July 20-21, 2004
Manufacturing Subcommittee, ACPS
Hilda F. Scharen

Summary Minutes of the Manufacturing Subcommittee
Advisory Committee for Pharmaceutical Science
July 20-21, 2004

This is the final report of the Advisory Committee for Pharmaceutical Science meeting held on July 20-21, 2004. A verbatim transcript will be available in about 2 weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder04.html#PharmScience

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The Manufacturing Subcommittee of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 20-21, 2004, at the Advisors and Consultant Staff Conference Room, 5630 Fishers Lane, Rockville, Maryland. Judy Boehlert, Ph.D, chaired the meeting.

Manufacturing Subcommittee of the Advisory Committee for Pharmaceutical Science Members (voting):
Judy Boehlert, Ph.D., Patrick DeLuca, Ph.D. (ACPS), Daniel Gold, Ph.D., Kenneth Morris, Ph.D., Thomas Layloff, Jr., Ph.D.[not in attendance], Garnet Peck, Ph.D., Joseph Phillips, G.K. Raju, Ph.D., Nozer Singpurwalla, Ph.D. (ACPS)

Acting Industry Representative (non-voting):
Paul H. Fackler, Ph.D.

Industry Representative (non-voting):
Gerald Migliaccio

Guest Speakers:
John Berridge, Ph.D., Jeffrey Macher, Ph.D., Tobias Massa, Ph.D., Jackson Nickerson, Ph.D., Fred Razzaghi

FDA Guest Speakers:
Gary Buehler, R.Ph., Jon Clark, M.S., H. Gregg Claycamp, Ph.D., CHP, Joseph Famulare, Brian Hasselbalch, Ph.D., David Horowitz, Esq., Ajaz Hussain, Ph.D., Stephen Moore, Ph.D., Moheb Nasr, Ph.D., Nga Tran, Dr.P.H (Contractor), Chris Watts, Ph.D.

FDA Participants:
Helen Winkle

Open Public Hearing Speakers:
July 20, 2004: None

July 21, 2004: None

These summary minutes for the July 20 and 21, 2004 of the Manufacturing Subcommittee meeting of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration were approved on ____08/12/04_____.

I certify that I attended the July 20 and 21, 2004, the Manufacturing Subcommittee meeting of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____//S//_____
Hilda F. Scharen, M.S.
Executive Secretary

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Judy Boehlert, Ph.D.
Chair

The Subcommittee received topic updates relative to ICH initiatives Q8, Q9, and proposed Q10, in addition to an overview of ASTM Committee E55. This was followed by presentations on ongoing activities pertaining to manufacturing science and

quality by design, focused on the evolving Chemistry, Manufacturing, and Controls review paradigm within the Office of New Drug Chemistry and the Office of Generic Drugs. They discussed and provided comments on a Current Good Manufacturing Practice (cGMP) risk model being developed at FDA. The Subcommittee then discussed and provided comments on a cGMP & quality system approach for the production of Investigational New Drugs (INDs), followed by discussions and comments on current efforts underway for the Process Analytical Technology (PAT), comparability protocol, and changes without prior approval initiatives.

Judy Boehlert, Ph.D. (Subcommittee Chair), called the meeting to order at 8:30 a.m. on July 20, 2004. The Subcommittee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Hilda Scharen, M.S. The agenda proceeded as follows:

Day 1: Tuesday, July 20, 2004

8:45	**Introduction to Meeting**	Ajaz Hussain, Ph.D. Deputy Director, Office of Pharmaceutical Science, FDA
9:00	**Topic Updates - Quality by Design**	
	(1) ICH Q8	John Berridge, Ph.D. Pfizer Ltd. (Representing EFPIA/JPMA/PhRMA)
	(2) ICH Q9	Fred Razzaghi, Consumer Healthcare Products Association (Representing EFPIA/JPMA/PhRMA)
	(3) Life Cycle Management for Process and System Control: An Industry Proposal	Tobias Massa, Ph.D. Eli Lilly & Co. (Representing EFPIA/JPMA/PhRMA)
	(4) ASTM E55 Committee: Pharmaceutical Applications of Process Analytical Technology	Donald Marlowe, FDA
10:30	*Break*	
10:45	**Introduction to Bayesian Approaches**	Nozer Singpurwalla, Ph.D. ACPS Committee Member
11:30	**Research and Training Needs: The Industrialization Dimension of the Critical Path Initiative**	Ajaz Hussain, Ph.D.
12:00	*Lunch*	
1:00	**Open Public Hearing**	
1:30	**Moving Towards the "Desired State": Manufacturing Science and Quality by Design as a Basis for Risk-based CMC Review**	Ajaz Hussain, Ph.D. (Topic Introduction)
	(1) Quality by Design and Specifications	Ajaz Hussain, Ph.D.
	(2) Manufacturing Science and Knowledge	G.K. Raju, Ph.D. Manufacturing Subcommittee
2:35	**Risk-based CMC Review Paradigm Under Quality by Design and Manufacturing Science Framework**	
	Opportunities, Challenges, Current Activities, and Next Steps:	
	(1) Office of New Drug Chemistry (ONDC)	Moheb Nasr, Ph.D., FDA

	(2) Office of Generic Drugs (OGD)	Gary Buehler, R.Ph., FDA
3:30	*Break*	
3:45	(3) Risk-based Development and CMC Question-based Review	Ken Morris, Ph.D. ACPS Committee Member
	(4) Topic wrap-up -- goals and next steps	Ajaz Hussain, Ph.D.
	Committee Discussion and Recommendations	

The meeting was adjourned at approximately 5:09 p.m. on July 20, 2004.

Judy Boehlert, Ph.D. (Subcommittee Chair), called the meeting to order at 8:30 a.m. on July 21, 2004. Hilda Scharen, M.S., read the conflict of interest statement into the record. The agenda proceeded as follows:

Day 2: Wednesday, July 21, 2004

8:45	**Introduction to Pharmaceutical Industry Practices Research Study**	David Horowitz, Esq., FDA
	Update on Pharmaceutical Industry Practices Research Study	Jackson A. Nickerson, Ph.D. , Washington University in St. Louis Jeffrey T. Macher, Ph.D., Georgetown University
9:15	**Pilot Model for Prioritizing Selection of Manufacturing Sites for GMP Inspection**	H. Gregg Claycamp, Ph.D., CHP, FDA David Horowitz, Esq.
10:15	*Break*	
10:30		Nga Tran, Ph.D., FDA (Contractor) Brian Hasselbalch, Ph.D., FDA
	Committee Discussion and Recommendations	
11:30	**Open Public Hearing**	
12:00	*Lunch*	
1:00	**cGMPs for the Production of Phase I Investigational New Drugs (INDs)**	Moheb Nasr, Ph.D. Joseph Famulare, FDA
	Committee Discussion and Recommendations	
1:45	**Applying Manufacturing Science and Knowledge: Regulatory Horizons**	
	(1) Process Understanding and PAT	Chris Watts, Ph.D., FDA
	(2) Comparability Protocol	Stephen Moore, Ph.D., FDA
2:45	*Break*	
3:00	(3) Changes Without Prior Approval	Jon Clark, M.S., FDA

Committee Discussion and Recommendations

3:30 **Meeting Conclusion and Summary Remarks** Ajaz Hussain, Ph.D.
Questions to the Committee*:*

Topic #1: *Developing a Risk-based CMC Review Paradigm in the Offices of New Drug Chemistry and Generic Drugs: Opportunities, Challenges, Current Activities, and Next Steps*

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.**

The Subcommittee strongly came to agreement that these current activities are helping to move in the right direction and are synergistic by providing more detailed information as to what is needed or the desired state, as well as, industry input.

Some members think that at this point both ICH and ASTM current activities are important, but will need to be reassessed in the future to ensure the efforts do not become duplicative.

The members emphasized it was important that all regulatory counterparts in Europe and Japan be kept abreast and involved. In fact, the members noted that there is a lot of interest by these counterparts with the ICH Q8, Q9, and proposed Q10 progressing in a harmonized fashion thanks to the continued commitment of the key players (industry, academia, regulators).

In addition, members commended the PAT team for their continued commitment and involvement that will lead to a finalized PAT Guidance and several workshops in the near future.

The Subcommittee concluded that the principles of science and management tools are helpful to move toward the desired state. However, the members agreed that a concrete example involving all parties (i.e. FDA, the innovators, the generics, etc…) for the generic and innovator drug companies are paramount to establish a "proof of principles", at which point the desired state can be laid out.

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 a 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.**

The Subcommittee expressed some concern regarding a clear demarcation of "minimum" and "optional" information. The members pointed out that the optional information will come in different degrees but not all of it will be available at the time of the NDA submission. The members added that regulatory flexibility is important for a greater process understanding and learning, as additional pharmaceutical development information becomes available.

The members concurred that FDA needs to assure that they will uniformly regulate across the industry and that pharmaceutical development information submitted will not delay the approval process, nor penalize the companies, as well as provide reduction in requirements for notification of changes in manufacturing (e.g., supplement submissions).

In conclusion, the Subcommittee emphasized that the companies need to have the choice between "minimum" and "optional" information providing incentives (i.e., companies being free to make changes to their own manufacturing process). The Subcommittee came to agreement that a working group should be established under the Subcommittee to address these specific questions.

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.**

The Subcommittee agreed that although Failure Mode Effect Analysis is a technical engineering basis to trace the course of events leading to failure, the tool only has a meaning when the levels and the processes are defined. The members think that Quality by Design and Manufacturing Science are fundamentals and priorities to achieve the goal. Failure Mode Effect Analysis can be a good starting point.

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?"

The members expressed some concerns with respect to the inordinate time it takes for generic drugs to be approved, which is mainly due to understaffing at the FDA. Also, the Subcommittee reinforced the need to cut down on approval time, and yet maintaining its efficacy, would be beneficial to both the drug manufacturers and society.

The Subcommittee emphasized that drug companies' concerns can be diminished by developing a concrete example of a faster and smoother approval process; this will benefit all stakeholders.

In addition, the members consider that training and education is important to strengthen process understanding. It was suggested that a working group could be formed under the Subcommittee to assist in developing an education program for both agency and industry staff.

Topic #2: *Pilot Model for Prioritizing Selection of Manufacturing Sites for GMP Inspection*

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

One member suggested distinguishing between different risks associated with the products and processing lines, although the Subcommittee recognized the importance of an effective quality system associated with pharmaceutical production.

One member suggested the use of a decision tree in order to prioritize sites according to the expected utilities.

In addition, the Subcommittee recommended that FDA consider the distribution of sites selected by the model to consider whether there is a representative balance between generic and innovator sites and between biotech and conventional manufacturing sites.

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

One member expressed concern that high volume of production should not be given too much weight as a criterion to prioritize sites for inspection and suggested a "volume-risk index" that would fully take into account factors that mitigate risks, some of which may be associated with high volume production.

The Subcommittee emphasized that historical inconsistency among investigator findings might limit the utility of such findings in prioritizing sites for inspection, but the Subcommittee recognized that this limitation should become less problematic over time as the new Pharmaceutical Inspectorate program is implemented.

The Subcommittee agreed that it would be crucial to ensure that the model promotes the correct incentives that encourage robust quality systems, continued availability of medically important drugs, and continuous improvement.

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

The members felt that companies with a high turnover of personnel might be a helpful indicator to include but that it may be difficult to obtain good data on this factor. One member stated that expert testimonies are a

positive step in the agency's risk-based analyses, but wanted to ensure that such testimonies would be formally incorporated into the analyses.

The members highlighted that understanding of high-risk areas is a helpful tool for both FDA and industry in allocating resources. The members emphasized that FDA needs to help industry understand the model ranking factors with appropriate transparency, to allow firms to improve their ranking by moving toward the desired state, and to allow them to appropriately allocate their internal resources.

The meeting was adjourned at approximately 4:00 p.m. on July 21, 2004.