Final Summary Minutes
Advisory Committee for Reproductive Health Drugs meeting
January 23 and 24, 2007

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/ohrms/dockets/ac/cder06.html#rhdac

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

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA. The meeting was called to order by Charles Lockwood, M.D. (Acting Chair, ACRHD); the conflict of interest statement was read into the record by Teresa Watkins (Designated Federal Official). There were approximately 160 persons in attendance. There were 5speakers for the Open Public Hearing Session (see below for a listing of the speakers).

Attendance:
Advisory Committee for Reproductive Health Drugs Members Present (voting)
Charles J. Lockwood, M.D. (Acting Chair), Maria Bustillo, M.D., Ronald S. Gibbs, M.D., Daniel Gillen, Ph.D., Julia V. Johnson, M.D., James R. Scott, M.D., Lorraine J. Tulman, DNSc, RN, FAAN (Consumer Representative), O. Lenaine Westney, M.D.

Advisory Committee for Reproductive Health Drugs Consultants (voting):
Elizabeth Shanklin-Selby (Patient Representative), Abbey Berenson, M.D., Paul Blumenthal, M.D., MPH, Eve Espey, M.D., MPH, Herbert Peterson, M.D., Diane Petitti, Ph.D., Bruce Stadel, M.D., MPH, James Trussell, Ph.D., Melissa Gilliam, M.D., MPH, Paula J Adams Hillard, M.D., Johanna Perlmutter, M.D.

Industry Representative (non-voting):
Jonathan Tobert (Industry Representative)

Advisory Committee for Reproductive Health Drugs Members Absent:
Arthur Burnett, II, M.D., Sandra Carson, M.D., James Liu, M.D., Diane Merritt, M.D., and William D. Steers, M.D.

FDA Participants:
Julie Beitz, M.D., Dan Shames, M.D., Scott Monroe, M.D., Phil Price, M.D., Shelley Slaughter, M.D., Lisa Soule, M.D., and Gerald Willett, M.D.

Open Public Hearing Speakers: Kirsten Moore, Amy Allina, Beth Jordan, Anita Nelson, and Kelly Blanchard

Designated Federal Official
Teresa A. Watkins

Issue:
On January 23 and 24, 2007, the Committee discussed current issues which influence the consideration for approval of oral and non-oral (i.e., transdermal and intravaginal) hormonal contraceptive drug products. Implantable and injectable hormone products were not discussed. Issues for discussion included clinical trial design, expectations for efficacy and safety outcomes, and measures of acceptability of the product to the user, including cycle control.

On January 23, 2007, the agenda proceeded as follows:

Call to Order and Introductions	Charles Lockwood, MD Acting Chair, Advisory Committee for Reproductive Health Drugs (ACRHD)
Welcome and Comments	Scott Monroe, MD Acting Director, Division of Reproductive and Urologic Products (DRUP)
Conflict of Interest Statement	Teresa Watkins, PharmD Designated Federal Official (ACRHD)
Topic 1 - Clinical Trial Design Issues	FDA – Phill Price, MD

Clinical Trial Design Issues Discussion Points

1. Should entry criteria be more reflective of actual clinical prescribing regarding BMI, smoking, and family history of thrombosis or thromboembolism?

--The consensus of the committee was that entry criteria should be more reflective of real world prescribing. Some expressed concern with including women with a personal history of venous-thromboembolism or those with a first degree relative with such a history, and posited that the Risk/Benefit issues for such patient need to be addressed when trials are designed. Others suggested that subgroup analyses could be performed to assess efficacy in special population (e.g., women with BMI > 35). Others expressed concern with the increased sample size that would likely be needed to achieve tight 95% confidence intervals for point estimates of efficacy in subgroups. However, the consensus of the committee was that active controlled trials might mitigate many of these concerns.

2. The Division has seen different efficacy results in foreign studies compared to U.S. studies (often better efficacy results in Europe). Should a certain minimum percentage of the subjects in Phase 3 studies be studied at U.S. sites?

-- General consensus of the committee was that for drugs that are going to be marketed in the United States, the clinical trials should enroll either a minimum percentage or a minimum number of U.S. subjects, particularly to address subpopulation under-represented in non-US populations (e.g., extremes of age and BMI). However, it was the committee's opinion that data from carefully conducted non-US sources should be considered.

3. Are there cultural or physical attributes in foreign populations that would render contraceptive study data from such populations less applicable to the U.S. population?

--The general opinion of the committee was yes.

4. Should a certain percentage of the study population represent "fresh starts" as opposed to "switchers?"

--The general opinion of the committee was no. However, "Switchers" may have lower pregnancy rates than "fresh starts" Again, the consensus of the committee was that active controlled trials would mitigate this concern.

5. Is there a role for active controlled trials; if so, under what circumstances?

YES = 19
NO = 0
Abstain = 0
Total = 19

--The committee strongly endorsed the concept that active controlled trials were warranted in most circumstances. They expressed a need to clearly define the active control and to, a priori, set reasonably wide confidence intervals for efficacy estimates based on meta-analysis of published data for presumptive control agents. One member suggested establishing three options for comparators: 1) a "gold standard" comparator employing an agent approved within the last ten years with a substantial market share; 2) a "market basket" of oral comparators; and 3) a direct comparator, which would have a similar formulation to the proposed product but differ in one aspect (e.g., a different dose of estrogen or a different progestin). Some expressed concern that permitting comparison with just any other hormonal product could lead to a progressive widening in acceptable efficacy values ("creep") and less decipherable results. Others expressed concerns with the feasibility of conducting active controlled trials under all circumstances since this might pose a barrier to the introduction of new inexpensive agents.

6. Should electronic diaries be recommended for pivotal contraceptive clinical trials?

--The general consensus of the committee is that they should be recommended but not required. Some expressed that although they "may" be a more reliable means of tracking data, they are not fool-proof and could artificially improve compliance (adherence). They don't always capture the information you may be looking for and they can be expensive.

7. The Division has typically used premature termination rates as an assessment of patient satisfaction in clinical trials. Would information obtained from validated Patient-Reported Outcome (PRO) instruments be more useful in contraceptive trials?

--*The general consensus of the committee was that if a validated Patient Reported Outcome (PRO) instrument was available, it would be extremely useful.*

8. Could a validated PRO instrument be used to obtain a secondary labeling claim of superiority (e.g., better cycle control)?

--*Concerns were expressed regarding issues of internal versus external validity for making such claims. The committee also expressed concerns that until standardized definitions of bleeding patterns are established, developing a validated PRO will be difficult, which limits the committee's ability to answer this question.*

Topic 2 - Efficacy and Risk/Benefit Assessment James Trussell, PhD/Daniel Gillen, PhD

Contraceptive Efficacy Assessment Discussion Points

9. Pearl Index versus life table analyses:
9a. What are the relative merits of each approach?
9b. Are there situations where one approach should be favored over the other? If so, what are they?
9c. How should divergent pregnancy rates calculated by the Pearl Index versus life table methods be considered in the approval process and in labeling?

--*The general feeling of the committee is that the Pearl index, although providing simplicity, is a less desirable analysis method in almost all circumstances. Life-table analysis should be the standard.*

10. How should divergent pregnancy rates, obtained in U.S. and non-U.S. populations, be considered in the approval process and in labeling?

--*The committee expressed the view that if data from the U.S. and non-U.S. populations differ dramatically, the U.S. data should take precedence.*

11a. Should "on-study pregnancies" be defined to include only those pregnancies that occur while subjects are within the treatment cycle or also include those pregnancies with an estimated date of conception that may have occurred within a certain number of days after the end of the last treatment cycle (e.g., 2, 5, 14 days – where the treatment cycle is defined to include the pill-free interval following active treatment)?

--*The committee felt that "on-study pregnancies" should be limited to those in which conception occurred during the established treatment cycle.*

11b. If yes, where should the cut-off be established or should it vary according to how reliably a drug inhibits ovulation?

--This question was not answered as the answer to part 11a was to only include those pregnancies for which conception occurred while subjects were within the established treatment cycle.

12. How can the life table analysis of pregnancy rates be adjusted for the use of back-up contraception midway through the exposure period, for example, back-up contraception used only during treatment cycle 6 in a 13-month treatment cycle?

--The committee indicated there were 4 ways to handle the situation.
1. You could exclude (censor) the patient's data entirely.
2. You could include relevant data up to the point of censoring (e.g., the 1st 5 months).
3. You could include all cycles in which back-up contraception was not used (e.g., months 1-5 and months 7-13).
4. You could include all cycles (e.g., 13 months) as it more accurately reflects "real-world" usage.

The data should be analyzed multiple ways, but the preference is to model the real world and include all the data, and assume it reflects typical use. Moreover, since strong preference would be given to active control trials in support of new applications such confounding was likely to occur in both the treatment and control arms to an equivalent degree.

13. How should the analysis of pregnancy rates be adjusted for the use of back-up contraception in extended cycle contraceptive trials? For example, in an 84/7 dosing regimen, should an entire 91 day cycle be considered non-evaluable, or should only a 28 day portion of the cycle be excluded from consideration of at risk cycles?

--The committee suggested analyzing the data with the back-up method data included, as well as with it removed, to discern any impact. Opinions included:
1. Censor the subject's data at end of the last cycle before she began to use back-up methods
2. Count it because all trials should be predicated on a pure intent to treat model.
3. Do not include data from the entire cycle (91 days).

Risk/Benefit Assessment Discussion Points

14. For historically controlled trials, should evaluation of pregnancy rate be based only upon the point estimate, the upper bound of the 95% confidence interval around that point estimate, or both?

--Question 14 was discussed both on Day 1 and Day 2.
Some members of the committee endorsed the concept that upper bounds of confidence intervals be used to confirm the substantial non-inferiority of new applications, but that arbitrary limits be avoided in order to promote the widest range of new contraceptive products being developed and brought to the market. However, because no consensus was reached on this issue, refer to the transcript for a more complete description of the discussion.

15a. Is there a pregnancy rate that would be unacceptably high, regardless of the risk/benefit balance of the product?
15b. If so, what would that rate be?

Questions 15a and 15 b were discussed on Day 1 and revisited on Day 2. The answer below reflects the input from Day 2.
The committee endorsed the concept that substantial flexibility should be exercised in accepting given point estimates and upper bounds of confidence intervals for new applications using active control trial formats. For example, for an agent with an indication or biologically plausible rationale for markedly lower risk or other positive side effects (e.g., lower rates of ovarian cancer) a reasonably high upper bound for a failure rate might be acceptable (e.g., 6 to 8%) whereas for a proposed new agent without novel claims or other positive features, a far narrower upper bound might be acceptable (e.g., 3%). However, the committee was unanimous in its desire to make clear that arbitrary limits be avoided in order to promote the widest range of new contraceptive products being developed and brought to the market. Please refer to the transcript for a more complete description of the discussion.-- Most abstained from giving and exact point estimate or upper confidence interval. The key point to emphasize is that you have to provide all the information to the clinician and the patient in an easily understandable format in labeling and then let them make the final decision on which product is most appropriate for the patient (i.e., caveat emptor).

16. Should the Division approve lower-dose products that have apparent decreased efficacy and possible decreased risk of serious adverse events as compared to higher-dose products (e.g., 20 µg estrogen vs. 30-35 µg estrogen contraceptive products)?

--The general opinion of the committee was yes. They expressed the view that 20 ug ethinyl estradiol oral contraceptives are still more effective than some approved and marketed, non-hormonal means of contraception (e.g. spermicides, condoms or diaphragms). They indicated there may be a place in therapy for some sub-populations who can't, shouldn't, or don't need to be on higher dose oral contraception (e.g. breastfeeding mothers, patients who have lupus, migraines, or patients who are prescribed oral contraceptives for acne). Some expressed the opinion that if it could be proven that a lower dose decreases the risk of venous thromboembolism, it could be useful to have available. The bottom line is that the risks versus benefits need to be conveyed to the patient.

Topic 3 – Translation Melissa Gilliam, MD/Paula Adams Hillard, MD

<u>Translation of Clinical Findings to "Real World" Discussion Points</u>
17. Can trial design be modified so as to provide results that are more reflective of actual effectiveness in the "real world"?

--The committee would like trials to expand entry criteria to include adolescents, women with higher BMIs, under-represented minorities, and other subpopulations. They would like clinical sites to be conveniently accessible in terms of location and the hours of operation to fit the needs of the study population.

18. Can trial design be modified so as to provide results that are more generalizable to U.S. subpopulations (e.g., enrolling more minorities and/or subjects from lower socioeconomic groups) who may have more real or perceived barriers that impact compliance?

--*The general opinion of the committee is yes, but there are cultural, language and logistical issues that need to be addressed so that minority subjects are approached in a more inclusive manner. The committee also suggested that there may be difficulty in enrolling enough subjects in those subpopulation groups to obtain meaningful information for them and therefore appropriate planning will be essential.*

19. Should clinical trials investigate new technologies that may facilitate compliance in "real world" use?

--*The consensus of the committee is yes. In general, new technologies should be investigated and once validated should then be incorporated into clinical trials, but you should not use unproven technology and risk introducing another confounding variable.*

Topic 4 – Cycle Control	James Trussell, PhD
5:40	Adjournment

On January 24, 2007, the agenda proceeded as follows:

Call to Order and Introductions	Charles Lockwood, MD Acting Chair, Advisory Committee for Reproductive Health Drugs (ACRHD)
Conflict of Interest Statement	Teresa Watkins, PharmD Designated Federal Official (ACRHD)
Welcome and Comments	Shelley R. Slaughter, MD, PhD Clinical Team Leader, Division of Reproductive and Urologic Products
Topic 4 – Cycle Control (cont.)	James Trussell, PhD

<u>Cycle Control Discussion Points</u>

20. Do the members of the Advisory Committee agree with the recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials proposed in the article by Mishell et al.?

--*The consensus is yes.*

21. How should the Division assess the impact of unscheduled bleeding on product acceptability?

--*The committee felt that the FDA should approve products based on their demonstrated safety and efficacy and allow the patient and clinician to determine acceptability. However, some members posited that data on the relative occurrence of scheduled and unscheduled bleeding should be provided in the product labeling.*

22. What objective measures beyond hemoglobin and hematocrit values, if any, should be employed to assess significant change in hematologic status?

--*The committee recommends no other measures.*

Topic 5 – Extended Dosing Regimens FDA – Gerald Willett, MD

Extended Dosing Regimens Discussion Points

23a. If the modified or extended dosing regimen does not expose a women to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product, does a Sponsor need to meet any criteria other than the criteria for efficacy and safety required for a traditional 21/7 product?

--*The consensus of the committee is no.*

23b. If so, what should these criteria be?

--*This question was not answered as part 23a is no.*

24. If the modified or extended dosing regimen exposes a woman to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product, what are the additional criteria that a Sponsor needs to meet to support approval for marketing?

--*It is difficult to predict in the pre-marketing setting what the long term safety implications of greater monthly quantities may be and therefore post-marketing surveillance is encouraged.*

25. In reviewing extended regimens, how should the Division balance a decrease in scheduled bleeding against an increase in unscheduled bleeding?

--*The committee felt the FDA does not need to balance these issues; rather they need to provide the relevant information to patients and clinicians in labeling.*

26. What cycle length should be used when analyzing cycle control in extended cycle products?

--*The established cycle length (e.g., 84/7)* should be used when analyzing cycle control in extended cycle products. *Some members suggested the FDA should convey in labeling that for the traditional 21/7 regimen that there are on average "x" number of days of scheduled*

bleeding and on average "y" number of unscheduled bleeding days and similar language used for the extended regimens. Others suggested describing qualitatively what to expect about bleeding and how it may change overtime.

Open Public Hearing

Topic 6 – Phase 4 commitments Diana Petitti, MD, MPH

Phase 4 Commitments

27. What designs should be considered for Phase 4 studies of hormonal contraceptives and what are the strengths and limitations of each type of design? What are the most important cost/benefit considerations and limitations of each design (e.g., a more rigorous design but a delay in obtaining outcome data)?

--*These studies are expensive. If a company is trying to make a new indication or safety claim (e.g., that their product is indicated in women at higher risk for venous thromboembolism because it poses a lesser risk), they should perform a randomized clinical trial, a very carefully designed and conducted prospective cohort study, or a case-control study nested in a large cohort. For effectiveness, a prospective observational study of representative populations is permissible. For general safety issues, observational data is permissible. Refer to Dr. Petitti's presentation for more detail.*

28a. Phase 4 commitments have generally been confined to obtaining information primarily or entirely related to safety issues. Can such studies be designed to obtain a better estimate of true "actual use" product effectiveness?

--*The committee consensus is yes.*

28b. If so, how best can this information be obtained?

-- *The general nature of the committee consensus was in support of the study designs discussed in Dr. Petitti's presentation.*

29. In addition to thrombotic and thromboembolic risk, are there other safety issues that should be addressed within long-term or large Phase 4 studies?

--*The committee suggested that Phase 4 studies should investigate known and potential benefits and harm, including thrombotic/thromboembolic disease, breast, endometrial, and ovarian cancer, pelvic inflammatory disease, endometriosis, dysmenorrheal, and other disorders. However, most contended that venous thromboembolism represented the major risk.*

Topic 7 – Labeling FDA – Lisa Soule, MD

Role and Impact of Labeling Discussion Points

30a. Can labeling information be made more useful for counseling patients to better inform patients about the likely effectiveness, safety, and other "acceptability considerations" (e.g., that a reduction in scheduled bleeding may be offset by an increase in unscheduled bleeding)?

--*The committee consensus was yes.*

30b. Would such information likely reduce discontinuation rates and improved actual product effectiveness?

--*The committee consensus was possibly. Studies are needed.*

31. Should product labeling be modified to include pregnancy rates or safety data for specific subgroups when available?

--*The committee consensus was yes. Some suggest that a structured synopsis or abstract that clearly states efficacy, effectiveness, and proven side effects/complications is very important. The wording should be concise, clear-cut, and understandable, in simple terminology, for example with absolute and attributable risks, not just odds ratios and confidence intervals.*

32. How do we communicate the risk of an unplanned pregnancy in the days or weeks immediately following discontinuation of a product?

--*The committee suggested that the patient should be told that the risk of pregnancy increases substantially as soon as she stops using hormonal contraceptives.*

33. How can labeling best communicate how to manage a situation where a patient misses pills?

--*The committee recommends following the World Health Organization recommendations on this issue.*

34. Should potential secondary, non-contraceptive, benefits of hormonal contraceptives be discussed in labeling?

--The committee took exception to the word "potential". The committee felt that only well-established, documented and replicated benefits should be included in the labeling, not unproven possible benefits. Labeling should identify the dosage for which benefits have been proven.

3:05 Adjournment

I certify that I attended the January 23 and 24, 2007 meeting of the Advisory Committee for Reproductive Health Drugs and that these minutes accurately reflect what transpired.

_____/s/_____
Teresa A. Watkins
Designated Federal Official
Chair, PADAC

_____/s/_____
Charles Lockwood, M.D.
Acting Chair, ACRHD