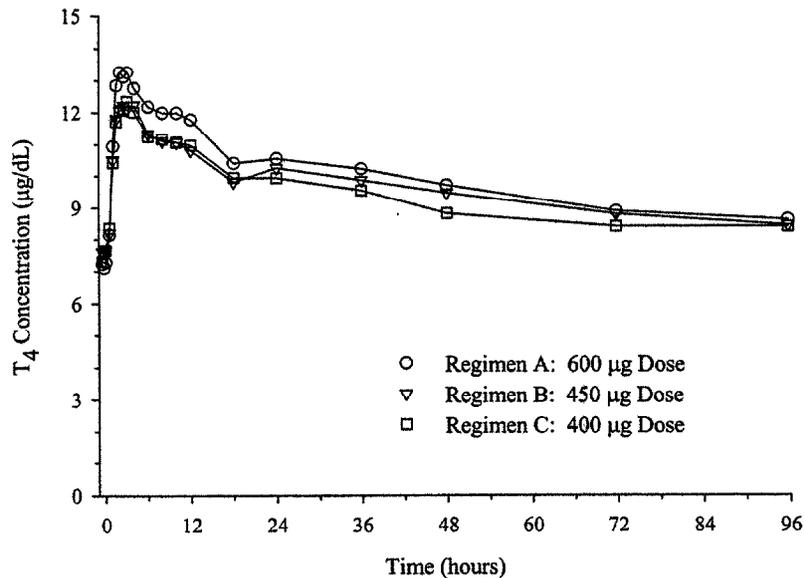


Figure 1. Mean Levothyroxine Concentration-Time Profiles on Study Day 1 Following Single Dose Administration of Levothyroxine Sodium – Uncorrected for Endogenous Baseline Concentrations.

36. Furthermore, the 400 and 450 mcg doses were found to be bioequivalent by a comfortable margin. The point estimate (the ratio of the AUC of the larger to the smaller

dose) was expected to be close to the dose ratio, 1.125, but was found (using the AUC values under the first correction method) to range from 1.01 to 1.04. The width of the 90 percent confidence intervals of the AUC ratios from this correction method ranged from 0.17 to 0.25. This is much narrower than the width of the acceptance range, 0.45 (*i.e.*, from 0.80 to 1.25).

37. Finally, the assay used by Abbott in the 417 Study, the DPC Coat-a-Count®, is an FDA-cleared radioimmunoassay, and is sufficiently sensitive to accurately measure the levothyroxine concentrations achieved in the study. Abbott conducted a validation study on the assay, which demonstrated an analytical sensitivity, defined as the lower limit of quantification ("LLOQ"), of 1.00 mcg/dL using 0.025 mL of serum. This is significantly lower than the lowest concentration of levothyroxine for any subject at any point in the 417 Study. Moreover, the mean peak levels in the study generally were in the 12 to 14 mcg range, even farther above the LLOQ of the assay.

38. Abbott's simulation and clinical studies demonstrate that levothyroxine products that differ by 12.5 percent are likely to be declared bioequivalent under FDA's recommended methodology, even when a baseline correction method for endogenous thyroid hormone is used. Where no baseline correction is used, levothyroxine products whose relative bioavailability differs by 25 or 33 percent are likely to be declared bioequivalent. These studies were well-designed, well-executed, and appropriately analyzed. I agree with the conclusions Abbott has drawn from the studies.

39. In conclusion, it is my opinion that the simulation and clinical studies conducted by Abbott were appropriately designed, conducted, and analyzed. FDA's recommended bioequivalence methodology, even with its baseline correction method, is

insufficiently sensitive to distinguish between significantly different doses of levothyroxine. The agency should consider convening an appropriate advisory committee or similar scientific meeting, to develop alternate methodologies for establishing the bioequivalence of levothyroxine drug products.

Declaration of Ronald J. Sawchuk, Ph.D.

Docket No. 2003P-0387/CP1

Dated: New Brighton, Minnesota
February 13, 2004



Ronald J. Sawchuk, Ph.D.