CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-045/S011

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

Date: February 18, 2004

Re: NDA 21-045 (SE6, serial 011, dated April 16, 2003)
Sponsor: Women's Capital Corporation
Product: Plan B® (levonorgestrel) Tablets, 0.75 mg
Indication: Emergency contraception

The sponsor submits this application to change the approved product, Plan B®, from a prescription to an over-the-counter (OTC) product. The dosage and instructions for use remain the same. The sponsor states that "the switch is needed because the current prescription requirement presents a major barrier to timely access and because delays in treatment reduce efficacy significantly."

The application consists of two pivotal OTC studies, 23 clinical supportive studies, and 14 clinical pharmacology studies. The two pivotal OTC studies consist of a label comprehension study (WCC/FHI # 9728) and an actual use study (WCC/FHI #9727). Study WCC/FHI # 9728 is designed to evaluate comprehension of the prototype OTC package label for Plan B® and study WCC/FHI # 9727 is designed to provide information on the ability of the target population to self-select and appropriately use the drug when labeled for OTC use.

Since the purpose of this application is to change an approved prescription product to an over-the-counter product, no efficacy studies are submitted. Thus, no statistical review for efficacy is required. Instead, these label comprehension and actual use studies are reviewed by the Division of Over-the-Counter Drug Products. In addition, the Division of Reproductive and Urologic Drug Products is conducting a thorough safety review.

Sonia Castillo, Ph.D.
Mathematical Statistician
HFD-715

Consult Memo

sNDA #: 21,045
Protocol Identification: Study 9727 (Plan B OTC Actual Use Study)
Drug Name: Plan B (levonorgestrel)
Dosage Form: Tablets **Strength:** 0.75 mg **Route/Admin:** Oral
Sponsor: Women's Capital Corporation
Proposed Indication: Emergency Contraception
Date Submission: 4/16/2003
Medical Reviewer: Jin Chen, M.D.

The following are answers to statistical questions from the medical reviewer during the review of supplemental new drug application seeking switch from prescription to the over the counter (OTC) of Plan B as an emergency contraceptive. These questions were discussed by the medical reviewer and the statistical reviewers in a meeting., and this memo mainly summarizes the discussion and questions/answers derived during the meeting. Questions are regarding the sample size calculation, missing data issues, interpretation of the statistical analyses, and data error rate issue from the actual use study of the submission.

1. **Please comment on the rationale of sample size estimate (p030 of vol 27)**

   Firstly, the Bonferroni method of adjustment for multiplicity by the sponsor is acceptable because it properly controls the overall false-positive rate. Adjusting for the multiplicity by Bonferroni in confidence interval estimation with respect to the contraindicated use and the incorrect use, the individual confidence level would be $1-\alpha/2$, which is $1-0.025 = 0.975$, given the family-wise error rate $\alpha = 0.05$.
   Secondly, the clinical input/assumption necessary for the sample size calculation are pre-specified in the protocol and are considered as reasonable. They are the true proportion in percentage of contraindicated/incorrect use (15 %) and the assumed error margin ($\pm$ 5 %).
   Lastly, based on these assumptions including clinical inputs, family-wise error rate, and Bonferroni multiplicity adjustment method, the sample size of 256 is appropriate by the normal approximation for a binomial distribution.

2. **Please comment on the approach that the sponsor handled the missing data (p031, vol 27).**

   In the calculation of the proportion, the definition of analysis set and the denominator of the proportion are crucial because they have direct impact on the

estimate of proportion. It would be useful to do some sensitivity analyses. When calculating the proportion of the contraindicated use, first categorize each subject in the ITT as contraindicated user, non-contraindicated user or undefined user due to insufficient data, then count members in each group and denote the group size as CU, NCU, and UD, respectively. Now there are two ways of estimation for the true proportion:

-method 1: CU/(CU+NCU);

-method 2: (CU+UD)/(CU+NCU+UD).

Method 1 is used by the sponsor in the report. But it ignores the missing data (or undefined users) and excludes them from the calculation. Method 2 used the number of ITT subjects in the denominator, where an undefined subject is assumed to be a contraindicated user. This method gives a conservative estimate for the proportion because the proportion by Method 2 is always greater than or equal to the one by Method 1. The true proportion of the contraindicated use may exist in-between the two proportions by Method 1 and Method 2.

3. **Please evaluate the statistical methods that the sponsor used to analyze data from AU study (the section I gave to you, which is also found in EDR dated 08-08-03A).**

   The statistical methods are acceptable and properly chosen. A concern was raised on the test result for the association between 'oral contraceptive use after receiving study drug (Yes/No)' and 'age group (< 17 yr./ ≥17 yr.)' because p-value(=0.1746) does not support the seemingly large observed difference in oral contraceptive use (36% for the group of < 17 yr. vs. 20% for the group of ≥17 yr.). However, the lack of a significant difference can be due to the exploratory nature of the analysis, in that the study was not a priori designed to test the statistical significance of the observed difference.

4. **The sponsor needs to provide details about computer problem during study which may have impacted the quality of study data entry (p029, vol 27) (Statistician?)**

   There is no specific statistical guideline in the situation like this: hardware data entry problem. But it seems reasonable for the sponsor to mend this anomaly *post hoc* by sampling data entry randomly and estimating the error rate and lower limit of interval for the rate before the final analysis.

Yongman Kim, Ph.D.
Mathematical Statistician

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yongman Kim
11/6/03 03:49:58 PM
BIOMETRICS

Stan Lin
11/6/03 06:09:44 PM
UNKNOWN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sonia Castillo
2/18/04 11:04:33 AM
BIOMETRICS

Screening of New NDA for Statistical Filing
Division of Biometrics II

NDA #: 21-045

Applicant: Women's Capital Corporation

Trade/Generic Name: PLAN B (levonorgestrel)

Indication: Emergency contraception

Date of Submission: April 16, 2003

Filing Date: June 9, 2003

User Fee Goal Date: February 20, 2004

Project Manager: Karen Anderson

Medical Reviewer: Daniel Davis, M.D.

Comments: This NDA is fileable from a statistical perspective.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	EDR data present
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	NA

Reviewer: S. Castillo

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sonia Castillo
6/10/03 12:16:03 PM
BIOMETRICS