ATTACHMENT 3: STABILITY BACKGROUND AND DATA PRESENTATION

I. INTRODUCTION

This attachment provides regulatory background on potency and stability, a discussion of the stability data that we requested from manufacturers of levothyroxine sodium products, and a presentation of the data provided to the agency.

II. GENERAL BACKROUND ON POTENCY AND STABILITY

Potency is a measure of the strength of a drug product, expressed in quantity of drug substance per dosage unit. For example, a 100-microgram (mcg) tablet that is 100% potent contains 100 mcg of the active pharmaceutical ingredient (API). If the tablet is only 95% potent, it contains only 95 mcg of the API and 95 mcg is the maximum amount of drug available to the patient, regardless of whether the product label says it contains 100 mcg.

With certain exceptions, a drug must conform to the standards for strength, quality, and purity, including described tests or methods of assay, set forth in an official compendium (e.g., the United States Pharmacopeia (USP)) (section 501(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 351)). USP monographs for compendial drug substances and drug products usually include acceptance criteria (allowable limits) for potency, along with a method by which the substances or products may be assayed. Potency specifications, both at time of release (release specification) and throughout the life of the product (shelf life specification), include a validated analytical procedure (assay) and a set of acceptance criteria that define the lowest and highest allowable values for potency. A product must meet its regulatory standards over its entire shelf life. Most USP monographs provide that drugs must meet a 90-110% potency specification.

Stability is whether a product maintains consistent quality, including potency, over time. If a product is not stable, it will degrade over time and lose potency. For example, a tablet that contains 100 mcg of the API at the time of release may degrade so that it contains only 90 mcg or even less at the time of expiry. Therefore, as part of the drug approval process and under post-approval regulations, manufacturers evaluate the potency of their products at different time points (e.g., every 3 months) over the shelf life of the product.

A. POTENCY DETERMINATION

Potency determination (assay) involves preparing a test sample from the drug product formulation and determining the amount of active ingredient present in that sample. For example, a specified quantity of tablets is dissolved in a solvent to create a solution with a target concentration. This solution then is compared to a solution that is prepared from a validated standard, as a point of reference. The test method is validated as being accurate, precise, rugged (provides statistically equivalent results when run by different analysts on different days using different equipment), robust (able to withstand small changes in spectrophotometric conditions), and specific (tablet and analytical method excipients do not interfere with the determination of the target analyte). In addition, the assay method is validated as *stability indicating* (degradation products are not included in the determination of the amount of active ingredient). The test results for the samples are recorded either in units (milligrams or micrograms) of active ingredient per tablet (e.g., 24 mcg per tablet), or alternatively, as a percent of the label claim (e.g., 96% labeled claim).

B. STABILITY TESTING

The purpose of stability testing is to provide evidence as to how the quality of a drug product varies with time under the influence of a variety of environmental factors (e.g., temperature, humidity, light), to establish a shelf life (expiration date) for a drug product, and to determine recommended storage conditions. Stability testing is also used to determine that a container closure system is suitable for long-term use (e.g., storage in a warehouse).

In a new drug application (NDA) or abbreviated new drug application (ANDA) submission, the sponsor is required to include data regarding the stability of the drug product, proposed expiration dating and a stability protocol, explaining how it will conduct long-term stability studies (21 CFR 314.50(d)(1)(ii) and 21 CFR 314.94(a)(9)). The stability protocol includes a shelf life specification (a quality standard that the drug product must meet throughout its shelf life), a testing schedule, container closure systems, and specified storage conditions.

A typical stability testing schedule includes test stations at Time 0 (typically representing initial release test results), every 3 months during the first year of storage, every 6 months during the second year of storage, and every year thereafter. Stability testing is carried out, at a minimum, throughout the current expiration dating period (shelf life) of the drug product.

A drug product is tested as packaged in all approved or proposed container closure systems (package presentations). For a solid oral dosage form, package presentations typically include an immediate container (bottle), closure (cap, equipped with innerseal and lining), and auxiliary packaging components (e.g., materials designed for physical protection of the product). At each time point in stability testing, tablets are taken from unopened bottles. The bottle from which the test product was removed is discarded and the next test uses new, unopened containers.

Stability testing takes place under controlled temperature and humidity conditions. If a product is to be labeled for room temperature storage, it is stability tested under International Conference on Harmonization (ICH) conditions of long-term storage (25º ± 2ºC and 60% ± 5% relative humidity (RH)).[1]

An expiration date is assigned to each package presentation based on the results of the stability testing. For example, 100-mcg tablets distributed in 100-count bottles by a manufacturer may have an expiration date different from the same tablets distributed in a 1000-count bottle. The expiration date for a product is determined by adequate stability data. For example, if statistical analyses of the stability data demonstrate that a product failed specifications for potency at 12 months, the product would be assigned an expiry to reflect a point in time at which it last met the test criteria (e.g., 10 months), and the date on the bottle would be 10 months from the date of manufacture.

Manufacturers are required to conduct stability tests on selected batches of drug product even after the product is approved (21 CFR 211.166). Typically, one batch of each strength in each package presentation is put on long-term stability testing each year. For example, a company might manufacture 12 batches of 100-mcg tablets in 100-count bottles each year and conduct release tests on each batch, but only one batch would typically be put aside for long-term testing over the product's shelf life.

A product's expiration date may change after it is approved. Depending on the results of stability testing over time, the expiration date may be extended or shortened. If the result of stability testing support a longer or shorter expiration date, the expiration date would be extended (e.g., from 12 months to 18 months) or shortened (e.g., from 12 months to 9 months).

C. RELATIONSHIP OF STABILITY TESTING TO REAL WORLD CONDITIONS

[1] Many products are also stability tested under accelerated (40ºC and 75% RH) and intermediate (30ºC and 60% RH) storage conditions to ensure that the drug product can withstand temporary excursions beyond the labeled storage conditions.

Generally, the results of stability studies represent the best case scenario stability profile. In other words, the drug products are tested under ideal conditions (controlled storage at 25ºC and 60% RH, with products taken from an original, unopened container, protected by an intact seal, not previously exposed to shipping conditions before sampling). In the real world, the environmental conditions more harshly affect the maintenance of the physico-chemical characteristics of the drug product. The following steps illustrate the sequence of events and environmental conditions that would apply to a typical, commercialized drug product:

- Step 1: The drug product is shipped from the manufacturer to a holding center, and then (after sale), to a warehouse. The product is subjected to shipping stress (e.g., bumping, dropping), and to temperature and humidity conditions outside the specified range from the stability studies.

- Step 2: The product is shipped from the warehouse to a pharmacy, where it is stored under variable conditions, depending on the ambient conditions in the pharmacy area. After the pharmacy receives a prescription for levothyroxine sodium, the original bottle is opened and tablets are dispensed into patient containers. Because the seal has been disrupted, the tablets remaining in the original bottle are no longer protected from humidity and oxygen. In addition, many pharmacies utilize *Baker cells* for dispensing and counting high-volume prescription drugs. Baker cells consist of a rotating hopper, into which the pharmacist empties large stock bottles (e.g., 1000-count or 5000-count presentations). When filling a prescription, the pharmacist designates the desired quantity of tablets to the Baker cell and the correct number automatically is disgorged through an outlet tube into a catch receptacle from which the pharmacist can pour the tablets into the patient bottle. The Baker cell subjects the tablets to open-air conditions, heat, and agitation and mixing stress.

- Step 3: The prescribed tablets (usually a one to three months supply) are "repackaged" into pharmacy containers, which are typically amber-colored plastic containers equipped with child-resistant closures. These container closure systems do not provide protection for the drug product, as they are not sealed from the environment, do not contain protective materials, and are opened by the patient at least once daily.

- Step 4: Some prescriptions are ordered through large central pharmacies and are delivered by mail. This can expose the drug product to extreme environmental conditions such as heat. For example, a mailbox in the central or southwestern United States during the summer months can experience internal temperatures well above 100º F.

- Step 5: Patients store their medications in a variety of non-controlled conditions (e.g., medicine cabinet in bathroom, pill-dispenser in purse).

III. LEVOTHYROXINE SODIUM DRUG PRODUCTS

More so than many other drug substances, levothyroxine sodium is stable only when stored under tightly controlled conditions (e.g., sealed container, room temperature or below, and protected from moisture, oxygen, light, and other chemical entities). The process of formulating levothyroxine sodium into a dosage form exposes the substance to many factors that cause the substance to degrade, such as:

- heat generated from tableting and granulation,
- moisture present in excipients and granulating solutions,
- oxidative conditions from exposure to atmosphere and metallic, manufacturing equipment, and
- chemical reactions with inactive formulation ingredients, such as lactose.

Historically, FDA recognized the need for patients to have available to them levothyroxine sodium products that are stable and consistent in potency (see Attachment 1: Regulatory History). As a result of

FDA review and oversight of chemistry, manufacturing and controls, levothyroxine sodium tablets products must meet the following standards for approval:

- Approved levothyroxine sodium products target release at 100% potency, without a stability overage.

- Approved levothyroxine sodium products conform to United States Pharmacopeia (USP) specifications of 90-110%, such that the maximum allowable loss of potency over shelf life is now 10% with respect to initial potency.

- Approved levothyroxine sodium products have expiration dating periods that are supported by stability data.

Note that some pre-NDA products were reformulated in order to improve their stability profiles to meet approval requirements.

A. STABILITY DATA FROM APPLICATION HOLDERS

FDA requested product stability data from manufacturers of all approved and marketed levothyroxine sodium products, manufactured between July 2003 and June 2005. The stability data requested from (and supplied by) the application holders were obtained from stability studies conducted according to the approved NDA and ANDA stability protocols. If changes in analytical methodology or product packaging were made after June 2005, the results would not be reflected in this dataset.

The stability data provided to the agency included reports for 12 different tablets strengths (25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg) in several different package presentations (100-count, 500-count, 1000-count, or unit-dose) for each application holder. FDA tabulated and evaluated the data.

For purposes of presentation in this background package, we have limited our discussion and evaluation of the requested stability data to four specified tablet strengths (25, 100, 125, and 150-mcg tablets). We selected 100 and 125 and tablet strengths because, according to IMS data, they are the most frequently prescribed. We chose 25 mcg because it is frequently prescribed to susceptible populations, such as newborns or the elderly for precise dosing titration (see Attachment 2). We chose 150-mcg to illustrate a point made in the next subsection (III.B of this Attachment).

The presentation includes graphical displays of the lot-by-lot data provided from each application holder, illustrating the changes in potency over time during stability storage (25ºC and 60% RH). Levothyroxine sodium tablets are stability tested according to the ICH, room-temperature stability protocol (described in section II.A of this Attachment). Because levothyroxine sodium dosage formulations typically cannot withstand ICH accelerated storage conditions (40ºC and 75% RH), they are stability tested using ICH intermediate storage conditions (30ºC and 60% RH).

B. GENERAL OBSERVATIONS FROM THE DATA

It is evident from the data that there is a trend of potency loss with some formulations showing potency loss approaching 10% of initial potency at the time of expiry.

There is variability within products produced by the same manufacturer. Some products exhibited a correlation between tablet strength and potency loss (e.g., increasing potency loss as tablet strength gets smaller), while others exhibited a correlation between package presentation and potency loss (e.g., increased potency loss in 1000-count bottles or unit dose presentations). As a result, the expiration dating periods for different strengths or presentations of a product varied.

As discussed, the current stability specifications allow for a 10% loss of potency during the expiration dating period. This has unintended consequences in the middle of the dosage range (i.e., 112, 125, 137, and 150-mcg tablets). Specifically, if a 150-mcg tablet loses 10% of its initial potency, it would contain 135 mcg of levothyroxine sodium and still meet current specifications for potency. However, this tablet would actually contain less levothyroxine than the labeled claim for the **next lower strength** (137-mcg tablet). This means that a patient taking a 150-mcg tablet at or near its expiry could receive a de facto dose for the 137-mcg tablet strength. From evaluation of the stability data provided for the 150-mcg tablets, this situation actually occurred in several cases. Some 150-mcg tablet lots tested to less than or equal to 137 mcg before expiry, remaining within specification (equal to or above 135 mcg). In other words, these lots of 150-mcg tablets deliver less levothyroxine sodium than the corresponding 137-mcg tablets at full potency. The graphs for the 150-mcg tablet lots illustrate this point.

In addition, there is variability between products from different manufacturers (i.e., some levothyroxine sodium tablets lost less than 5% of initial potency within their labeled expiry, while other products lost approximately 10% of initial potency within their labeled expiry). Expiration dating periods vary between these products, from a minimum of 8 months to a maximum of 24 months. These general observations are based on the stability data derived from product batches manufactured between June 2003 and July 2005 provided by each manufacturer. The data were not collected in a single trial designed to assess comparative, side-by-side stability profiles between products.

Because the stability studies represent optimal storage conditions, as opposed to real world conditions (section II.C of this Attachment), the actual physico-chemical changes to levothyroxine sodium tablets may be more pronounced than those indicated by the stability studies. At this time, the agency does not have data for levothyroxine sodium drug products exposed to typical commercial-market conditions (e.g., shipping, non-uniform storage, pharmacy handling, hot mailbox, moist bathroom). However, it is reasonable to expect that these conditions would not improve the stability outcome of these products over that observed from the stability data presented.

C. INTERPRETING THE CHARTED STABILITY DATA

The data are presented on graphs showing potency (mcg of T4 per tablet) versus stability storage time (months of storage). The following are explanations regarding tabular presentation of the stability data:

- The presentations indicate the 90% and 95% potency levels. (Note that the presentations for the 150-mcg tablet lots illustrate the next lower strength (137-mcg) instead of the 95% potency level.)

- The summary stability data is presented lot-by-lot, as it was provided to us. We did not manipulate the data submitted. The potency of levothyroxine sodium (*mcg of T_4 per tablet*) is plotted against stability storage time (*Months*) at controlled conditions (*25C and 60% RH*) in approved container closure systems. This represents ICH "room temperature" long-term storage conditions (25º ± 2ºC and 60% ± 5% RH).

- A separate chart is provided for each package presentation (e.g., 100-count bottles and 1000-count bottles). Data are not presented for unit dose blister packaged products. Each chart uses standardized scales and reference points. For each presentation, the stability storage time (*Months at 25C and 60% RH*) ranges from 0 to 24 months. The potency (*mcg of T_4 per tablet*) is standardized as follows:
    - 25-mcg tablets: ranges from 22 to 26 mcg of T_4 per tablet (88 to 104% label claim)
    - 100-mcg tablets: ranges from 87 to 105 mcg of T_4 per tablet (87 to 105% label claim)
    - 125-mcg tablets: ranges from 112 to 130 mcg of T_4 per tablet (89.6 to 104% label claim)

- 150-mcg tablets: ranges from 130 to 155 mcg of T_4 per tablet (86.7 to 103.3% label claim)

- Occasionally, the plot of potency versus stability storage time indicates an apparent increase in potency (e.g., the potency value at 9 months is higher than the potency value at 6 months). This scenario is not unusual for drug product (or substance) stability data and reflects the factor of analytical method variability. Fresh bottles from the same lot are opened for every stability test station and testing is destructive (i.e., future tests cannot be run on the same tablets or on tablets from the same container).

- Several stability plots contain unconnected data points. This reflects missing data points (e.g., a stability study containing potency test results for 0, 3, and 9 months, but none for 6 months).

- Because we requested stability data over a two year time frame (from July 2003 to June 2005), the stability plot for a particular lot may end at a point in time that does not reflect the product's expiration date. For example, one lot may end at 6 months because that was all the data collected as of June 2005. Or, because a manufacturer may keep its product on stability testing longer than its expiration date, one lot may end at 24 months, even though the product's expiration date is 18 months.

SUMMARY OF DATA

A. Product and Expiration Date

Levo-T (Alara, NDA 21-342) is packaged in 100 and 1000-count bottles. The current expiration dating period is 18 months for all presentations.

Synthroid (Abbott, NDA 21-402) is packaged in 100 and 1000-count bottles and unit dose blister packages. The current expiration dating period is 9 months for the 100-count bottled presentation and for unit-dose presentations, and 15 months for the 1000-count bottles.

Levoxyl (King, NDA 21-301) is packaged in 100 and 1000-count bottles and in unit-dose blister packages. The current expiration dating period is 18 months for 25 to 200-mcg bottled presentations and 12 months for 300-mcg tablets in bottles and for unit-dose presentations.

Thyro-tabs, now using tradename Levothroid (Lloyd, NDA 21-116, packaged by Forest), is packaged in 100 and 1000-count bottles. The current expiration dating period is 18 months for higher strength tablets (100 to 300-mcg), 12 months for intermediate-strength tablets (50 to 88 mcg), and 8 months for the 25-mcg tablets.

Unithroid (Jerome Stevens, NDA 21-210) is packaged in 100 and 1000-count bottles. The current expiration dating period is 24 months for all presentations.

Mylan's product (ANDA 76-187) is packaged in 100, 500 and 1000-count bottles. The current expiration dating period is 18 months for all strengths and package presentations.

Genpharm's product (ANDA 76-752) is packaged in 100 and 1000-count bottles. The current expiration dating period is 24 months for all strengths and package presentations.

B. Blinded Summary of the Data

Note: Blinded data are presented in random order and include summaries of stability data for strengths and/or package presentations that are not included in the graphs.

Brand A: It is noted that the applicant manufactured a relatively small number of batches over the requested time period, and that the stability submission comprised a relatively small quantity of data. There was no observable difference in stability profile between the presentations. The submitted data consisted of either 1 or 2 batches, each split into the presentations. The loss of potency was relatively minimal (occasional lots lost up to 6% potency through expiry, while many lots tested to essentially the same potency at expiry as they did at the onset of stability).

Brand B: Only two stability batches contained any data below 97% of the label claim at any time. There was no significant difference with respect to strength or package presentation.

Brand C: The typical loss of potency was 4 to 6 % through expiry. There was a consistently smaller decline in potency during stability storage for certain package presentations compared to the other(s). There was no observable stability trend related to tablet strength.

Brand D: Certain package presentations typically lost about 10% of potency through expiry. The other presentations lost 6-9% potency through expiry.

Brand E: Only one stability batch contained any data below 95% of the label claim at any time tested. There was no significant difference with respect to strength or package presentation.

Brand F: The loss of potency was calculated from the potency at release, as opposed to being calculated from the onset of stability testing. One package presentation experienced the most significant decline (typically 8-10% loss through expiry). The typical loss of potency ranged from 5-10% at expiry for the other package presentations.

Brand G: Certain tablet strengths lost on the average, approximately 8-10% of initial potency through expiry, and some lots exhibited more than a 10% decrease in potency within a short period after expiry. Others lost between 2-7% of initial potency through expiry.