October 19-20, 2004
ACPS
Hilda F. Scharen

Advisory Committee for Pharmaceutical Science (ACPS)
October 19-20, 2004

This is the final report of the Advisory Committee for Pharmaceutical Science meeting held on October 19-20, 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

All external requests should be submitted to the Freedom of Information office.

The Advisory Committee for Pharmaceutical Science of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 19-20, 2004, at the Advisors and Consultant Staff Conference Room, 5630 Fishers Lane, Rockville, Maryland. Art Kibbe, Ph.D., chaired the meeting.

Advisory Committee for Pharmaceutical Science Members (voting):
Arthur H. Kibbe, Ph.D., Patrick P. DeLuca, Ph.D., Meryl H. Karol, Ph.D., Melvin V. Koch, Ph.D., Michael S. Korczynski, Ph.D., Marvin C. Meyer, Ph.D., Kenneth Morris, Ph.D., Cynthia R.D. Selassie, Ph.D., Marc Swadener, Ed.D., Nozer Singpurwalla, Ph.D., Jürgen Venitz, M.D., Ph.D.

Advisory Committee for Pharmaceutical Science Consultants (voting):
Gordon Amidon, Ph.D., M.A., Judy Boehlert, Ph.D., Carol Gloff, Ph.D.

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

Guest Speakers:
Shahid Ahmed, M.S.

FDA Guest Speakers:
Lucinda Buhse, Ph.D., Jon Clark, M.S., Jerry Collins, Ph.D., Joseph Contrera, Ph.D., Ajaz Hussain, Ph.D., Monsoor Khan, R.Ph., Ph.D., Steven Kozlowski, M.D., Vincent Lee, Ph.D., Quian Li, Sc.D., Robert Lionberger, Ph.D., Robert O'Neill, Ph.D., Amy Rosenberg, M.D., John Simmons, Ph.D., Keith Webber, Ph.D., Helen Winkle, Lawrence Yu, Ph.D.

FDA Participants:
Gary Buehler, R.Ph.

Open Public Hearing Speakers:
October 19, 2004:
Saul Shiffman, Ph.D.

October 20, 2004: None.

These summary minutes for the October 19 and 20, 2004 of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration were approved on _____11/16/04_____.

I certify that I attended the October 19 and 20, 2004, meeting of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration meeting and that these minutes accurately reflect what transpired.

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

_____//S//_____
Art Kibbe, Ph.D.
Chair

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The Committee received updates pertaining to the ACPS Manufacturing Subcommittee, the ACPS Parametric Tolerance Interval Test (PTIT) Workgroup, and the Good Manufacturing Practices (GMPs) for the 21st Century initiative. Additionally, the Committee reviewed and discussed: research opportunities under the Critical Path Initiative, the Office of Pharmaceutical Science (OPS) plans and activities designed to take the organization towards the "desired state" of science and risk-based regulatory policies and practices as articulated under the GMPs for the 21st Century Initiative, and specific topics related to pharmaceutical equivalence and bioequivalence of generic drugs.

Art Kibbe, Ph.D. (Committee Chair), called the meeting to order at 8:30 a.m. on October 19, 2004. The Committee 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, October 19, 2004

8:30	Call to Order	Arthur Kibbe, Ph.D. Chair, ACPS
	Conflict of Interest Statement	Hilda Scharen, M.S. Executive Secretary, ACPS
8:45	Introduction to Meeting OPS Update Pharmaceutical Quality for the 21st Century	Helen Winkle, Director, Office of Pharmaceutical Science, (OPS), CDER, FDA
9:00	Subcommittee Reports Manufacturing Subcommittee	Judy Boehlert, Ph.D. Chair, Manufacturing Subcommittee
9:30	Parametric Tolerance Interval Test for Dose Content Uniformity Current update on the Working Group Committee Discussions and Recommendations	Robert O'Neill, Ph.D. Director, Office of Biostatistics (OB), Office of Pharmacoepidemiology and Statistical Science (OPaSS), CDER, FDA
9:45	Break	
10:00	The Critical Path Initiative – Challenges and Opportunities Topic Introduction and OPS Perspective	Ajaz Hussain, Ph.D. Deputy Director, OPS, CDER, FDA
	Research Opportunities and Strategic Direction	Keith Webber, Ph.D. Acting Director, Office of Biotechnology Products (OBP), OPS, CDER, FDA
	Informatics and Computational Safety Analysis Staff (ICSAS)	Joseph Contrera, Ph.D. Director, Informatics and Computational Safety Analysis Staff(ICSAS), OPS, CDER, FDA
	Office of New Drug Chemistry (ONDC)	John Simmons, Ph.D. Director, Division of New Drug Chemistry I, ONDC, OPS, CDER, FDA
	Office of Generic Drugs (OGD)	Lawrence Yu, Ph. D. Director for Science, Office of Generic Drugs (OGD), OPS, CDER, FDA
12:00	Lunch	
1:00	Open Public Hearing	

2:00	Office of Biotechnology Products Current research and future plans	Amy Rosenberg, M.D. Director, Division of Therapeutic Proteins,OBP,OPS,CDER,FDA
		Steven Kozlowski, M.D. Director, Division of Monoclonal Antibodies, OBP, OPS, CDER, FDA
	Office of Testing and Research Current research and future plans	Jerry Collins, Ph.D. Director, Laboratory of Clinical Pharmacology, Office of Testing and Research (OTR), OPS, CDER, FDA
		Lucinda Buhse, Ph.D. Director, Division of Pharmaceutical Analysis, OTR, OPS, CDER, FDA
		Mansoor Khan, R.Ph., Ph.D. Director, Division of Product Quality Research, OTR, OPS, CDER, FDA
3:30	Break	
	Wrap-up and Integration	Jerry Collins, Ph.D.
	Challenges and Implications	Vincent Lee, Ph.D. Senior Pharmacist, OPS, CDER, FDA
	Committee Discussion and Recommendations	
5:00	Adjourn	

The meeting was adjourned at approximately 5:35 p.m. on October 19, 2004.

Day 2: Wednesday, October 20, 2004

8:30	Call to Order	Arthur Kibbe, Ph.D.
	Conflict of Interest Statement	Hilda Scharen, M.S., FDA
8:45	Science in Regulation -- Visionary Overview	Arthur Kibbe, Ph.D.
9:15	The "Desired State" of Science- and Risk-based Regulatory Policies	Ajaz Hussain, Ph.D., FDA
	(1) Organization Gap Analysis	Helen Winkle
	(2) Scientific Gap Analysis	Ajaz Hussain, Ph.D.
	(3) Policy Gap Analysis	Jon Clark, M.S. Associate Director for Policy Development, OPS, CDER, FDA
10:30	Break	
	(4) Generic Pharmaceutical Association (GPhA) Perspective	Shahid Ahmed, M.S. Vice Presdient, Regulatory Affairs American Pharmaceutical Partners (representing GPhA)

	(5) Pharmaceutical Research and Manufacturers of America (PhRMA) Perspective	Gerry Migliaccio, Ph.D. Vice President, Global Quality Operations, Pfizer, Inc. (representing PhRMA)
	Committee Discussion and Recommendations	
12:00	Lunch	
1:00	Open Public Hearing	
2:00	Pharmaceutical Equivalence and Bioequivalence of Generic Drugs (1) The Concept and Criteria of BioINequivalence	
	Concept of BioINequivalence	Lawrence Yu, Ph.D., Director for Science, Office of Generic Drugs (OGD), OPS, CDER, FDA
	Criteria of BioINequivalence	Qian Li, Sc.D. Mathematical Statistician, OB, OPaSS, CDER, FDA
	Committee Discussion and Recommendations	
3:00	Break	
	(2) Bioequivalence Testing for Locally Acting Gastrointestinal Drugs	
	Topic Introduction	Lawrence Yu, Ph.D.
	Scientific Principles	Gordon Amidon, Ph.D. Professor of Pharmacy and Professor of Pharmaceutical Sciences, College of Pharmacy, University of Michigan
	Regulatory Implications and Case Studies	Robert Lionberger, Ph.D. Chemist, OGD, OPS, CDER, FDA
	Committee Discussion and Recommendations	
4:30	Conclusion and Summary Remarks	Ajaz Hussain, Ph.D. Helen Winkle
5:00	Adjourn	

***Questions to the Committee**:*

Topic #1: Critical Path Initiative

Are we focusing on the appropriate Critical Path topics? Are there others that we should be addressing through our research programs? How should we identify Critical Path issues in the future and how should we prioritize them?

The Committee thanked the presenters for their in-depth presentations. The Committee agreed that FDA is focusing on the right Critical Path topics to improve drug development and processing. The members felt that the FDA knowledge base puts the Agency in a unique position to identify some of the problems. However, they added that since FDA does not have all the information, collaboration with Industry and Academia is necessary in order to achieve the critical pathway.

In addition, the members highlighted that a science-based approach is necessary to define the metrics and the desired state. The committee discussed several metrics, which are helpful to measure effectiveness of the program,

such as the multiple review cycle and tracking of FDA personnel turnover. Also, the members suggested that a Bayesian approach may be the best way to reduce the review cycle time for drug approval.

The members underlined that collaboration and trust are essential for a science-based approach to the regulatory arena and commended FDA on their research efforts and collaboration with NIH. The members emphasized that it is a challenge for Industry to contribute to the knowledge base due to the legal pressure placed on them; intellectual property rights and trust complicate the collaboration effort. Also, the members underlined that better communication between FDA and Industry can help make the approval process more predictable for the sponsor. The members added there is an acute need for fundamental research and public funding. The members underlined that manufacturing has been a neglected area in the United States, compared to Europe.

In addition, the committee felt that Academia would be the best group to pursue the continued research projects needed to contribute to the science-based approach and be hypothesis driven, in order to achieve the Critical Path issues of the future. In conclusion, the committee felt a reduction in risk with knowledge sharing is necessary in achieving scientific truth, as well as, compliance not to be a barrier to the scientific knowledge. Finally, the members stressed that as the rate of technology advancement increases, an internal committee needs to also be considering the questions of the future, in order to handle the prospective paradigm shifts.

Topic #2: The Concept and Criteria of BioINequivalence
Please comment on the following recommendations:

- **If bioinequivalence is demonstrated for any one pharmacokinetic parameter that is prespecified, then bioinequivalence is demonstrated for the products.**
- **Bioinequivalence must be demonstrated for all three pharmacokinetic parameters for bioinequivalence to be demonstrated for the products, where the error rate is controlled at 5%, and if any one pharmacokinetic parameter is not prespecified.**

The committee recognized the difficulty of a developing a science-based response to this problem. The members recommended that the existence of prior information must be included in the determination of bioinequivalence. In addition, the members argued that if the area under the curve (AUC) is picked, this gives no information about the rate; the Cmax captures both the rate and extent of absorption. Some suggested that the criteria for establishing bioinequivalence must include all three metrics of Cmax, AUCt and AUC∞, while the others recommended that one metric be sufficient.

In conclusion, the Committee highlighted that it is a hurdle to prove bioinequivalence, as the bounds used have to disapprove all three metrics. The committee agreed that bioinequivalence is a challenge for FDA, in the light of diminished Agency resources, but prior information such as failed biostudies could answer some of these questions.

Topic #3: Bioequivalence Testing for Locally Acting Gastrointestinal Drugs.
Please comment on the following recommendations:

- **For locally acting GI drugs, is PK, if measurable, an in vivo test sensitive to formulation performance and useful as a part of a determination of bioequivalence?**
- **Are there any drug specific issues that would aid FDA in interpreting the results of a PK study on a GI acting drug with respect to a conclusion about bioequivalence?**
- **When is it possible to use dissolution testing alone to demonstrate bioequivalence of GI acting drugs?**
- **When should comparative clinical trial studies be conducted to demonstrate bioequivalence?**

The Committee discussed the use of dissolution testing to establish bioequivalence for drugs that act in the GI tract. The members added that in vitro testing is good if there is control over the test. The members emphasized that dissolution tests are needed early on in the process, in order to narrow down the variables. Further, pharmacokinetics studies are useful to assure safety of the test product.

In addition, the members stressed that dissolution tests are formulation tests, and can be a surrogate for clinical tests. The Committee discussed that dissolution tests can be very discriminating if the study is designed well. Although the committee felt that the Agency had all the data necessary to do dissolution testing for the products being discussed, dissolution test procedures can be simple for some drugs, but complicated for others. The Committee argued that

when a lot of background information is available, the dissolution test could be used. However, the members added that when doing dissolution testing, careful attention needs to be paid to the calibrator.

The members emphasized that as local acting products, such as GI, nasal, or topical are part of the Critical Path Initiative, they could contribute to the timely approval of generic drugs.

In conclusion, the Committee agreed it was difficult to reach a consensus, but that in order to prove bioequivalence in vitro dissolution along with pharmacokinetics should be acceptable.

The outgoing Chair praised the committee and the FDA staff for the great work that has been accomplished over the last three years. He especially recognized Ms. Winkle and Dr. Hussain for their leadership of these efforts.

The meeting was adjourned at approximately 4:35 p.m. on October 20, 2004.