

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.