MEMORANDUM

TO: Members, ACPS Manufacturing Subcommittee

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

DATE: June 22, 2004

RE: ACPS Manufacturing Subcommittee Meeting July 20-21, 2004

Dear Subcommittee Members and Invited Guests,

We look forward to meeting with you on July 20-21, 2004, to discuss several important scientific topics at the next meeting of the Advisory Committee for Pharmaceutical Science (ACPS) Manufacturing Subcommittee.

DAY 1 (July 20, 2004)

Over the last year FDA has discussed the topics of manufacturing science and quality by design at a conceptual level. These discussions were essential to establish a shared vision for the future and for describing the "desired state" for pharmaceutical development and manufacturing and how these changes will be incorporated into the regulatory framework. These efforts have now progressed into the implementation phase within FDA and beyond (e.g., ICH, and ASTM). On July 20, we will provide the Subcommittee an update on ongoing activities and other plans for moving toward the desired state. The selected presentations and proposals for discussion are:

1. Progress Report on Ongoing Activities (Attachments 1-6)

   Updates will be provided on ICH efforts on pharmaceutical development (Q8), risk (Q9), and quality systems (proposed Q10). Additional information relative to ICH activities is available at the ICH Website (www.ICH.org).

   Dr. Chris Watts will update the Subcommittee on the PAT Guidance status and will provide a progress report on the ASTM E55 Committee: Pharmaceutical Applications of Process Analytical Technology activities. A background article from ASTM's May 2004 *Standardization News* is provided for your information.

2. Moving Toward the "Desired State": Manufacturing Science and Quality by Design as a Basis for Risk-based CMC Review (Attachments 7-9)

   Two perspectives on the description, utility and implementation options for manufacturing science and quality by design into FDA's CMC review process will be presented. We have requested Dr. G.K. Raju to provide his perspective on "Manufacturing Science and Knowledge", and I will provide a perspective on "Quality by Design and Specifications".

3. Developing a Risk-based CMC Review Paradigm in the Offices of New Drug Chemistry and Generic Drugs: Opportunities, Challenges, Current Activities, and Next Steps

   Moheb Nasr (Director, Office of New Drug Chemistry) and Gary Buehler (Director, Office of Generic Drugs) will provide their perspective on incorporating a risk-based CMC review process for those two offices under the manufacturing science and quality-by-design framework. They will also discuss the opportunities and challenges they have identified in implementing these concepts in the day-to-day activities of their offices.

   Following these perspectives, a brief summary of discussions between Professor Ken Morris and CMC review leaders in ONDC and OGD will be provided. Over the past eight months we have invited Professor Morris to visit FDA to conduct "brainstorming sessions" on the discussion topics to identify challenges and to help address how to work toward the "desired state."

Questions to the Subcommittee:

(1) Do you agree that current activities within ICH and ASTM are helping us move toward the desired state? We also seek your recommendations on how to ensure these activities are synergistic.

(2) To facilitate movement toward the desired state, FDA is providing incentives by ensuring that use of new technologies and additional information, above a minimum acceptable submission standard (e.g., PAT guidance, ICH Q8, etc.), will not be regulatory requirements but will be opportunities for companies to demonstrate higher level of process understanding and risk mitigation and, therefore, a basis for regulatory flexibility (e.g., reduced need for prior approval supplements).

- ***a. For implementation of these concepts, a clear demarcation of "minimum" and "optional" information is necessary. Please recommend how such demarcation criteria can be developed and implemented.***
- ***b. Quality by design and manufacturing science are considered foundations for rational risk-based decisions. Please recommend how these principles should be linked to risk tools such as Failure Mode Effect Analysis.***

(3) What other current activities and/or planned activities in the ONDC and OGD would you recommend to help move their practices toward the "desired state?"

4. Pharmaceutical Communities Research and Training Needs: The Industrialization Dimension of the Critical Path Initiative (Attachment 10)

   This discussion will focus on the ***Industrialization Dimension of the Critical Path Initiative***. The Subcommittee is requested to share their perspective and recommendations on what OPS should do to address the challenges outlined by this initiative. Suggestions would include possible collaborations with our OPS laboratories (e.g., Office of Testing and Research), academia, and industry (e.g. PQRI, NSF Center for Pharmaceutical Process Research, others), as well as other opportunities.

5. Introduction to Bayesian Approaches (Attachment 11)

   Without the effective and correct use of prior knowledge we often "re-invent the wheel." At OPS we are currently exploring the utility and applications of Bayesian approaches in CMC review. We have requested Professor Nozer to share with the Subcommittee his perspective on the utility of Bayesian approaches in regulatory decision making. This is an awareness topic and, therefore, Professor Nozer's presentation will be an "Introduction to Bayesian Approaches." Additional background information is available at http://www.prous.com/bayesian2004/index.asp, a website containing presentations from a May 20004 workshop on Bayesian Approaches sponsored by FDA, NIH, and Johns Hopkins University.

DAY 2 (July 21, 2004)

Discussion will start with the introduction of current thinking on cGMPs for the production of Phase I INDs. The discussion will be followed by an update on some ongoing academic research intended to identify factors associated with high quality pharmaceutical manufacturing. There will also be several presentations setting the stage for discussion on the risk-based pilot model in development for prioritizing the selection of manufacturing sites for cGMP inspection. The day will conclude with further updates on current topics successfully applying the manufacturing science and knowledge concepts we will be discussing during the course of our meetings.

1. cGMPs for the Production of Phase I Investigational New Drugs (INDs) (Attachment 12)

   This presentation will encompass two areas of current thinking. From the review perspective, being discussed are relevant CMC issues that focus mainly on safety and that don't hinder drug development at the early IND stages (proof of concept). Additionally, a presentation will be given on the draft guidance to show our reasonable expectations at Phase I of drug development.

2. Pharmaceutical Industry Practices Research Study

   In order to better focus on a risk-based approach in regulating pharmaceuticals, the Agency has entered into a number of collaborations with industry, academia and other government organizations. One of these collaborations is with Professors Macher and Nickerson of Georgetown University and Washington University, respectively. Their study is focused on obtaining a better understanding of those factors which lead to superior manufacturing performance in the pharmaceutical industry. The information from their study will help the Agency identify those factors that predict manufacturing performance to assist in developing targets for identifying risks to product quality. Professors Macher and Nickerson will share an update of their research study with the Subcommittee.

3. Pilot Model for Prioritizing Selection of Manufacturing Sites for GMP Inspection (Attachment 13)

These presentations will discuss how risk management concepts and tools can be used to prioritize FDA's limited resources for GMP inspections. Speakers will discuss how *risk ranking and filtering* techniques that have been applied in other contexts can assist FDA in quantifying and aggregating diverse risks, such as risks to quality associated with different manufacturing facilities. FDA will describe its first iteration of a pilot model to prioritize sites for GMP inspections, with the understanding that this is only the beginning of a process that will benefit from successive iterations and continuous improvement to achieve the goal of better allocation of scarce inspectional resources.

Questions to the Subcommittee:

(1) Can you identify alternative approaches that would systematically prioritize manufacturing sites for GMP inspections?

(2) In what areas would additional data provide the most value added in prioritizing manufacturing sites for GMP inspections?

(3) Are there other metrics that should be incorporated, e.g., measuring process control?

4. Applying Manufacturing Science and Knowledge: Regulatory Horizons (Attachments 14-16)

The cGMP 21st Century initiative has stimulated the Agency to be forward thinking with respect to regulatory decision making, with emphasis on quality by design and process understanding/knowledge. Three presentations will focus on updating areas where manufacturing science and knowledge concepts are being applied and incorporated into ongoing activities within CDER: (1) Process Understanding and PAT, (2) Comparability Protocol, and (3) Changes Without Prior Approval.

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 Bob King (kingr@cder.fda.gov).