Pregnancy Labeling Subcommittee of the Reproductive Health Drugs Advisory Committee

June 3, 1999

Holiday Inn, Silver Spring, MD

Committee
Greene, Michael M.D.
Dattel, Bonnie J., M.D.
Hammond, Mary G., M.D.
Lemons, James A., M.D.
Conover, Elizabeth Ann, M.S.
Chong, Cynthia M., M.D.
Scott, Julia R., R.N.
Jones, Ken Lyons, M.D.
Wisner, Katherine L., M.D.
Rosene-Montella, Karen, M.D.
Briggs, Gerald, B. Pharm.
Wier, Patrick, Ph.D.
Andrews, Elizabeth B., Ph.D.,
Mitchell, Allen, M.D.*
Cragan, Janet Darden, M.D.
Taylor, Alan, Ph.D.
O'Loughlin, Victoria, Ph.D.

FDA
Sandra L. Kweder, M.D.
Rose E. Cunningham
Kathryn J. Aikin, Ph.D.
Joseph J. DeGeorge, Ph.D.
Heidi M. Jolson, M.D., M.P.H.
Evelyn M. Rodriguez, M.D., M.P.H.
Rachel E. Behrman, M.D.
Florence Houn, M.D., M.P.H., F.A.C.P.
Marianne C. Mann
Linda S. Brophy
David E. Morse, Ph.D.
Murray Lumpkin, M.D.

Invited Guests/ Guest Speakers
Eric Holmboe, M.D.
Francois Meyer, M.D.

*Participated by Telecon

These summary minutes for the June 3, 1999, meeting of the Pregnancy Labeling Subcommittee of the Reproductive Health Drugs Advisory Committee were approved on 13 Sept 99.

I certify that I attended the June 3, 1999, meeting of the Pregnancy Labeling Subcommittee of the Reproductive Health Drugs Advisory Committee and that these minutes accurately reflect what occurred.

Kimberly L. Topper
Executive Secretary

See Attached Fax
Michael Greene, M.D.
Chairperson

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The meeting was called to order at 8:10 am. There were 58 non FDA attendees and 49 FDA attendees. Dr. Greene welcomed the guests and each subcommittee member introduced themselves. Dr. Allen Mitchell was participating in the meeting by teleconference. The Conflict of Interest statement was read for the record.

Dr. Sandra Kweder introduced the topics to be covered and set the stage for the day's discussion and identified the objectives. The presentation covered definitions, the introduction of the labeling issues, pregnancy categories, experiences in applying these categories, an update on the 9/97 Part 15 Hearing recommendations, and the Task Force activities.

Dr. David Morse presented an Integrated Approach to the Evaluation of Non-Clinical Reproductive Toxicity Data. The presentation covered the activities of the Pregnancy Integration Working Group and the Integration Tool for Positive Reproductive Toxicity Results.

Dr. Eric Holmboe presented the Perils and Pitfalls of Talking about Medical Risks. The presentation covered the definition of risk, understanding risk, elements of risk, elements of risk: identification, elements of risk: permanence, elements of risk: timing, and elements of risk: value. Also covered was how to communicate risk, qualitative-vs-quantitative, errors in risk interpretation and the perception of risk.

Dr. Rachael Behrman presented the Concept Paper covering the Model Pregnancy Labeling format, the process, clinical management, summary risk assessment, and discussion of data sections.

Dr. Kit Aikin presented the Pregnancy Labeling Evaluation of Physician Focus Groups. The presentation covered the recruitment of the participants, their impressions of the labels, their current thinking on the availability of information, format and the wish list.

The committee held discussion on the morning presentations and stopped for lunch at 12:00.

The committee reconvened at 1:10 and immediately held the Open Public Hearing. The following requested time to present in advance: Cindy Pearson, Executive Director, and Doris Haire, American Foundation for Maternal and Child Health. The following spoke from the floor: George P. Giacoia, Pediatric Pharmacology Unit, NIH, Barbara Heiser, Executive Director, National Alliance for Breastfeeding Advocacy, Mildred S. Christian, President, Argus International, Inc., and Dr. Robert Brent, past member of the Fertility and Maternal Health Drugs Advisory Committee.

Dr. Francois Meyer gave a presentation on the European Labeling Initiative. He confirmed that the EU was having the same difficult time addressing the issue. Dr. Sandra Kweder presented the questions for the committee and a lively discussion was held on the following questions:

Format and Content

1. Please provide comment on the usefulness of the proposed reorganization of the Pregnancy (and Fertility and Lactation) section of labeling that separates information into three subsections (Clinical Management; Summary Risk Assessment; Discussion of Data). Can this be refined or improved?

   - *Although current letter categories are not useful it would be helpful if there were a shorthand way of communicating large amounts of data.*
   - *A brief summary statement that physicians may use in discussions with patients is a good idea.*
   - *Keep it simple, but have a very brief summary of underlying information.*
   - *It was suggested that the Discussion of Data not be included in the package insert and to make this information available on the WEB or other places. It was also proposed by our members that Fertility need not be included in this as it is very different than Pregnancy and Lactation.*
   - *It is important to have a way of denoting quality of underlying data.*
   - *Overall, may be best to have visit summary presented first.*
   - *The Concept paper proposal is good - ensure that the Clinical Management statements are closely related to the Risk Assessment. Some guidance could be given but be careful not to be directive.*

2. How specific and detailed should recommendations be in the Clinical Management statements (e.g., types and frequency of testing and monitoring)? Are there circumstances under which providing specific recommendations about management would be inadvisable? If so, can you provide examples?

   - *In the Clinical Management section try not to go beyond what is known. It is difficult to project human exposure from animal studies.*
   - *It is difficult to articulate, or even know, what standard of care is. It*

often varies regionally, so we need to be very careful

- *Rather than being directive, it may be most useful to provide some clinical construct for risk information.*
- *Consider using the term "Clinical Considerations" instead of Clinical Management.*
- *Only provide specific recommendations/directions when the data is very FIRM.*
- *We must search for a systematic way for reviewers to articulate the quality of the data.*
- *Standard templates would be very useful.*
- *If there is firm evidence of a risk then a Management Plan would be appropriate. Clarification would be necessary depending if the insert were being written for the consumer or the physician.*
- *We should consider including recommendations to seek expert advice where appropriate.*

3 In the summary risk assessment, how can appropriate context for the reader be provided, such as risks to pregnancy associated with the maternal disease state or baseline population rates of the adverse outcomes in question?

- *The AHCPR categorizes studies on the basis of the quality of the study.*
- *The language must be very clear and understandable. Try not to use "medicalese" but provide the full information so the laymen is able to understand and comprehend the data that is available.*
- *Extensive data would be needed to back up the Clinical Management and Summary Risk Assessment sections.*
- *It is important to acknowledge ignorance and controversy in the Risk Assessment up front.*
- *It would be very helpful to include specific distinctions of risk by trimester.*
- *May be useful to have standard statements or formats that address baseline risks of birth defects or information on risk related to maternal condition.*

4 Can the committee provide guidance on the relative merits of quantitative (e.g., risk ratios) vs. qualitative (e.g., high/low) descriptions of risk for this section of the label?

- *Risk Ratio should not be used - if it is a small number to begin with it will still be a small number.*

- *Use absolute risk not relative risk. Making predictions of risk when viewing animal studies could be done if it is supported by data.*
- *Indicate if it is potential or known risk.*
- *Be concerned with ethnic, sex, religious views used in the perception of data. Men like numbers, but women see things in absolutes and clear concise definitions are critical.*
- *Confidence intervals have a role in this issue as they convey the amount of data.*
- *Be wary of overstating risk based on animal data, simply because it is available*

5. What should the goals be for the Discussion of Data subsection? How should information be selected for inclusion?

- *The current suggested subheadings may be too much detail. Instead, we might consider :*

  Suggested subheadings of interpretations:
  1) Hazard Characterizations - including the conditions under which they occur
  2) Exposure Levels of Concern
  3) Biomarkers - to make the bridge between human and animal data
- *It is important, to the extent possible, to move the translation of data from laboratory terms to those that are more clinically relevant.*

Risk Communication

6. In the setting where little is known about risk, how should this lack of information be communicated in a manner that is optimally informative?

- *Admit our ignorance - make a distinction where risk is undetermined or data is not available.*
- *Use caution in making the assumption that all drugs within a class are teratogenic. Just because one is it does not mean the rest are.*

7. How can uncertainty associated with predictive value of animal studies, particularly in the absence of human data, best be communicated?

- *Do not talk about the uncertainties - discuss with weighted evidence.*

8. Is there risk or other descriptive language that has acquired sufficient unintended connotation that it should be avoided in providing advice or in summary risk statements? Are there examples and can you suggest alternatives?

- *Be very cautious of terms like - caution, placental barrier, crosses the placenta, and probability.*
- *The lay public and physician/scientists define the terms very differently. Long and technical terms are frightening to some.*
- *Consider using operational titles.*
- *Stick to the facts and do not use interpretative words.*

The meeting was adjourned at 4:25

These minutes are a brief outline of the actual events and are not intended to cover the meeting in detail. A verbatim transcript is available.