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TSH-Based Protocol, Tablet Instability, and Absorption Effects on L-T_4 Bioequivalence

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Background: FDA Guidance for pharmacokinetic (PK) testing of levothyroxine (L-T_4) for interbrand bioequivalence has evolved recently. Concerns remain about efficacy and safety of the current protocol, based on PK analysis following supraphysiological L-T_4 dosing in euthyroid volunteers, and recent recalls due to intrabrand manufacturing problems also suggest need for further refinement. We examine these interrelated issues quantitatively, using simulated what-if scenarios testing efficacy of a TSH-based protocol and tablet stability and absorption, to enhance precision of L-T_4 bioequivalence methods.
Methods: We use an updated simulation model of human thyroid hormone regulation quantified and validated from data that span a wide range of normal and abnormal thyroid system function. *Bioequivalence:* We explored a TSH-based protocol, using normal replacement dosing in simulated thyroidectomized patients, switching brands after 8 weeks of full replacement dosing. We simulated effects of tablet potency differences and intestinal absorption differences on predicted plasma TSH, T_4, and triiodothyronine (T_3) dynamics. *Stability:* We simulated effects of potency decay and lot-by-lot differences in realistic scenarios, using actual tablet potency data spanning 2 years, comparing the recently reduced 95–105% FDA-approved potency range with the original 90–110% range.
Results: A simulated decrease as small as 10–15% in L-T_4 or its absorption generated TSH concentrations outside the bioequivalence target range (0.5–2.5 mU/L TSH), whereas T_3 and T_4 plasma levels were maintained normal. For a 25% reduction, steady-state TSH changed 300% (from 1.5 to 6 mU/L) compared with <25% for both T_4 and T_3 (both within their reference ranges). *Stability:* TSH, T_4, and T_3 remained within normal ranges for most potency decay scenarios, but tablets of the same dose strength and brand were not bioequivalent between lots and between fresh and near-expired tablets.
Conclusions: A pharmacodynamic TSH-measurement bioequivalence protocol, using normal L-T_4 replacement dosing in athyreotic volunteers, is likely to be more sensitive and safer than current FDA Guidance based on T_4 PK. The tightened 95–105% allowable potency range for L-T_4 tablets is a significant improvement, but otherwise acceptable potency differences (whether due to potency decay or lot-by-lot inconsistencies) may be problematic for some patients, for example, those undergoing high-dose L-T_4 therapy for cancer.

Introduction

Levothyroxine (L-T_4) treatment requires precision dosing (1–3), and has been described as a narrow therapeutic index drug (3–5), making careful determination of equivalence between L-T_4 preparations particularly important. Unfortunately, it is practically impossible to measure effects of L-T_4 at its eventual target sites, because the mechanism of action for L-T_4 is indirect and ubiquitous; exogenous L-T_4 is absorbed, passed through blood circulation, and finally converted to hormonally active triiodothyronine (T_3) intracellularly throughout the body (2). This complicates development of precise bioequivalence standards.

Current FDA Guidance for bioequivalence of L-T_4 preparations is based on T_4 pharmacokinetic (PK) analysis following a very high 600 μg dose of L-T_4 (6). The original Guidance (6,7) provoked multiple criticisms and counterarguments (2–4,8–13), and has since evolved to include constant baseline subtraction of predose T_4 levels from the 600 μg PK response data (14). We addressed this issue using our first-generation simulation model of this system, with our results strongly supporting this evolutionary step (15). However, several issues remain, including concerns that current Guidance lacks the sensitivity to detect clinically significant differences between preparations (2,8). Although the FDA has given assurances that differences between equivalent products should

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never exceed 9% (2,16), clinicians point out that tablet potency differences "approaching 9% are clinically significant" (2). As a result, TSH measurement—the primary clinical indicator of thyroid function—rather than T_4 has been promoted as a potentially more sensitive pharmacodynamic bioequivalence measure (2,8,12). Clinicians, researchers, and three medical societies (8) have brought this alternative to the attention of the FDA (16,17), but the FDA has not accepted this approach thus far, as T_4 has a more direct biological relationship with hormonally active T_3 (16).

Instability and inconsistency in L-T_4 tablet potency over time and between lots have also been ongoing FDA concerns (7,17–20), with multiple product recalls due to inconsistent potency and instability (18,21–24). These issues exacerbate bioequivalence concerns, as bioequivalence testing depends on the presumption that brands are at least intrabrand bioequivalent before testing them for bioequivalence against each other. A recent FDA study (19) revealed that while some brands, doses, and lots maintained potencies quite close to their labeled dose throughout the study, others decreased in potency significantly during their shelf life. In some cases L-T_4 content dropped below that of fresh tablets from the next dose-strength below; for example, potency of some 150 μg tablets decreased 10% to 135 μg within shelf life, below the 137 μg tablet potency (19). Based on this study and ongoing product recalls (21–24), the FDA recently further restricted the acceptance range in the Guidance for L-T_4 stability, which now requires 95–105% potency during product shelf life, updated from the range 90–110% (25). This requisite potency range is used to determine the shelf life for a given brand. The FDA establishes a shelf life that predictively keeps tablet potency within the target range based on manufacturer-collected stability data for the L-T_4 formulation (7).

We address three issues in assessment of bioequivalence here, using our second-generation simulation model of human thyroid hormone (TH) regulation, recently quantified and validated against data that span a wide range of normal and abnormal thyroid system function (26). In brief, the nonlinear dynamic feedback control system (FBCS) model includes thyroid secretion, TSH secretion with feedback regulation by T_3 and T_4, distribution, metabolism, and elimination of TH in and from all tissue pools—including T_4 to T_3 conversion, plasma protein binding effects, and a gut absorption submodel, for exogenous TH dosing.

We first test the comparative efficacy of a bioequivalence protocol based on TSH rather than T_4 measurements, using smaller L-T_4 doses in simulated thyroidectomized patients with no endogenous T_4 pool to confound bioequivalence measurements. We explore (a) tablet potency and (b) intestinal absorption differences in this assessment. Third, we examine bioequivalence issues posed by intrabrand as well as interbrand variations in potency and tablet stability, testing the adequacy of the new standards by computer simulation of these variations in the FBCS model, using actual potency data collected over 2 years as exogenous input to the model via the gut submodel (19).

Methods

Simulation model

The model has two major components: the brain submodels (26), and the TH secretion and distribution and elimination (D&E) submodels (15), updated in (26). The brain submodels incorporate circadian TSH secretion regulated by T_3 and T_4 in brain, and a simple one-compartment TSH degradation model. The six-compartment TH D&E submodel includes nonlinear Michaelis-Menten–based $T_4 \rightarrow T_3$ conversion in slow and fast tissue pools, as well as plasma protein binding. An explicit gut submodel provides for oral L-T_4 inputs and adjustment of gut absorption rates. All are detailed in (26).

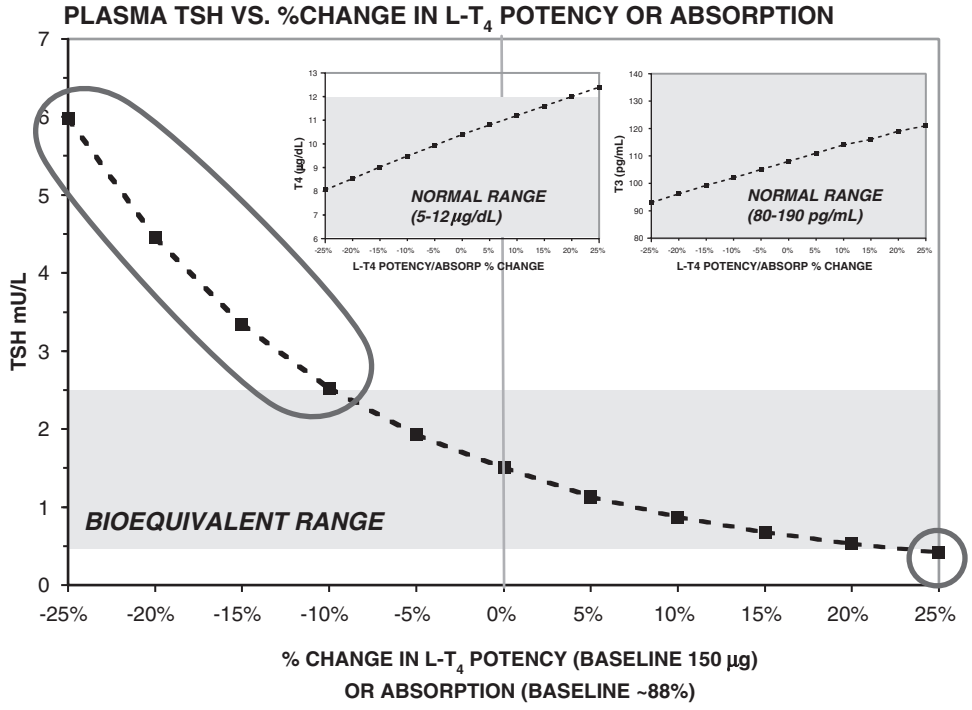

FIG. 1. Steady-state simulated TSH, triiodothyronine (T_3), and thyroxine (T_4) in response to changes in tablet potency or absorption rate. Simulated Potency Protocol: Brand A (normal potency) until titrated to 0.5–2.5 TSH range; measure TSH, T_3, and T_4. Switch to Brand B; measure TSH, T_3, and T_4 at 8 weeks. Shading indicates normal ranges for T_4 and T_3 (5–12 μg/dL T_4, 80–190 pg/mL T_3), and target range for establishing bioequivalence (0.5–2.5 mU/L TSH). Simulated Absorption Protocol: Same as above, but changed levothyroxine (L-T_4) gut absorption instead of drug potency. Results are the same, because the net effects of potency and absorption changes on plasma T_4 are the same.

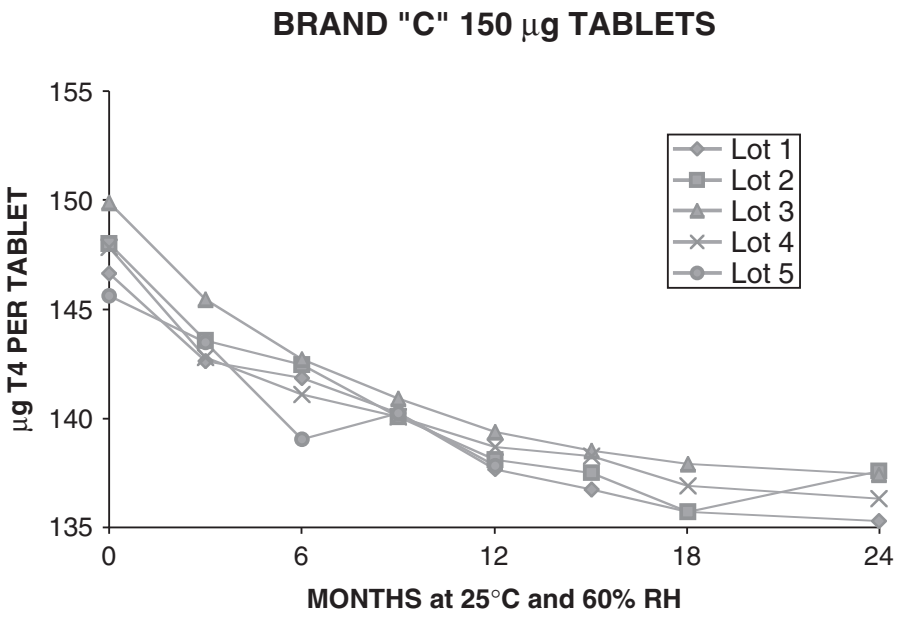

FIG. 2. Stability data for five different lots of 150 μg tablets over 24 months [adapted from (19)].

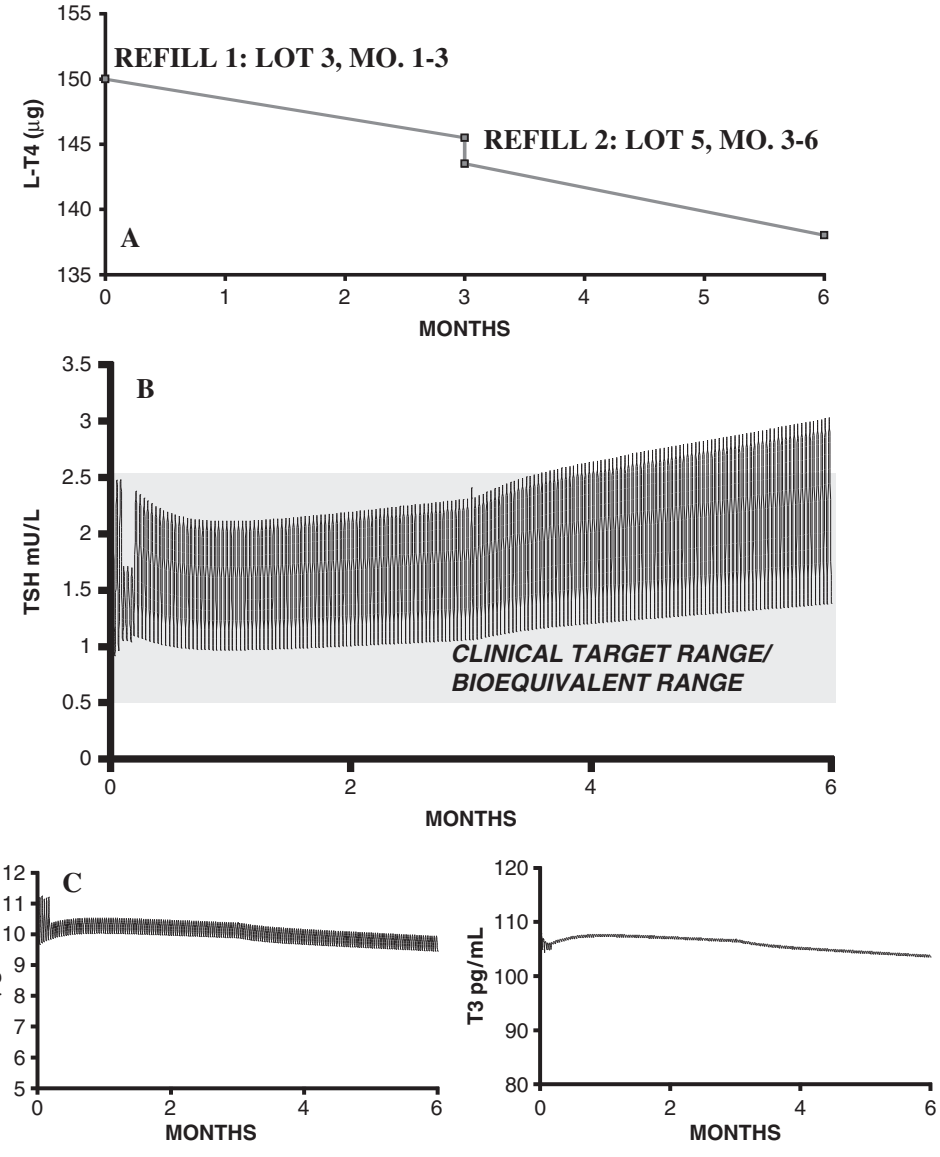

FIG. 3. Scenario *1a* (95–105% potency range, data based): L-T_4 instability and lot-by-lot potency difference effects for 150 μg tablets of Brand C (19) on plasma TSH, T_3, and T_4. Shifts in plasma TSH, T_4, and T_3 concentrations (panels **B** and **C**) in response to switching lots of the same brand of L-T_4 upon refilling (daily tablet potency given in panel **A**). T_4 and T_3 are plotted within their normal ranges, 5–12 μg/dL and 80–190 pg/mL, respectively.

Differences in tablet potency and intestinal absorption rate effects on L-T_4 bioequivalence determinations via TSH measurement

We assumed a target range of 0.5–2.5 mU/L TSH for positively establishing bioequivalence, a typical clinical target range for patients on replacement TH (27). We simulated thyroidectomized patients given standardized 150 μg L-T_4 daily over 8 weeks, reducing plasma TSH nominally to 1.5 mU/L and raising plasma T_4 and T_3 concentrations to $\sim$10 μg/dL and $\sim$1 ng/dL. They were then switched to L-T_4 preparations with a range of altered potencies or a range of different L-T_4 absorption rates (ranges shown along *x*-axis of Fig. 1). After another 8 weeks on these simulated regimens, TSH, T_3, and T_4 concentrations were again evaluated [protocol suggested by Drs. James Hennessey and Steven Sherman (28,29)].

L-T_4 stability and lot-by-lot differences

We simulated the effects of potency decay and lot inconsistency on hormone levels in thyroidectomized patients receiving 150 μg/day L-T_4. We tested two different stability criteria scenarios: (a) the current 95–105% allowable potency range; and (b) the original 90–110% potency range, to quantify the improvement. We did this in two ways, first (*1a* and *b*) using real tablet stability data [FDA potency data for "Brand C" at 150 μg L-T_4 shown in Fig. 2 (19)], and second, (*2a* and *b*) a more extreme acceptance bounds analysis simulation, explained below.

1. Data based acceptance bounds analysis. *1a—(95–105% potency range, data based):* Based on Brand C data for 150 μg L-T_4 tablets (19), the current 95–105% FDA allowable potency range for L-T_4 tablets yields a shelf life of about 6 months; that is, most lots stay roughly within the 95–105% range over 6 months. We consider a typical 3-month mail order supply of L-T_4, taken from a single lot of Brand C L-T_4 at the time of the refill. We simulate the potency of each daily dose by linearly interpolating between the nearest data points as in Figure 2.

We simulated effects of potency decay on plasma hormone levels using a starting 3-month supply of fresh tablets from Lot 3 (months 1–3 of Lot 3 in Fig. 2), followed by a

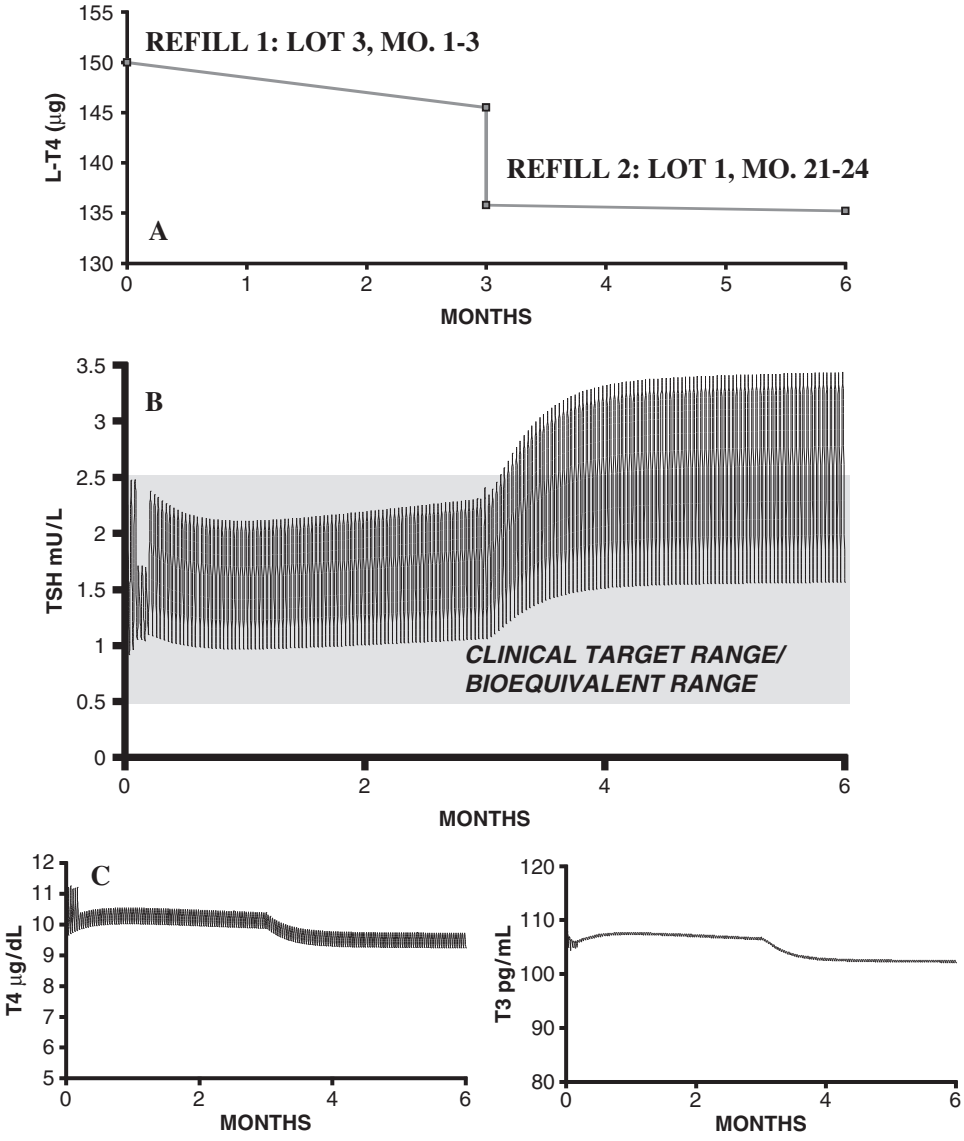

FIG. 4. Scenario *1b* (90–110% potency range, data based): L-T_4 instability and lot-by-lot potency difference effects for 150 μg tablets of Brand C (19) on plasma TSH, T_3, and T_4. Dramatic shifts in plasma TSH, T_4, and T_3 concentrations (panels **B** and **C**) in response to switching lots of the same brand of L-T_4 upon refilling (daily tablet potency given in panel **A**). T_4 and T_3 are plotted within their normal ranges, 5–12 μg/dL and 80–190 pg/mL, respectively.

simulated 3-month refill using half-expired tablets from Lot 5 (months 3–6 of Lot 5 in Fig. 2), which for example might have been purchased at a different or the same pharmacy. The complete time course profile of simulated daily potency is shown in Figure 3A. We chose these two 3-month refills from these two lots because they demonstrated the largest change in tablet potency possible for a patient to experience on refilling, using a 95–105% allowable potency range and Brand C data.

1b—(90–110% potency range, data based): We next tested the original 90–110% FDA allowable potency range, which yielded a roughly 2-year shelf life. We simulated 3 months using fresh tablets from Lot 3 (months 1–3 of Lot 3 in Fig. 2) as in Scenario *1a*, followed by a simulated 3-month refill, in this case using near-expired tablets from Lot 1 (months 21–24 of Lot 1 in Fig. 2), as shown in Figure 4A. As in *1a*, these two lots and 3-month periods provide the largest change in tablet potency upon refilling, in this case with the less restrictive acceptance range yielding a longer estimated shelf life.

2. Theoretical acceptance bounds analysis. Here we predict the outcome of a patient taking regular daily doses at the extremes of the allowable potency range. This gives a sample of the hormone concentration ranges anticipated at both the earlier FDA target potency range of 90–110% and current target potency range of 95–105%.

2a—(95–105% potency range): We simulated a constant daily dose of 105% (157.5 μg/day) of the normal 150 μg dose for the first 3 months, followed by 3 months of tablets at 95% potency (142.5 μg/day), as shown in Figure 5A.

2b—(90–110% potency range): Here we simulated a constant daily dose of 110% (165 μg/day) of the normal 150 μg dose for the first 3 months, followed by 3 months of tablets at a constant 90% potency (135 μg/day), as shown in Figure 6A.

3. L-T_4 potency range for TSH bioequivalence. We additionally computed the widest potency range for maintaining simulated TSH concentrations within the clinical target/bioequivalence range of 0.5–2.5 mU/L.

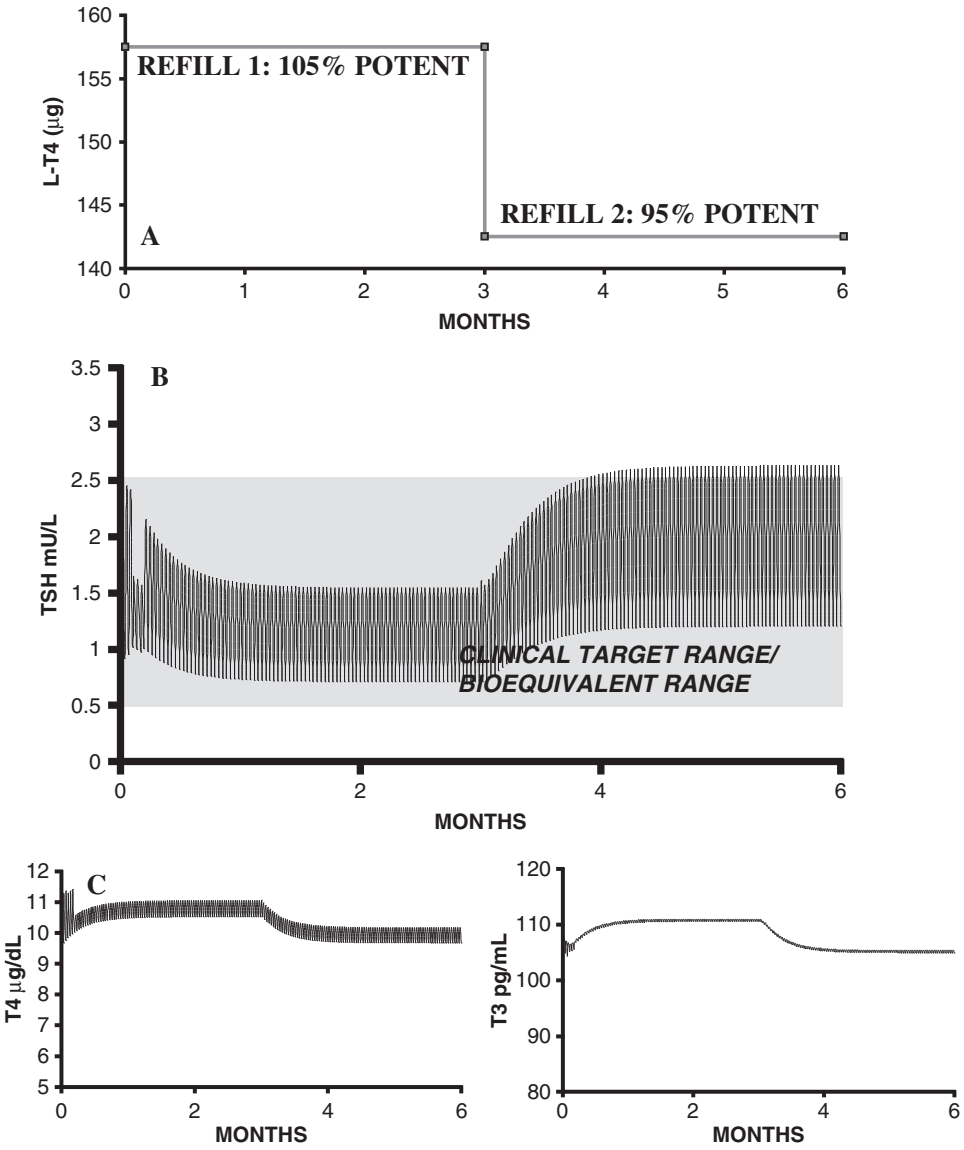

FIG. 5. Scenario *2a* (95–105% potency range, limiting case): L-T_4 potency difference effects on plasma TSH, T_3, and T_4 for 150 μg tablets. Shifts in plasma TSH, T_4, and T_3 concentrations (panels **B** and **C**) in response to switching from 105% to 95% of normal tablet potency upon refilling (daily tablet potency given in panel **A**). T_4 and T_3 are plotted within their normal ranges, 5–12 μg/dL and 80–190 pg/mL, respectively.

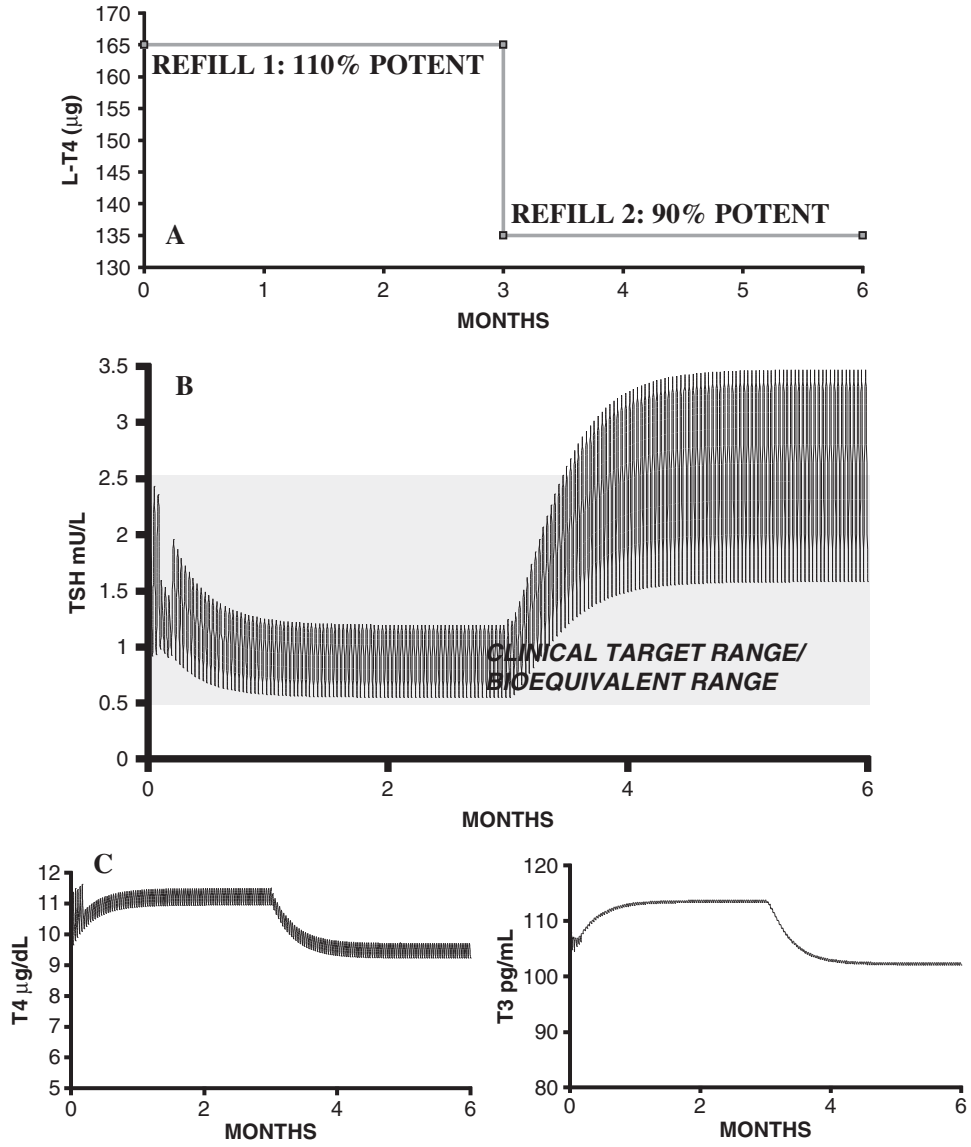

FIG. 6. Scenario *2b* (90–110% potency range, limiting case): L-T_4 potency difference effects on plasma TSH, T_3, and T_4 for 150 μg tablets. Shifts in plasma TSH, T_4, and T_3 concentrations (panels **B** and **C**) in response to switching from 110% to 90% of normal tablet potency upon refilling (daily tablet potency given in panel **A**). T_4 and T_3 are plotted within their normal ranges, 5–12 μg/dL and 80–190 pg/mL, respectively.

Results

Bioequivalence of L-T_4 preparations

Simulated hormone measurements before and after switching simulated preparations are given in Figure 1. A decrease in L-T_4 potencies or absorption differences as small as 10–15% (from 150 to 135 μg L-T_4, from ~88% to 79% absorption) generated TSH concentrations outside the bioequivalence target range (0.5–2.5 mU/L TSH), whereas T_3 and T_4 plasma levels were maintained within their normal ranges (T_4: 5–12 μg/dL, T_3: 80–190 pg/mL) (1).

L-T_4 stability and lot-by-lot differences

(1) Simulated responses to decaying L-T_4 tablet potencies are given in Figures 3 and 4. In Scenario *1a*, daily average plasma TSH levels showed an increase from ~1.5 to 2.2 mU/L over 6 months of simulated therapy. In *1b*, daily average plasma TSH levels showed an increase from ~1.5 to 2.5 mU/L over 6 months of simulated therapy. We also analyzed "Brand F" data from Duffy (19), the other brand of 150 μg tablets in the FDA stability study (not shown), with similar results to Brand C results.

(2) The responses to Scenarios *2a* and *b* are shown in Figures 5 and 6. Scenario *2a*, using the updated 95–105% target potency range, yields concentrations slightly outside the clinical/bioequivalent target range of 0.5–2.5 mU/L TSH when tablet potency is at 95%—the lower end of the acceptable range.

(3) An allowable potency range of 96–104% maintained TSH concentrations within the clinical target range of 0.5–2.5 mU/L TSH.

Discussion

Bioequivalence of L-T_4 preparations

Our results support at least adding TSH measurements to current bioequivalence protocols, preferably in treated thyroidectomized patients—one of the real patient populations receiving the drug therapeutically, rather than in normal volunteers. Alternatively, the greater sensitivity of the pharmacodynamic variable TSH shown in our results supports

the possibility of an effective purely TSH-based protocol for L-T_4 tablet bioequivalence standards, such as the one tested here, rather than the T_4 PK analysis specified in current FDA Guidance. Effects of oral L-T_4 differences in potency and gut absorption on plasma TSH, T_3, and T_4, detailed in Figure 1, demonstrate that TSH is a much more sensitive measure of bioequivalence than T_4 or T_3. For a 25% drop in L-T_4 potency, steady-state TSH changes by $\sim$300%, from 1.5 to 6 mU/L, whereas both T_3 and T_4 remained within their reference ranges (changing by 23% and 14%, respectively). Use of treated thyroidectomized patients would also allow for a significantly smaller and likely safer L-T_4 dose: $\sim$150 versus the 600 μg used in current L-T_4 bioequivalence testing.

Our results also show that TSH exhibits a notable one-sided sensitivity. Whereas simulated TSH is highly sensitive to inadequate dosage, it is somewhat less sensitive to overdosing. This effect stems from system nonlinearities captured by our quantified model of TH inhibition of TSH secretion. It also mirrors similar saturation/one-sided sensitivity effects seen in actual human data (4,30,31), with our overall results fairly closely matching those reported by Carr *et al.* (31). In most patients studied, a roughly 25% decrease or increase ($\pm$25 μg) in daily L-T_4 maintenance dosages yielded TSH levels above 5.6 or below 0.5 mU/L—the asymmetric upper and lower limits of the reference range used by Carr *et al.* (31). In our Figure 1, a simulated 25% drop in daily dose increases TSH to $\sim$6 mU/L, well above our reference range limit of 2.5 mU/L, and a 25% increase decreases TSH below 0.5 mU/L.

For implementation of this protocol in actual subjects, randomization of drug administration is suggested, with multiple study arms. For example, (arm 1) patients titrated on Brand A and then switched to Brand or generic B; (arm 2) patients titrated on Brand B or generic and then switched to Brand A; (arm 3) patients titrated on Brand A and then "switched" to Brand A; (arm 4) patients titrated on Brand B or generic and then "switched" to Brand B or generic (29). This would eliminate or minimize the possibility of any one-sided TSH sensitivity adversely affecting the bioequivalence assessment. Randomization/multiple study arms would also be important for this protocol because of the lack of data on reproducibility of bioequivalence testing using a different pharmacodynamic standard such as TSH (29).

L-T_4 stability and lot-by-lot differences

Responses to stability and lot-by-lot difference effects (Figs. 3 and 4) show TSH extending outside its clinical target range/bioequivalent target range of 0.5–2.5 mU/L, even though T_3, T_4, and TSH levels remained within their normal ranges (TSH: 0.5–5 mU/L; T_4: 5–12 μg/dL, T_3: 80–190 pg/mL). However, Scenario *1a* (Fig. 3), with the current acceptance range, produced TSH levels only slightly outside the clinical/bioequivalent target range, and only when tablet potency had actually approached or dropped below the 95% limit of the allowed potency range. On the other hand, Scenario *1b* (Fig. 4) using the earlier acceptance range gave TSH concentrations consistently outside the target range when using near-expired tablets, clearly justifying the Guidance range acceptance reduction. The big jump ($\sim$50%) in simulated TSH shown in Figure 4, panel B, is particularly disconcerting. The Guidance range reduction is further confirmed by Scenarios *2a* and *b*, which show that simulated TSH extends significantly beyond the target range when given tablets at 90% potency, but only slightly outside the target range when given 95% potent tablets. In the results for Scenario 3, we found a potency range of 96–104% for 150 μg L-T_4 tablets sufficient to keep simulated TSH within the clinical target/bioequivalence range (0.5–2.5 mU/L TSH).

Together, these what-if simulation scenarios support the adequacy of the narrowed 95–105% potency acceptance range for L-T_4 tablets in the 2006 update to the FDA Guidance. However, some of our simulations, even with the updated standards, push the limits of acceptance. While hormone level changes of the magnitude seen in our simulations are unlikely to be harmful to patients taking relatively low doses of L-T_4, they could pose a problem for patients taking larger doses, such as those undergoing hormone-suppression therapy for cancer (12). Further, much of the tablet stability data we used for predicting outcomes via simulation/data comparisons were generated under fairly ideal conditions, and L-T_4 tablet stability is known to be sensitive to factors such as light, temperature, and moisture (32–37). The stability data we used (19) were generated in idealized, controlled environments, at normal temperature and relative humidity, with tablets kept in sealed containers with desiccants. Duffy (19) notes that patients are unlikely to be so meticulous, so that actual stability of L-T_4 taken by patients is likely worse than these findings. Also, our simulation model is based on and predicts only population average results, so it is likely that TSH levels would extend outside the normal range in some patients under real-world circumstances.

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Disclosure Statement

No competing financial interests exist.

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