

MEMORANDUM

TO: Members, Advisory Committee for Pharmaceutical Science

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

DATE: September 27, 2005

RE: ACPS Meeting October 25-26, 2005

Dear ACPS Members and Invited Guests,

We look forward to meeting with you on October 25-26, 2005, to discuss several important scientific topics. On the first day Ms. Helen Winkle will outline the goals and objectives for this meeting and provide you a brief update on Office of Pharmaceutical Science (OPS) ongoing initiatives and activities.

DAY 1: Topic #1

The first discussion topic will be a continuation of the May 2005 ACPS meeting discussion on a Quality-by-Design (QbD) approach to pharmaceutical quality assurance and control of drug dissolution or release rate characteristics of solid oral drug products. In our presentation at the May 2005 meeting, we extended invitations to all stakeholders to consider our proposed tactical plan as a first step and to develop their own proposals for addressing the challenges and opportunities identified in the ACPS discussions. Both innovator (PhRMA) and generic (GPhA) trade associations and the USP are planning to present their perspectives and proposals at the October 2005 meeting. An FDA working group has been working to further develop the proposed tactical plan and will present their expanded proposal. These presentations will follow the presentations by the three stakeholders (PhRMA, GPhA, and USP). We hope the background information provided and the presentation content will be sufficient to give the ACPS members an adequate opportunity to evaluate these different perspectives and proposals, to highlight areas of common understanding of this topic, and to identify where relevant scientific areas of disagreement exist among all the stakeholders.

The key questions posed to the committee are:

1. What are the important areas of agreement and disagreement among the various stakeholders?
2. What are the relevant scientific areas of disagreement among the stakeholders that the FDA should seek to establish consensus through additional efforts?
3. Should FDA develop a new guidance document on a QbD approach to dissolution rate specification? If so, what should be the critical elements FDA should include in

- the proposed guidance document to distinguish it from the current regulatory approach for decisions related to dissolution rate specification setting?
4. What additional considerations are necessary to leverage these efforts further and to make this proposed approach to dissolution specification a model for subsequent QbD approaches to regulatory specifications setting for other critical quality attributes?

Day 1: Topic #2

Day 1 will conclude with a progress report by the ACPS Working Group on the Parametric Tolerance Interval Test (PTIT) for Dose Content Uniformity of Inhalation Products. This is a collaborative working group of FDA and Industry [represented by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)] scientists that was formed to resolve issues related establishing regulatory specifications for dose content uniformity for inhalation products. Dr. Robert O'Neill will present the group's progress report and seek your recommendation on their findings, progress, and planned next steps. A meeting of this working group will be held on October 4, and following that meeting, we may provide you additional background material(s) prior to the October 2005 meeting of the ACPS. For your reference, the information related to previous ACPS discussions on this topic can be located at the following websites:

http://www.fda.gov/ohrms/dockets/ac/04/slides/4034S1_03_O%27Neill.htm
http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4078S1_03_O%27Neill.htm

We seek your recommendation on:

1. An equitable approach to conclude this effort. We believe these protracted efforts to resolve a debate on specification setting need to be concluded soon.
2. In retrospect, would an approach based on QbD principles be a more efficient approach for resolving similar debates?

DAY 2: Topic #1

We plan to introduce to you a new topic, “alcohol induced dose dumping” in our format of an “awareness topic”. Unintended, rapid drug release, in a short period of time, of the entire amount, or a significant fraction of the drug contained in a modified release dosage form, is often referred to as “dose dumping”.

Depending on the therapeutic indication and the therapeutic index of a drug, dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or both. In theory, concomitant consumption of alcoholic beverages along with these products might be expected to have the potential to induce dose dumping. This potential mechanism leading to dose-dumping from an oral modified-release dosage form has not previously attracted significant attention in the pharmaceutical science literature or in regulatory

assessment process. A recent FDA finding of an unfavorable risk versus benefit profile of a product (<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydromorphoneHCP.pdf>) due to alcohol-induced dose dumping necessitates development of a general regulatory approach to address the issue.

Two presentations are planned to provide you with information on: (1) the basis for clinical concern associated with alcohol-induced dose dumping, and (2) our current thinking and progress towards developing a general regulatory approach to minimize this risk for all approved and new modified release dosage forms. Although no specific questions on this topic are posed to ACPS, through the planned presentations and ACPS discussions we seek your input on this topic and general recommendations on the principles underpinning our current thinking and proposed approach for risk minimization.

Day 2: Topic #2

The OPS review offices – the Office of New Drug Chemistry, the Office of Generic Drugs and the Office of Biotechnology Products – have already initiated or are developing programs to implement the principles of Quality-by-Design and risk-based regulatory decision making in their day-to-day activities. These programs are being tailored to accommodate differences among these offices with respect to their regulatory processes, work-load, timelines, and stakeholders. However, it is desired and expected that the underlying scientific and risk assessment principles adopted for these programs be common and be able to address the level of complexity of the products, manufacturing processes, analytical and knowledge uncertainty in the regulatory applications of products regulated by these offices.

As these programs mature and are implemented we intend to provide updates to the ACPS to seek their input on approaches that OPS should consider to coordinate these programs, measure their progress, and to ensure that:

1. The founding scientific and risk assessment principles adopted by these programs are based on the common principles of quality-by-design
2. The implementation plans by these offices are consistent with the complexity of the products, manufacturing processes, analytical and knowledge uncertainty in the regulatory applications of products regulated

Day 2: Topic #3

Following up on a topic brought to the Committee during its May 2005 meeting, we will discuss the progress toward developing a “peer review” program to assess the quality of laboratory research in the Office of Pharmaceutical Science (OPS). Currently, we have two different mechanisms within the OPS to evaluate the research programs: one which was established for the Office of Testing and Research and another that is utilized by the Office of Biotechnology Products. We will provide an update since the last ACPS meeting and will seek ACPS discussion and recommendations on potential strategies and structures being considered.

Day 2: Topic #4

To conclude this meeting we selected an important topic – the state of US pharmaceutical science and engineering education – to highlight issues we believe need the attention of the entire pharmaceutical community. We believe that our journey towards the 21st Century "Desired State" for pharmaceutical quality will need to enhance the pharmaceutical education system in the USA. We plan to present different perspectives on this issue and seek your input on how OPS/CDER/FDA should bring this to the attention of key decision makers in the education community.

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).