CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201110Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 70,875

Duramed Research, Inc.
ATTENTION: Jennifer Norman
Director, Clinical Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Norman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Progesterone Vaginal Ring.

We also refer to the meeting between representatives of your firm and the FDA on June 16, 2009. The purpose of the meeting was to discuss the preclinical program, the clinical trial results, and the overall design of your electronic NDA submission for Progesterone Vaginal Ring.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}
Shelley R. Slaughter, MD, PhD
Medical Officer Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 16, 2009
TIME: 11:00 a.m.
APPLICATION: IND 70,875
DRUG NAME: Progesterone Vaginal Ring
TYPE OF MEETING: Type B, Pre-NDA
MEETING CHAIR: Shelley Slaughter, M.D., Ph.D.
MEETING RECORDER: Celia Peacock, M.P.H., R.D.

FDA Participants

Shelley, Slaughter, M.D.	Medical Team Leader	Division of Reproductive and Urologic Products (DRUP)
Celia Peacock, M.P.H., R.D.	Regulatory Project Manager	DRUP
Scott Monroe, M.D.	Director	DRUP
Phill Price, M.D.	Medical Officer	DRUP
Christos Mastroyannis, M.D.	Medical Officer	DRUP
Audrey Gassman, M.D.	Medical Officer	DRUP
Krishan Raheja, Ph.D.	Phamacologist	DRUP
Mahboob Sobhan, Ph.D.	Statistical Team Leader	Division of Biometrics III
Doanh Tran, Ph.D.	Clinical Pharmacology	Division of Clinical Pharmacology III

Duramed Research Participants

Joseph A. Carrado, M.Sc., R.Ph.	Vice President, Global Regulatory Affairs
Matt Hall, Director	Clinical Operations
Amy Hummel, M.S.	Senior Associate, Clinical Regulatory Affairs
Keith Earle, D.V.M.	Director, Toxicology
Kathleen Reape, M.D.	Vice President, Women's Health R&D
Jennifer Norman, R.Ph.	Director, Clinical Regulatory Affairs
Keith Earle, D.V.M.	Director, Toxicology
Keith Liu, Ph.D.	Director, Biostatics
Heather Golarz	Senior Clinical Program Manager, Clinical Operations

QUESTIONS, DIVISION RESPONSES, AND FURTHER DISCUSSION:

Clinical Questions

Question 1: Duramed maintains that the results from the pivotal clinical trial DR-PGN-302, along with those from the Phase 1 studies 10617222 and DR-201-102 and Phase 2 studies DR-PGN-201 and DR-PGN-202 (summaries provided in Attachment 1 support the submission of the proposed NDA for the indication of supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. Does the Division concur?

FDA response:

No, we do not concur.

a. We remind you of our recommendations made on multiple occasions during your drug development program (beginning with the June 13, 2007 end of Phase 2 Type B meeting and continuing into 2009) that your Phase 3 study (s) be stratified and powered to demonstrate efficacy in each of the age groups represented by women less than 35 years of age and women 35-42 years of age. We specifically refer you to the following comments on Study DR-PGN-302 provided by the Division in ADVICE LETTERS dated August 27, 2008 and March 09, 2009:

   August 27, 2008 – "We do not agree that a study powered only to demonstrate efficacy in the population of women less than 35 years of age will be adequate for an indication for support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women. The proposed study will not adequately address efficacy and safety in the population of women 35 years of age or greater. Such women represent approximately 50% of women undergoing ART procedures and would be expected to constitute approximately 50% of the potential users of the progesterone vaginal ring. Therefore, it is not acceptable if the sample size for the subgroup of older women is underpowered for assessing the efficacy of the progesterone vaginal ring."

   March 09, 2009 – "Study DR-PGN-302, with only 200 subjects in the age range of 35-42 years old, is inadequately powered to assess efficacy in this population. We continue to strongly recommend that randomization and the primary analyses be stratified and powered in terms of ovarian reserve as assessed by the age of the subject (subjects < 35 years old and subjects ≥ 35 to 42 years old).

b. The Division continues to have concern that the formulation of the DR-2011-progesterone vaginal ring (release rate of 14 mg/day of progesterone) provides insufficient progesterone for supplementation of corpus luteal function and maintenance of early pregnancy. The issue of whether or not the progesterone vaginal ring provides sufficient supplementation is a review issue not only for efficacy, but for the safety (spontaneous abortion rate) of this product as well.

c. Pending a determination by the Office of New Drug Quality Assessment (ONDQA) of the potential impact of the change in manufacturing site for DR-2011, a bioequivalence study may be required to bridge the drug products used in clinical trials and the to-be-marketed product.

Discussion During The Meeting:

The Sponsor emphasized that the vaginal ring design has accommodated the maximum amount of progesterone possible and the release rate is at the maximum.

The Sponsor acknowledged the Division's recommendation to power the pivotal study (s) to demonstrate efficacy in women < 35 years old and women ≥ 35 to 42 years old. However, the Sponsor clarified that because of some "internal constraints", they had made the choice to power their study only for women less than age 35. The Sponsor also noted an approved product whose primary study was powered only for subjects < 35 years of age.

The Division relayed that it was not in a position to advise the Sponsor as to whether or not an application with the above noted studies would be fileable; that determination would depend on the results of the Division's review at the time of submission. However, the Division again noted its concern regarding the very limited information on women in the older population.

The Sponsor indicated that it would internally consider conducting a separate study in women age ≥ 35-42.

Regarding the potential impact of the change in manufacturing site for DR-2011, the Sponsor stated that they plan to discuss the need for a bioequivalence study in a separate CMC Pre-NDA meeting with ONDQA. The Sponsor inquired what the primary endpoint would be if a bioequivalence study is performed. The Division stated that serum concentrations of exogenous progesterone are quantifiable and that they could be used for bioequivalence assessment.

Question 2: Does the Division agree with the proposed presentation of the safety listings, categorization, and definitions for the Clinical Study Report for DR-PGN-302, as presented in the Clinical Summary below (pages 14-21)?

FDA response:

No.

We also request the following safety listings:

a. In the safety datasets, please include the treatment (progesterone ring or Crinone) and the MedDRA terms, the PT (preferred term), and also the adverse event term as described by the investigator.

b. We recommend that proposed Table 8 [Incidence of Treatment-Emergent Adverse Events – Safety Cohort (4% or more)] needs to include all treatment-emergent adverse events in the safety cohort as 1% or greater in Study PGN-DR-302. In addition, the TEAE table needs to reflect the number of subjects that had each event, not the total number of events.

c. Provide a secondary summary table of the number of overall adverse events by site and treatment group.

d. Provide an additional safety table of all subject who had a reported event of ovarian hyperstimulation syndrome (OHSS), categorized by severity (mild, moderate and severe) using standardized categorization criteria. In addition, provide the definitions used to classify OHSS.

Discussion During The Meeting:

The Division clarified item b above to state that Table 8 should include for the safety cohort, treatment-emergent adverse events at 2% or greater and not 1 % as indicated above.

Question 3: As per the Guidance for Industry: E3 Structure and Content of Clinical Study Reports (July 1996), Duramed plans to include as Appendix 16.3 of the Clinical Study Report for DR-PGN-302, copies of case report forms only for subjects that died, experienced a serious adverse event and/or discontinued study participation due to an adverse event. Does the Division agree that inclusion of these categories will be sufficient?

FDA response:

No.

In addition, we request the following:

a. Submit case report forms for all subjects with serious and/or severe ovarian hyperstimulation.

b. Submit the stimulation cycle sheet (if applicable) with all case report forms submitted for the above categories.

c. Provide a Table that lists the number and types of vaginal infections reported during treatment with the ring or the gel.

No additional discussion during the meeting.

Question 4: Pending the inclusion of final data from the ongoing studies (Phase 1, Phase 3 and preclinical), does the Division agree with the presentation of information in the proposed labeling (provided in Attachment 2)?

FDA response:

We believe that it is premature to discuss labeling at this point with the exception of noting that all submitted labeling submitted should be in PLR format as outlined in the Physician Labeling Rule (PLR) that took effect on June 30, 2006.

No additional discussion during the meeting.

Preclinical Question

Question 5: Progesterone is a well-characterized drug that is widely marketed throughout the world. Also, the silicone elastomer (b) (4) component of the vaginal ring has met the biocompatibility and genotoxicity testing criteria of the ISO 10993 Part 10 guidelines and has been previously approved for use as a biological implant. Duramed is currently conducting study DR-201-001 entitled, "An Intravaginal Safety Assessment Study of a Surgically Implanted Progesterone Vaginal Capsule Formulation for 30, 60, 75 and 90 Days in the Mature New Zealand White Female Rabbit" (protocol provided in Attachment 3).

Does the Division concur that the nonclinical program (consisting of Study # DR-201-001, a 10-Day Intravaginal Irritation Study of Progesterone in Female New Zealand White Rabbits (Study # (b) (4)) and biocompatibility/genotoxicity results of the silicone elastomer (b) (4)) is adequate to support the NDA filing?

FDA response:
Yes, we concur that the nonclinical program is adequate, based on the information available for long term use of progesterone by the intravaginal route of administration for the same indication, coupled with the safe use of the DR-2011 formulation in your Phase 1 and Phase 2 clinical studies.

No additional discussion during the meeting.

Administrative Questions

Question 6: Duramed plans to request a waiver of pediatric studies as per 21 CFR § 314.55 (c) (2) as this product is not intended for pediatric use based on its indication. Does the Division concur with this plan?

FDA response:
Yes, we concur with your plans to request a waiver of pediatric studies.

No additional discussion during the meeting.

Question 7: Duramed plans to submit the NDA in CTD format as a hybrid electronic submission without an .xml backbone. Documents and data files will be arranged in separate folders as recommended in the eCTD guidance. A hyperlinked PDF Table of Contents outside folders will act as a backbone and link to the files in the folders. Does the Division concur with this plan?

FDA response:
Yes, we concur providing you have an eCTD waiver.
See: http://www.fda.gov/cder/regulatory/ersr/waiver.htm.

No additional discussion during the meeting.

Question 8: Does the Division concur that the Proposed Overall Table of Contents/Content Plan (provided in Attachment 4) will constitute a fileable NDA?

FDA response:
No, we do not concur. Please refer to our response to Question 1.
In addition, upon filing, do not use 1.1.7 for Form 3674. Rather, Form 3674 should be included under 1.2, Cover Letters, and the leaf should be titled "FDA form 3674". Also note that FDA does not utilize 5.3.7 for case report forms and individual patient listings. Instead, those should be included in a folder with the study to which they pertain.

No additional discussion during the meeting.

Question 9: No formal integrated efficacy or safety analyses are planned, given the differing patient populations and wide disparity in numbers of subjects between Phase 2 (N=9) and Phase 3 (N=1299) trials. Does the Division agree with this plan?

FDA response:
Yes, we concur that Phase 2 should not be integrated with Phase 3 studies for the analyses of efficacy and safety.

No additional discussion during the meeting.

Question 10: Duramed plans to include in Module 2 a Clinical Overview (Module 2.5), but not a Clinical Summary (Module 2.7) for the same reasons outlined in Question 8 above. Similarly, a Nonclinical Overview (Module 2.4), but not a Nonclinical Summary (Module 2.6), will be included given the size and scope of the nonclinical program as outline in Question 4 above. Does the Division agree with this plan?

FDA response:
The Clinical discipline concurs with your plans to include in Module 2, a Clinical Overview (Module 2.5), but not a Clinical Summary (Module 2.7).

No additional discussion during the meeting.

Additional Clinical Comments for Study DR-PGN-302

a. We request that you provide demographic tables that include: past obstetrical history including gravidity, parity, previous abortions, and ectopic pregnancy information.
b. Submit the duration of use of the progesterone vaginal ring in all subjects that achieved pregnancy.
c. Submit subgroup analyses of the primary efficacy endpoint (ongoing pregnancy) by ovarian reserve as measured by Day 3 serum FSH, age of female partner and the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm in injection (ICSI)] and day of embryo transfer (Day 3 or 5).

d. Present additional analyses of ongoing pregnancy rate that examine sub-stratification of clinical data based on BMI and infertility diagnosis (based on your classification system).

e. Report the outcomes (live births, terminations, multiple gestations, birth defects) of all pregnancies that occurred in study DR-PGN-302 in tabular form.

f. Submit the analysis files (in addition to raw data files), preferably, in SAS transport format and the corresponding data definitions as part of module 5.

Additional Clinical Pharmacology Comments

1. The progesterone vaginal ring (DR-2011) was initially stated to release (b) (4) mg/day. It was subsequently changed to (b) (4) 14 mg/day. It is not clear how the release rates were calculated. It is also not clear why the stated release rate was changed twice without a reported change in formulation composition. The NDA should address these 2 comments. Release rate calculation should be based on the residual amount of progesterone remaining in DR-2011 following vaginal placement of the ring for 7 days.

Discussion During The Meeting:

The Sponsor clarified that a release rate of (b) (4) mg/day was estimated based on in vitro data whereas (b) (4) 14 mg/day release rates were calculated based on residual amount following in vivo application of the ring. (b) (4) The Sponsor did not have this information during the meeting but stated that they would provide it in the NDA.

2. Provide the following in the NDA:
   - Raw and calculated pharmacokinetic parameters data files for studies DR-PGN-201, 10716222, and DR-201-102. Provide the files in SAS Transport (.XPT) format.
   - Method validation report(s) for progesterone assay(s) used in clinical studies.
   - Bioanalytical reports for studies DR-PGN-201, 10716222, and DR-201-102.
   - A summary outlining the manufacturing site changes and what bridging studies were conducted to ensure that the products from different manufacturing sites had similar bioavailability. Include a table of all clinical studies and the associated drug products (i.e., products from different manufacturing sites) that were used.

No additional discussion during the meeting.

ACTION ITEMS:

- Finalize meeting minutes within 30 days.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 70875	DURAMED RESEARCH INC	PROGESTERONE (VAGINAL RING)

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

/s/

PHILL H PRICE
07/15/2009
I am signing as a proxy for Dr. Shelley Slaughter, M.D. PhD.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,875

MEETING MINUTES

Duramed Research, Inc.
Attention: Patricia Thomas
Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Ms. Thomas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DR-2011 (progesterone vaginal ring).

We also refer to the End-of-Phase 2 clinical meeting between representatives of your firm and the FDA on June 13, 2007. The purpose of the meeting was to discuss the Phase 2 clinical study results and the proposed Phase 3 clinical plans for DR-2011.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call John Kim, R.Ph., J.D., Regulatory Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

MEETING DATE: June 13, 2007 **TIME:** 11 am – 12:30 pm

LOCATION: Food and Drug Administration
White Oak Building 22, Conference Room 1417
10903 New Hampshire Avenue
Silver Spring, MD 20993

APPLICATIONS: IND 70,875

DRUG NAMES: DR-2011 (progesterone vaginal ring)

SPONSOR: Duramed Research, Inc.

TYPE OF MEETING: Type B, End-of-Phase 2

MEETING CHAIR: Shelley R. Slaughter, M.D., Ph.D.

MEETING RECORDER: John Kim, R.Ph., J.D.

FDA ATTENDEES:
Scott Monroe, M.D. – Acting Director, Division of Reproductive and Urologic Products (DRUP)
Shelley R. Slaughter, M.D., Ph.D. – Clinical Team Leader, DRUP
Audrey Gassman, M.D. – Medical Officer, DRUP
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment (DPMA), Office of New Drug Quality Assessment (ONDQA)
Doanh Tran, R.Ph., Ph.D. – Clinical Pharmacologist, Office of Clinical Pharmacology @ DRUP
Mahboob Sobhan, Ph.D. – Team Leader, Division of Biometrics II
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

DURAMED ATTENDEES:
G. Fred Wilkinson – President, Chief Operating Officer
Keith Liu, Ph.D. – Director, Biostatistics
Diane Harrison, M.D. – Senior Director, Clinical Operations
Charlene Sanders, M.D. – Senior Director, Clinical Regulatory Affairs
Patricia Thomas, M.P.H. – Director, Clinical Regulatory Affairs
Chandra Vattikonda, Ph.D. – Senior Director, Scientific Affairs
Keith Earle, D.V.M. – Associate Director, Preclinical Toxicologist
Mark Coriolan, B.S. – Associate, Clinical Regulatory Affairs
(b) (4)

BACKGROUND:
The Sponsor requested this End-of-Phase 2 clinical meeting to discuss (b) (4) proposed Phase 3 clinical protocols: (b) (4) DR-

PGN-302 for luteal phase supplementation. DR-2011 is a progesterone-containing silicone ring drug delivery system that has an average *in vitro* release rate of 16 mg/day over (b) (4) 7 days. The *in vivo* release rate is estimated to be 16 mg/day when vaginally inserted for 7 days.

DISCUSSION POINTS:
The discussions are generated from the Sponsor's specific questions that follow.

Question a: *Does the agency agree that the results described for Study DR-PGN-201 and the ongoing Study DR-PGN-202 indicate evidence of effectiveness and tolerability to proceed with the Phase 3 clinical program?*

FDA Response: No. We do not believe that you have provided sufficient dose-finding evidence from the results of the Phase 2 study DR-PGN-201 to proceed into Phase 3 development. We also have serious concerns that the progesterone vaginal ring does not support a sufficient level of serum progesterone ((b) (4) ng/mL) to support an ART pregnancy. The rationale for our concerns includes:

- In the mid-luteal phase in normal women, serum progesterone levels range between (b) (4) and (b) (4) ng/mL. Your proposed serum progesterone levels are inadequate based on this standard physiologic marker.
- Nine of ten of subjects treated with the vaginal ring had bleeding or spotting compared to none in the group treated with progesterone vaginal gel in study DR-PGN-201.
- The largest meta-analysis (Daya and Gunby, 2004) suggests that there is an advantage of IM over vaginal progesterone for ongoing pregnancies and livebirths despite a theoretical "first pass effect".

The Division recognizes that using serum progesterone levels and endometrial biopsy results, may not, alone or in combination, be optimal surrogate markers for pregnancy outcomes for either luteal supplementation (b) (4) after Assisted Reproductive Technology treatment. However, these two surrogates are the most standardized and accepted of the markers used. The results of DR-PGN-201 appear to indicate that the decreased secretory transformation and the low serum progesterone levels seen point towards inadequate progesterone delivery of the vaginal ring.

Sponsor Response: *Sponsor contends that its product provides the maximum amount at a consistent reliable dosing compared to the approved products. In addition, the Sponsor believes that there will be success with this product based on clinical outcomes in the Phase 2 studies.*

FDA Response: The Sponsor is reminded that to proceed on to Phase 3 based on the results of Study DR-PGN-201 is to proceed at your own risk that the ultimate outcome does not provide the efficacy and safety results that you have anticipated, given our preceding discussion. Sponsor is also referred to the discussion by the FDA under Question d – Study design –d. and under Question e – Study design-b.

Question b: *The Phase 3 program is designed to support the approval of a marketing application for DR-2011 (Progesterone vaginal ring) in the treatment of progesterone*

supplementation (b) (4) *as part of an Assisted Reproductive Technology treatment for infertile women with progesterone deficiency. Does the Agency concur?*

FDA Response: As above, we do not concur that you are ready to proceed into Phase 3. In addition, we do not concur with the outlines of the Phase 3 protocol outlines as presented in this submission. Initial comments on the Phase 3 outlines are in the answers to questions (d) and (e).

Question c: *Does the Agency agree with the Phase 3 plan as adequate support for the proposed indications for Duramed's to-be-marketed DR-2011 (Progesterone Vaginal Ring) product as stated below:*

(b) (4)

2) *Progesterone supplementation as part of an Assisted Reproductive Technology treatment for infertile women with progesterone deficiency*

FDA Response: It is premature to agree to the Phase 3 plan without adequate dose-finding. As previously stated, we continue to recommend that you perform additional dose-finding studies. We however, do recommend that the indications be:

1) For pregnancy by progesterone supplementation as part of an Assisted Reproductive Technology (ART) treatment for infertile women

(b) (4)

The exact wording will be discussed at the time of labeling negotiations.

(b) (4)

(b) (4)

[redacted]

Question e: *Does the agency agree with Duramed's study design for DR-PGN-302?*

FDA Response: No. The Agency has serious concerns that the amount of progesterone delivered is inadequate based your initial pharmacokinetic measurements. In addition, we do not agree with the study design as outlined. Initial comments on Study DR-PGN-302 are listed below:

Study Design Issues:

a. We recommend double-blinding or at a minimum investigator and ultrasonographer be blinded.
b. The primary efficacy analysis should be based on a two-sided 95% confidence interval. A lower confidence limit of (b) (4)% is not acceptable for the progesterone vaginal ring. The non-inferiority limit for the phase 3 study should be defined as equal to or greater than -10% of a two-sided 95% confidence interval when compared to an active progesterone comparator. You should report the percentages of the difference of the lower limit of the 95% confidence intervals to the first decimal point. We also remind you that the livebirth per transfer rate in the 2004 CDC clinical pregnancy rate per cycle using fresh embryos is 33% and your study should demonstrate that your product will be comparable to this standard.
c. The primary efficacy analysis should include all subjects who completed oocyte retrieval and have received at least one dose of progesterone (m-ITT cohort).

d. **Randomization** and **analyses** should be stratified and **powered** by ovarian reserve as measured by Day 3 serum FSH and age of female partner (< 35 years of age, 35-42 years of age). The Division feels strongly that this information is critical in order to appropriately advise the physician who treats and the patient who falls in the age greater than 35 range (up to 60% of the ART population for luteal supplementation). The Division further recommends a sub-stratification of data based on BMI, the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm injection (ICSI)] and infertility diagnosis. The analysis of data relative to sub-stratification groups can be descriptive. Studies should be powered to demonstrate differences in these (sub-stratification) groups only if specific claims regarding these are sought.
e. The Division recommends that ovarian reserve (serum FSH) be measured in a central laboratory. The entry criteria should include evaluation of a serum FSH level on Days 2, 3, or 4. Subjects with a serum FSH of 15 IU/L or greater obtained on cycle Day 2, 3 or 4 should be excluded.
f. The Division recommends that if you choose to perform one study for this indication, either all of the sites or a majority of subjects be treated at US sites, as practices of ART are significantly different in non-North American countries.
g. We remind you that these are not all the comments on the study design, and would recommend that the completed protocols be submitted for review.

Question f: *Duramed is considering including a QOL assessment in both the non-donor and donor phase 3 studies. Does the Agency have any recommendations for a particular QOL tool to use for this purpose?*

FDA Response: Claims for QOL would only be acceptable based on development of a validated instrument. The Sponsor should refer to the guidance entitled, "*Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*."

Additional Discussion:

The Division recommended that an additional drug-ring interaction study should be performed to look at the effects of vaginal creams and gels on the PK/PD parameters of the progesterone vaginal ring. In the absence of data, this will be a labeling issue. The Sponsor indicated that it will address this in the labeling as a contraindication unless there is a broader use of the product beyond the ART population.

The Division repeated its recommendation for a dose-finding study in which a dose response is seen with several doses. If the Sponsor elects to proceed at its own risk into Phase 3 without additional dose-finding study, the Agency advised that the Sponsor should conduct one study first to confirm dosing.

The Sponsor indicated that an update CMC amendment will be submitted for review in lieu of an EOP2 CMC meeting.

The Division indicated that the Phase 3 protocols should be submitted for review. The Division will provide written comments, but will welcome a teleconference. The Sponsor also has the option of submitting the Phase 3 protocols as a Special Protocol Assessment request.

ACTION ITEM:

- The Project Manager will provide meeting minutes within 30 days of the meeting date.

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

/s/

Shelley Slaughter
7/2/2007 05:18:10 PM
I concur.