Global Experience:
Levothyroxine Quality and Safety

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Genpharm's Product

- Genpharm is an affiliate / subsidiary of Merck KgaA, Darmstadt Germany
- Merck is a leading supplier of levothyroxine products worldwide
- Unique process and formulation using gelatin to stabilize levothyroxine (US patent #6,646,007 and 10/661.588 pending)

Genpharm's Product

- Originally submitted NDA for Novothyrox, approved May 31, 2002
  - Not marketed
- Later submitted ANDA approved June 16, 2005
- AB rated to both Synthroid and Levoxyl

The Concern

- FR 62:157 August 14, 1997
- "… lack of stability and consistent potency has the potential to cause serious health consequences…"
- All existing and new levothyroxine sodium products must have an approved application after August 14, 2000
- Deadline later changed to August 14, 2001

The Concern

- Consistent in Potency and Bioavailability
- Patient Safety / Adverse Drug Experiences
- Formulation Changes
- Stability

Bioavailability / Bioequivalence

- Genpharm bioavailability vs. oral solution is approximately 99% (NDA)
- Linearity across strengths also demonstrated (NDA)
- Bioequivalence studies (ANDA)
  - Synthroid
  - Levoxyl

Potency / Content Uniformity

- 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"
- May also be concerns about potency of individual tablets (content uniformity)

Range in Observed Assay Values Between Lots

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%

Observed Minimum and Maximum Assay Values of Individual Tablets

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%

Safety

- 62 countries
- >33 years
- 9.7 billion tablets sold 2001-2005
- Currently approximately 7 million patients taking Merck levothyroxine products worldwide
- Only levothyroxine product approved by FDA and European Commission
- Merck product is safe and effective

Formulation

- European product is white
- US / Canadian marketed product contains colors to differentiate strengths
- No changes since approval (ANDA)
- Any changes would require approval since the formulation is subject of an approved application

Stability

- FDA have publicly stated that the approved Levothyroxine Sodium products have varying shelf life, up to 24 months
- Genpharm's product is approved with the longest (i.e. 24 months) shelf life
- Demonstrated by excellent assay results at 24 months time point

Lowest Observed Assay at 24 Months

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 %

Assay Over Shelf Life

- Since Levothyroxine Sodium is considered to be an unstable drug, expect large decrease in tablet assay over shelf life
- Mean change in % label claim over the shelf life was 3.1%

Conclusion

- Genpharm / Merck Levothyroxine Sodium:
  - Correct and Consistent Potency
  - Stable
  - Safe