

TO: Members, Advisory Committee for Pharmaceutical Science

FROM: Helen Winkle
Acting Director, Office of Pharmaceutical Science, CDER, FDA

Date: February 11, 2003

Re: Advisory Committee for Pharmaceutical Science Meeting on March 12 and 13

Dear ACPS Members:

I want to start by welcoming all of the new members to the advisory committee. We look forward to your participation on the committee and the value you will add in assisting us in the Office of Pharmaceutical Science (OPS) by providing your scientific input on various important issues in our regulatory processes. There will be a training session on March 11, 2003 to familiarize each of the new members with the CDER (Center for Drug Evaluation and Research) programs and regulatory functions. I hope that each of the new members will be able to attend that training session.

The attached backgrounder packet provides available information on each of the topics to be discussed at the advisory committee meeting on March 12 and 13, 2003. Although several of these topics will be "awareness" topics for future discussion, there are several topics where your input will be important. Please review backgrounder packet. If you have any questions prior to the meeting, do not hesitate to contact me.

March 12, 2003

Subcommittee Updates/Future Subcommittees

The ACPS is in the process of finalizing its subcommittee structure. The ultimate objective is to have subcommittees established under the parent advisory committee that represent the various scientific disciplines that support product review including: Chemistry, Manufacturing Controls (Manufacturing), Pharmacology/Toxicology, Clinical Pharmacology, Biopharmaceutics, and Microbiology. These two sessions will address the subcommittee structure and provide information on the specific goals and objectives of the newly formed and proposed individual subcommittees.

- ***PAT Subcommittee*** – The PAT Subcommittee has been sunsetted and issues previously discussed by that subcommittee's membership will now fall under the preview of the Manufacturing Subcommittee. Dr. Tom Layloff, chair of the PAT Subcommittee, will provide information on the accomplishments of the PAT Subcommittee, and recommend topics for future discussion by the Manufacturing Subcommittee.

- ***Manufacturing Subcommittee*** - This new subcommittee, which will be chaired by Dr. Judy Boehlert, will focus on a number of topics that relate directly to how we ensure the quality of pharmaceutical manufacturing in both the product review and inspection (GMP – Good Manufacturing Practices) processes. This subcommittee will serve as a forum in the future for vetting a number of issues under the FDA GMP initiative, “Pharmaceutical cGMPs in the 21st Century – a Risk-Based Approach.” The first meeting of this subcommittee will be on March 21, 2003. Dr. Ajaz Hussain will provide an overview of this subcommittee as well as an update on the progress of the aseptic processing working groups under the Product Quality Research Institute (PQRI).
- ***Clinical Pharmacology Subcommittee***. This newly formed subcommittee met for the first time October 23, 2002. Dr. Jurgen Venitz will present an update of that meeting.
- ***Biopharmaceutics Subcommittee***. Dr. Hussain will explain the role of this subcommittee, which is currently being established, and provide an overview of proposed topics for future consideration.
- ***Microbiology Subcommittee***. There are a number of new issues on the horizon dealing with issues of new microbiological technology and their application to regulatory decision-making. Dr. Peter Cooney will present on the role of this new subcommittee and possible topics for consideration. This subcommittee will meet for the first time in June or July 2003.
- ***Pharmacology/Toxicology Subcommittee***. This subcommittee, which is an offshoot of the Nonclinical Studies Subcommittee of the advisory committee, will deal with issues relating to the regulatory policies and processes for pharmacology and toxicology. Dr. Bob Osterberg will present on this subcommittee and its role under the advisory committee. This subcommittee will meet for the first time June 10, 2003.

Topical Dermatological Drug Product Nomenclature

There are a number of questions and issues regarding the existing classification of dosage forms for topical drugs. The definitions of ointment, paste, lotion, cream and gel vary widely. The CDER working group that has been created to establish a scientific basis for a systematic and coherent classification of dosage forms for topical drugs, under Dr. Yuan-yuan Chiu, will present their findings and evaluation for consideration and recommendation by the advisory committee.

The background documentation includes information used by the working group in evaluating various definitions for topical dosage forms along with their recommendation for definitions to be used by the Agency in classification. There will be two guest speakers, Dr. Keith Marshall and Dr. Herb Carlin, who will share their knowledge on this topic.

Questions for the ACPS:

- 1. The appearance and feel of a topical dosage form is part of the proposed definitions. In conversations with practitioners and evaluation of the literature, words such as greasy, non-greasy and cooling are often used when describing these dosage forms. Is there any value in including these attributes in the proposed definitions?*
- 2. Laboratory work found viscosity to be the most discriminating property that separated lotions from creams. In addition most literature sources describe lotions as liquids and creams as semi-solids. In the proposed definitions, lotion is distinguished from cream based on "pourability" which we found in the lab to be a viscosity less than 30,000 cp using the Brookfield viscometer at 25 ° C and 5 rpm. Is this reasonable?*
- 3. Laboratory work found LOD to be a discriminating property that separated ointments from creams. In addition, a review of current submissions to the Office of New Drug Chemistry and the Office of Generic Drugs found that ointments had large percentages of hydrocarbons or PEGs in their bases. In the proposed definitions, ointment is distinguished from cream based on the proportions of volatiles (<20% LOD) and composition (Hydrocarbons or PEGs>50%). Is this reasonable?*
- 4. The distinction between hydrophilic and lipophilic creams is made based on the composition of the continuous phase. Is there any value in including these two types of creams in the definitions?*
- 5. (a) Gel is distinguished from cream based on the presence of sufficient quantities of a gelling agent to form a three-dimensional, cross-linked matrix. Is this reasonable? Should "sufficient quantities" be defined? Which literature sources should be used as references? (b) Some currently marketed "gels" contain an emulsifier that gives the dosage form an opaque appearance. Should the presence of an emulsifier in a formulation preclude a dosage form from being classified as a gel? Should it then be considered a cream instead of a gel? (c) What is the most appropriate analytical technique that can be used to identify the three-dimensional structure of a gel?*
- 6. Is the overall approach taken in the proposed definitions appropriate?*

Topical Dermatological Bioequivalence

Determining bioequivalence for approving generic drug topical dermatological products has been complicated over the years based on the limitations in testing of topical products. FDA has researched methods for determining bioequivalence for topical products, specifically dermatopharmacokinetics (DPK), but has been unable to specifically identify a method which adequately addressed therapeutic equivalence of the products. Transcripts of advisory committee meetings from 10/23/98, 11/17/00, and 11/29/01 where DPK was discussed are available at the following FDA Internet Website: <http://www.fda.gov/cder/audiences/acspage/pharmaceuticalmeetings1.htm>.

The draft guidance on DPK has been withdrawn as a result of recommendations from the advisory committee at the November 2001 meeting. Based on input from that advisory committee meeting, FDA would like to take a fresh look at topical dermatological bioequivalence and how best to ensure regulatory and scientific soundness in review of generic products. Dr. Dale Conner, Director, Division of Bioequivalence, Office of Generic Drugs, will provide an overview of the generic drug approval process and the past efforts expended in the Agency in developing a regulatory policy for determining bioequivalence of topical generic products. Dr. Dena Hixon, Associate Director for Medical Affairs, Office of Generic Drugs will talk about issues relating to clinical “bioequivalence” for all generic products and the issues that arise in approving these products. Dr. Jonathan Wilkin, Director, Division of Dermatological and Dental Drug Products, Office of New Drugs, will discuss the clinical perspective on therapeutic equivalence of topical products and the specific challenges associated with these products. Dr. Ajaz Hussain will wrap up the discussion by presenting FDA’s proposed future direction for ensuring therapeutic equivalence of topical products.

Since we are now revising our strategy on how to address this issue, FDA is presenting this as an “awareness” topic for the advisory committee in preparation for more in depth discussion at future meetings. FDA will also seek input from the advisory committee regarding our current proposed direction and whether we should be considering additional alternatives.

Comparability Protocol

For various reasons, NDA/ANDA applicants often need to make changes to the approved manufacturing process. Applicants are responsible for assessing, prior to distribution of a product, the effect of any postapproval Chemistry, manufacturing and Controls (CMC) changes on product quality as they may relate to the safety or effectiveness of the product. Comparability protocol is a well defined, detailed, written plan for assessing the effect of specific CMC changes in product quality. Applicants are required to submit a supplemental application (prior approval or changes being effected) for any CMC change that has a substantial or moderate potential to affect product quality. Filing a comparability protocol with FDA can facilitate the implementation of postapproval CMC changes. Dr. Yuan-yuan Chiu, Director, Office of New Drug Chemistry will provide an overview. Dr. Stephen Moore and Nancy Sager will talk on this topic.

MARCH 13, 2003

Research in Office of Pharmaceutical Science (OPS)

This topic is being shared with the committee as an “awareness” topic. As the committee considers topics, it is important for them to be aware of the research capabilities within OPS as a possible resource for addressing regulatory and scientific issues. Dr. Hussain will provide a general overview of OPS’s current research program including

highlighting several major research programs in the Office of Research and Testing (OTR). Dr. Nakissa Sadrieh will present on the Center's Rapid Response Team (RRT). This team was created in November of 2000 to provide timely and specific research support (both laboratory-based and literature-based) for designated scientific questions which arise in the CDER review divisions. The goal of the team is to provide the review divisions with sound scientific data, or literature, which can be used to make regulatory decisions. Dr. Sadrieh will share several of the projects with the committee.

The background information includes a fact sheet on the Rapid Response Team and a list of completed and ongoing projects.

Dose Content Uniformity – Parametric Tolerance Interval Test for Aerosol Products

This is an “awareness” topic.

CDER has published two guidances for chemistry, manufacturing and controls (CMC) documentation of orally inhaled and nasal drug products (OINDP) – a draft guidance on *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - CMC Documentation*, and a final guidance on *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - CMC Documentation*. These guidances include recommendations for dose content uniformity (DCU) or spray content uniformity (SCU), also referred to as delivered dose uniformity.

As a result of the issuance of these two guidances, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) submitted a proposal entitled *A Parametric Tolerance Interval Test for Improved Control of Delivered Dose Uniformity of Orally Inhaled and Nasal Drug Products* (15 November 2001), which requested that this test replace the DCU and DCU through container life tests, as well as the SCU and SCU through container life tests. This test measures the metered dose at beginning, middle and end lifestages, to assess whether the product delivers the labeled number of full medication doses throughout the life of the MDI.

Conceptually, FDA agrees with this recommendation; however, there are still questions that need to be addressed. Dr. Wallace Adams will introduce the topic. Dr. Bo Olsson will present IPAC-RS's proposal. Dr. Walter Hauck will be available for questions regarding the statistical aspects of the proposal.

The background material includes an explanation of the guidances and the proposal along with appropriate reference material

Bioavailability / Bioequivalence of Endogenous Drugs

In approving endogenous drug products for market a number of challenges arise in evaluating bioavailability and bioequivalence in new drug applications (NDAs) for innovator products and abbreviated new drug applications (ANDAs) for generic products.

This topic is being presented to the advisory committee as an “awareness” topic and to discuss our scientific reasoning behind our decision-making processes on endogenous drug products.

Dr. Dale Conner will present the topic. He will provide an overview of the issues and our current scientific thinking and present the various attributes that we evaluate and the logic that is applied in making regulatory decisions on the products. Although each product is evaluated on its individual characteristics, there is a logical progression and rationale employed in the FDA evaluation process including how baseline should be corrected. FDA will present two case studies on how we have evaluated two products for approval including levothyroxine sodium tablets and two other examples. Dr. Stephen Johnson will present these case studies. Abbott Laboratories will present its recently accepted recommendations for baseline correction for levothyroxine sodium.

TO: Members, Advisory Committee for Pharmaceutical Science

FROM: Helen Winkle
Acting Director, Office of Pharmaceutical Science, CDER, FDA

Date: March 7, 2003

Re: Errata to Memo dated February 11, 2003 regarding ACPS Meeting March 12 and 13, 2003

In the section "Bioavailability / Bioequivalence of Endogenous Drugs", the last sentence should read as follows

"Abbott Laboratories will present an overview of research it conducted on baseline correction methods for levothyroxine sodium. Some of Abbott's research findings were recently adopted by FDA for bioequivalence testing on levothyroxine products. Abbott will also discuss other approaches for baseline correction."

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.