# MEMORANDUM

TO: Members, Advisory Committee for Pharmaceutical Science

FROM: Ajaz S. Hussain, Ph.D.
Deputy Director, Office of Pharmaceutical Science, CDER, FDA

DATE: March 16, 2004

RE: ACPS Meeting April 13-14, 2004

Dear ACPS Members and Invited Guests,

We look forward to meeting with you on April 13-14, 2004, to discuss several important scientific topics at the next meeting of the Advisory Committee for Pharmaceutical Science.

On April 13, Ms. Helen Winkle will provide opening remarks and will outline the goals and objectives of the 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, we will present the progress report from the Clinical Pharmacology Subcommittee for your assessment and recommendations. The subcommittee met on November 17-18, 2003, to discuss a number of topics including:

- Quantitative analysis using exposure-response
- Pediatric bridging studies: pediatric decision tree
- Drug interactions
- Pharmacogenetics: Integration into new drug development

If you wish to review the briefing information, presentation slides, and meeting transcripts, please look at the following internet websites:

http://www.fda.gov/ohrms/dockets/ac/03/briefing/3998B1_01_TOC.htm
http://www.fda.gov/ohrms/dockets/ac/03/questions/3998Q1_Draft.htm
http://www.fda.gov/ohrms/dockets/ac/03/slides/3998s1.htm
http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3998T1.htm
http://www.fda.gov/ohrms/dockets/ac/03/slides/3998s2.htm
http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3998T2.htm

## DAY 1

On April 13, 2004, three topics will be discussed:

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

At the October 21, 2003, ACPS meeting this topic was discussed. Approaches were presented to address the issues related to development and regulatory acceptance of this statistical approach for developing a standard for delivered dose uniformity of inhalation products. The FDA and the industry, represented by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), have been working on this topic for over three years and the progress has been very slow. The October 2003 meeting of ACPS provided FDA with an excellent opportunity to clearly articulate the challenges and the subsequent committee discussion provided valuable insight on potential approaches for resolving the issues with PTIT.

Following this meeting, FDA and the IPAC-RS discussed several approaches for moving forward to efficiently resolve the remaining issues. At this Advisory Committee meeting, we will present the proposal that was developed for moving forward. This proposal recommends the formation of a working group under the ACPS which will consist of key FDA Directors representing the disciplines of statistics (Dr. Robert O'Neil; FDA lead), clinical (Dr. Badrul Chowdhry), new drug chemistry (Dr. Moheb Nasr) and generic drugs (Dr. Lawrence Yu), along with several IPAC-RS nominees. Dr. O'Neil will present the details of this proposal and the IPAC-RS will also provide its perspective.

The presentations and discussions in April will focus primarily on the proposed process, the goals for the Working Group, and the reporting timeline. We look forward to the ACPS recommendations on the Working Group's activities and its proposal for resolving the PTIT issues.

**ACPS ACTION**

***The ACPS is requested to: 1) evaluate this proposal for the formation of a working group under ACPS supervision, 2) recommend improvements necessary for realizing the group's goals and objectives, and 3) recommend reporting requirements and a timeline for completing this project.***

Following the October 2003 ACPS meeting, I wrote an article (as a part of my presentation to the XI Respiratory Drug Delivery conference in April 2004) on this topic outlining some of the challenges and opportunities from my own perspective. This article is included in the background packet (Attachment #1) for your perusal.

If you wish to review the ACPS discussions on PTIT from the October and March 2003 meetings, you can find this information on the following websites:

http://www.fda.gov/ohrms/dockets/ac/03/briefing/3996b1.htm
http://www.fda.gov/ohrms/dockets/ac/03/slides/3996s1.htm
http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3998T2.htm
http://www.fda.gov/ohrms/dockets/ac/03/briefing/3926b2.htm

2. Progress Report and Planned Next Steps for the Process Analytical Technology (PAT) Initiative

Topics to be covered include:

- Status of the training and certification program for the PAT Review and Inspection Team (Attachment #2)
- Training on "Rapid Microbial Methods" (Attachment #3)
- Process for finalizing the draft PAT guidance (Attachment #4)
- Formation and progress of the ASTM's E55 Committee, Pharmaceutical Applications of PAT (Attachment #5)
- Perspectives on PAT for your consideration (review articles, Attachment #6)
- PAT continuing efforts: Conferences and Meetings (Attachment #7) and collaborations (Attachment #8)

**ACPS ACTION**

***The ACPS is requested to provide its assessment of the progress in the PAT initiative and to recommend how we may improve the impact, effectiveness, and efficiency of this program.***

3. PAT Applications for Products in the Office Of Biotechnology Products in OPS/CDER and in the Center for Biologics Evaluation and Research (CBER)

The PAT Initiative, which was launched at the July 2001 ACPS meeting, was developed through collaboration among CDER, CVM, and ORA. In October 2003, the Office of Biotechnology (OBP) was formed in OPS/CDER through a transfer of staff from CBER to CDER. Because staff in this new office and in CBER were not part of the first PAT training and certification program, the scope of the draft guidance did not cover the products regulated by these organizations. As planned, the final PAT guidance will retain the same scope, and will exclude OBP/OPS/CDER and CBER products even though the PAT framework outlined in the draft guidance is broad and applicable to many different manufacturing environments. This is because the training of FDA staff is essential to implement this framework. The discussion will include identification of challenges for implementing the PAT framework in other parts of CDER and in CBER.

**ACPS ACTION**

***The ACPS is requested to consider the best way to expand the scope of the PAT framework to include products in OBP and CBER. In addition, ACPS is requested to provide input on the following questions:***

- ***What technologies are available now to evaluate the characteristics of protein products in real time during manufacturing?***

- ***What tools would allow us to understand the manufacturing process better?***

- ***What processes in biological drug manufacturing would benefit the most from implementation of PAT?***

- ***For processes or products that do not currently allow direct product quality monitoring, what other strategies do you recommend for product quality control in addition to control of in-process parameters?***

- ***What additional elements should be incorporated in a training and certification program for reviewers and inspectors of biotechnology PAT applications?***

## DAY 2

On April 14, 2004, two bioequivalence topics will be discussed along with an update on topical bioequivalence (discussed at the October 2003 meeting). A brief introduction to regulatory aspects of nanotechnology will also be presented as an awareness topic.

1. Bioequivalence of Highly Variable Drugs.

   The term "highly variable" in the context of bioequivalence evaluation has been generally applied in the scientific literature to those drugs or drug products that exhibit intra-subject variability equal to or greater than 30% CV for measure of rate (peak drug concentration [Cmax]) or extent of absorption (area under the drug concentration in blood/plasma - time curve [AUC]). High intra-subject variability poses many challenges for establishing bioequivalence. This issue has been discussed for many years and has not been completely resolved. This discussion will reexamine the challenges and seek ACPS advice on several questions (Attachments #9 & 10).

   ### ACPS ACTION

   ***ACPS is requested to provide advice on the following issues:***

   - ***That "highly variable drugs or drug products can be defined as those exhibiting intra-subject variability of 30% CV or greater in AUC or Cmax."***

   - ***Comment and recommendations on two approaches for addressing the challenges:***

   - ***Expand bioequivalence limits from 80-125%, and restrict the mean T/R difference, e.g., ± 20? What information is necessary to properly set these new confidence interval limits?***

- ***Reference Scaling: Scale current bioequivalence criterion based on the reference variability in each study and restrict the mean T/R difference as above.***

2. The Concept and Criteria of BioINequivalence

At first glance, this may appear to be an odd topic; however, FDA sometimes receives submissions containing studies intended to show bioINequivalence between two drug products. Often these are from innovator companies that conduct studies to challenge FDA's approval of generic versions of innovator drug products. This discussion is intended to 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.

The Office of Generic Drugs has developed a proposal for discussion at the ACPS meeting (Attachment #11). 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. The document also provides thoughts on several statistical issues.

**ACPS ACTION**

***ACPS will be requested to discuss the following questions:***

- ***Does the ACPS agree with the distinction between demonstrating bioINequivalence and failure to demonstrate bioequivalence?***

- ***Does the ACPS recommend a preferred method for evaluating the three pharmacokinetic parameters for bioINequivalence?***

    1. ***If bioINequivalence is demonstrated for any one pharmacokinetic parameter, then bioINequivalence is demonstrated for the products.***

    2. ***BioINequivalence must be demonstrated for all three pharmacokinetic parameters for bioINequivalence to be demonstrated for the products.***

    3. ***There should be one pre-selected pharmacokinetic parameter used for bioINequivalence testing. If so, which one?***

    4. ***The three pharmacokinetic parameters should be evaluated for bioINequivalence with statistical corrections to the level of significance for each parameter in order to maintain an overall significance level of 0.05.***

3. Update on Topical Bioequivalence Method Development

   Following the October 2003 ACPS meeting, FDA staff developed a scientific paper that reviews the challenges for establishing pharmaceutical and bioequivalence (hence, therapeutic equivalence) of topical products. The attached manuscript (Attachment #12) was developed in collaboration with Dr. Jonathan Wilkin and it further develops the "Q3" concept that was introduced to ACPS in October 2003. At this ACPS meeting we will provide a brief overview of the proposal outlined in this manuscript to seek your general impressions and thoughts -- for example, are we on the right track? We plan to publish this manuscript to initiate scientific dialog before we bring the concept to the ACPS as a formal proposal.

4. Nanotechnology: An Awareness Topic (Attachment #13)

   Nanotechnology is a very rapidly growing area of science and technology. It is expected to lead to the development of many novel and sophisticated applications in drug delivery. Historically, nanometer-sized materials (e.g., silver and gold colloids) have been used in medicine. Additionally, many current pharmaceutical materials and drug delivery systems (e.g., particles, micro-emulsions, and liposomes) can have materials with dimensions in the nanometer range.

   The safety and efficacy of these products are currently being addressed adequately within the established regulatory system. However, the extensive research and development activities in nanotechnology are expected to lead to the development of more complex drug delivery systems, drug-device combination products, and other products regulated by the FDA. To ensure that FDA is ready to meet this responsibility, a multi-disciplinary discussion group has been assembled at the Agency level in the Office of Commissioner. This group is proactively gauging the growth of nanotechnology in anticipation of the complexity of future submissions to the FDA. As such, the Agency needs adequate regulatory procedures in place to deal with the challenges of the nascent technology.

   The purpose of the brief discussion at the April 2004 Advisory Committee is to share information on CDER/FDA activities and emerging plans to address the regulatory needs of nanotechnology-based products. At a future meeting of the Advisory Committee, we will discuss and seek advice on our approach to address nanotechnology-based products.

We are looking forward to a very stimulating discussion with you on the selected topics. Have a safe and enjoyable journey to Rockville, MD. The meeting will be held at the 5630 Fishers Lane building in Rockville. If you need any additional information please do not hesitate to contact me (hussaina@cder.fda.gov) or Bob King (kingr@cder.fda.gov).