

IV. DISSOLUTION TESTING IN VITRO

Dissolution studies can be performed using an appropriate method developed by a sponsor⁴ or the current USP method. For each tablet strength to be marketed, multi-point dissolution studies should be performed on three production-sized batches using 12 tablets per batch. The time points used should be 10, 20, 30, 45, 60, 80, 100, and 120 minutes, or until 80 percent of the labeled claim is dissolved, so that a complete profile may be obtained. Dissolution testing should include lots used in the bioavailability studies.

V. FORMULATION

The composition of the formulation for each tablet strength of levothyroxine sodium to be marketed should be provided in the NDA.

VI. BIOWAIVER

For tablet strengths not studied in the dosage-form proportionality study (see section III. C), the sponsor should request biowaivers and provide appropriate formulation information as well as in vitro dissolution data as covered under 21 CFR 320.22(d)(2). Specifically, all of the following conditions should be met:

1. The dosage-form proportionality study among the to-be-marketed tablet strengths of levothyroxine sodium (low, medium, and high strengths) has been found acceptable, and proportionality has been shown among the strengths included in the study (also see section III. C. *Data Analysis*).
2. For tablet strengths to be covered under the waiver request, they should differ only in the amount of levothyroxine sodium and filler needed to maintain the tablet weights.
3. Multi-point dissolution profiles are similar across tablet strengths using an *f2* test. If both test and reference products dissolve 85 percent or more of the label amount of the drug in ≤ 15 minutes, the *f2* test is not necessary.⁴ The dissolution method as well as dissolution data have been found acceptable by the Agency.

Sponsors whose products do not meet the above conditions should contact the Division of Pharmaceutical Evaluation II for further guidance.

⁴ See FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

VII. ASSAY VALIDATION

Assays used for both in vivo and in vitro studies should be fully validated, reproducible, precise, accurate, specific, stable, and linear. If commercial kits are used, they should be validated in-house at the analytical site where the assay for the study is performed. Please note that the validation data from the kit manufacturer alone is insufficient.

REFERENCES

Farwell A. P., and L. E. Braverman, 1996, "Thyroid and Antithyroid Drugs," *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*, 9th ed. pp. 1383-1409, McGraw-Hill.

Paul T. L., J. Kerrigan, A. M. Kelly et al., 1988, "Long-term Thyroxine Therapy Is Associated with Decreased Hip Bone Density in Premenopausal Women," *JAMA*, vol. 259, pp. 3137-3141.

**Advisory Committee for Pharmaceutical Science
March 12-13, 2003**

Additional information relating to topics on the agenda for March 12-13, 2003 became available after the background packet was mailed. Information on two topics is provided below.

1. A Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century: A Progress Report

FDA has a major agency-wide initiative on "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk Based Approach," a two-year program which applies to pharmaceuticals, including biological human drugs and veterinary drugs. On February 20, 2003 FDA announced significant interim steps toward meeting the goals of this two-year initiative. These documents may be viewed at the following website: <http://www.fda.gov/cder/gmp/index.htm>. The committee members will be given an update on this initiative and one the draft guidances, Comparability Protocols, is a topic on the agenda.

2. Bioequivalence / Bioavailability of Endogenous Drugs

Issue: Bioavailability and bioequivalence assessments of drug products containing endogenous drugs require special considerations with respect to study design and data analysis. These special considerations have not been outlined in the general guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations" (<http://www.fda.gov/cder/guidance/3615fnl.pdf>) (Issued 7/2002, Posted 7/2002). FDA has provided drug specific recommendations, for example: Potassium Chloride (slow-release tablets and capsules) In Vivo Bioequivalence and In Vitro Dissolution Testing (<http://www.fda.gov/cder/guidance/old195fn.pdf>) (Revised 6/6/1994, Posted 6/22/1998); and

Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing (<http://www.fda.gov/cder/guidance/3645fnl.pdf>) (Issued 2/2001, Posted 3/8/2001)).

FDA is currently developing additional science-based regulatory policy for other endogenous substances. It may be desirable to develop general decision criteria on how to study bioavailability and demonstrate bioequivalence for endogenous drugs.

Objective of this "awareness topic" discussion: The goal of this discussion is to provide information to ACPS on the challenges for bioavailability and bioequivalence assessment of endogenous drugs and current regulatory approaches and thoughts. A more detailed discussion on this topic is planned for future ACPS (possibly at the first Biopharmaceutics Sub-Committee) meetings. Therefore, at this meeting we only seek the ACPS recommendations on what information or data may be needed to make future discussions as productive as possible.

For this discussion we have selected two case studies as examples - Bioavailability assessment of levothyroxine Sodium tablets and bioequivalence assessment of potassium chloride (slow-release tablets and capsules).

Note: A few months ago Abbott Labs provided the agency data from a study related to the FDA guidance "Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing." This study illustrates several aspects that need to be considered with respect to study design and data analysis of endogenous drugs. We have, therefore, invited them to share this information with you. Abbott has raised with FDA some issues related to the impact of their study results on the bioequivalence assessment of levothyroxine. This is not a topic for discussion at this ACPS meeting. During the open public session several speakers have requested time to express their opinions on the issue of bioequivalence of levothyroxine products. Again, these do not directly apply to this discussion. The FDA welcomes these opinions and will collect these for consideration in an appropriate manner.

Docket No. 97N-0314/CP2

Knoll Pharmaceutical's Citizen Petition Regarding Synthroid

CONFIDENTIAL APPENDIX

This appendix contains trade secret and confidential commercial information. It is included to more fully explain the agency's position as set forth in the public response to Knoll's citizen petition concerning Synthroid dated December 15, 1997.

**THIS DOCUMENT CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION
AND SHOULD NOT BE PUBLICLY DISCLOSED.**

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