

MEMORANDUM

TO: Members, Advisory Committee for Pharmaceutical Science

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

Date: 19 September 2002

RE: ACPS meeting October 21 and 22, 2002

Dear ACPS Members and Invited Guests,

We look forward to meeting you on 21 & 22 October 2002 to discuss several important scientific topics. On October 21, the Non-Clinical Studies and the Process Analytical Technology subcommittees will report on their progress and future plans. Following these reports information on the following topics will be presented to update the committee on our progress (topics 1 and 2) and to seek advice on several issues and questions outlined in this memorandum and the attached background information packet.

October 21, 2002 Topics

1. **Update: Risk-Based CMC Review.** Dr. Yuan-yuan Chiu first introduced this topic at the 15 November 2000 ACPS meeting. The goal of this initiative is to develop and adopt a risk assessment and management approach for the CMC review of post-approval manufacturing changes as well as for the review of original ANDAs. The current thinking is that under this program drugs considered “low risk” with respect to quality will receive reduced CDER oversight over information and data submission. Specifically, most of the manufacturing changes will not require a submission of a supplement (Prior Approval or Changes-Being-Effectuated) to the application. The amount of data and information to be submitted in the annual report of an approved application will also be minimized. The same concept and practice will also apply to original ANDAs after necessary regulation changes. This initiative does not exempt firms from performing necessary studies to evaluate the effects of changes to the quality, safety and efficacy of the drug, or from generating necessary data and information to support the approval of an original ANDA. Such data and information will be kept on site and made available during FDA inspection. Only firms with acceptable GMP compliance records will qualify for this program.

The CDER Risk-Based CMC Review working group has adopted a three-tier risk assessment and management approach that categorizes risk as into quality risks, safety/clinical risks, and risk of GMP non-compliance. They have attempted to quantify quality risk by developing scientific attributes and criteria for identifying “low risk” drugs, and a list of drugs that meet these quality criteria. The group’s current thinking on how to assess quality risk with respect to the drug substance and drug product will be

presented to the ACPS (See the Risk Decision Trees in the background packet - Attachment #1).

The information presented at the November 2000 meeting and the committee discussions (starting on page #25 of the transcripts) are archived at the following FDA Internet web-sites. In her presentation Dr. Chiu will provide a summary of these previous discussions.

<http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s1.htm>

<http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3657t1.pdf>

At the October 2002 meeting we do not plan to put forward specific questions to you. The working group would appreciate any comments and suggestions the committee may have for improving this emerging risk criteria. At a future meeting we plan to discuss with you this topic in detail along with our data analysis.

2. **Update: Blend Uniformity Analysis.** The Product Quality Research Institute's (PQRI) recommendations on the use of stratified sampling of dosage units to document adequacy of powder blending process were presented and discussed at the May 8, 2002, meeting of the ACPS. The committee was in general agreement with this proposal and suggested additional peer review before acceptance by the agency. The ACPS transcripts of this discussion (starting on page #138) meeting are available at the following FDA Internet web-site.

<http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3860T2.pdf>

A group of senior CDER staff representing offices of Pharmaceutical Science, Generic Drugs, New Drug Chemistry, and Compliance reviewed these recommendations. Individuals on this group were not members of the PQRI's BU Working Group. The Office of Biostatistics served as a consultant to the review group on statistical issues.

The group concluded that during routine production of solid dosage forms, the proposed concept of stratified in-process dosage unit analysis can serve as a method to document adequacy of powder blend and to assure drug content uniformity. However, the group felt that a few questions needed further clarification and/or scientific justification. These questions were communicated to the PQRI on August 14, 2002 (See Attachment #2a).

In parallel to the FDA review, Prof. DeLuca (Member of ACPS and the Editor of the AAPS electronic journal PharmSci Tech) subjected these recommendations to additional peer review by inviting selected scientists to evaluate the proposal (See Attachment #2b).

We anticipate the issues identified in the FDA review will be addressed by PQRI prior

to the October 2002 ACPS meeting and that we will be able to share with you our decision and planned next steps with respect to policy development and implementation. In the event these issues are not resolved, we will seek ACPS input on how best to resolve these. We have invited Drs. Massa (Chair, PQRI Steering Committee) and Garcia (Chair, PQRI BU Working Group) to attend the October 2002 meeting.

3. **Regulatory Issues related to crystal habits - polymorphism**. This topic was introduced at the May 2002 meeting as an "awareness" topic to identify and frame the key questions for further deliberations. At that meeting, FDA staff and invited experts provided an overview on several regulatory science issues related to polymorphism including characterization, setting specification for a new drug candidate, and impact on approval of generic drugs. The ACPS transcripts of this discussion (starting on page #204) are available at the following FDA Internet web-site.

<http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3860T2.pdf>

On June 7, 2002 the Office of Generic Drugs, as part of its Science Training Series, organized a symposium on polymorphism. Several experts were invited to share their knowledge and thoughts on this topic. Prof. David Grant (Theory and Origin of Polymorphism), Prof. Kenneth Morris (Methods for Characterization), Dr. Harry Brittain (Effects of Pharmaceutical Processing on Polymorphs), Prof. Nair Rodriguez-Hornedo (Effects of Crystallization on Properties of Drugs), and Prof. Leslie Benet (Considerations of Polymorphism in Therapeutic Equivalence). This symposium was an excellent continuing education experience for FDA staff.

A background paper for the ACPS meeting was developed by FDA staff and is attached for your review (Attachment #3). It provides current scientific thinking on issues related to monitoring and controlling drug substance polymorphs during manufacturing. Decision trees for solid oral dosage forms or liquids containing undissolved drug substances are developed to determine if there is a scientific need to establish polymorph acceptance criteria for drug substance and drug product. Although, the focus of this paper is on generic drug process (ANDAs) we expect the scientific discussions at the ACPS meeting will be relevant to both new and generic drugs. We have invited Profs. Morris, Brittain, and Benet to attend this meeting and to share with you their assessment of the FDA current thinking.

Based on the information presented in this manuscript the following questions are put forward for discussion:

- A. Do the proposed decision trees adequately address the key polymorph issues (stability and bioavailability) that should be considered in FDA's regulatory assessment on an ANDA?*
- B. Decision Tree#1. Are there other issues with respect to characterization of*

polymorphic forms that FDA should consider?

- C. *Decision tree #3 suggests that it is not necessary to have a polymorph specification for a drug product if/when the most stable polymorphic form is used or the form used is in a previously approved product that was developed without extraordinary formulation or manufacturing process development effort.*

Please comment on methods, approaches, and challenges for establishing specification for polymorphs in drug products. Also, in your experience, how often would you anticipate that such a specification necessary?

Please comment on the concept "extraordinary formulation or manufacturing process development effort" suggested in this decision tree.

- D. *What additional considerations, if any, should be addressed on the issue of manufacture-ability or "process-ability" when different polymorph forms are present?*

October 22, 2002 Topics

4. **Goals and Objectives: The proposed ACPS subcommittee on Pharmaceutical Manufacturing.** This subcommittee will address regulatory science issues in the area of manufacturing from both review and inspection (cGMP) perspectives. The new FDA initiative "Pharmaceutical cGMP's for the 21st Century" (See Attachment #4) will be a major focus of this committee. The PAT Subcommittee may eventually be incorporated into this committee.

It is envisioned that the CDER's Office of Pharmaceutical Science and the Office of Compliance will bring issues for discussion to this committee. Often this will be a team effort, on occasions and depending on topic area, only one of the offices may take the responsibility for topic discussion.

We plan to outline the goals and objectives and identify several topics for discussion. Industry representatives from PhRMA and GPhA have been invited to share their perspective with you.

5. **Aseptic Manufacturing.** This is a new topic for discussion at the ACPS and is an example of a manufacturing inspection issue that also has regulatory review impact. In order to have appropriate expertise we have invited several experts in microbiology and aseptic manufacturing to participate in the meeting.

In 1987, FDA's Center for Drug Evaluation & Research, Center for Biologics, and Office of Regulatory Affairs issued formal guidance in lieu of publishing regulations specific to

sterile drugs. Because of the need to control many variables during aseptic processing, the 1987 guidance was entitled "Guideline on Sterile Drug Products Produced by Aseptic Processing." It provided industry with the Agency's current thinking on areas where a lack of understanding was found to exist at the time. The document provided better definition of minimal cGMP standards needed to conduct operations in a manner that prevents contamination of a sterile drug. The Agency stated the intention to update the guideline from time to time when it "recognized the need through its regulatory efforts and through comments submitted by interested persons." With this knowledge, and following evolution in technology, standards and understanding of aseptic processes, FDA embarked on the task of updating this guidance in 1997. ***In a revised guidance document FDA plans to address areas for which improved clarity and explanation are needed to better facilitate industry compliance. The goal of this ACPS discussion is to identify these areas.***

To facilitate and to focus the ACPS discussion the FDA staff have developed a background paper that describes FDA's current thinking on the topics that we have identified as important topics for inclusion in the proposed guidance (See Attachment #5a). FDA staff members will make presentations to introduce these issues and offer their perspectives. In addition, we have invited the Parenteral Drug Association (Russ Madsen) to share their view on this topic. Although not confirmed at this time, we hope to have a presentation in the general area of risk assessment /hazard analyses of airborne contamination.

Questions for the ACPS and invited guests:

- A. Does the concept paper identify the most relevant topics for guidance development in the area of aseptic manufacturing?***
- B. Is the FDA's current thinking on these topics, as outlined in the concept paper, well grounded in science and is it sufficiently detailed to provide industry with clarity on FDA expectations with respect to assuring appropriate quality of sterile drugs produced by aseptic processing?***
- C. What (additional) considerations are needed to ensure that the proposed guidance: (1) contributes to the improvement of aseptic manufacturing processes across the industry, (2) help guide the FDA inspection process, and (3) encourages innovation in the aseptic manufacturing arena.***
- D. Please address the above questions broadly and also on the following specific topics: (1) Sterilization options; (2) Aseptic processing design, evaluation and contamination prevention, (3) Media fills, (4) Environmental monitoring and (5) Personnel issues.***