April 13-14, 2004
ACPS
Hilda F. Scharen

Advisory Committee for Pharmaceutical Science
April 13-14, 2004

The Advisory Committee for Pharmaceutical Science of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 13-14, 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., Charles L. Cooney, Ph.D., Patrick P. DeLuca, Ph.D., Melvin V. Koch, Ph.D., Meryl H. Karol, Ph.D. (April 13 only), Marvin C. Meyer, 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., Thomas Layloff, Ph.D. (April 13 only)

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

Industry Representative (non-voting):
Gerald Migliaccio

Guest Speakers:
Leslie Benet, Ph.D., Laszlo Endrenyi, Ph.D., Charles DiLiberti, M.S.

FDA Guest Speakers:
Ali Afnan, Ph.D., Dale Conner, Pharm.D., Barbara Davit, Ph.D., Sam Haidar, Ph.D., Ajaz Hussain, Ph.D., Chris Joneckis, Ph.D., Robert Lionberger, Ph.D., Robert O'Neill, Ph.D., Brian Riley, Ph.D., Nakissa Sadrieh, Ph.D., Donald Schuirmann, M.S., Chris Watts, Ph.D., Keith Webber, Ph.D., Helen Winkle, Lawrence Yu, Ph.D.

FDA Participants:
Gary Buehler, R.Ph.

Open Public Hearing Speakers:
April 13, 2004:
Parrish M. Galliher, Troy J. Logan, Leo Lucisano, Robert Mattes

April 14, 2004:
Dr. Jeffrey A. Staffa, Consillium, LLC (paper submission only)

These summary minutes for the April 13 and 14, 2004 of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration were approved on _____.

I certify that I attended the April 13 and 14, 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 an update from the Clinical Pharmacology Subcommittee, and on the formation of a Working Group for Parametric Tolerance Interval Test for Dose Content Uniformity, and discussed the following: Process Analytical Technology (PAT) – Next Steps, PAT Applications for products in the Office of Biotechnology Products (OBP), Bioequivalence of Highly Variable Drugs, Bioinequivalence, Topical Bioequivalence. A topic awareness presentation was made on Nanotechnology. The members and the invited consultants were provided the background material from the FDA prior to the meeting.

Art Kibbe, Ph.D. (Committee Chair), called the meeting to order at 8:30 a.m. on April 13, 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, April 13, 2004

Introduction to Meeting OPS Update **Pharmaceutical Quality for the 21st Century**	Helen Winkle Director, Office of Pharmaceutical Science (OPS), CDER, FDA
Subcommittee Reports Clinical Pharmacology	Jürgen Venitz, M.D., Ph.D. Chair, Clinical Pharmacology Subcommittee
Parametric Tolerance Interval Test for Dose Content Uniformity	Ajaz Hussain, Ph.D. Deputy Director, OPS, CDER, FDA
Moving Forward -- An Approach for Resolution	Robert O'Neill, Ph.D., FDA
Committee Discussions and Recommendations	
Break	
Process Analytical Technology (PAT) – Next Steps	Ajaz Hussain, Ph.D.
Finalizing PAT Guidance	Chris Watts, Ph.D., FDA
Standards Development	Ali Afnan, Ph.D., FDA
Rapid Microbial Methods	Bryan Riley, Ph.D., FDA
Committee Discussions and Recommendations	
Lunch	

Open Public Hearing

Leo Lucisano, Regional Director, CMC Regulatory Affairs, GlaxoSmithKline

Parrish M. Galliher, Founder, President and CEO, Xcellerex, LLC

Troy J. Logan, Pharmaceutical Segment Manager, Siemens Energy & Automation

Robert Mattes, Laboratory Instrumentation Scientist, Foss-NIR Systems

PAT Applications for products in the Office of Biotechnology Products Overview and Issues	Keith Webber, Ph.D., FDA
	Christopher Joneckis, Ph.D., FDA
	Charles Cooney, Ph.D. Massachusetts Institute of Technology
	Melvin Koch, Ph.D. University of Washington

Tom Layloff, Ph.D.
Principal Program Associate
Management Sciences for Health

Break

Committee Discussion and Recommendations

The meeting was adjourned at approximately 4:30 p.m. on April 13, 2004.

Art Kibbe, Ph.D. (Committee Chair), called the meeting to order at 8:30 a.m. on April 14, 2004. Hilda Scharen, M.S., read the conflict of interest statement into the record. The agenda proceeded as follows:

Day 2: Wednesday, April 14, 2004

Bioequivalence of Highly Variable Drugs	Lawrence Yu, Ph.D., FDA
Why Bioequivalence of Highly Variable Drugs is an Issue?	Charles DiLiberti, M.S., Barr Labs, Inc. .
Highly Variable Drugs: Sources of Variability	Gordon L. Amidon, Ph.D., University of Michigan
Clinical Implications of Highly Variable Drugs	Leslie Benet, Ph.D., University of California, San Francisco
Bioequivalence Methods for Highly Variable Drugs	Laszlo Endrenyi, Ph.D., University of Toronto

Break

Bioequivalence of Highly Variable Drugs: Case Studies	Barbara Davit, Ph.D., FDA
FDA Perspectives	Sam Haidar, Ph.D., FDA
Bioequivalence of Highly Variable Drugs Q & A	Dale Conner, Pharm.D., FDA

Committee Discussion and Recommendations

Lunch

Open Public Hearing: No speakers

BioINequivalence – Concept and Definition	Lawrence Yu, Ph.D., FDA
Statistical Demonstrations of BioINequivalence	Donald Schuirmann, M.S., FDA

Break

BioINequivalence Q & A Committee Discussion and Recommendations	Lawrence Yu, Ph.D., FDA
Update -- Topical Bioequivalence	Lawrence Yu, Ph.D., FDA
Establishing Bioequivalence of Topical Dermatological Products	Robert Lionberger, Ph.D., FDA

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Future Topics - Nanotechnology Nakissa Sadrieh, Ph.D., FDA

Conclusion and Summary Remarks Ajaz Hussain, Ph.D., FDA

Questions to the Committee*:*

Topic #1: Parametric Tolerance Interval Test (PTIT) for Dose Content Uniformity of Aerosol Products
Evaluate this proposal for the formation of a working group under ACPS supervision
Recommend improvements necessary for realizing the group's goals and objectives
Recommend reporting requirements and a timeline for completing this project

The Committee agreed on the proposal for the formation of a working group under the supervision of the Advisory Committee for Pharmaceutical Science. The Committee accepted the outlined process for how the working group will function and the proposed timelines. The committee emphasized the importance of clinical representation on this working group, as this is the essence of risk based management.

Topic #2: PAT Applications for Products in the Office Of Biotechnology Products in OPS/CDER and in the Center for Biologics Evaluation and Research (CBER)

1. What technologies are available now to evaluate the characteristics of protein products in real time during manufacturing?
The Committee agreed it is difficult to judge how well the developed tools are applied. The members felt that this was an important question, as it relates what is being made to its therapeutic efficacy and safety. The Committee argued that asking the right questions and understanding what is to be known will drive the creation of new technologies.

2. What tools would allow us to understand the manufacturing process better?
The Committee emphasized that data collection/mining is important. However, the members felt that a correlation of cause/effect and critical thinking about the analytical data are crucial.

3. What processes in biological drug manufacturing would benefit the most from implementation of PAT?
The members recognized that variability control is key. The committee suggested that the goal is to identify how much variation is allowed at each critical step, while still maintaining a good product.

4. For processes or products that do not currently allow direct product quality monitoring, what other strategies do you recommend for product quality control in addition to control of in-process parameters?
The Committee agreed that critical thinking needs to be applied to understanding what needs to be measured and what we know about the product. The members added that can be measured may not be helpful and it is important to find the technology to measure what is needed.

5. What additional elements should be incorporated in a training and certification program for reviewers and inspectors of biotechnology PAT applications?
The Committee felt there is a need to emphasize critical thinking and problem solving in the training. In addition, the members felt it was important to incorporate the science of uncertainty and its quantification in the training programs. Also, the committee agreed that the PAT Guidance is a framework, applicable to any manufacturing and will apply to the Office of Biotechnology Products; not originally part of the initial training and certification activities.

Topic #3: Bioequivalence of Highly Variable Drugs
1. ACPS is requested to provide advice on the following issues:
That "highly variable drugs or drug products can be defined as those exhibiting intra-subject variability of 30% CV or greater in AUC or Cmax."
The Committee suggested the need to understand where the variability originated. The members added that prior knowledge of all biostudies may help set more appropriate specifications to make decisions.

2. Comment and recommendations on two approaches for addressing the challenges:

1. **Expand bioequivalence limits from 80-125%, and restrict the mean T/R difference, e.g., ± 20? What information is necessary to properly set these new confidence interval limits?**
2. **Reference Scaling: Scale current bioequivalence criterion based on the reference variability in each study and restrict the mean T/R difference as above.**

The Committee emphasized that Highly Variable (HV) drugs focus on HV drug product. The members emphasized there is an undue reliance on the use of confidence intervals to make decisions, thus a paradigm shift is in order. The members agreed that the use of reference scaling and good scientific methods could reduce the variability in the short term. However, in the long term, the Committee felt a Decision Tree would be useful in understanding what the problem is, as well as the real fundamentals i.e. physical and chemical parameters. The Committee added that the role of decision trees is not merely an understanding of a problem, but a necessary step for making coherent, science based decisions. In conclusion, the Committee agreed that a limit on the point estimate should also be used along with reference scaling.

Topic #4: The Concept and Criteria of BioINequivalence

1. **Does the ACPS agree with the distinction between demonstrating bioINequivalence and failure to demonstrate bioequivalence?**

The Committee felt that there was a need to separately define bioINequivalence, not just as failure of the bioequivalence test. The members argued it was important to focus on the clinical relevance with the therapeutic index. The Committee discussed both Area under the Curve (AUC) and Cmax as metrics important for bioequivalence and bioINequivalence.

2. **Does the ACPS recommend a preferred method for evaluating the three pharmacokinetic parameters for bioINequivalence?**
   - **If bioINequivalence is demonstrated for any one pharmacokinetic parameter, then bioINequivalence is demonstrated for the products.**
   - **BioINequivalence must be demonstrated for all three pharmacokinetic parameters for bioINequivalence to be demonstrated for the products.**
   - **There should be one pre-selected pharmacokinetic parameter used for bioINequivalence testing. If so, which one?**
   - **The three pharmacokinetic parameters should be evaluated for bioINequivalence with statistical corrections to the level of significance for each parameter in order to maintain an overall significance level of 0.05.**

The Committee agreed on a general understanding of bioINequivalence to move forward recognizing it is not a simple matter. In addition, the members felt this is an important concept, especially how it applies to the entire regulatory scenario. There was no consensus at this point as to a final criteria pertaining to the three pharmacokinetic parameters.
In addition, the members' felt that the criteria used for approving bioequivalence is very good. However, the Committee felt that the criteria used to define bioINequivalence is very difficult, with the criteria and confidence interval both needing to be outside the boundary.
In conclusion, the committee agreed that these discussions will force people to ask questions of why a product is bioequivalent and will lead to mechanistic understanding.

The meeting was adjourned at approximately 4:15 p.m. on April 14, 2004.