



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Rockville MD 20857

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Re: Docket Nos. 2003P-0126/CP1 and 2003P-0387/CP1

Dear Dr. Leonard and Messrs. Rogers, Safir, Cunningham, Sporn, Parker, Fox, and McCormick:

This letter responds to two citizen petitions submitted to the Food and Drug Administration (FDA) concerning the appropriate bioequivalence methodology and approval standards for abbreviated new drug applications (ANDAs) for levothyroxine

sodium tablets. King Pharmaceuticals, Inc., and its subsidiary Jones Pharma Inc. (hereafter Jones) submitted a petition dated March 28, 2003, and submitted a supplement to that petition dated March 16, 2004. Abbott Laboratories (Abbott) submitted a petition dated August 25, 2003, and submitted supplements to that petition dated December 22, 2003, January 9, 2004, February 9, 2004, February 25, 2004, April 15, 2004, and June 4, 2004. Jones asks FDA to:

- Refrain from approving or accepting for filing any ANDAs or supplemental ANDAs for levothyroxine sodium tablets that attempt to establish bioequivalence to any reference drug using the bioavailability standards set forth in FDA's February 2001 guidance *Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* (BA guidance) or the bioequivalence standard announced by FDA at the March 12-13, 2003, meeting of the Pharmaceutical Science Advisory Committee
- Convene a joint meeting of the Pharmaceutical Science Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee to evaluate, in a public forum, appropriate methodologies for establishing bioequivalence between levothyroxine tablet drug products
- Stay approval or acceptance for filing of any ANDA or supplemental ANDA for levothyroxine tablets basing bioequivalence on the standards set forth in the BA guidance or the methodology announced by FDA at the March 12-13, 2003, meeting of the Pharmaceutical Science Advisory Committee until the joint advisory committee meeting has convened, FDA has established a new bioequivalence methodology consistent with the petition, and bioequivalence studies in accordance with the new methodology have been submitted; or, until FDA responds to the petition

Abbott asks FDA to:

- Immediately halt the use of FDA's bioequivalence methodology in reviewing any ANDAs or supplemental new drug applications (NDAs) for levothyroxine sodium tablets that seek a therapeutic equivalence rating to Synthroid
- Halt review of any pending applications that rely on FDA's bioequivalence methodology or any other methodology that has not been shown to be sufficiently sensitive to distinguish levothyroxine products that may differ by clinically relevant amounts
- Refer the issue of the proper bioequivalence methodology for levothyroxine products to an appropriate advisory committee, with joint representation from the Pharmaceutical Science Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee

- Establish through a public process consistent with good guidance practices the most accurate and sensitive methodology available for demonstrating the equivalence of levothyroxine products, including a valid method for addressing baseline levels of endogenous hormone and valid statistical criteria that take into account the narrow therapeutic range of levothyroxine sodium

For the reasons that follow, both petitions are denied.

I. Background Concerning Levothyroxine Sodium Products and the Petitions

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T4). Thyroid hormones affect protein, lipid, and carbohydrate metabolism, growth, and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart.

Levothyroxine sodium was first introduced into the market before 1962 without an approved NDA, apparently in the belief that it was not a new drug. Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function, such as cretinism, myxedema, nontoxic goiter, or hypothyroidism. The diminished or absent thyroid function may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine sodium may also be used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

From 1987 to 1994, FDA received at least 58 adverse drug experience reports about levothyroxine sodium drug products, half of which involved prescription refills for patients who had used the products for many years. In addition, from 1990 until 1997, there were at least 10 recalls of these products for inadequate content uniformity, subpotency, and/or stability failures. Because of these potency and stability problems, FDA published a notice in the *Federal Register* of August 14, 1997 (62 FR 43535), declaring levothyroxine sodium a "new drug" and requiring NDA submissions for all currently marketed and any future levothyroxine sodium products.

FDA approved the first levothyroxine sodium NDA on August 21, 2000, for Jerome Stevens Pharmaceutical's Unithroid product. FDA has approved six other NDAs for levothyroxine sodium since that time. FDA approved Jones' NDA for Levoxyl on May 25, 2001, and Abbott's NDA for Synthroid on July 24, 2002. FDA also approved Mylan's ANDA with an AB rating to Unithroid on June 5, 2002. FDA did not approve any other ANDAs for levothyroxine sodium prior to issuing this response to the citizen petitions.

On May 8, 2002, Abbott submitted a request for a meeting to Dr. David Orloff, Director, Division of Metabolic and Endocrine Drug Products (DMEDP), Center for Drug Evaluation and Research (CDER), FDA, and other CDER officials. The company

requested that these officials meet with Abbott to discuss the results of its simulation study, the suitability of the current bioequivalence requirements for levothyroxine sodium, and the potential impact on public health and patient care resulting from FDA's bioequivalence standard for levothyroxine sodium products. Dr. Orloff denied Abbott's request for a meeting as premature and requested that Abbott submit the full report of its study results for DMEDP's consideration. Abbott submitted this report on October 10, 2002. Abbott's study used baseline correction to account for naturally occurring levels of levothyroxine (T4) in patients who took Synthroid. In its October 10, 2002, letter, Abbott relied on the study to challenge FDA's bioequivalence method because FDA's method for determining bioavailability did not use any baseline correction.

Dr. Orloff responded to Abbott by letter dated January 14, 2003. Dr. Orloff explained that DMEDP agreed with Abbott that baseline correction would improve the accuracy of bioequivalence testing for levothyroxine sodium products. Thus, Dr. Orloff concluded that FDA would adopt one of those methods tested by Abbott in its study.

Abbott then notified Dr. Robert Meyer, Director, Office of New Drug Evaluation II (ODE II), CDER, by letter dated February 12, 2003, that Abbott was appealing Dr. Orloff's decision under FDA's dispute resolution procedures. Abbott argued that the baseline correction method selected by FDA was still inadequate. On February 13, 2003, Abbott presented the results of its study at a meeting with various officials from CDER's Office of Generic Drugs and Office of Pharmaceutical Science.

In a letter dated March 7, 2003, Dr. Meyer affirmed Dr. Orloff's decision and denied Abbott's appeal. Dr. Meyer concluded that FDA's method of baseline correction was the most appropriate of the methods tested in Abbott's study to establish bioequivalence for levothyroxine products. On March 13 and 14, 2003, the Advisory Committee for Pharmaceutical Science met to discuss bioequivalence methods for endogenous drugs. FDA officials announced at the meeting the baseline correction method for bioequivalence tests of levothyroxine sodium drug products, as described by Drs. Meyer and Orloff in their letters to Abbott. Abbott representatives discussed the results of its Study M02-147 at the meeting.

Jones Pharma submitted its citizen petition dated March 28, 2003, challenging FDA's bioequivalence method for levothyroxine sodium products. Abbott then appealed Dr. Meyer's decision by letter dated April 4, 2003, to Dr. John Jenkins, Director, Office of New Drugs, CDER. By letter dated May 15, 2003, Jane Axelrad, Associate Director for Policy, CDER, requested that Abbott withdraw its appeal and submit a citizen petition instead challenging FDA's bioequivalence method because the matter would be more appropriately resolved in a public forum. Abbott agreed and submitted its citizen petition dated August 25, 2003.

II. Summary of Statutory Basis for ANDA Approval and Relevant Regulations

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic

Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To gain approval, an ANDA must show, among other things, that the generic version has the same active ingredient in the same strength and dosage form, that it has the same labeling (with certain limited exceptions), and that it is bioequivalent to a listed drug (i.e., a previously approved drug product). 21 U.S.C. 355(j)(2)(A); 355(j)(4). The scientific premise underlying the Hatch-Waxman Amendments is that drug products that are pharmaceutically equivalent and bioequivalent are, therefore, therapeutically equivalent, and may be substituted for each other.

FDA regulations define pharmaceutical equivalents as follows:

Pharmaceutical equivalents means drug products in identical dosage forms that contain identical amounts of the identical active ingredient, i.e., the same salt or ester of the same therapeutic moiety, [but] do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. 21 CFR 320.1(c).

In addition, under the Hatch-Waxman Amendments and FDA regulations, a generic drug product is bioequivalent to the reference listed drug if

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . . . 21 U.S.C. 355(j)(8)(B)(i)); see also 21 CFR 320.1(e) and 320.23(b).

FDA regulations at 21 CFR part 320 establish acceptable methodologies for determining the bioequivalence of drug products. The courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence requirements. See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

Based on these statutory and regulatory requirements, FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with current good manufacturing practice regulations. FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*), Preface at viii.

III. Regulatory Requirements for Content and Format of Levothyroxine Sodium ANDAs

To obtain approval of an ANDA, such as for levothyroxine sodium, an applicant must demonstrate that the generic drug product is therapeutically equivalent to its reference listed drug and thus may be substituted for the reference listed drug. An ANDA applicant must submit extensive evidence to support a finding of therapeutic equivalence. Demonstrating bioequivalence is only one part of that evidence.

FDA's regulations at 21 CFR 314.94 describe the numerous requirements for the content and format of an ANDA. In addition to bioequivalence requirements, this provision sets forth other requirements concerning the physical and chemical nature of a generic product, as described below.

First, the generic drug product must be the same as its reference listed drug in that it must contain the same active ingredient, use the same route of administration, be in the same dosage form, and be of the same strength. 21 CFR 314.94(a)(5) and (6). These requirements ensure that the generic drug product is the same drug in the same strength as its reference listed drug.

Second, a generic applicant for a solid oral dosage form such as levothyroxine sodium may use inactive ingredients different from those used in the reference listed drug. However, the applicant must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that these inactive ingredients do not affect the safety or efficacy of the proposed drug product. 21 CFR 314.94(a)(9).

Third, an ANDA applicant must submit the same chemistry, manufacturing, and controls (CMC) information as required in an NDA. The required CMC information includes, among other things:

A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, specifications relating to stability, sterility, particle size, and crystalline form.

A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product); a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications and analytical methods

needed to assure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, specifications relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating.

21 CFR 314.50(d)(1).

These CMC requirements provide substantial assurance that the quality of the generic product (that contains the same active ingredient as the reference product) will be equal to that of the reference listed drug.¹

IV. Bioequivalence Testing for Generic Levothyroxine Sodium Drug Products

As can be seen from the extensive list of requirements enumerated in sections II and III above, bioequivalence testing is only part of the evidence that ensures that the generic drug product is the same as its reference listed drug. Bioequivalence testing is conducted in support of an ANDA submission to confirm that the generic and reference listed drug products, which contain the same active ingredient and are pharmaceutically equivalent, will perform similarly in the human body. Bioequivalence testing verifies that the active ingredient in a generic drug product will be absorbed into the body to the same extent and at the same rate as its corresponding reference listed drug product.

Bioequivalence studies are not only performed as part of the ANDA process, but also conducted by innovators to confirm equivalence between formulations when it is necessary to make manufacturing and/or formulation changes. For example, often the marketed drug product is different in formulation or method of manufacture from the product used in the pivotal clinical trials of safety and efficacy used to support the NDA. These differences may be the result of formulation changes necessary to scale up production from a small-scale (laboratory) size to a large-scale (commercial) size. After

¹ FDA's guidance for industry on *Levothyroxine Sodium Products Enforcement of August 14, 2001, Compliance Date and Submission of New Applications* states that the finished levothyroxine sodium product should be formulated to contain 100 percent of the labeled claim of the active ingredient when the product is released.

In addition to the application standards described above, the United States Pharmacopeia (USP) sets forth standards for the content of levothyroxine sodium drug products, as for most other drug products. The USP permits a levothyroxine sodium drug product to contain from 90 to 110 percent of the labeled dose. Although FDA recommends that levothyroxine sodium products contain 100 percent of their labeled claim of active ingredient at the time of release, the USP range accounts for the natural fluctuations in the potency of drug products resulting from the numerous complexities involved in pharmaceutical manufacturing. These variations in potency are considered a natural part of the manufacturing process. This USP standard is the same whether the levothyroxine sodium product was approved under an NDA or under an ANDA. Thus, to the extent there is a range of variation in the amount of active ingredient in levothyroxine sodium products, the permitted range is no different for an innovator product than for a generic product. The USP also sets forth a standard for the *in vitro* dissolution of levothyroxine sodium tablets. Innovator and generic products must satisfy the same standards.

approval, the innovator may modify the scale of production runs, equipment, manufacturing process, formulations, dosage forms, ingredient specifications, source of supplies, and method of synthesis of the active ingredient. In these cases, the marketed or reformulated product must demonstrate bioequivalence to the original formulation to confirm that the safety and efficacy of the product with the new formulation is the same as that of the product with the original formulation. Thus, the bioequivalence studies that generic companies must conduct to support an ANDA are the same as the bioequivalence studies that innovator companies must submit to an NDA to support formulation or manufacturing changes.

The design FDA recommends for a bioequivalence study of levothyroxine sodium products is consistent with FDA's general recommendation for bioequivalence testing of orally-administered drug products, whether conducted in support of an ANDA or NDA.² FDA recommends that a bioequivalence study of levothyroxine sodium products be performed using a single-dose, fast, two-treatment, two-sequence crossover design with at least a 35-day washout period between treatments. In a crossover study, study subjects receive the test (generic) and reference (innovator) products in separate sequences (either test before reference or reference before test), with a period between treatments of no drug administration (the "washout" period). The 35-day washout period is recommended because of the long half-life of levothyroxine. This period ensures that levothyroxine from the previous dose is cleared from the body before the second dose is administered. FDA recommends that the study be conducted in healthy subjects, usually 24-36 normal adults. As explained in section VI below, three initial plasma concentration measurements should be taken before dosing with the test and reference products to establish the baseline of endogenous levothyroxine for each study subject. FDA recommends that single doses of the test and reference drug products be administered to the subjects during the respective treatment phases, and the plasma concentrations of the drug be measured over time. FDA recommends that applicants use a 600 microgram (mcg) dose of levothyroxine sodium. A 600 mcg dose achieves plasma concentrations well above the baseline levels in study subjects. For each subject, the mean of the three pre-dose measurements should be subtracted from the post-dose plasma levothyroxine levels prior to calculation of the various pharmacokinetic parameters to correct for the presence of endogenous levothyroxine.

To evaluate the rate and extent of levothyroxine absorption, the measured plasma concentrations for each subject should be plotted graphically against time of measurement. The graph depicts the plasma sampling time on the horizontal (x) axis and corresponding plasma drug concentration on the vertical (y) axis. The relevant pharmacokinetic parameters calculated from these data include the "area under the plasma concentration vs. time curve" (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the extent of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant pharmacokinetic parameter is the maximum or "peak" drug concentration (C_{max}). C_{max} is used to reflect the rate of absorption.

² Guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (General Considerations guidance).

It is important to analyze the pharmacokinetic parameters statistically because of the variability inherent in human subjects. This variability means that if the same subject receives the *same* drug product on two different occasions, the resulting plasma concentrations will not be exactly the same. Because of this inherent variability, it is possible that if a single individual takes two *different* products on separate occasions, there may be a measurable difference in the pharmacokinetic parameters. In this situation, it is not clear whether this difference is the result of a difference between the products, or the result of variability in the individual's endogenous hormone levels. Thus, FDA recommends that ANDA or NDA applicants use statistical methods to estimate more accurately those differences in pharmacokinetics that result from the two product formulations.

When considering the results from bioequivalence studies, it is important to understand what statistical tests are used and how FDA uses the results of these statistical tests to determine whether two products are bioequivalent. To understand the statistical tests for bioequivalence, one must first understand the relevant statistical terms, particularly the definition of "mean" and "confidence interval." The statistical term "mean" is frequently used in describing bioequivalence study results. The mean is the average of all the differences in pharmacokinetic values observed in the small group of study subjects.

A "confidence interval" is used to address the factor of variability. Just as there is variation in pharmacokinetic values within an individual at different treatments, there is also variation in these values between treatment groups. Thus, if the same bioequivalence study is repeated in another small group of subjects, the second study's mean may be different from the first study's mean. Therefore, FDA defines a "confidence interval" to provide greater assurance that a single study's mean reflects accurately the results for other study groups. Essentially, the confidence interval provides an estimated range that is likely to contain the mean if the drug were given to the entire population. A confidence interval specifies the preferred degree of "confidence" (i.e., likelihood) that the estimate accurately reflects the results for the entire population.

In analyzing bioequivalence studies, FDA always uses a 90 percent confidence interval. For example, the ratio of the mean AUC or C_{max} values for a small study (reflecting the average difference between the test and reference products for all of the study subjects) could be 99 percent. Furthermore, a statistical analysis of the data could determine that the 90 percent confidence interval for this small study is a range of 90 percent to 110 percent in the ratio of pharmacokinetic values. This confidence interval shows that for the entire population, the ratio of the mean AUC or C_{max} between test and reference products is likely (with a 90 percent probability) to be between 90 percent and 110 percent. If the small study used a greater number of subjects to more accurately reflect the general population's results, then the 90 percent confidence interval would be smaller (i.e., a smaller range of the possible pharmacokinetic values in the general population, such as 95 to 105 percent).

FDA determines whether a study shows that two products are bioequivalent based on the confidence interval and not on the mean value of the study. The results of a study are expressed as a confidence interval for the ratio of test to reference products. To decide whether two products are bioequivalent, the calculated confidence interval is compared to an acceptance interval. The acceptance interval (also referred to as acceptance limits) is expressed as two numbers that provide upper and lower limits on the confidence interval. If the confidence interval is contained within this acceptance interval, then FDA concludes that the study demonstrates bioequivalence; if not, then the study does not demonstrate bioequivalence. The acceptance interval is a fixed standard, while the confidence interval is determined from the data in a particular study.

FDA considers that products are equivalent when the 90 percent confidence intervals for pharmacokinetic parameters are entirely within an 80 percent to 125 percent acceptance interval. The choice of the 80 to 125 percent acceptance interval reflects decades of scientific data on the variability of product characteristics (such as potency) within and between batches, as well as biological variability in patients. From these data, FDA concluded that the variability in pharmacokinetic values allowed under this acceptance interval would not adversely affect clinical outcomes, because this variability is within the range of differences that can already arise due to other product specific and biological factors.³ FDA has not found any clinical problems resulting from the thousands of drug products approved with passing bioequivalence results based on the current criteria.

It is important to note that the 80 to 125 percent boundaries are acceptance limits for the confidence interval and not a judgment about the acceptable mean differences between test and reference products. The sample mean pharmacokinetic values for the test and reference products lie at the center of the confidence interval. Because this confidence interval must fall within the 80 to 125 percent boundaries, these statistical criteria limit the acceptable range in which the mean values can stray from the 100 percent ratio. The actual mean differences FDA found for drugs tested and analyzed under this statistical procedure were much smaller than the 80 to 125 percent boundaries. In the 1980s, FDA reviewed 224 bioequivalence studies that passed the 80 to 125 percent criterion.⁴ In these studies, the observed mean difference in AUC between the brand name and the generic product was approximately 3.5 percent. This analysis was repeated for the 127 bioequivalence studies conducted for generic drugs approved in 1997.⁵ The average observed difference in AUC in these studies was approximately 3.3 percent.

Figure 1 below is provided to graphically illustrate the relationship between the mean value obtained from a bioequivalence study, the 90 percent confidence interval for that bioequivalence study, and FDA's acceptance limits of 80 to 125 percent. The center of

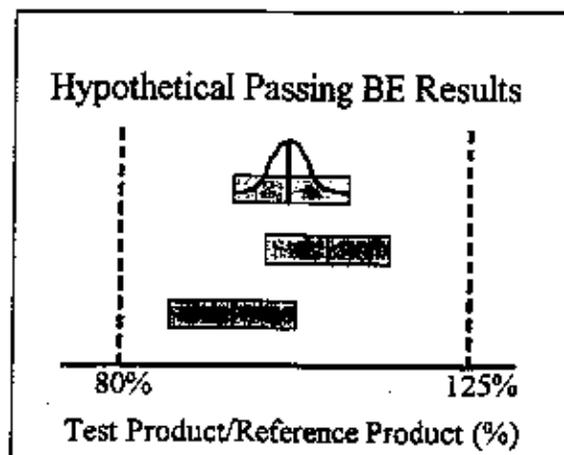
³ Dighe, S.V., and Adams, W.P., "Bioequivalence: A United States Regulatory Perspective," in: *Pharmaceutical Bioequivalence* (Welling P.G. et al., eds.), pp. 347-380, 1991.

⁴ Nightingale, S., and J.C. Morrison, "Generic Drugs and the Prescribing Physician," *JAMA*, 258:9, Sept. 4, 1987.

⁵ Henney, J.E., "Review of Generic Bioequivalence Studies," *JAMA*, 282:21, Dec. 1, 1999.

each box is the mean value from a bioequivalence study, while the entire box represents the confidence interval from the same bioequivalence study. Because the 80 to 125 percent acceptance limits are bounds on the confidence intervals, the mean values from the passing bioequivalence studies must be closer to 100 percent. The figure illustrates that the actual mean differences between test and reference listed products will be much smaller than FDA's bioequivalence acceptance criterion of 80 to 125 percent.

Figure 1: Hypothetical results from bioequivalence (BE) tests for approved generic drugs



V. Abbott's Study M02-417

Abbott's Study M02-417 submitted in support of Abbott's petition was a three-way crossover study using 33 healthy subjects. Each subject received doses of 400, 450, and 600 mcg of levothyroxine sodium in random order. Plasma levels of both T4 and TSH were measured until 96 hours after dosing. Between each treatment period there was a washout period of 44 days or 53 days.

When Abbott analyzed the data without using baseline correction to subtract endogenous levels of T4, the 400, 450, and 600 mcg doses were all found to be bioequivalent to each other. Abbott then concluded that the data should be baseline corrected.

Abbott analyzed the T4 data in its study using three baseline correction methods:

Method 1: The pre-dose baseline value of T4 on the day of dosing was subtracted from each post-dose concentration. The pre-dose baseline value was calculated as the average of the three concentrations measured at -0.5, -0.25, and 0 hours prior to dosing in each period.

Method 2: For each time of post-dose sampling, the observed concentration was corrected assuming that the endogenous T4 baseline level at 0 hours declines according to a half-life of 7 days.

Method 3: Subjects' T4 concentrations were sampled repeatedly for 24 hours before dosing. The T4 concentration for each time of post-dose sampling was corrected by subtracting the concentration observed at the same time of day during the 24 hours preceding the dose.

When baseline correction Method 1 was used, the 400 and 450 mcg doses could both be distinguished from the 600 mcg dose in bioequivalence results, but they could not be distinguished from each other.

VI. Baseline Correction Makes Bioequivalence Results for Levothyroxine Sodium Products More Rigorous

As explained in detail below, FDA's bioequivalence methodology for levothyroxine sodium drug products uses baseline correction to make the comparison between two drug products.

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine, more commonly called T4. T4 is the active ingredient in levothyroxine sodium drug products. The T4 in the body that comes from a levothyroxine sodium drug product (exogenous T4) and the T4 that is produced by the body itself (endogenous T4) are identical. Therefore, when the plasma level of T4 is measured in a bioequivalence study that compares two levothyroxine sodium products, there is no way to determine what amount of T4 was contributed by the drug products and what amount was already present in the body.

In a pharmacokinetic study, baseline correction is a way of estimating the amount of endogenous drug and subtracting that amount from the total plasma or blood level of the measured pharmacokinetic parameter. Specifically, in a bioequivalence study comparing two levothyroxine sodium products, baseline correction provides an estimate of the amount of endogenous T4 and subtracts that amount from the total measured plasma levels of T4. By subtracting the estimated amount of endogenous T4, the bioequivalence comparison more closely reflects the difference between the two drug products.

In the human body, a feedback system regulates thyroid hormone production. In this system, when T4 levels increase, endogenous production of T4 decreases, and when T4 levels decrease, endogenous production of T4 increases. From what we know about that feedback system, it is clear that introducing relatively large amounts of exogenous T4 (from a levothyroxine sodium drug product) would have some effect in decreasing the body's production of endogenous T4. However, there is no scientific data to quantitatively determine the size of this effect. Accordingly, any method of baseline correction applied to the results of a bioequivalence study comparing levothyroxine sodium products must make an assumption about the effect of exogenous T4 on the body's production of T4.

Abbott's study presented three methods of baseline correction. Each of these methods makes a different assumption about the effect of exogenous T4 on the body's production of T4.

Abbott's Method 1 assumes that exogenous T4 has no effect on the level of T4 naturally produced in the body; thus baseline levels of T4 measured prior to dosing are the same as baseline levels of T4 after dosing. For this method, Abbott corrected the post-dose plasma level data by subtracting the average of three pre-dose measurements of T4.

Abbott's Method 2 assumes that exogenous T4 completely suppresses the natural T4 production in the body. The rate of elimination or removal of T4 is well known and expressed in the product labeling as the half-life (the time for half the T4 present to be removed). If the exogenous dose of T4 stops the endogenous production of T4 and elimination continues, the baseline levels of T4 will decrease after dosing. Using the half-life and the measured pre-dose concentration, the new baseline can be estimated at each sampling time. Abbott corrected post-dose plasma level data by subtracting the estimated baseline concentrations of T4 from the measured levels of T4.

Abbott's Method 3, like Method 1, assumes that exogenous T4 has no effect on the level of T4 naturally produced in the body, and thus baseline levels of T4 for 24 hours before dosing would be the same as the levels for 24 hours after dosing. Method 3 was based on multiple measurements of baseline T4 throughout a 24-hour period prior to dosing. These baseline values were subtracted from the values at the same time points that were measured after dosing.

Based on its review of Abbott's study, FDA adopted baseline correction as part of its bioequivalence methodology for the approval of generic levothyroxine sodium products. Baseline correction of bioequivalence comparisons of levothyroxine sodium products is appropriate for the following reasons. First, bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. See 21 U.S.C. 355(j)(8)(B)(i); 21 CFR 320.1(e) and 320.23(b). As applied to levothyroxine sodium products, this definition requires FDA to determine whether there is a significant difference between the exogenous T4 from these drug products in order to evaluate bioequivalence. Comparisons of total T4 concentrations that also include endogenous T4 do not reflect the rate and extent of absorption of the drug solely from the drug product.

Second, as supported by Abbott's study, the presence of endogenous T4 biases the results of a bioequivalence comparison in favor of demonstrating equivalence. When baseline levels are included in these comparisons, the difference in T4 that is attributable to the

difference between the two drug products is a smaller percentage of the total measured difference in T4. When baseline levels are subtracted from the data, however, the same difference in T4 that is attributable to the difference between the two drug products becomes a much larger percentage of the bioequivalence comparison. For example, if a hypothetical endogenous drug has an AUC of 100 total units for the reference product and 99 total units for the test product, the difference between the two products would appear to be 1 percent. If these total values were then adjusted for the endogenous amount of 90 units, this amount would be subtracted from the 100 total units for the reference product and 99 total units for the test product. Thus, with baseline correction, the real difference between the products would be calculated as 10 percent (10 remaining units for the reference product compared to 9 remaining units for the test product). Therefore, two products are less likely to be found equivalent with baseline correction, because the larger the baseline amount that is subtracted, the more difficult it is for the products to pass the test.

FDA evaluated the three methods of baseline correction and concluded that the bioequivalence results in Abbott's study were similar (i.e., closely aligned values) for these three methods. FDA chose Method 1 as part of its bioequivalence methodology for levothyroxine sodium because it is both the most conservative method (i.e., most difficult to demonstrate bioequivalence) and requires the least number of blood draws from study subjects. The baseline T4 levels subtracted from total T4 results in Method 1 are higher than with Method 2 and similar to Method 3. Subtracting more AUC from bioequivalence results makes it harder for two products to demonstrate bioequivalence.

In summary, FDA's bioequivalence methodology includes measuring baseline levels of endogenous T4 using three pre-dose samples. The mean of these three measurements is subtracted from the post-drug levels of the various pharmacokinetic parameters to correct for the presence of endogenous T4.

VII. Abbott's Study Does Not Demonstrate That FDA's Bioequivalence Method Will Allow the Approval of Products That Differ by 12.5 Percent

The petitioners assert that FDA would approve as equivalent two levothyroxine sodium products that differ by 12.5 percent in the delivery of levothyroxine sodium. Abbott Petition at 28-35; Jones Petition at 6-7. The petitioners base this assertion on the fact that Abbott's study found two products at different dosage strengths, one containing 400 mcg of levothyroxine sodium and one containing 450 mcg of levothyroxine sodium, to be bioequivalent. The petitioners conclude that FDA's bioequivalence method is inadequate because of this flawed comparison.

This assertion is invalid, however, because the petitioners base their argument on Abbott's use of doses significantly lower than the 600 mcg dose FDA recommends for bioequivalence testing. As discussed below, bioequivalence tests using doses significantly lower than the FDA-recommended dose can bias the results of the bioequivalence comparison in several ways. Furthermore, Abbott's claim that FDA would approve levothyroxine sodium products differing by 12.5 percent is also invalid

because Abbott wrongly assumes that such different products, particularly in dosage strength, could be approved as the same under FDA requirements.

A. Doses Lower than 600 mcg Do Not Accurately Reflect the Results of Bioequivalence Testing Using 600 mcg Doses

The petitioners' claim that FDA would approve as bioequivalent two products that differ by 12.5 percent is unfounded, because this claim is based on the use of doses that are significantly lower than the 600 mcg dose recommended by FDA.

FDA recommends the 600 mcg dose of levothyroxine sodium for bioequivalence testing to provide T4 levels that are sufficiently higher than endogenous levels in study subjects. The use of a higher dose provides greater assurance that the bioequivalence test measures accurately the rate and extent of absorption of the drug. At lower doses, such as the 400 and 450 mcg doses used in Abbott's study, the total amount of measured T4 consists of a greater percentage of endogenous T4 than at a higher dose, such as the 600 mcg dose recommended by FDA. When more of the measured concentration of T4 consists of endogenous T4 ("the noise"), the bioequivalence comparison is less sensitive to the actual differences in T4 concentrations that are present from administering the drug product ("the signal"). FDA's recommended use of this higher 600 mcg dose is a more conservative approach in addressing this "signal to noise" effect, because it is less likely that the presence of endogenous levels of T4 will bias the test results in favor of bioequivalence (i.e., making it more difficult to show bioequivalence).

FDA has not recommended any dose greater than 600 mcg for bioequivalence testing because there is limited data available in the literature on subjects' responses to doses larger than this amount. There is also no assurance, based on the literature, that a dose higher than 600 mcg would not present a safety concern. Accordingly, FDA chose the 600 mcg dose as the highest recommended dose for which there was evidence of safety and effectiveness.⁶

It is also important to note that FDA recommends a 600 mcg dose for the same reason that the petitioners advocate baseline correction—to more accurately measure the differences that are due to administration of exogenous levothyroxine sodium, rather than other factors. Despite Abbott's arguments to the contrary (Abbott Petition at 33), it is not inconsistent to use both baseline correction and a 600 mcg dose for bioequivalence tests. In fact, both of these recommended steps help ensure a more accurate bioequivalence result.⁷

⁶ Another problem with using lower doses, such as the 400 and 450 mcg doses in the Abbott study, is the resulting increase in assay variability. Using a larger dose, such as 600 mcg, makes the bioequivalence comparison more precise because it reduces this assay variability. Abbott argues that the current assay method for T4 "provides adequate precision." Abbott Petition at 35. However, using a larger dose reduces the risk of any imprecise measurements from this assay variability.

⁷ Abbott argues that FDA must issue the 600 mcg standard by notice and comment rulemaking. Abbott Petition at 34, n. 29. FDA, however, has not applied the recommendation as a rule under the Administrative Procedure Act, 5 U.S.C. 551. An applicant could use a different approach if it satisfied

Abbott's comparisons in its study between the 400 mcg and 450 mcg doses are irrelevant to the sensitivity of FDA's bioequivalence method, because these doses are significantly smaller than the 600 mcg dose recommended by FDA.⁸ Abbott's study, in fact, did not show any inaccurate bioequivalence findings in the comparisons of results to the 600 mcg dose. As explained above, the presence of endogenous levels of T4 is more likely to bias the results of bioequivalence studies at lower administered doses, such as the 400 mcg and 450 mcg doses. FDA recommended the use of the 600 mcg dose to ensure the increased sensitivity of the bioequivalence test and decrease the risk of inaccurate bioequivalence findings, such as alleged by petitioners based on Abbott's study results. Thus, the conclusion Abbott draws from its study (that FDA would approve as equivalent doses that differ by 12.5 percent) is invalid because Abbott achieved its study results only by its choice of doses that are significantly lower than the 600 mcg dose FDA recommends for bioequivalence testing.⁹

B. Products With Different Dosage Strengths Would Not Be Approved as Bioequivalent and the Same Under FDA Approval Requirements

The principle underlying petitioners' arguments concerning Study M02-417 is that products differing by 12.5 percent in dosage strengths could be approved as the same labeled dosage amount.¹⁰ In arguing that FDA would approve as bioequivalent two products that differ by 12.5 percent, petitioners ignore the fundamental requirements for bioequivalence testing, as well as for drug approvals generally, that would prevent such flawed findings of bioequivalence.

FDA's scientific concerns and the requirements of the applicable statutes and regulations. In the context of this 600 mcg recommendation, FDA has explained carefully how Abbott's comparison of the 400 and 450 mcg doses is irrelevant to the validity of FDA's bioequivalence method. Furthermore, it is important to note that Abbott raises inconsistent arguments in challenging FDA's recommendation of a 600 mcg dose for bioequivalence testing. Abbott asserts that FDA's justification for its choice of a 600 mcg dose is arbitrary, but Abbott also admits that it is within FDA's discretion to choose the dose to be used for bioavailability and bioequivalence testing. Abbott Petition at 35, 41.

⁸ Abbott argues that FDA's acceptance of Mylan's bioequivalence study using a 500 mcg dose undermines the Agency's recommendation to use a 600 mcg dose. Abbott Petition at 32. FDA notes, however, that Mylan included two other bioequivalence studies using 600 mcg doses.

⁹ Abbott also argues that "no amount of potency and dissolution testing can assure bioequivalence when the applicable in vivo methodology is itself incapable of distinguishing among products known to deliver different amounts of the drug." Abbott's April 15, 2004, supplement at 7. FDA does not disagree. However, Abbott's statement is irrelevant because Abbott's study does not demonstrate that FDA's bioequivalence methodology for levothyroxine sodium is inadequate.

¹⁰ To the extent the petitioners also assert that FDA's bioequivalence method fails to distinguish between 12.5 percent differences in bioavailability between products, the petitioners fail to provide any relevant evidence in support of this argument. Petitioners rely on Abbott's Study M02-417 to support their argument, but this study tested whether or not products with different dosage amounts of levothyroxine sodium, and not products with known differences in bioavailability, could be found bioequivalent.

First, the petitioners ignore the essential ANDA approval requirement that the generic product must be the same strength as the innovator product. For this reason, a bioequivalence study compares two products "administered at the same molar dose." 21 CFR 320.1(e). Thus, the comparison between the 400 mcg and 450 mcg dosage strengths, relied upon by petitioners in challenging FDA's recommended bioequivalence method, is inapplicable under FDA's regulations for bioequivalence.¹¹

Second, the petitioners wrongly assume that bioequivalence testing should ensure that the drug content of the compared two products is the same. For example, Jones states: "FDA must develop new acceptable criteria for bioequivalence in levothyroxine sodium tablet products . . . capable of distinguishing between drug products that differ by as little as 12.5% in drug content and by rate of absorption and total body distribution." Jones Petition at 3. Bioequivalence testing, however, is not a method to determine drug content. Bioequivalence testing of levothyroxine sodium drug products determines whether the body absorbs the same amount of active ingredient at the same rate (within the statistical criteria) from two different levothyroxine sodium products. 21 CFR 320.1(e). Drug content, on the other hand, is measured in vitro by a chemical assay. Thus, the petitioners' request that FDA develop a bioequivalence test to distinguish between differences in drug content is inconsistent with the purpose and definition of the bioequivalence test.

Third, petitioners ignore other regulatory requirements that would prevent products differing in dosage strength from being approved as the same. These requirements, such as the submissions for chemistry and manufacturing controls, ensure that products are manufactured at their specified doses and maintain their potency and stability. FDA's current good manufacturing practice regulations ensure that approved products are manufactured and marketed at their labeled dosage strength. Thus, to the extent petitioners argue that FDA's bioequivalence method allows the approval of drug products varying in dosage strength by 12.5 percent as the same, this concern is unfounded.

VIII. Other Criticisms of FDA's Bioequivalence Methodology for Levothyroxine Sodium Products

The petitioners criticize a number of aspects of FDA's bioequivalence methodology for levothyroxine sodium products. These criticisms are discussed below.

A. Intrasubject Variability

Abbott asserts that FDA is likely to approve as equivalent levothyroxine sodium products that, in fact, are not equivalent because the intrasubject variability of levothyroxine sodium is low. Intrasubject variability means that pharmacokinetic values for the same subject are different when the subject is tested at different times.

¹¹ A bioequivalence study that was properly designed to test FDA's bioequivalence methodology for levothyroxine sodium would compare two levothyroxine sodium products that had been intentionally made to differ in bioavailability, but contained the same labeled amount and content of levothyroxine sodium at a total dose of 600 mcg.

In general, as Abbott asserts, when intrasubject variability is low, there is a greater risk that products that are not in fact bioequivalent could be found bioequivalent. Abbott Petition at 20-21. However, Abbott's conclusion that FDA will approve levothyroxine sodium products that are not bioequivalent ignores the fact that FDA's bioequivalence methodology for levothyroxine sodium uses baseline correction. Intrasubject variability with levothyroxine sodium is relatively low when the data are not baseline corrected to subtract endogenous T4 levels. With baseline correction, however, the intrasubject variability of levothyroxine sodium is higher and is similar to that for other approved drug products. Thus, baseline correction adequately addresses the potential problem of intrasubject variability.

B. Washout Period

In a crossover study, it is possible for the first treatment to have an effect (referred to as "carryover") on the result of the second treatment. Carryover may occur when testing a drug with a long half-life if the washout period between treatments is not long enough. Therefore, the washout period needs to be sufficient for nearly all of the drug given in the first treatment to be eliminated from the subjects' bodies before they receive the drug given in the second treatment. The major concern in these types of studies is that any carryover that occurs is not equal between the test and reference products. This unequal carryover, if it occurs, can bias the results of the study. If carryover between the two products is equal, this effect does not bias the study results.

Abbott's Study M02-417 used washout periods of 44 and 53 days. Abbott states that its study shows there are carryover effects of up to 53 days with supra-therapeutic doses of levothyroxine sodium, such as the 400, 450, and 600 mcg doses used in Abbott's study. For this reason, Abbott suggests that an appropriate bioequivalence study should use a washout period longer than the 35 days FDA recommends or use another method to account for the carryover effect. Abbott Petition at 8, 41.

Abbott has not established that a longer washout period or another method of addressing carryover is necessary to correct FDA's bioequivalence methodology for levothyroxine sodium products. Abbott's study provided evidence only that there may be unequal carryover effects when *different doses* are administered. Abbott's study does not demonstrate that there will be unequal carryover when the *same dose* is used, as in bioequivalence studies submitted for approval of generic levothyroxine sodium products. Furthermore, FDA's review of the bioequivalence study submitted for approval of Mylan's ANDA referencing Unithroid identified no statistically significant sequence effects and thus no unequal carryover. Nor did FDA's review of the studies submitted by NDA applicants for levothyroxine sodium products comparing tablet formulations to a standard solution identify any such sequence effects. These results are evidence that Abbott's study comparing different doses is not relevant to bioequivalence studies that use the same dose.

C. Comparing T3

The USP monograph for levothyroxine sodium permits levothyroxine sodium products to contain up to 2 percent T3. Jones states that because T3 is the active thyroid hormone, bioequivalence testing for levothyroxine sodium products should also compare serum T3 levels. Jones Petition at 9.

FDA disagrees. In general, FDA recommends that bioequivalence studies measure only the parent drug released from the dosage form, rather than the metabolite. General Considerations guidance at 18. The rationale for this recommendation is that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. General Considerations guidance at 18. In addition, although T3 is a metabolite of T4, it is also directly produced in the body; thus, measuring T3 would not be a true indicator of the absorption of T4 from levothyroxine sodium products.

D. Confidence Interval

The petitioners suggest that FDA consider narrowing the bounds of the 90 percent confidence interval for bioequivalence testing of levothyroxine sodium products.¹² Jones Petition at 10; Abbott Petition at 36-38. Neither petitioner, however, has presented scientific evidence to show that tighter acceptance criteria are necessary to ensure that non-bioequivalent levothyroxine sodium products are not rated bioequivalent.

1. **Petitioners fail to show the necessity for narrowing the acceptance limits for the confidence interval**

Abbott suggests that it is particularly important to narrow the statistical acceptance criteria for levothyroxine sodium because it is a narrow therapeutic range drug. Abbott Petition at 37. FDA does not believe that it is necessary to narrow the statistical acceptance criteria for bioequivalence studies simply because the drug being studied has a narrow therapeutic range. In the General Considerations guidance, FDA recommends that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs, but the Agency does not recommend changing the normal acceptance criterion of 80 to 125 percent. General Considerations guidance at 20. In fact, FDA has approved other drugs with narrow therapeutic ranges, such as digoxin, phenytoin, and warfarin, without changing the acceptance criteria, and there is no documented scientific evidence of safety or efficacy problems with these drugs. To the extent petitioners argue that FDA's statistical standards are insufficient to ensure a meaningful bioequivalence result for levothyroxine sodium products, FDA has already explained in section VI above how its baseline correction method ensures greater accuracy in the bioequivalence measurement.

¹² Although Jones refers to narrowing the confidence interval itself, we assume that Jones is actually recommending that the bounds of the 90 percent confidence interval be narrowed.

As explained in section IV above, FDA's statistical analysis for bioequivalence considers both the mean values for pharmacokinetic factors and the individual variation in values. In practice, because of the intrasubject variability in the responses of human subjects to drugs, the mean bioavailability values of an innovator and a generic product must be very close to satisfy FDA's bioequivalence acceptance criteria. FDA's two surveys of passing bioequivalence studies (224 studies reviewed in the 1980s and 127 reviewed for generic drugs approved in 1997) found observed mean differences in AUC between the brand name and the generic product of about 3.5 percent and 3.3 percent, respectively.¹³ As explained in section VIII.A above, the intrasubject variability of levothyroxine sodium is higher with baseline correction and similar to that for other approved drugs. These studies demonstrate that FDA's statistical standards are sufficient to ensure that drugs, including levothyroxine sodium, with unacceptable differences in relevant pharmacokinetic values are not found bioequivalent.¹⁴

Furthermore, if the bounds on the confidence interval were narrowed, it would be necessary to use many more subjects to give the study sufficient statistical power. Using more subjects would make bioequivalence testing more expensive (in both the NDA and ANDA contexts). Raising the cost of bioequivalence testing on a speculative, non-scientific basis would be inconsistent with the principles of the Hatch-Waxman Amendments to make low-cost, generic drugs available to the public. In addition, using more subjects without a strong scientific justification would also be inconsistent with the basic principle that no unnecessary human research should be done.

2. Petitioners' challenge to the acceptance limits for levothyroxine sodium bioequivalence tests undermines their own NDA approvals

In challenging FDA's statistical analysis for bioequivalence, petitioners implicitly challenge FDA's statistical analysis for their own NDA approvals. It is important to understand that the same bioequivalence methodology used to approve generic drugs is used when an innovator product is compared to itself. There are many circumstances in

¹³ The evidence from these surveys also invalidates the simulation study that Abbott's petition discusses. Abbott Petition at 8-11. Abbott asserts that the simulation shows that a test levothyroxine sodium product that delivers 15 percent less or more of levothyroxine than a reference product would have a 26 percent (or 42 percent) chance of being declared bioequivalent to the reference product (by both C_{max} and AUC) in a 36-subject study that used the 80 to 125 percent acceptance criterion. However, the simulation assumes that the test and reference products differ by 15 percent in the delivery of levothyroxine — an assumption that is exceedingly unlikely. The standard deviation around the mean AUC difference of 3.5 percent from the 1980s survey was 2.84 percentage points. The 15 percent mean AUC difference assumed in Abbott's simulation would be four standard deviations from the mean. The probability of such a result is less than 1 percent. A 15 percent difference between an innovator and a generic product in the amount of active ingredient would also not be possible because of the CMC requirements for ANDA applicants.

¹⁴ With regard to these surveys, Abbott argues in its June 4, 2004, supplement that "only the confidence intervals around [the] mean measurements should be considered in evaluating the true differences between products." Abbott's June 4, 2004, supplement at 10-11. In fact, the mean values in the surveys are relevant to FDA's evaluation of Abbott's simulation and study because Abbott claims that FDA's bioequivalence method cannot distinguish mean differences of 12.5 or 15 percent.

which an innovator conducts bioequivalence studies, for example, when the formulation to be marketed is different from the formulation used in clinical studies. Moreover, after approval, the innovator may modify the scale of production runs, equipment, manufacturing process, formulations, dosage forms, ingredient specifications, source of supplies, and method of synthesis of the active ingredient. When such significant changes are made, FDA accepts the results of the innovator's bioequivalence study to demonstrate equivalence between the "old" and "new" products using the same bioequivalence criteria used to evaluate generic drugs.

In fact, FDA used the same confidence interval bounds to accept data analyses from NDA applicants seeking approval for levothyroxine sodium products. Sponsors for levothyroxine sodium products approved under NDAs, including Abbott's Synthroid and Jones' Levoxyl, conducted studies to demonstrate that different dosage strengths were proportionally equal to each other (e.g., six 100 mcg tablets are bioequivalent to two 300 mcg tablets).¹⁵ The study design used for that demonstration is essentially the same as that used to show whether a generic levothyroxine sodium product is bioequivalent to its reference listed drug, except that bioequivalence studies now require analysis of baseline corrected data. All other aspects of the study, including the dose used, the washout period, and the acceptance limits for the 90 percent confidence interval, are the same. It is illogical to believe that these features of a study, particularly the 80 to 125 acceptance range for a 90 percent confidence interval, were acceptable for the purpose of showing dosage proportionality, but not acceptable to show equivalence between an innovator and a generic product.

From the clinical point of view, it is just as important that dosage strengths within a product line be proportional as it is that generic products be therapeutically equivalent to their reference listed drugs. Titrating patients to the proper dose to control their hypothyroidism would not be possible if different dosage strengths were not proportional. For example, the clinician needs to know that a 50 mcg tablet is equivalent to two 25 mcg tablets. When clinicians prescribing Synthroid and Levoxyl adjust their patients' doses, they are relying on the same study design that is used to conclude that a generic version of Synthroid or Levoxyl is equivalent to Synthroid or Levoxyl.

3. FDA is not required to promulgate through notice and comment rulemaking its statistical analysis for bioequivalence testing for levothyroxine sodium products

Abbott also argues that FDA's failure to narrow the confidence interval for levothyroxine sodium indicates that the Agency is applying the 80 to 125 percent acceptance criterion as a rule. Abbott contends that if the Agency treats the 80 to 125 criterion as a rule, then it must adopt that rule through notice and comment rulemaking. Abbott Petition at 37. As discussed below, FDA does not find this argument persuasive.

¹⁵ See FDA's guidance on *Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing*.

FDA has clarified its statistical analysis of bioequivalence data in its guidance for industry on *Statistical Approaches to Establishing Bioequivalence* and in the Orange Book. The 80 to 125 acceptance criteria is a scientific judgment about the best statistical practices to use in bioequivalence testing and is not an appropriate subject for notice and comment rulemaking. FDA's statutory duty to evaluate generic drugs for approval requires the Agency to use its scientific judgment when analyzing bioequivalence data to determine whether there is a "significant difference" in the rate and extent of absorption of the drug. 21 U.S.C. 355(j)(8)(B)(i). FDA has established by notice and comment rulemaking those specific types of evidence appropriate for the design of bioequivalence studies. 21 CFR 320.24. FDA has also established by notice and comment rulemaking general principles to be followed for the design of a bioequivalence study. 21 CFR 320.26. These regulations establish the general parameters and requirements for bioequivalence studies.

FDA recommended the statistical analyses for these study results as guidance to allow for appropriate adjustments to the analysis in individual cases. This approach through guidance, rather than binding rulemaking, provides both FDA and applicants with flexibility in determining the most appropriate analysis for individual bioequivalence tests.

FDA has not applied this recommendation as a rule, but instead has and would vary the acceptance criteria in an appropriate case. As Abbott acknowledges, FDA is willing to adjust this statistical standard (either by narrowing or widening the confidence interval acceptance criteria) in those circumstances where the real differences permitted under the standard would be clinically significant. For example, FDA widened the bounds of the confidence interval acceptance criteria when the Agency approved generic albuterol inhalers, because the parameter being compared was a pharmacodynamic one (FEV1—forced expiratory volume at 1 minute) and because subject responses were highly variable. The petitioners, however, have failed to justify an amendment of this standard for levothyroxine sodium products. In fact, the only evidence submitted by Abbott demonstrates that the Agency's baseline correction method increases the accuracy of FDA's bioequivalence methods.

IX. Levothyroxine Sodium Tablets Behave Like Solutions

Evidence about the relative bioavailability of levothyroxine sodium drug products compared to a solution formulation of levothyroxine sodium provides further assurance that FDA-approved products will be therapeutically equivalent. The primary difference between a tablet and a solution formulation of the same drug is that before the tablet formulation can be absorbed it must dissolve, while the solution formulation is already dissolved. A solution formulation is orally absorbed as rapidly and completely as possible for that drug. The faster the tablet dissolves, the more likely the tablet formulation would be absorbed at the same rate and extent as a solution formulation. Thus, differences in bioavailability between a tablet and a solution are a measure of the effect of the formulation and manufacturing of the tablet product on its bioavailability. All solution

formulations of the same drug are considered to be equivalent to each other.¹⁶ Therefore, if the drug from all tablet formulations is absorbed to the same rate and extent as from a solution, then these tablet formulations would all be considered equivalent to each other.

Each NDA sponsor conducted an in vivo study to determine the relative bioavailability of its tablet formulation of levothyroxine sodium compared to a reference oral solution. Table 1 below shows the results of that comparison for seven products.

Table 1: Relative bioavailability of tablets versus a solution

Sponsor	AUC ₄₈ ratio (90% CI)	C _{max} ratio (90% CI)
Stevens	99 (93-102)	97 (93-101)
Jones	98 (96-101)	95 (91-98)
Alara/Mova	99 (96-102)	98 (94-102)
GenPharm	99 (97-101)	99 (95-102)
Abbott	93 (90-96)	84 (81-87)
Lloyd	94 (91-98)	91 (86-96)
Vintage	94 (92-97)	93 (91-96)

Each row of the above table lists the mean ratio of either AUC or C_{max} between the NDA product and the reference oral solution. The values in parentheses are the 90 percent confidence interval around each mean value. For all of the products in Table 1, the difference between the AUC of total T4 for the tablet and the AUC of total T4 for the solution ranges from 1 to 7 percent, and the mean difference is 3 percent. The differences in C_{max} range from 1 to 7 percent, except for Abbott's Synthroid product at 16 percent.

These observed differences are small relative to the variability inherent in levothyroxine sodium tablets and in the physiology of drug absorption. The mean variability in the levothyroxine dosage form proportionality studies submitted to FDA was approximately 6 percent. This 6 percent variation, determined from subjects' response to doses of 12x50 mcg and 6x100 mcg tablets from the same manufacturer, is approximately the same as the observed differences between the tablets and a solution. In addition, the mean differences

¹⁶ One of the principles of FDA's bioavailability and bioequivalence regulations is that the in vivo bioavailability or bioequivalence of certain drug products is self-evident when there is no question that the drug substance is released from the drug product. 21 CFR 320.22(b); General Considerations guidance. The simplest example of this principle is a parenteral drug product. There is no issue about whether a parenteral drug product is absorbed because it enters the bloodstream directly. FDA regulations consider the bioequivalence of oral solutions to be similarly self-evident. 21 CFR 320.22(b)(3).

between the tablets and a solution are also smaller (with the exception of Abbott's Synthroid product) than the within-product differences in potency (10 percent) that are permitted by the USP.

The fact that the observed differences between the tablets and a solution are relatively small indicates that all of these products were manufactured and formulated in such a way that they dissolve quickly in the body and do not use any excipients that interfere with absorption. These seven products do not have identical formulations. They use different excipients in different combinations and proportions and are manufactured using different processes and under different conditions. The similar performance of these seven different products is evidence that the FDA approval process leads to products of high quality.

These results provide further assurance that FDA will not approve products as bioequivalent that are in fact inequivalent. Under the applicable statutory and regulatory requirements, FDA will not permit any future levothyroxine sodium product to use an excipient that was not present in an already approved product without providing evidence that the new excipient does not interfere with the absorption of the drug. In addition, any levothyroxine sodium product approved in the future would be subject to the same manufacturing process controls and standards as the currently approved products. Because future products would be subject to the same constraints and standards, it is expected that these products would be of a similar quality to that of the currently approved products, would dissolve quickly in the body, and would not be significantly different from their reference listed drugs. These similarities would provide greater assurance that future approved levothyroxine sodium products would in fact be bioequivalent to their reference listed products.

X. Bioequivalence Testing in Athyrotic Patients Measuring TSH

The petitioners suggest that FDA should consider measuring TSH (thyroid stimulating hormone) rather than T4 in bioequivalence testing for levothyroxine sodium products. Jones Petition at 10; Abbott Petition at 41. Jones states that TSH is "the true indicator of thyroid hormone balance" because physicians use TSH to diagnosis hyperthyroidism or hypothyroidism and to adjust patients' dosages. Jones Petition at 3-4. Jones also asserts that TSH is a much more sensitive measure than T4 or T3. Jones Petition at 4.

The petitioners also suggest that FDA consider recommending that bioequivalence testing for levothyroxine sodium products use athyrotic patients as study subjects. Jones Petition at 10; Abbott Petition at 41. Athyrotic patients have no endogenous production of thyroid hormone and must use levothyroxine sodium therapy (or other thyroid replacement therapy) to maintain normal metabolic functioning. Abbott suggests that a bioequivalence study using athyrotic patients would be more accurate than a bioequivalence study in normal subjects. Abbott Petition at 40.

TSH levels change slowly in response to administration of levothyroxine sodium. It typically takes at least six weeks for TSH levels to reflect a change in the amount of levothyroxine sodium given a patient. Thus, in a bioequivalence study using TSH as the

measured endpoint, TSH levels could not be measured until subjects had been receiving levothyroxine sodium for at least six weeks. Such a study would have to be conducted in patients because it would be unethical to expose normal subjects to levothyroxine sodium for such an extended period of time. Thus, the petitioners' two suggestions—measuring TSH and testing in patients—are inextricably linked.

Contrary to Abbott's assertion, a bioequivalence study measuring TSH in athyrotic patients would be a much less accurate and reliable way to compare the rate and extent of absorption of two drug products than the bioequivalence methodology FDA recommends. The purpose of bioequivalence testing is to measure the release of the drug substance from the drug product. Measuring T4, the active ingredient in levothyroxine sodium products, accomplishes that purpose, but measuring TSH does not. TSH is not a direct measure of any property of drug products, but instead is a pharmacodynamic endpoint that measures an effect in the body resulting from drug administration.

In addition, using TSH as the endpoint to be measured in bioequivalence testing would be less accurate than measuring T4 because both the inter-subject variability and intra-subject variability of TSH are high. TSH levels in patients receiving the same dose of levothyroxine sodium can vary greatly. A range of TSH values from 0.5 to 5.4 international units/milliliter (IU/mL) is considered normal. Even in an individual patient, the TSH value does not remain constant. In clinical practice, it is not unusual for a patient receiving the same dose of the same levothyroxine sodium product to have, for example, a TSH of 3 at one doctor's visit, a TSH of 2 at the next visit, and a TSH of 1.5 at the next visit. Even though the TSH values differ, the patient is clinically and biochemically euthyroid (i.e., no symptoms of thyroid dysfunction and thyroid function tests within normal limits) at each visit. This clinical experience of variability is supported by a study that observed the intra-subject variability of TSH to be up to 200 percent.¹⁷ Because there is so much inherent inter-subject and intra-subject variability in TSH levels, a bioequivalence test measuring TSH levels would not accurately reflect the contribution of the drug product. Therefore, TSH is not an appropriate measure for bioequivalence testing.

The type of concerns with pharmacodynamic endpoints discussed above are the reason that FDA regulations recommend the use of such an endpoint only when the active ingredient cannot be measured directly in biological fluids. 21 CFR 320.24(a) provides:

An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section only when appropriate methods are not available for

¹⁷ Dong, B.J., et al., "Bioequivalence of Generic and Brand-name Levothyroxine Products in the Treatment of Hypothyroidism," *JAMA*, 277:1205-1213, April 16, 1997.

measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

T4, the active ingredient of levothyroxine sodium, is readily measurable in plasma. Thus, under FDA regulations, T4 is the recommended endpoint for bioequivalence studies. The petitioners have failed to provide any legitimate scientific justification under the regulations as to why the measurement of T4 is inadequate for a bioequivalence determination.

In sum, for all the reasons discussed above, a bioequivalence study of levothyroxine sodium using athyrotic patients would not be an accurate and reliable way to compare the amount of drug released from two drug products. FDA's bioequivalence method for levothyroxine sodium, which uses normal subjects and measures T4, is a more accurate study design.

XI. Abbott's Concerns About Clinical Consequences From Product Substitution Are Unfounded

Abbott submitted a number of declarations from endocrinologists and clinical study reports to emphasize the need for precise dosing of levothyroxine sodium, particularly for the treatment of thyroid cancer and hypothyroidism in certain patient populations. In its February 9, 2004, supplement to the petition, Abbott states: "[T]he expert declarants describe the critical importance of titrating patients to precise doses of levothyroxine, and how a change in dose of as little as 9 or 12 percent can put patients at serious risk."¹⁸ Supplement at 2. Abbott appears to rely on these declarations and studies to argue that harm would result in patients being switched from Synthroid to another levothyroxine sodium product that differed in dosage amounts by 9 to 12.5 percent.¹⁹ For example, the

¹⁸ Abbott's reference to a 9 percent difference derives from its misrepresentation of FDA's response denying Knoll Pharmaceuticals' citizen petition asking FDA to find Synthroid to be generally recognized as safe and effective. (Knoll manufactured Synthroid prior to Abbott's acquisition of the product.) The confidential appendix to FDA's response contained a description of a hypothetical patient who received different amounts of levothyroxine sodium from one refill to the next. (FDA has not previously disclosed anything from the Confidential Appendix. However, because Abbott has discussed the appendix in its citizen petition, the Agency is briefly discussing the appendix only to refute Abbott's mischaracterization of FDA's petition response.) The amounts differed by 19 percent – not the 9 percent Abbott asserts. In this hypothetical, the tablets from one refill would have contained a higher dose than the one prescribed; the tablets from the other refill would have contained a lower dose than the one prescribed. FDA's conclusion about the effect of the two doses on the hypothetical patient was: "On the first dose, the patient is likely to be mildly hyperthyroid, while on the second dose, the patient is likely to be mildly hypothyroid." FDA described this hypothetical scenario as an example of a possible clinical risk to patients taking unapproved levothyroxine sodium tablets.

¹⁹ Jones also included one study in its petition (Carr, D., et al., "Fine Adjustments of Thyroxine Replacement Dosage: Comparison of the Thyrotropin Releasing Hormone Test Using a Sensitive

concluding paragraph of the declaration of Jerome M. Hershman states: "[T]he substitution of two different manufacturers' levothyroxine products, that differ from one another by 12.5%, or even as little as 9%, can have a clinically significant effect on patients." The underlying premise of Abbott's argument appears to be that if FDA applies its current standards for levothyroxine sodium products, then the Agency will approve as therapeutically equivalent products that differ by 9 to 12.5 percent.

Abbott's premise is incorrect. As explained in section VII above, FDA's standards for levothyroxine sodium products will not allow products that differ by 9 percent or more in potency or bioavailability to be rated therapeutically equivalent. Thus, Abbott's submitted declarations and studies concerning the adverse clinical effects from products differing in potency and bioavailability fail to show that FDA's bioequivalence standards for levothyroxine sodium products are inadequate.

With regard to potency, products that are rated as therapeutically equivalent must contain the same amount of active ingredient. As explained in section VII above, Abbott's focus on bioequivalence testing as a means to ensure the approval of levothyroxine sodium products with proper potency and stability is misplaced. Instead, numerous other requirements in the Act and FDA's regulations, such as those concerning submissions on chemistry, manufacturing, and controls, ensure that drug products are manufactured and released at the proper dosage amounts and maintain their potency.

With regard to bioavailability, as discussed in section IV above, FDA's two reviews of passing bioequivalence studies (224 studies reviewed in the 1980s and 127 reviewed for ANDAs approved in 1997) found that the average observed differences in AUC were 3.5 and 3.3 percent, respectively. There is no evidence to suggest that a difference in bioavailability of 3.3 or 3.5 percent would have any clinical consequences, even for the patients most in need of precise dosing (e.g., thyroid cancer patients).

Finally, Abbott inappropriately asks the Agency to "quantify the clinically acceptable difference that may be allowed between substitutable (*i.e.*, "AB" rated) levothyroxine products." Abbott Petition at 40. In making this request Abbott also relies on the flawed assumption that FDA will rate two levothyroxine sodium products as therapeutically equivalent when there are significant differences in potency and bioavailability between the products. As described above, FDA's therapeutic equivalence ratings ensure that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Thus, there is no need for FDA to quantify any clinically acceptable difference in substitutable products.

Thyrotropin Assay with Measurement of Free Thyroid Hormones and Clinical Assessment," *Clinical Endocrinology (Oxf)*, 28:325-333, 1988) that the firm states shows that changes of 25 mcg from the optimum levothyroxine sodium dose "can render a patient hyperthyroid or hypothyroid." Jones Petition at 3.

XII. TSH Levels Naturally Fluctuate

Several physicians who commented on Abbott's petition asserted that it is important that patients be maintained on a single brand of levothyroxine sodium.²⁰ One comment stated that changing brands of levothyroxine sodium can result in a change in TSH.²¹ The assumption underlying this comment is that patients' TSH levels do not fluctuate when they take only one brand of levothyroxine sodium. However, the evidence FDA gathered in support of declaring levothyroxine sodium a new drug indicated that patients who were maintained on Synthroid, for example, *did* experience variations in TSH.

It is important for physicians to recognize that there are many reasons for TSH levels to fluctuate that are unrelated to the characteristics or quality of levothyroxine sodium products. Many drugs affect thyroid hormone pharmacokinetics and metabolism. The labeling for Synthroid and Levoxyl contains an extensive list of drugs that may affect thyroid hormone levels. For example, commonly used antacids may reduce the efficacy of levothyroxine sodium products by binding T4 and delaying or preventing the absorption of T4. These effects, in turn, may alter TSH levels through feedback interaction at the level of the pituitary. One study found that TSH levels were affected when patients took an iron tablet at the same time they took their levothyroxine sodium dose.²²

One textbook states that the most likely reason for fluctuating TSH levels is patients' failure to take their levothyroxine sodium tablets regularly.²³ It is also well known that serum TSH has a diurnal variation and pulsatile secretion. A mean peak level of 3.1 mU/L at 2 a.m. and a mean trough level of 0.7 mU/L at 4 p.m. have been documented in normal subjects.²⁴ Yet, physicians do not typically require that blood tested for TSH levels be drawn at a particular time of day. There is also evidence that the following factors can be responsible for changing TSH levels: change of season,²⁵ calorie restriction,²⁶ change in body temperature,²⁷ and exercise.²⁸

²⁰ Comments by Dr. Jerome Hershman and Dr. Stephen Brunton.

²¹ Comment by Dr. Lawrence C. Wood, M.D., CEO and Medical Director of the Thyroid Foundation of America.

²² Campbell N.R. et al., "Ferrous Sulfate Reduces Thyroxine Efficacy in Patients with Hypothyroidism," *Annals of Internal Medicine*, 117(12):1010-1013, Dec. 15, 1992.

²³ *Harrison's Principles of Internal Medicine - 15th Edition*, Chapter 330, Disorders of the Thyroid Gland, by J. Larry Jameson and Anthony P. Weetman, 2001.

²⁴ Brabant, G. et al., "Physiological Regulation of Circadian and Pulsatile Thyrotropin Secretion in Normal Man and Woman," *Journal of Clinical Endocrinology and Metabolism*, 70:403-409, 1990.

²⁵ Nicolau, G.Y. et al., "Circadian and Circannual Rhythms of Hormonal Variables in Elderly Men and Women," *Chronobiol. Int.*, 1(4):301-319, 1984.

In summary, while some physicians may believe that fluctuations in patients' TSH levels result primarily from the use of allegedly inferior levothyroxine sodium products or from the substitution of one approved levothyroxine sodium brand for another, there are numerous other factors that have the potential to affect TSH levels.

XIII. Request for Advisory Committee and Additional Meetings

Both Jones and Abbott request that FDA refer the issue of the proper bioequivalence methodology for levothyroxine sodium products to an advisory committee. Jones specifically asks that the Agency convene a joint meeting of the Pharmaceutical Science Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee. Jones Petition at 1. Abbott asks that FDA consult an "appropriate advisory committee" with joint representation from the Pharmaceutical Science Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee. Abbott Petition at 38-41.

In support of this request, Abbott cites section 404 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act) (21 U.S.C. 360bbb-1). This provision of the Modernization Act states:

If, regarding an obligation concerning drugs or devices under this Act or section 351 of the Public Health Service Act, there is a scientific controversy between the Secretary and a person who is a sponsor, applicant, or manufacturer and no specific provision of the Act involved, including a regulation promulgated under such Act, provides a right of review of the matter in controversy, the Secretary shall, by regulation, establish a procedure under which such sponsor, applicant, or manufacturer may request a review of such controversy, including a review by an appropriate scientific advisory panel described in section 505(n) or an advisory committee described in section 515(g)(2)(B). Any such review shall take place in a timely manner. The Secretary shall promulgate such regulations within 1 year after the date of the enactment of the Food and Drug Administration Modernization Act of 1997.

Abbott's reliance on the Modernization Act for its requested relief is misplaced. First, the statutory provision cited by Abbott explicitly states that it is applicable when there is "no other right of review" of the matter in controversy. Here, Abbott and Jones had, and exercised, the right of review of the issues raised in

²⁶ Chacon, F. et al., "Chronobiological Features of the Immune System," *European Journal of Clinical Nutrition*, 56 Suppl 3:S69-72, Aug. 2002.

²⁷ O'Malley et al., "Circadian Rhythms of Serum Thyrotrophin and Body Temperature in Euthyroid Individuals and Their Responses to Warming," *Clin Sci (Lond.)*, 67(4):433-437, Oct. 1984.

²⁸ Scheen, A.J. et al., "Effects of Exercise on Neuroendocrine Secretions and Glucose Regulation at Different Times of Day," *American Journal of Physiology*, 274(6 Pt 1):E1040-9, June 1998.

their respective citizen petitions. Abbott initially pursued its challenge to FDA's bioequivalence method through the dispute resolution procedure under 21 CFR 314.103. DMEDP, and then ODE II, considered Abbott's challenge and issued written decisions. Then, at FDA's request, Abbott presented its challenge to the Agency through the citizen petition process under 21 CFR 10.30. Jones also filed a citizen petition raising similar issues. The above regulations establish a right of review for the bioequivalence issues raised by petitioners, and Abbott and Jones have in fact proceeded through these regulations.

Even if the Modernization Act requirements were applicable here, neither the statute nor the Agency's regulations guarantee any person the right to an advisory committee meeting. Instead, the above-cited statutory provision simply creates a process by which a request for an advisory committee meeting may be made.²⁹ Furthermore, FDA's advisory committee regulations, particularly 21 CFR 14.172, state that an advisory committee meeting may be requested but do not require FDA to grant the request. In any event, Abbott has already had the opportunity to discuss the results of its Study M02-417 at the March 13, 2003, advisory committee meeting.

Abbott also suggests that FDA has refused to meet with Abbott officials to discuss its challenge to the Agency's bioequivalence methodology for levothyroxine sodium. Abbott Petition at 14-18; Abbott April 15, 2004, supplement. This suggestion mischaracterizes the Agency's actions. Abbott presented the results of its Study M02-417 to CDER officials in a meeting on February 13, 2003. CDER officials then carefully considered Abbott's challenge of FDA's bioequivalence method in its appeals to DMEDP and ODE II.

Furthermore, Abbott has fully presented its views concerning FDA's approval standards and bioequivalence methodology to the Agency through the citizen petition process. Abbott's original petition was dated August 25, 2003. Abbott has supplemented that petition six times—most recently on June 4, 2004. The petition and its supplements include numerous articles and declarations by Abbott's experts. FDA has carefully considered all of Abbott's submissions in evaluating levothyroxine sodium bioequivalence issues.

In its April 15, 2004, supplement, Abbott also alleges that FDA's "inability to fulfill its fundamental obligation under the law to consider all relevant information, and to provide sponsors with an opportunity to have disputes heard before an advisory committee or panel of experts, jeopardizes the deference that FDA is ordinarily due when it engages in scientific decision making." Abbott's April 15, 2004, supplement at

²⁹ In a supplement to its petition dated December 22, 2003, Abbott makes the following argument: "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)." Supplement at 4. The case cited is not on point; it simply contains the words "bereft of meaning."

10 (footnote omitted). Specifically, Abbott insists that FDA hold a public workshop with the American Thyroid Association (ATA) to discuss issues concerning levothyroxine sodium before responding to Abbott's petition. At ATA's request, CDER officials met with ATA representatives on September 16, 2003. At the meeting, ATA presented various issues concerning levothyroxine sodium products for further discussion and consideration by FDA. ATA also requested a workshop with FDA as a forum for these discussions and submitted a proposed workshop agenda to Dr. Steven Galson, Acting Director, CDER, by letter dated December 30, 2003. Dr. Galson then explained in a letter to ATA dated February 19, 2004, that although FDA was committed to plan and hold a workshop to discuss various levothyroxine issues, FDA would respond first to Abbott's and Jones' citizen petitions before considering further any workshop to discuss the Agency's position with respect to levothyroxine issues.³⁰ Abbott's insistence that the Agency hold a workshop with ATA on levothyroxine sodium bioequivalence methods prior to issuing a response to its petition is misguided. Based on the numerous and thorough submissions by Abbott and others, FDA has been able to evaluate these citizen petitions without the need for a workshop to further elucidate the issues. Furthermore, Abbott's request ignores FDA's citizen petition procedures at 21 CFR 10.30, which do not provide the petitioner with the right to a public meeting (much less a meeting between FDA and a third party) to discuss the issues raised in its petition.³¹

³⁰ This correspondence is filed in the docket for these citizen petitions.

³¹ Abbott argues in its June 4, 2004, supplement that FDA does not have the legal authority to issue findings of therapeutic equivalence, particularly as "AB" ratings in the Orange Book, through applications or supplements submitted under section 505(b)(2) of the Act, but only through ANDAs submitted under section 505(j) of the Act. Abbott's June 4, 2004, supplement at 13-14. Abbott also argues that FDA must issue standards for assigning therapeutic equivalence ratings for NDAs through notice and comment rulemaking. *Id.* at 14. Abbott seeks to amend the relief it requested in its petition to include asking FDA to determine that the Agency lacks the authority to assign therapeutic equivalence ratings outside the scope of section 505(j).

For the following reasons, FDA will not address the substance of these arguments in this petition response. First, Abbott delayed raising these arguments until 8 months after submitting its original petition. Yet, Abbott was already on notice that FDA would accept NDAs seeking AB ratings for levothyroxine sodium products. FDA explained this position publicly as early as 1999. In the draft guidance for industry on *Levothyroxine Sodium* (issued August 1999), FDA stated that "[a]n NDA applicant may submit a bioequivalence study comparing its levothyroxine product to one previously approved. If the products are bioequivalent, they will be AB-rated to each other." Guidance at 4. In fact, FDA's position on therapeutic equivalence ratings for levothyroxine sodium applications is not unusual or new, because the Agency has approved numerous other applications in the past that sought therapeutic equivalence determinations (as AB ratings) for drug products through section 505(b), rather than section 505(j). Despite being on notice of FDA's position for several years, Abbott waited until the "eleventh hour" in the context of this citizen petition, after the filing of five supplements and numerous comments by other parties, to raise this argument.

Second, Abbott's arguments about FDA's therapeutic equivalence ratings are unrelated to the arguments in Abbott's citizen petition and previous supplements. The petition and supplements, as well as the comments submitted by interested parties, focus on the appropriateness of FDA's bioequivalence method for levothyroxine products. These bioequivalence issues are quite different from the therapeutic equivalence issues that Abbott now raises. Thus, FDA believes that these new arguments would be more appropriately

In conclusion, Abbott has had ample opportunity to present the information and views on which its petition relies. The public has had the opportunity to comment on the presentations by Abbott and Jones and has, in fact, done so. Thus, no additional meetings, presentations, or workshops are needed before the Agency issues this response. FDA has carefully considered all of the issues raised by the petitioners and has explained its position thoroughly in this petition response. Contrary to Abbott's assertion, the Agency has fulfilled its obligation under the law to consider all relevant information in ruling on these petitions.³²

XIV. GGPs

Abbott asserts that FDA is required by its good guidance practice (GGP) regulations to publish a guidance recommending the bioequivalence method for levothyroxine sodium products. As explained below, however, FDA is not required to issue the bioequivalence methodology through GGPs.

First, the bioequivalence methodology for levothyroxine sodium products is clearly described by the General Considerations guidance. This guidance recommends specific

raised and addressed in a separate citizen petition. FDA will respond more fully to these arguments in a separate citizen petition response in the future.

Finally, FDA already has considered these therapeutic equivalence issues in the context of a previous citizen petition. As Abbott notes on page 13 of its June 4, 2004, supplement to this petition, the firm presented its arguments concerning therapeutic equivalence ratings to the Agency in its July 10, 2002, comments on a 2001 citizen petition submitted by Pfizer Inc. (Pfizer) and Pharmacia Corporation (Pharmacia). See citizen petition submitted by Morgan, Lewis & Bockius, LLP, on behalf of Pfizer and Pharmacia, at 25-29 (Docket No. 2001P-0323/CP1). FDA, in denying in part and granting in part the Pfizer citizen petition, affirmed the Agency's position allowing therapeutic equivalence ratings through 505(b)(2) applications. See FDA's October 14, 2003, citizen petition response at 32-33. Although FDA agreed with Pfizer's contention that the Agency could not assign therapeutic equivalence ratings to the drugs at issue because of a difference in salts of the same active moiety, FDA did not agree with Pfizer that it lacked statutory authority to make therapeutic equivalence ratings through 505(b)(2) applications or that it was required to promulgate procedures for such ratings through notice and comment rulemaking. *Id.*

³² On February 10, 2004, Jerome Stevens Pharmaceuticals, Inc. (JSP) submitted a citizen petition concerning levothyroxine sodium (Docket No. 04P-0061). JSP amended its petition on March 31, 2004. That amendment publicly revealed that JSP had submitted a supplemental NDA containing a bioequivalence study comparing its product Unithroid to Synthroid and seeking that Unithroid be AB-rated to Synthroid. The amendment also revealed that JSP had engaged in a dispute resolution procedure with FDA concerning its supplemental NDA.

In its June 4, 2004, supplement, Abbott requests that FDA and/or JSP disclose the material submitted to FDA in JSP's dispute resolution, including JSP's supplemental NDA. Abbott alleges that "[s]uch disclosure would allow Abbott and others to refine the conclusions reached in the simulation and study." Abbott's June 4, 2004, supplement at 13. JSP's bioequivalence study was submitted in support of its application, and the information in that study is confidential under FDA's regulations. 21 CFR 314.430(d)(1). Moreover, this information is irrelevant to the issues raised in Abbott's citizen petition.

steps in the study design and data handling for bioequivalence studies, including for sample collection and sampling times. General Considerations guidance at 6-11, 21-23. In particular, the guidance recommends that bioequivalence studies measure only the parent drug released from the dosage form. General Considerations guidance at 18. For levothyroxine sodium, this recommendation means that T4 should be measured. Furthermore, bioequivalence testing for levothyroxine sodium products is actually relatively simple because the drug is easily absorbed and can be measured in plasma.

The baseline correction method in the bioequivalence test for levothyroxine sodium products is an analytical step that does not warrant guidance. Abbott correctly states that “[f]or guidance documents that set forth initial interpretations of regulatory requirements or deal with ‘complex scientific’ or ‘highly controversial’ issues, FDA’s GGP regulations direct the agency to publish in the *Federal Register* an announcement that a draft guidance is available, accept and review comments, and publish a final draft before implementation.” Abbott Petition at 42; 21 CFR 10.115(c). However, GGPs do not require FDA to publish a specific guidance concerning bioequivalence for levothyroxine sodium products, particularly for an analytical step in determining bioequivalence (i.e., the baseline correction method). This method for levothyroxine sodium products is not an “interpretation” of a regulatory requirement for bioequivalence. FDA has already provided its interpretation of the bioequivalence regulatory requirement in the General Considerations guidance. Nor is the bioequivalence method for levothyroxine sodium products “scientifically complex,” because the test only involves measuring the drug (T4) minus its appended salt (sodium) in plasma. To the extent Abbott asserts that FDA’s baseline correction method should be issued through guidance, this method merely involves the subtraction of a pre-dose average measurement from the dosing measurements.

Moreover, despite petitioners’ claims to the contrary, FDA’s baseline correction method for bioequivalence tests of levothyroxine sodium products is not “highly controversial.” Abbott and Jones regard the issue as controversial because both firms may lose significant market share if FDA approves generic versions of Synthroid and Levoxyl. As Jones states: “It will not be possible for Jones to recoup this market share. . . .” Jones Petition at 10. However, the economic interests of an NDA applicant do not make an issue “controversial” under the GGP requirements.

Second, communicating with potential generic drug applicants is a routine part of FDA’s business that is conducted by letter responses to questioners, and not by the issuance of guidance documents. In 2002, the Office of Generic Drugs received 744 requests for information. In 2003, the Office of Generic Drugs received 971 requests for information. In 2002, FDA approved 321 generic drug products. If FDA were required to answer questions from potential generic drug applicants by issuing guidance documents, it would be impossible for the Agency to fulfill its responsibility under the Act to approve every generic drug that meets the statutory standards.

Third, FDA has publicly announced that it would cease its former practice of developing drug-specific bioequivalence guidances. On October 27, 2000, FDA published a notice in the *Federal Register* announcing the availability of the General Considerations guidance. 64 FR 64449. The notice stated that the guidance "provides general information on how to comply with the BA and BE requirements for orally administered dosage forms under the bioavailability and bioequivalence requirements regulations." The notice further stated that the guidance "is one of a set of planned core guidances designed to reduce or eliminate the need for FDA drug-specific guidances." The Agency has not issued any new drug-specific bioequivalence guidances since it made the General Considerations guidance available.³³

XV. Request for Stay

In its petition, Jones asks the Agency to stay approval or acceptance for filing of any ANDA or supplemental ANDA for levothyroxine sodium tablets basing bioequivalence on the standards set forth in the BA guidance or those announced by FDA at the March 12-13, 2003, meeting of the Pharmaceutical Science Advisory Committee until (1) the joint advisory committee meeting has convened, (2) FDA has established a new bioequivalence methodology consistent with the petition, and (3) bioequivalence studies in accordance with the new methodology have been submitted; or, until FDA responds to the petition.

Jones argues that it will suffer irreparable harm if FDA does not grant the request for stay. In support of this argument, Jones asserts that the approval of a generic levothyroxine sodium tablet product will result in lost market share for Jones that will never be recovered, the approval of a generic that is not actually bioequivalent to its reference listed drug will lead to a loss of goodwill among patients for Jones' products, and the approval of a generic levothyroxine sodium product will create confusion in the marketplace as physicians begin prescribing the generic products. Jones Petition at 10-11. Jones further asserts that some patients are likely to experience adverse clinical responses to generic products due to alleged 12.5 percent differences in actual drug content. Jones Petition at 11. Jones concludes that these adverse patient outcomes will result in a permanent loss of patient confidence in Jones' product and a resulting loss of sales. Jones Petition at 11. Jones also argues that the public interest favors granting a stay because of the confusion in the marketplace that would be generated by generics coming on the market and then disappearing. Jones Petition at 11.

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action:

³³ One drug-specific guidance has been revised. On December 30, 2003, FDA published a notice of availability of a draft guidance for industry on *Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing*. The guidance was revised to advise sponsors that the Agency no longer recommends conducting in vivo bioequivalence testing for generic clozapine tablets in healthy subjects. This revision was necessary because a high number of healthy subjects experienced serious adverse effects such as hypotension, bradycardia, syncope, and asystole during clozapine bioequivalence studies.

The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:

- (1) The petitioner will otherwise suffer irreparable injury.
- (2) The petitioner's case is not frivolous and is being pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
- (4) The delay resulting from the stay is not outweighed by public health or other public interests.

FDA will not address Jones' irreparable injury argument or whether or not Jones' petition has been filed in good faith and is not frivolous. Instead, FDA has determined that Jones as failed to demonstrate sound public policy grounds for the stay or that the delay would be outweighed by public health or other public interests.

Jones has not articulated sound public policy grounds supporting a stay. The only public interest argument Jones can assert is that there would be confusion in the marketplace generated by generics coming on the market and then "disappearing." This objection assumes that the Agency's current standards for approval of ANDAs for levothyroxine sodium will, upon considered public examination, be found inadequate. This assumption is too speculative and too unlikely to form the basis of a public policy argument for grant of a stay. As explained above, FDA's bioequivalence method with baseline correction is sound, and the petitioners have failed to demonstrate any need for FDA to withhold application of this standard, such as for referral to an advisory committee. This conclusion is strengthened further because Jones itself does not offer an alternative bioequivalence methodology or ANDA approval standards, but merely states a few suggestions which, it acknowledges, "may contain flaws." Jones Petition at 10. Thus, because the merits of Jones' challenge to FDA's bioequivalence method are unpersuasive, Jones fails to provide any legitimate public policy grounds to stay the application of this method.

Moreover, the levothyroxine sodium market currently consists of seven approved levothyroxine sodium products and a generic version of one of those products. It is difficult to understand how the approval of generic versions of Levoxyl and Synthroid would add greatly to any confusion that already allegedly exists from the existence of multiple products.

Finally, even assuming that Jones' confusion argument was a valid public policy reason to grant a stay, the adverse effects on applicants and consumers associated with a delay resulting from a stay are not outweighed by this reason. One of the purposes of the Hatch-Waxman Amendments was to foster the availability of low-cost generic drugs. This important public policy would be frustrated if FDA were to grant the stay Jones

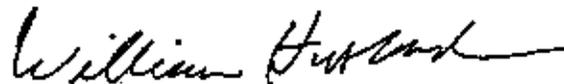
requests. Levoxyl and Synthroid have significant market shares, and the policies behind the Hatch-Waxman Amendments dictate that these products not be shielded from generic competition. Grant of a stay for the actions requested by Jones would potentially delay generic competition for many years.

For all of these reasons, FDA concludes that granting the stay requested by Jones would not be in the public interest. Thus, FDA denies Jones' request for a stay.

XVI. Conclusion

For all of the reasons discussed above, FDA affirms that its bioequivalence methodology for levothyroxine sodium products (comparing baseline-corrected T4) is scientifically sound. Therefore, FDA denies the petitions and the petition for stay.

Sincerely yours,



William K. Hubbard
Associate Commissioner
for Policy and Planning