MEMORANDUM

TO: Members, Advisory Committee for Pharmaceutical Science

FROM: Ajaz S. Hussain, Ph.D.

Deputy Director, Office of Pharmaceutical Science, CDER, FDA

DATE: September 24, 2004

RE: ACPS Meeting October 19-20, 2004

Dear ACPS Members and Invited Guests,

We look forward to meeting with you on October 19-20, 2004, to discuss several important scientific topics.

On October 19, Ms. Helen Winkle will provide opening remarks and will outline the goals and objectives for this meeting. She will also provide a brief overview on the progress we've made in the FDA initiative, *Pharmaceutical cGMP's for the 21st Century*.

Following this, Dr. Judy Boehlert will provide a progress report from the Manufacturing Subcommittee for your assessment and recommendations. The subcommittee met on July 20-21, 2004, to discuss a number of topics including:

- Moving Toward the "Desired State": Manufacturing Science and Quality by Design as a Basis for Risk-based CMC Review
- Developing a Risk-based CMC Review Paradigm in the Offices of New Drug Chemistry and Generic Drugs: Opportunities, Challenges, Current Activities, and Next Steps
- Pharmaceutical Communities Research and Training Needs: The Industrialization Dimension of the Critical Path Initiative
- cGMPs for the Production of Phase I Investigational New Drugs (INDs)
- Pilot Model for Prioritizing Selection of Manufacturing Sites for GMP Inspection

The briefing information, presentation slides and meeting transcripts are available at the following FDA internet websites:

http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4052b1.htm
http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4052s1.htm
http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4052T1.htm
http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4052s2.htm
http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4052T2.htm

DAY 1

The following three topics will be discussed:

1. Parametric Tolerance Interval Test (PTIT) for Dose Content Uniformity of Aerosol Products.

   At the April 2004 ACPS meeting this topic was discussed. The formation of a joint FDA-Industry [represented by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)] Working group was recommended. This group was formed to resolve issues to allow FDA to adopt the use of the PTIT procedure. Dr. Robert O'Neill will present the group's progress report and seek your recommendation on their findings, progress, and planned next steps.

   For your reference the information related to the previous ACPS discussion on PTIT (the April 2004 meeting) can be located at the following websites:

   http://www.fda.gov/ohrms/dockets/ac/04/slides/4034S1_03_O'Neill_files/frame.htm
   http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4034T1.htm

2. The Critical Path Initiative -- Challenges and Opportunities.

   Attached as part of the background information is the Agency's white paper entitled "Challenge and Opportunity on the Critical Path to New Medical Products". The OPS and its offices will present their proposals under this initiative to seek your assessment and recommendations. We would appreciate your considerations on these proposals for their relevance and priority.

DAY 2

Discussion on the second day will cover OPS science and policy management plans and selected topics on bioequivalence assessment. Prior to these discussions, we have requested Professor Kibbe to share with us his overview and perspective on his experience as the senior member and outgoing Chairperson of the ACPS.

1. OPS Plans and Activities Moving Towards the "Desired State.

   We will be presenting our thoughts on the following topics:

   Organization Gap Analysis -- Helen Winkle
   Scientific Gap Analysis -- Ajaz Hussain
   Policy Gap Analysis -- Jon Clark

   Shortly, the Agency will be publicly releasing a comprehensive 2-year status report on the *Pharmaceutical cGMPs for the 21 Century* initiative. This informative document will be separately provided to you (by email) as an additional background piece in preparation for discussions at the meeting.

2. The Concept and Criteria of BioINequivalence.

This discussion is intended to further articulate criteria for establishing bioINequivalence. Such criteria may be useful to communicate and guide the review of studies intended to establish bioINequivalence and for companies conducting such studies.

This continues previous discussion on this topic (April 2004 meeting). If you wish to review the ACPS discussions on the BioINequivalence topic from the April 2004 meeting, you can find this information on the following websites:

http://www.fda.gov/ohrms/dockets/ac/04/slides/4034S2_09_Yu_files/frame.htm
http://www.fda.gov/ohrms/dockets/ac/04/slides/4034S2_10_Schuirmann_files/frame.htm
http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4034T2.htm

The Office of Generic Drugs has further refined its proposal for discussion at the ACPS meeting. This proposal introduces the concepts and criteria of bioequivalence, bioINequivalence, failing to demonstrate bioequivalence, and failing to demonstrate bioINequivalence. It also explains the statistical criteria used to claim bioINequivalence for one pharmacokinetic parameter and presents the pros and cons of several strategies to collectively evaluate the three pharmacokinetic parameters.

ACPS ACTION

ACPS will be requested to discuss the following question:

What is your preferred method for evaluating the three pharmacokinetic parameters for bioinequivalence?

- **If bioinequivalence is demonstrated for any one pharmacokinetic parameter that is prespecified, then bioinequivalence is demonstrated for the products.**
- **Bioinequivalence must be demonstrated for all three pharmacokinetic parameters for bioinequivalence to be demonstrated for the products, where the error rate is controlled at 5%.**
- **FDA should allow sponsors of bioinequivalence studies to make their own choice on picking up strategies; sponsors should prespecify the choice in study protocols before the study is conducted.**

3. Bioequivalence Testing for Locally Acting Gastrointestinal Drugs.

For drugs whose site of action is the gastrointestinal (GI) tract, determination of bioequivalence is more complicated as local drug concentrations cannot be measured directly. The goal of this topic is to present to the committee background on some of the scientific issues involved in developing bioequivalence methods for locally acting drugs that target the GI tract. In the past FDA has acted on a case by case basis, but for the future we would like to identify the key scientific principles for consistent and efficient identification of bioequivalence methods. We

will discuss and seek ACPS input on the following issues related to bioequivalence of locally acting GI drugs:

- Role of pharmacokinetic studies
- Role of in vitro tests including dissolution and binding assays
- Role of clinical studies

ACPS ACTION

We would like the committee to comment on the following questions:

- **For locally acting GI drugs, is PK, if measurable, an *in vivo* test sensitive to formulation performance and useful as a part of a determination of bioequivalence?**

- **Are there any drug specific issues that would aid FDA in interpreting the results of a PK study on a GI acting drug with respect to a conclusion about bioequivalence?**

- **When is it possible to use dissolution testing alone to demonstrate bioequivalence of GI acting drugs?**

- **When should comparative clinical trial studies be conducted to demonstrate bioequivalence?**

We are looking forward to a very stimulating discussion with you on the selected topics. Have a safe and enjoyable journey to Rockville, MD. If you need any additional information please do not hesitate to contact me (hussaina@cder.fda.gov) or Bob King (kingr@cder.fda.gov).