ATTACHMENT 1: REGULATORY HISTORY AND CURRENT ISSUES

INTRODUCTION

This attachment provides members of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) and the Advisory Committee for Pharmaceutical Science (ACPS) the regulatory history of how oral levothyroxine sodium drug products have been made available to the American public. This attachment also describes current regulatory issues involving approved levothyroxine sodium products.

DEVELOPMENT AND REGULATION OF LEVOTHYROXINE SODIUM PRODUCTS

Synthetic levothyroxine (T4) products became commercially available in the 1950's without an approved new drug application (NDA), apparently in the belief that levothyroxine sodium was not a new drug. Over the next 4 to 5 decades, levothyroxine sodium products became the preferred drug over dessicated thyroid preparation for replacement therapy. That T4 from these products underwent *in vivo* conversion to the active T3, similar to endogenous T4, reassured clinicians that levothyroxine sodium products allowed for better management of thyroid disorders with a lower risk of iatrogenic hyperthyroidism. By 1997, there were at least 37 manufacturers or re-packagers of levothyroxine sodium tablets.

While much information regarding thyroid hormone action has been established, including its half-life, protein binding, receptor-binding, and cellular and tissue/organ effects, absence of information regarding manufacturing, stability, and potency of levothyroxine sodium products raised concerns about whether these products could reliably and predictably be used for their labeled indications. Between 1990 and 1997, the agency became aware of multiple recalls due to sub-potency, stability failures, and occasionally super-potency. In certain situations, due to poor stability performance, manufacturers released final drug product with a stability "overage" (i.e., more than 100% of labeled claim) to address the rapid degradation of the product and to allow a practical shelf life meeting USP potency specifications of 90-110%.[1]

Such reports raised concerns of both safety and effectiveness for these products and therefore, on August 14, 1997, the FDA announced in a Federal Register notice (62 FR 43535) that oral drug products containing levothyroxine sodium were considered new drugs subject to approval under Section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355). The document called for NDAs for levothyroxine sodium products from sponsors wishing to market such products in the United States after August 14, 2000. This deadline was later extended to August 14, 2001 (65 FR 24488). FDA also issued guidance in July 2001, titled *Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications*, outlining the agency's exercise of its enforcement discretion in allowing sufficient time for physicians to switch their patients from unapproved products to approved products and allowing time for manufacturers of approved products to scale up their production and introduce their products into the market in sufficient quantities to address the medical needs of millions of patients.

The agency also issued a guidance in February 2001 titled, *Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing*, to assist manufacturers in the submission of an NDA, outlining the study designs necessary to demonstrate the pharmacokinetics,

[1] USP potency specifications of 90-110% include an upper bound beyond 100% to address issues of assay variability, whereas the lower bound of 90% addresses the issue of drug degradation over time.

dosage-form proportionality, and bioavailability of the to-be-marketed formulation, and provided information on *in vitro* dissolution testing. Since thyroid hormone had been used extensively in clinical practice, applicants were not required to conduct clinical studies to demonstrate safety and efficacy, but instead could rely on published literature to support the proposed labeled indications.

Some pre-NDA products were reformulated to improve their stability profiles to meet approval requirements. As a result of FDA review and oversight of the chemistry, manufacturing and controls for levothyroxine sodium tablets, the following improvements have been noted. Approved levothyroxine sodium products:

- target release at 100% potency, without a stability overage,
- conform to USP specifications of 90-110%, such that the maximum allowable loss of potency over shelf life is now 10% with respect to initial potency, and
- have expiration dating periods that are supported by stability data.

As a result of these regulatory actions stemming from the initial Federal Register notice of August 14, 1997, the agency has approved 7 NDAs for levothyroxine sodium products under section 505(b)(2) of the Act (an NDA relying on published literature to support the proposed labeled indications). After the August 14, 2001, deadline, an unapproved levothyroxine product without an NDA pending before the agency was subject to agency enforcement action. After this date, applications for levothyroxine sodium were to be submitted as abbreviated new drug applications (ANDAs) to be reviewed in the Office of Generic Drugs under Section 505(j) of the Act. Synthroid®, Unithroid®, and Levoxyl® have been relied upon as the reference listed drugs in ANDAs. The agency has approved two ANDAs for levothyroxine sodium products.

Table 1 lists the approved products and their dates of approval.

Table 1. Approved Levothyroxine Sodium Drug Products as of August 2006

Name of Drug	Manufacturer/Application Holder	Date of Approval	NDA/ANDA
Unithroid®	Jerome Stevens	August 21, 2000	NDA 21210
Levoxyl®	Jones Pharma	May 25, 2001	NDA 21301
Levo-T®	Alara	March 1, 2002	NDA 21342
Novothyrox®	Genpharm	May 31, 2002	NDA 21292*
Synthroid®	Abbott	July 24, 2002	NDA 21402
Levothroid/Thyrotabs®	Lloyd/Forest	October 24, 2002	NDA 21116
Levolet®	Vintage	June 6, 2003	NDA 21137
Levothyroxine sodium	Mylan	June 5, 2002	ANDA 76187
Levothyroxine sodium	Genpharm	June 16, 2005	ANDA 76752

* Re-submitted to Office of Generic Drugs (OGD) and reviewed and approved under ANDA 76752

CURRENT ISSUES CONCERNING APPROVED LEVOTHYROXINE PRODUCTS

In addition to approving two generic products, FDA has approved several supplements to the NDAs establishing bioequivalence between certain levothyroxine sodium products. Such findings established these products to be AB-rated (interchangeable) to one another. As a result, as with generic products, it is possible that a product established as interchangeable for a specified prescribed product could be substituted when filling a prescription for the specified prescribed product.

Manufacturers of certain approved levothyroxine sodium products have challenged FDA's reviews of the ANDAs and NDA supplements and the methodology used to establish bioequivalence. In that same light,

three medical societies voiced their objections to the agency's determination that several marketed levothyroxine sodium products were bioequivalent to one another. FDA has defended its bioequivalence standards and approvals of these levothyroxine sodium products in response to these challenges and objections. In response to these expressed concerns, FDA held a joint public meeting with the American Thyroid Association, the Endocrine Society, and the American Association of Clinical Endocrinologists in May 2005 to discuss FDA's regulatory standards and methodological approaches for determining therapeutic equivalence between levothyroxine sodium drug products. At the May 2005 meeting, FDA explained how its bioequivalence methods and determinations of AB ratings for levothyroxine sodium products are scientifically sound.

The most notable concern expressed by the societies' representatives was the contention that FDA's bioequivalence methodology would fail to distinguish products that differ from each other by as much as 12.5%, which could be clinically significant. Two speakers presented a slide containing the FDA-approved range of doses of levothyroxine sodium and the percent differences in active ingredient between each dosage strength (e.g., 100 mcg, 112 mcg). One speaker highlighted that stepwise increases or decreases within the dosage strengths of 88 mcg, 100 mcg, 112 mcg, 125 mcg, and 137 mcg represented a change of less than 12.5% (range 9-12%) which would be similar to "changes that clinicians make deliberately every day."[2] According to the society representatives, the failure of FDA's bioequivalence method to distinguish products that differ from each other by these dosage amounts would be clinically significant. This concern can be expressed in the following hypothetical example: if a patient who has been adequately treated at 100 mcg of product A is switched to 100 mcg of product B, and if the difference in potency varies between the products by 12%, it might result in the patient receiving as little as 88 mcg or as much as 112 mcg of active ingredient, doses that might otherwise be too little or too much for the patient.

Given the expressed concerns at the meeting about the clinical significance of differences in dosage amounts between these products, FDA is considering further the clinical significance of such dosage differences, particularly with regard to the potency and stability of these products. While the relationships between products for dosing consistency may matter, a fundamental issue that first must be understood and addressed is the consistency of dosing within a given product over time and from prescription to prescription. For example, if a product degrades over time after it is released for marketing, it is important to consider whether the product dispensed under a prescription, which may be newly released or close to its expiry date, will have the same potency as a product subsequently dispensed under a prescription, which may be in a different point in its shelf life. This issue of within product variability, which was not the focus of the May 2005 meeting, is now the focus of this advisory committee meeting. The question before the joint committee is whether, under current FDA approval standards for potency, these levothyroxine sodium products demonstrate durable stability over time such that there would not be an increase or decrease in potency, possibly as large as that between doses used in titration, for physicians to be concerned about whether their patients are receiving a predictable, consistent dose even when not switching between products (i.e., for the same product, at point of prescription fill to the next refill). Attachment 2 of the memorandum provides more detailed background on clinical issues for levothyroxine sodium products, and attachment 3 of this memorandum provides more detailed background on potency and stability standards.

CONCLUSIONS

The agency believes that potency for a product (intraproduct potency) is important and must be maintained within a clinically relevant range over the product's shelf life period to ensure that patients will receive the prescribed effective dosage strength throughout the product's labeled expiry period. This

[2] For example, see presentation by Dr. James V. Hennessey, Joint Public Meeting on Equivalence of Levothyroxine Sodium Products, May 23, 2005 (Docket No. 2005N-0137).

is particularly important for a narrow therapeutic index drug, such as levothyroxine sodium. FDA acknowledges that significant variability in potency between levothyroxine sodium products also could result in serious clinical consequences. Because medical societies' representatives have suggested that percent differences between dosage strengths within a product as low as 9% could be clinically significant, it is important to evaluate whether currently approved levothyroxine sodium products meet the expectations outlined by the societies even absent a substitution of one product for another. That is, the agency feels intraproduct issues must be reasonably addressed before considering any interproduct issues, as the former issues are fundamental to the latter.

As a result, earlier this year, the agency requested product stability data from manufacturers of all approved and marketed levothyroxine sodium drug products, manufactured between July 2003 and June 2005. FDA's presentation of this data is included in Attachment 3 of this memorandum.