Summary Minutes
Advisory Committee for Reproductive Health Drugs Meeting
December 15, 2003

A verbatim transcript is available and posted on the FDA dockets website at:
http://www.fda.gov/ohrms/dockets/ac/cder03.html#ReproductiveHealth

I certify that I attended the December 15, 2003, meeting of the Advisory Committee for Reproductive Health Drugs and that these minutes (see below) accurately reflect what transpired at that meeting.

Approval Date: _____

_____ _____
Jayne E. Peterson, R.Ph., J.D., Acting Executive Secretary Linda Giudice, M.D., Chair

All external requests for the a written copy of the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from Johnson and Johnson, Pharmaceutical Research & Development, LLC (J & J was an FDA invited participant in the AC meeting). The meeting was called to order by Linda Giudice, (Committee chair); the conflict of interest statement was read into the record by Jayne Peterson (Acting Executive Secretary). There were approximately 200 persons in attendance. There were twelve (12) speakers for the Open Public Hearing session (see below for a listing of the speakers).

Attendance:
Advisory Committee for Reproductive Health Drugs Members Present (voting):
Linda Giudice, M.D. (Chair), Susan Crockett, M.D., Nancy Dickey, M.D., Scott Emerson, M.D., Ph.D., W. David Hager, M.D., Vivian Lewis, M.D., Larry Lipshultz, M.D., George Macones, M.D., Valerie Montgomery Rice, M.D., Joseph Stanford, M.D.

Advisory Committee for Reproductive Health Drugs Members Absent:
Arthur Burnett, Jr., M.D., Charles Lockwood, M.D., Lorraine Tulman, Ph.D.

Advisory Committee for Reproductive Health Drugs Consultants (voting):
Irwin Rosenberg, M.D., Ralph Green, M.D., Katherine Wenstrom, M.D., Michael Greene, M.D., Barry Shane, Ph.D., Tsunenobu Tamura, M.D., Phillip Darney, M.D. Note: Patrick Stover, Ph.D. was scheduled to present and participate in the meeting but was unable to attend the meeting (see meeting agenda below). Instead Dr. Barry Shane presented on his behalf.

Non-Prescription Drugs Advisory Committee Member Present (voting):
Sonia Patten, Ph.D.

Acting Industry Representative (non-voting):
Jonathan Tobert, M.D., Ph.D.

National Institutes of Health (NIH) Participant (non-voting):
James Mills, M.D., M.S.

Centers for Disease Control (CDC) Participant (non-voting):
Joseph Mulinare, M.D., MSPH

FDA Participants (non-voting):
Daniel Shames, M.D., Donna Griebel, M.D., Scott Monroe, M.D., Lisa Soule, M.D., Jeanne Rader, Ph.D., Elizabeth Yetley, Ph.D.

Open Public Hearing Speakers:

Spina Bifida Association of America/Spina Bifida Foundation: Eileen Carlson/Douglas Sorocco
Reproductive Health Technology Project: Kristen Moore
John Grossman, M.D. (representing self)
National Association of Nurse Practitioners in Women's Health: Susan Wysocki
Association of Reproductive Health Professionals: Felicia Stewart
Association of Women's Health Obstetric and Neonatal Nurses: Claudia Ravin
Healthy Mothers/Healthy Babies: Anita Boles
Dr. Sonya Oppenheimer
Planned Parenthood Federation of America: Vanessa Cullins
Douglas Rose (representing self)
American College of Nurse Midwives: DeAnn Williams
American Society of Reproductive Medicine: Richard Falk, M.D.

Issue: The public health issues, including the safety and potential clinical benefit, associated with combining folic acid and an oral contraceptive into a single combination product. **(Note: The goal of this plan is to reach women of child-bearing potential either who currently take oral contraceptives and conceive while on the OC or who discontinue the OC and immediately conceive).**

FDA Presentations

Folate Nutrition and Metabolism and Influence on Neural Tube Defects (NTDs)	Barry Shane, Ph.D. Professor, Dept. of Nutritional Sciences and Toxicology University of California, Berkeley
Folic Acid and Safety	Patrick J. Stover, Ph.D. Associate Professor of Nutritional Biochemistry Cornell University
Folic Acid Fortification in the U.S.: Planning, Implementation, and Monitoring	Elizabeth Yetley, Ph.D. Lead Scientist for Nutrition Center for Food Safety and Applied Nutrition (CFSAN), FDA
Assessing the Impact of Fortification on the Epidemiology of NTDs	Joe Mulinare, M.D., MSPH National Center on Birth Defects and Developmental Disabilities Centers for Disease Control and Prevention (CDC)
Folic Acid Supplementation and Fortification in Nova Scotia (via telecon)	Michiel Van den Hof, M.D. Division Head, Maternal/Fetal Medicine Dalhousie University, Halifax, Nova Scotia
What is the Minimum Effective Dose of Folic Acid for Preventing NTDs?	James L. Mills, M.D., M.S. Chief, Pediatric Epidemiology Section Epidemiology Branch Div. of Epidemiology, Statiststics and Prevention Research, NICHD, NIH

Invited Sponsor Presentations (Johnson and Johnson, Pharaceutical Research & Development, L.L.C.)

Proposal Background and Overview	Andrew J. Friedman, M.D. Director, Women's Health Care Research Ortho-McNeil Pharmaceutical, Inc.
Neural Tube Defects: Efficacy and Safety of Folic Acid	Godfrey P. Oakley, Jr., M.D., MSPM Visiting Professor, Dept. of Epidemiology Rollins School of Public Health Emory University
Need for Increased Folic Acid Intake Among Reproductive Age Women	Anna Maria Siega-Riz, Ph.D., R.D. Associate Professor of Maternal and Child Health and Nutrition University of North Carolina at Chapel Hill
Oral Contraceptive Use, Pregnancy Intendedness and Folic Acid Intake	Andrew M. Kaunitz, M.D. Professor and Assistant Chairman University of Florida Health Science Center
Summary and Conclusion	Andrew J. Friedman, M.D.

Questions to the Committee:

1. **Are further increases in folic acid intake, beyond what is available from fortified cereals, likely to result in public health advances in preventing further neural tube defects?**

   Vote: Yes: 18 No: 0

   The Committee Members felt that folic acid intake above the current levels being ingested by women of child bearing potential would be beneficial.

   Sources of folic acid include: normal food intake, fortified cereals and enriched grains, and vitamin supplements. Recommendations for pregnant women (pre-pregnancy and early pregnancy) are to increase folic acid intake by 400 mcg/day, however, many women do not reach this goal. Adequate folic acid is most important the first four to six weeks of pregnancy, however, many women are unaware of this. Data were presented that suggested that:
   - *since the Federal fortification program was begun in 1998, in general, daily folic acid intake has been increased by approximately 200 micrograms/day and the incidence of NTDs in the U.S. has decreased by an estimated 30%;*
   - *further decreases in the NTD rate may still be possible.*

2. **Can we define a subpopulation among women of reproductive age that needs additional folic acid?**

   ****Note: This question was reworded by the committee to read, "Is it necessary to define a subpopulation among women of reproductive age that needs additional folic acid?" and the vote was taken based on this re-wording.**

   Vote: Yes: 4 No: 14

   If yes, what subpopulation should receive additional folic acid and how would you identify this population?

   The majority of the Committee Members felt that all women of reproductive age (regardless of their current folic acid intake) could be candidates for further folic acid supplementation and that identification of any specific subpopulation was not necessary. The several that felt that subpopulation(s) could be identified mentioned: women taking folate antagonists (such as valproic acid). Additionally, a few Committee Members mentioned that because of the concern that women taking folic acid supplemented vitamins might be already ingesting 1000 mcg/day of folic acid (which is the daily maximum recommended by the Institute of Medicine) , they would exclude these women as candidates for additional folic acid.

3. Are there any safety issues associated with folic acid supplementation targeted at reproductive-age women? If so,

Vote: Yes: 7 No: 11

a. What are they?

The Committee Members were somewhat split on this issue. Several felt strongly that although toxic levels of the drug is per se not a safety issue, the potential of folic acid to mask pernicious anemia would be a concern. They also expressed concern that increased folic acid intake could impact the activity of antifolate drugs such as antiepileptics (valproic acid) and methotrexate.

b. Would these safety issues not be a concern below a certain level of supplementation? If so, what is that level?

4. Would the benefit of prior folic acid use persist if conception occurs after discontinuation of folic acid?

Vote: Yes: 12 No: 2 Abstain: 1

If so, for how long will the benefit persist?

The majority of the Committee Members expressed agreement that even following discontinuation of folic acid, the benefits exist. They further agreed that increased red cell folate levels (following folic acid supplementation) would be maintained for up to 90 days following discontinuation.

5. Is an oral contraceptive pill a reasonable delivery vehicle if additional folic acid supplementation is likely to provide public health advances in preventing further neural tube defects?

Vote: Yes: 18 No: 0

a. If so, would 400 mcg be a reasonable dose?

Vote: Yes: 18 No: 0

While the Committee Members voted that 400 mcg of folic acid would be a reasonable dose to add to an oral contraceptive pill, many stated that this dose might not be ideal and that additional studies should be conducted to further define a dose.

b. If 400 mcg is not appropriate, what dose of folic acid should be provided?

The Committee Members did not provide a recommendation for alternative dosing.

The meeting adjourned at approximately 5:00 p.m.