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Before Food and Drug Administration Public Meeting on Levothyroxine Sodium Therapeutic Equivalence
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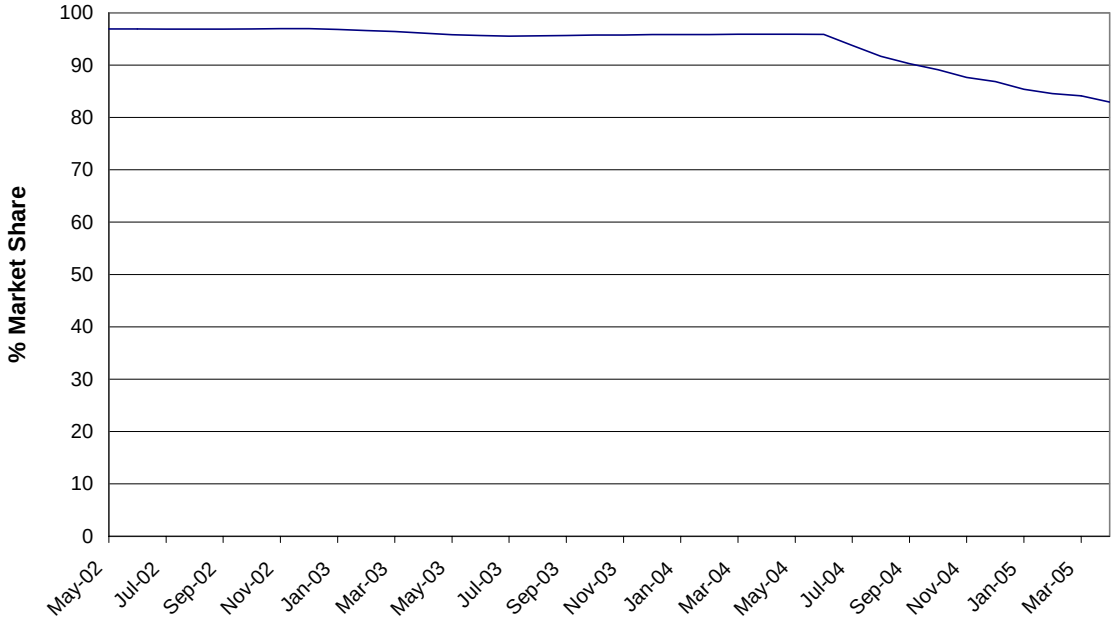
> Phil: What would you do if you were stuck in one place and every day was exactly the same, and nothing that you did mattered?
> Ralph: That about sums it up for me.
> -- Groundhog Day (Columbia Pictures, 1993)

This hearing is simply the latest round in a decades-long debate in which discredited scientific arguments are repeated and uncorroborated clinical anecdotes recycled in an effort to generate enough confusion to maintain the market share of the brand name medication, Synthroid, and, to a lesser extent, Levoxyl. The only new wrinkle is that, instead of speaking for itself, the manufacturer now lurks behind three professional societies, all of which, according to their web sites, receive funding from Synthroid's manufacturer, Abbott Laboratories.

Abbott's tactics have paid off. Synthroid is the second most frequently prescribed drug in the United States.[1] Although Synthroid was the last of the major versions of levothyroxine to receive a New Drug Application (NDA), it still received 82% of levothyroxine prescriptions in March 2005. As the graph demonstrates, this percentage is only declining very slowly.

Synthroid Share of Levothyroxine Market
May 2002-April 2005



The company's "success" has been to the detriment of the public health. Let us assume that, in the absence of company obfuscation and physician gullibility, Synthroid's market share would drop to 33% (more than many brand name drugs can muster after generic competitors arrive) and that, for simplicity's sake, the total levothyroxine market is equal to that of Synthroid alone or $873 million.[2] As we have seen, Synthroid does have the lion's share of the market and it is more expensive than other forms of levothyroxine, so this assumption is approximately correct. Let us further assume that the price of generic levothyroxine is half that of Synthroid (the CVS Pharmacy website in early May listed the price of 30 125µg Synthroid tablets as $21.39, compared to $9.99 for a similar quantity of Unithroid). The potential savings to taxpayers, out-of-pocket payers and insurers from reversing this unjustified domination of the levothyroxine market by Synthroid is thus $214 million per year (82%-33% * 0.5 * $873 million). Clearly, much more than the results of a technical debate over bioequivalence is at stake here. (We recognize these estimates to be optimistic in the sense that it would likely take years for so large an erosion of Synthroid's market share to take place. In addition, it is possible that Synthroid's competitors may not be as inexpensive as Unithroid; the CVS Pharmacy website listed Levoxyl's price as $17.79 for 30 125 µg tablets.)

Part of the confusion in this area stems from the fact that the Food and Drug Administration (FDA) has declared six of the eight approved levothyroxine formulations to be the Reference Listed Drug (RLD). Companies can only claim bioequivalence (and thus substitutability) for those particular RLD formulations to which they have specifically compared their formulation. The result is a confusing patchwork of drugs that are bioequivalent to some formulations, but not to others. To date, only seven of 28 possible pairs (25%) have been declared bioequivalent (these receive an "AB" rating in the FDA's Orange Book), as illustrated in the table below ("levothyroxine" is Mylan's version).

Levolet							
Levothyroxine							
Levoxyl	AB		AB				
Novothyrox							
Synthroid	AB		AB				
Thyro-Tabs							
Unithroid			AB	AB		AB	
	Levo-T	Levolet	Levothyroxine	Levoxyl	Novothyrox	Synthroid	Thyro-Tabs

Because only AB-rated pairs can be substituted according to the FDA, it is no wonder that the status quo persists largely unaltered. This is an ideal situation for the government, perhaps under the Agency for Healthcare Research and Quality's Centers for Education & Research on Therapeutics (CERTs) to sponsor studies examining the bioequivalence of key pairs, especially of the low-priced generics to Synthroid and Levoxyl. The savings to be gained by the Medicaid program alone would easily pay for such research. The FDA (and the specialty societies that insisted upon this meeting) should also be educating physicians and pharmacists about the permitted substitutions.

Abbott has complained that the criteria used by the FDA to determine bioequivalence are not rigorous enough. It is important to note that although the FDA is willing to declare as bioequivalent drugs with areas under the curve (AUCs), peak concentrations (C_{max}s) and times to peak concentrations (T_{max}s) within a range of 80-125% of each other, this range actually applies to the 90% confidence interval. For a 90% confidence interval to fall within that range, the mean value must be quite close to 100%. As the FDA's Dr. Conner noted at the Advisory Committee for Pharmaceutical Science meeting of March 13, 2003 (the previous Groundhog Day):

> [T]he mean data or the point estimates that we see in normal bioequivalence studies don't generally fall outside of 10 percent and most of them are around 3 percent either way because essentially the confidence interval has a width around that mean and it doesn't really take much movement away from center to cause the edge of that confidence interval to go over our limit and fail. So if you're really just talking about mean data, the means never really get a chance to get out anywhere close to the plus or minus 20 percent.[3]

So when Abbott or its advocates cite the range as evidence for laxity, the degree of tolerance is being overstated. They also frequently do not recognize that because, under FDA guidelines, the bioequivalence study is conducted with 600 µg of levothyroxine, well beyond the dose clinically used in practice (and a dose that produces blood levels considerably in excess of endogenous levels), the likelihood of detecting a difference between two formulations is increased, making the test of bioequivalence more stringent.

The suggestion to add thyroid-stimulating hormone (TSH) to T_3 and T_4 as part of any bioequivalence determination flies in the face of all existing practice in the bioequivalence field. (Of course, TSH retains an important in clinical management.) All other things being equal, if a drug formulation can get approximately the same amount of drug into the blood in approximately the same amount of time, it should have the same biological effect. If we are to accept the notion that TSH must be evaluated for levothyroxine bioequivalence, must we then demonstrate similar reductions in blood pressure or cholesterol for antihypertensive or cholesterol-lowering drugs that we wish to be declared bioequivalent?

Abbott is exploiting the particular biological behavior of TSH. As it well knows, TSH levels are subject to a number of influences, including diurnal changes, assay variability, other drugs and ambient temperatures. Moreover, TSH behaves in a distinctly non-linear fashion; a change of 1 mIU/L from 4 mIU/L may well have some clinical significance, but a similar change at 40 mIU/L is meaningless. Indeed it is these two sources of "noise" that the company is seeking to exploit. For, with enough noise, no two formulations can be proved bioequivalent without extremely large studies. Dr. Conner of the FDA went even further at the March Advisory Committee meeting:

> I would tend to guess that if you did that study [using TSH] on two lots of any manufacturer's product, it would probably fail, if that study was done, with that level of variability.
>
> In fact, I would even go out on a limb and say that you might fail testing if you took the same lot and just randomly divided it into two sections and studied it in a crossover fashion and did the same study, you would have a pretty decent chance of failing identical stuff from the same lot, given that study and that level of variability.[4]

There is a still more fundamental question: Is TSH a reliable predictor of clinical outcome? In a recent commentary, Dr. Anthony Toft stated that, "There is simply no evidence, other than anecdotal, that an increase (or decrease) in thyroxine tablet content of up to 12.5%, which could theoretically occur if a generic preparation of thyroxine were substituted for a branded preparation at prescription refill, will induce subclinical or overt hyper- or hypothyroidism."[5] At the 2003 Advisory Committee Meeting, Dr. Lesko of the FDA made a similar point:

> First of all, TSH is not a blood pressure. Blood pressure is a surrogate endpoint for clinical effectiveness and blood pressure has been correlated with mortality and morbidity. TSH has not been correlated in any prospective study that I'm aware of with clinical symptomatology of thyroid disease.[6]

This view is consistent with a major scientific review of subclinical thyroid disease, ironically commissioned by the three professional societies that have forced today's meeting. The review found that the available data were "insufficient" to show a benefit upon lipid levels, cardiac dysfunction, systemic hypothyroid symptoms or neuropsychiatric symptoms from treating patients with TSH's of either 4.5-10 mIU/L or >10mIU/L. Furthermore, the review found "no evidence" that treatment at either of these TSH levels had an impact upon adverse cardiac endpoints.[7]

Moreover, the proposal to include TSH in bioequivalence testing is not even consistent with FDA regulations. Bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[8] The regulations go on to define a hierarchy of acceptable measurements with measurement of the active ingredient at the top and measures of the pharmacological effect of the drug only third.[9] Moreover, the regulations permit this less-desirable approach "only when appropriate methods are not available for measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s)."[10] Abbott would literally have the FDA break or rewrite existing regulations.

As is well known, the history of bioequivalence determinations for levothyroxine is one sullied by data suppression, data manipulation, plagiarism,[11] private investigations and legal threats.[12,13] The longer Abbott drags out this proceeding, the more it seems that when the company acquired the patent rights to Synthroid in 2001 it also procured the previous owner's predilection for bullying and data manipulation.

[1] Drug Topics. Top 200 Brand-name Drugs by Units in 2004. Available at: http://www.drugtopics.com/
[2] Drug Topics. Top 200 Brand-name Drugs by Retail Dollars in 2004. Available at: http://www.drugtopics.com/
[3] Dale Conner, FDA. Transcript of the Meeting of the Advisory Committee for Pharmaceutical Science, March 13, 2003, p. 158.
[4] Dale Conner, FDA. Transcript of the Meeting of the Advisory Committee for Pharmaceutical Science, March 13, 2003, p. 207.
[5] Toft A. Which thyroxine? Thyroid 2005;15:124-6.
[6] Lesko L, FDA. Transcript of the Meeting of the Advisory Committee for Pharmaceutical Science, March 13, 2003, p. 201.
[7] Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. Journal of the American Medical Association 2004;291:228-38.
[8] 21 CFR 320.1(e)
[9] 21 CFR 320.24(b)
[10] 21 CFR 320.24(b)(3)
[11] Mayor GH, Orlando T, Kurtz NM. Limitations of levothyroxine bioequivalence evaluation: analysis of an attempted study.
American Journal of Therapeutics 1995;2:417-32.
[12] Rennie D. Thyroid storm. Journal of the American Medical Association 1997;277:1238-43.
[13] Lurie P, Wolfe SM. Letter to FDA Commissioner David Kessler urging him to begin a safety and efficacy review of all pharmaceuticals marketed in the U.S. prior to 1938 (including Synthroid). Available at: http://www.citizen.org/publications/release.cfm?ID=6035.