Background Document:

Joint Advisory Committee Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and the Advisory Committee for Pharmaceutical Science (ACPS)

Meeting Date: October 4, 2006

Presentation by Genpharm Inc.

Background:

Genpharm originally submitted a New Drug Application for Levothyroxine Sodium Tablets (brand name Novothyrox) which was approved by FDA on May 31, 2002. For commercial reasons, this product was not marketed. Genpharm later filed an Abbreviated New Drug Application for Levothyroxine Sodium Tablets, which was approved on June 16, 2005. This product has been marketed in the United States since September 2005.

Genpharm Inc., located in Toronto, Canada, is an affiliated subsidiary of Merck KGaA, Darmstadt, Germany . Merck is a leading supplier of Levothyroxine Sodium Tablets in many parts of the world.

Marketing History:

The Merck brands of Levothyroxine Sodium Tablets have been marketed in Europe for more than twenty years. The product is currently marketed in 62 countries. In 1999, Merck developed a new formulation which replaced the original one. This new formulation has an excellent drug product stability profile and is the formulation registered in the United States. Merck has sold more than 9.7 billion tablets in the past 5 years. Currently there are approximately seven million patients treated with Merck Levothyroxine Sodium Tablets worldwide.

FDA Regulatory Action:

A notice was published in the Federal Register on August 14, 1997 (FR62:157) [i] which required all companies marketing Levothyroxine Sodium to submit New Drug Applications for approval by August 14, 2000. This deadline was later extended to August 14, 2001 and provisions for phased withdrawal of unapproved products were also published.

The supplementary information published with the Federal Register notice highlighted four main areas of concern which prompted the action taken by FDA and required new drug status to ensure that data and formulation changes would be reviewed and evaluated by FDA prior to implementation by manufacturers. The concerns were as follows:

1) “Levothyroxine Sodium Products Must Be Consistent in Potency and Bioavailability”
2) Adverse Drug Experiences
3) Formulation Change
4) Stability Problems

Each of these will be discussed below with respect to the product currently approved and supplied to the United States market by Genpharm.

Potency and Bioavailabilty:

FDA required applicants for Levothyroxine Sodium products to demonstrate bioavailability of their formulations with respect to an orally ingested solution of Levothyroxine Sodium and also linearity of response across several strengths of tablets. Genpharm submitted a New Drug Application containing the clinical study documentation requested by FDA on June 27, 2000. The relative bioavailability of our formulation compared to an equal nominal dose of oral Levothyroxine Sodium solution is approximately 99%. This demonstrates that Genpharm's formulation has excellent bioavailability and is safe for use.

Genpharm has also performed and submitted to FDA, bioequivalence studies comparing our formulation with two other FDA approved formulations, Synthroid (Abbott Laboratories) and Levoxyl (Jones Pharma). The results of these studies demonstrate that patient safety will not be compromised by substitution with the Genpharm formulation for patient's who have been controlled on one of the other formulations.

The Federal Register notice stated "… tablets of the same dosage strength from the same manufacturer vary from lot to lot in the amount of active ingredient present." The table below presents the range in tablet assay values, observed at release testing for Genpharm's Levothyroxine Sodium product manufactured over a two year period.

Strength	Range of Assay Value (% LC)
25 mcg	96.9% - 103.4%
50 mcg	102.4% – 104.8%
75 mcg	100.7% – 102.9%
88 mcg	98.6% – 102.6%
100 mcg	96.7% - 103.1%
112 mcg	97.0% - 101.9%
125 mcg	96.5 % - 101.5%
150 mcg	101.1% - 103.0%
175 mcg	99.8% - 101.6%
200 mcg	97.1% - 102.4%
300 mcg	99.6% - 104.9%

The data demonstrate consistency between lots within a strength and all results are compliant with the specification approved by FDA.

Potency as represented by Assay values is normally based on testing of a composite sample of multiple tablets. It may be more relevant to consider the observed results and variability in the testing of individual tablets. The table below presents the minimum and maximum tablet assay values observed in content uniformity testing of individual tablets for Genpharm's Levothyroxine Sodium product manufactured over a two year period.

Strength	Range of Assay Value (% LC)
25 mcg	97.9% - 106.9%
50 mcg	100.2% – 105.9%
75 mcg	98.0% – 104.8%
88 mcg	99.0% – 106.6%
100 mcg	95.4% - 106.5%
112 mcg	98.3% - 103.8%
125 mcg	96.7 % - 104.8%
150 mcg	98.5 % - 103.2%
175 mcg	97.3% - 103.9%
200 mcg	98.4% - 105.4%
300 mcg	98.2% - 107.2%

The results demonstrate excellent consistency in potency and are all compliant with the approved content uniformity specification which is more restrictive than the standard USP criteria of 85.0 – 115.9% label claim.

Adverse Drug Experiences:

The Federal Register notice highlighted concerns about inconsistencies in potency resulting in adverse drug experiences, particularly when patients were switching brands. To date, Genpharm has not received any reports of this nature specific to the US brands. Since the focus of this discussion is the quality issues associated with Levothyroxine Sodium products, adverse drug experiences will not be discussed further.

Formulation Change:

The formulation marketed by Genpharm in the United States is the same as the formulation sold by Merck worldwide, except that the US product has colors added to aid in the differentiation of the tablet strengths. In most other countries, all tablets are white. No formulation changes have been made since approval, and since the product is now subject of an approved application, any changes need to be supported by bioequivalence and quality data and submitted for regulatory approval prior to implementation. This will obviate any of the concerns raised about formulation changes in the Federal Register notice.

Stability Problems:

Levothyroxine Sodium is generally considered to be an unstable drug substance and the Federal Register notice highlighted several examples of warning letters, recalls and unusual storage conditions on labeling from the period prior to 1997. FDA has stated publicly that products approved since 1997 have varying shelf life, ranging from 9 to 24

months and that all products meet the required potency at the end of shelf life of < 10% loss in potency. [ii]

Genpharm's product has an approved shelf life of 24 months, and is therefore, based on the FDA approval is one of the most stable products available on the US market. Presented below is a summary of the lowest Assay values observed at the 24 months test point for completed stability studies on the product.

Strength	Lowest Assay Value (% LC)
25 mcg	95.3 %
50 mcg	99.4 %
75 mcg	100.3 %
88 mcg	98.8 %
100 mcg	97.7 %
112 mcg	97.9 %
125 mcg	99.9 %
150 mcg	97.7 %
175 mcg	95.6 %
200 mcg	98.8 %
300 mcg	97.4 %

The lower limit for Assay in the USP monograph is 90.0% label claim and the FDA has stated that this is the standard they are applying to the approved products for shelf life. The data above show that the Genpharm product demonstrates results above these limits at the approved shelf life. In fact, the mean loss in potency over the shelf life is 3.1% label claim.

Conclusion:

Currently approved Levothyroxine Sodium products, in particular, Genpharm's Levothyroxine Sodium Tablets are consistent in potency, bioavailability and stability. Therefore they are safe and effective for use and no further regulatory action is warranted.

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[i] Federal Register Vol 62, No. 157, Thursday, August 14, 1997 pp 43535 - 43538

[ii] Presentation by Dr. David Orloff, FDA Summary, Public Meeting for Levothyroxine Sodium Therapeutic Equivlance, May 23, 2005, Washington, DC