October 21-22, 2003
ACPS
Hilda F. Scharen

Advisory Committee for Pharmaceutical Science
October 21-22, 2003

The following is an internal report, which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov.dockets/ecomments. Slides shown at the meeting will be available at the same website.

All external requests for the meeting transcripts should be submitted to the CDER 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 21-22, 2003, at the Best Western Washington Gateway Hotel, 1251 West Montgomery Avenue, Rockville, Maryland. The meeting was chaired by Art Kibbe, Ph.D.

Advisory Committee for Pharmaceutical Members (voting):
Arthur H. Kibbe, Ph.D., Joseph Bloom, Ph.D., Patrick P. DeLuca, Ph.D., Robert Gary Hollenbeck, Ph.D., Michael S. Korczynski, Ph.D., Marvin C. Meyer, Ph.D., Lemuel A. Moye, M.D., Ph.D., Wolfgang Sadee, Dr.rer.nat., Cynthia R.D. Selassie, Ph.D.

Advisory Committee for Pharmaceutical Consultants(voting):
Judy Boehlert, Ph.D., Nozer Singpurwalla, Ph. D., Jürgen Venitz, M.D., Ph.D.

Acting Industry Representative (non-voting):
Efraim Shek, Ph.D.

Guest Speakers:
Annette L. Bunge, Ph.D., Michael Golden, John R. Murphy, Ph.D., Darlene Rosario

FDA Guest Speakers:
Wallace Adams, Ph.D., Lucinda Buhse, Ph.D., Yuan-Yuan Chiu, Ph.D., Frank Holcombe Jr., Ph.D., Ajaz Hussain, Ph.D., Moheb Nasr, Ph.D., Vilayat Sayeed, Ph.D., Jonathan Wilkin, M.D., Lawrence Yu, Ph.D.

FDA Participants:
Gary Buelher, R.Ph., Ph.D.

Open Public Hearing Speakers:
October 21-22, 2003:
No speakers were signed-up to participate in the Open Public Hearing

These summary minutes for the October 21 and 22, 2003 of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration were approved on __11/05/03_____.

I certify that I attended the September 17, 2003, meeting of the Manufacturing Subcommittee of the Advisory Committee for Pharmaceutical Science of the Food and Drug Administration meeting and that these minutes accurately reflect what transpired.

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

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

October 21-22, 2003
ACPS
Hilda F. Scharen

The Committee received an update from the subcommittee and discussed the following: Parametric Tolerance Interval Test for Dose Content Uniformity; Risk-based CMC Review Proposals; Nomenclature issues and challenges; Research Plan for Generics –Bioequivalence of Topical Products. 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 October 21, 2003. 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 21, 2003

Welcome and Introduction to the Meeting	Ajaz Hussain, Ph.D., FDA
Subcommittee Reports	
ACPS Manufacturing Subcommittee Update	Judy Boehlert, Ph.D.
Clinical Pharmacology Subcommittee Report	Jürgen Venitz, M.D., Ph.D.
Draft PAT Guidance	
PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance	Ajaz Hussain, Ph.D., FDA
Questions/Discussion	
Break	
Parametric Tolerance Interval Test for Dose Content Uniformity	
Dose Content Uniformity: Parametric Tolerance Interval Approach	Ajaz Hussain, Ph.D., FDA
PTIT for DCU of OINDP: Approach to Resolution of Identified Issues	Wallace Adams, Ph.D., FDA
Lunch	
IPAC-RS Presentations Pharmaceutical Product Quality Assurance Through CMC Drug Development Process	Darlene Rosario, Aradigm
Zero Tolerance Criteria Do Not Assure Product Quality	John R. Murphy, Ph.D
Summary and Status of IPAC-RS Proposal for Improved Control of Delivered Dose Uniformity (DDU) of Orally Inhaled and Nasal Drug Products	Michael Golden, GlaxoSmithKline
Break	
Committee Discussion and Recommendations	

The meeting was adjourned at approximately 4:39 p.m. on October 21, 2003.

Art Kibbe, Ph.D. (Committee Chair), called the meeting to order at 8:30 a.m. on October 22, 2003. Hilda Scharen, M.S, read the conflict of interest statement into the record. The agenda proceeded as follows:

Day 2: Wednesday, October 22, 2003

Risk-based CMC Review Proposals

Risk-based CMC Review Current Thinking	Yuan-yuan Ciu, Ph.D.
Risk-based CMC Review	Vilayet Sayeed, Ph.D.
An example of Process Understanding Directed Risk-Based CMC Review Proposals Oversight of Post-Approved Change	Ajaz Hussain, Ph.D., FDA
Risk-Based CMC Review Proposals: Issues and challenges	Moheb Nasr, Ph.D., FDA
Committee Discussion	

Break

Nomenclature

Pharmaceutical Nomenclature: Issues and challenges	Moheb Nasr, Ph.D., FDA
FDA Perspective on Dosage Form Nomenclature	Dan Boring, R.Ph., Ph.D.
Defining Orally Disintegrating Tablets	Frank Holcombe Jr., Ph.D.
Topical Dosage Form Classification – an Update	Lucinda Buhse, Ph.D.
Committee Discussion	

Lunch

Research Plan for Generics – Bioequivalence of Topical Products

Office of Generic Drugs Research Programs	Lawrence X. Yu, Ph.D.
Dermatopharmacokinetics: Improvement of methodology for assessing bioequivalence of topical products	Annette L. Bunge, Ph.D. Colorado School of Mines
The Pursuit of Alternative Methodologies For Demonstrating Bioequivalence for Generic Topical Dermatologic Drug Products: DPK, Q3, Cakes and 2 PIs	Jonathan Wilkin, M.D., FDA
Committee Discussion	
Conclusion and Summary Remarks	Ajaz Hussain, Ph.D., FDA

Adjourn

***Questions to the Committee**:*

Topic #1: Nomenclature

1) What are the factors that the Agency should consider in determining (a) whether a new dosage form name is warranted and (b) how such a dosage form should be defined?

The Committee agreed we are facing many challenges with new dosage forms and new technologies by using older names and terminology, which actually do not make sense. The committee discussed Orally Disintegrating Tablets (ODT) and that there are no standards methods for disintegration testing of ODT if a product is substituted with another.

The members emphasized the difference between dissolution versus disintegration and that the intent of disintegration, as a less restrictive term, is that the tablet does not stay in mouth. In addition, the Committee agreed that the tablet is not intended to be swallowed but rather absorbed in mouth or gastro-intestinal tract.

The committee recognized the clear need to use naming, as a means, to distinguish between chewable versus OD tablets; i.e. if a tablet doesn't disintegrate rapidly you have to chew it.

The Committee felt that the focus should be on the dosage form and not the name of the drug and concluded that a new name for a dosage form is not necessary.

The Committee proposed that as soon as a new dosage form brings either convenience or becomes a labeling aspect, the intended use for a particular product really needs to be re-examined, as well as the relevant criteria for classifying these products.

2) Is it reasonable or useful to include a quantifiable attribute when defining a dosage form or distinguishing between closely related dosage forms where appropriate? Can such an approach be viewed as too arbitrary in some cases and too rigid in other cases?

The Committee discussed the necessity of having quantifiable attributes outweigh the possible consequences of not having one. The Committee members argued that if the dosage form is meant to define an attribute, then that attribute should be included in the definition. In the context of Quality by Design, the Committee argued that aspects of the naming or labeling of a product is associated with the attributes, as it implies the intended use of the drug or product.

The Committee emphasized that the name definition should apply only to the mode of administration of the product, and thus needs to be as simple as possible. The members recommended that the labeling or guidance could be sufficient in addressing the intended use of the product.

The Committee agreed the non-specific definition of ODT is confusing and one has to be cautious when describing a disintegration time. Overall the Committee agreed that nomenclature is complex, not a purely scientific issue, and challenges remain in ensuring the intended use of the product is reflected in the label.

3) Is the proposed criterion, i.e. an in-vitro disintegration time of less than 60 seconds, reasonable for defining an orally disintegrating tablet?.

The Committee members discussed whether a disintegrating tablet implies it rapidly disintegrates or not. Although, the intended purpose of OD is for the tablet not to be kept in the mouth for a long period of time i.e. oral disintegration, the terminology of " rapidly disintegrating" could have some misleading implications from a therapeutic perspective. Also, it was felt that OD describes the route of administration or the mechanism rather than the release time.

The Committee agreed that 60 seconds was too long a time description for disintegration of an ODT. Although the Committee felt that it is not productive to include a time constraint, it was generally agreed that there is a need to have a requirement for disintegration time for each product but not to include it in the name of the product. The Committee felt that FDA should decide on the time description based on the different dosage forms developed.

4) Has the update on topical dosage forms presented today addressed the questions/comments raised by the ACPS at the March 2003 meeting?

The Committee felt there was a dramatic improvement in the presented flowchart and although there will always be a "gray" area(lotion being an emulsion), it fit well with classic expectations.

Dermatopharmacokinetics (DPK)

1) What type of studies should be conducted to validate the DPK method?

The Committee felt that the dissolution isn't going to give the same estimate on how well the drug gets out of the delivery form, gets out of the dosage form, and is absorbed into the body as a biostudy.

The Committee defined DPK as an in vitro test and as one approach to assess the release rate of the drug from a complex formulation. It was felt that DPK is a reasonable approach to look at that aspect of drug release from the product. The Committee felt optimistic about the reduction in variability presented but would like to see more reproducible results in different labs. The members agreed that the key aspect of DPK is to indicate the difference in the vehicle.

Q3: Structural Similarity

2) What type of data is needed to demonstrate that two products are Q3 equivalent?

The Committee felt that there are 2 aspects to Q3: one as a simple solution to a system and another more complex and unclear how it can serve as a support. The Committee agrees on predictability of behavior of these systems in a complex environment and predictability in-vivo, and generalizing capabilities by using fundamental attributes for comparing different formulations.

3) How should the Q3 concept be validated or demonstrated

- **Demonstration that we can detect changes in manufacturing processes?**
- **Demonstration that we can detect formulations with known differences?**
- **Demonstration that drug release rates are identical?**

The Committee felt that careful thought needs to be placed into how we approach validation first principles and identified variability in the substrate as a key aspect to be applied over time and in the patient. The Committee agreed that as there is nothing similar to first principles in a clinical trial assessment, how well can a product be characterized and compared in a meaningful way.

The Committee concluded that because dermatological products are for local effects, developing a system by product could be a solution. Also, the Committee agreed that one is better off with comparing two systems rather than just one. The Committee concluded that as we try to equate it to bioquivalence, in a traditional way, it makes it more difficult to come to a simple answer.

Bioequivalence for topical products

4) What role should Q3 and DPK play in the demonstration of bioequivalence for topical products?

- **Under what circumstances should Q3 equivalence be sufficient to justify a wavier of in vivo bioequivalence tests?**
- **Under what circumstances should Q3 equivalence and a DPK method in healthy subjects be sufficient to determine bioequivalence?**

The Committee discussed the goal is to find something to assess release of drugs at steady state and DPK indicates how fast the product comes out of the barrier. The Committee agreed that cadaver skin is as good a test method as DPK for in vitro diffusion and could be more controllable.

The Committee agreed that though there are theoretical shortfalls in analysis of any of these systems, the goal is to evaluate the behavior of the dosage form, the activity of the drugs and the related aspects.

The Committee concluded that the because there are different perspectives on each side it is difficult finding a common ground. The agreement is to move toward constructing a portfolio approach looking at a combination of tests or to test different indications and be able to anticipate challenges.

The meeting was adjourned at approximately 3:45 p.m. on October 22, 2003.