MEETING MINUTES

Date: January 27, 1998 **Time:** 10:30 AM- 12:00 PM **Location:** Parklawn; Rm 17B-43

IND: **Drug Name:** Cenestin (synthetic conjugated estrogens) Tablets

External Participant: Duramed Pharmaceuticals, Inc

Type of Meeting: Pre-NDA

Meeting Chair: Dr. Lisa Rarick **External Participant Lead:** Mr. John Rapoza

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Tatiana Pavalova M.D., Ph.D. - Clinical Pharmacology Fellow
Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Robert Seevers, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Mei-Ling Chen, Ph.D. - Director, Division of Pharmaceutical Evaluation II (DPE II) (HFD-870)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Constituents:

Ms. Kathryn Hanford, Sr. Biostatistician, MDS Harris
Mr. Ken Phelps, V.P. Corporate Projects, Duramed
Mr. John Rapoza, V.P. Regulatory Affairs, Duramed
Dr. Ruth Stevens, Director of Pharmacokinetics, Phoenix International
Mr. William Stoltman, Director Regulatory Compliance, Duramed
Dr. Suman Wason, Medical Director, Phoenix International
Dr. George Wright, Consultant

Meeting Objectives:
To discuss the format for the proposed NDA by Duramed for their conjugated estrogens product.

Background:
Duramed proposes to reference their ANDA submitted on September 1994, for the Chemistry, Manufacturing and Controls section of their proposed NDA. The sponsor filed the IND on July 18, 1997. Clinical studies for the NDA were discussed in a Pre-IND meeting for IND on June 19,

1997. Duramed is pursuing the route of a 505(b)(2) with one clinical trial for the indication of reduction of vasomotor symptoms.

Discussion Points: (See attached)

- the sponsor plans to lock the clinical database on February 10, 1998, and file the NDA in March 1998; a total of 451 patients were screened with 109 completers; only 11 withdrew from the study
- the 1992 labeling guidance for estrogen drug products does not suggest an initial dose of 1.25 mg
- although Duramed plans to include the clinical sites in the clinical study report, the sponsor does not plan to analyze the data from each study center separately because the numbers would not be large enough to give sufficient power for efficacy
- the sponsor does not plan to stratify or analyze the clinical data by dosage strength because the numbers would not be large enough to provide sufficient power to prove efficacy for each dosage strength
- The sponsor does not plan to submit the data or information in an electronic format

Decisions reached:

Proposed Actions (see attached)

1. ANDA Reference:
   a. it would be acceptable to refer to ANDA 40-115 for the CMC sections of the NDA that are unchanged from the ANDA; although the original volumes will be available for review, the exact volume and page numbers of the ANDA must be referenced
   b. at least 24 months of room temperature and 12 months of accelerated stability data on 3 batches of the drug product would be required with the appropriate data analysis to support the proposed 48 month expiration dating period; Duramed claims to have 48 months of data
   c. the post-approval stability commitment should use ICH conditions, i.e., 25 C°/60 RH
   d. any unidentified impurity greater than 0.1% should be identified and qualified (see attached)
2. the sponsor should contact the Chief Mediator's Office for details concerning the qualifications for a small business exemption from User Fees
3. Duramed seeks a 3 year market exclusivity-acceptable
4. the 0.625 mg dose will likely be appropriate as the initial starting dose for the indication of reduction of vasomotor symptoms
5. Clinical Study report
   a. the overall analysis of the data presented in the meeting package appears to be adequate; however, the sponsor should also provide more descriptive results by study center, even if sample sizes are insufficient to have statistically significant results, in order to address the internal consistency of the data; in addition to a summary table of site listings, the NDA should contain the following information regarding each study center:
      1. baseline values and descriptions of the primary (not secondary) efficacy variable results
      2. descriptions of the adverse event data
      3. complete case report forms on dropouts
   b. classification of concomitant medications
      the sponsor will include data listings of the concomitant medications, they will not be classified into WHO groupings -- acceptable

c. clinical data by dosage strength
   1. the data should be stratified and summarized by dosage strength
   2. any waiver for intermediate doses should be justified by appropriate data
   3. a description of the number of women titrated to the various doses should be included in the NDA and possibly in the **Clinical Studies** subsection of the labeling; they can be summarized in a table
   4. effectiveness could be described according to the way the study was randomized

6. the sponsor seeks to submit summaries of their four definitive studies for the Clinical Pharmacology and Biopharmaceutics studies with reference to the ANDA for complete results; the sponsor does not plan to report the pilot bioequivalence study performed prior to these studies—**acceptable**
7. the sponsor will provide SAS data sets for Biometrics and Biopharmaceutics and diskettes of the labeling
8. the sponsor should apply for a categorical exemption to filing an EA (see attached)

Other Issues

- Chemistry
  - the trade name Cenestin (synthetic conjugated estrogens) has been submitted to the Nomenclature Committee and were found to be acceptable
  - the shape and the color of the tablet on the carton should be changed; the sponsor agreed to change the color of the tablet on the label to colorless and the shape of the tablet to round from oval
  - the company name should be a smaller font than the product name and placed on the bottom of the paragraph
  - the phrase, "Keep out of reach of children" should be included on the label for all sizes
  - the validation methods used in the clinical study should be provided in the NDA
  - manufacturing sites may be re-inspected
  - upon review, other issues that arise will be addressed
- Biopharmaceutics
  - *in vivo* studies and comparative dissolution data for the 0.625 mg and 1.25 mg strengths are available in the ANDA; the sponsor should request waivers for the three additional doses; Duramed agreed to submit formulation information and comparative dissolution data and profiles for all five strengths of available batches to support the waiver request for *in vivo* studies
  - dose proportionality data should be submitted for the 0.625 mg and 1.25 mg doses
  - a Pharmacokinetics section will be added to the label according to the estrogen labeling guidance
  - proposed dissolution specifications could be based on data generated from the Duramed bio-lots
- Statistics
  - the primary variable in the study comparing estrogen to placebo is the absolute number of reduction of VMS symptoms at 4, 8, and 12 weeks; percentage change will also be examined for consistency with absolute change
  - the sponsor proposes the intent-to-treat population as those who had at least one tablet and 4 weeks of data; FDA prefers the ITT to include patients with any data; the last observation should be carried forward so that the most recent data is available; a discussion of the impact of losses-to-follow up should be included

- "n" numbers, min, max, and standard deviations (SD) (difference in square means) should be added to all tables
- confidence intervals should be at the 95% level
- observed means, in addition to least square means, should be presented
- in Table 3 entitled, "Statistical Summary of Absolute Change in MSVS at Weeks 4, 8, and 12, Intent-to-Treat Analysis, the baseline and ranges should be added
- the reference to dropouts should be more descriptive, the inclusion of a Kaplan Meier chart of time to discontinuation is recommended
- the minimum and maximum ranges should be included in the demographic summary for continuous variables
- sample sizes should be added to Figure 1

Action Items:

Item:	Responsible Person:	Due Date:
• contact Office of Chief Mediator for update on PDUFA small business exemption	Duramed	before filing NDA

/7

2/11/98

Signature, minutes preparer

Concurrence, Chair 1/27/98

drafted: dm/January 24, 1998/i53731mm.pnd

cc:
NDA Arch:
HFD-580
HFD-580/LRarick/Tvan der Vlugt/RSeevers/MRhee/KRaheja/AJordan/LKammerman/ADorantes
HFD-580/JMercier

Concurrence:
LPauls, JSafran, RSeevers, ADorantes, LKammerman 02.03.98
MRhee, MChen 02.04.98/LRarick 02.05.98/Tvander Vlugt 02.09.98
TPavlova 02.10.98

Attachment 1

PRE-NDA CONFERENCE: SYNTHETIC CONJUGATED ESTROGENS TABLETS

Proposed NDA Actions

1. We plan to reference the currently filed ANDA #40-115 on Synthetic Conjugated Estrogens Tablets for Chemistry manufacturing and Controls sections of the NDA. We intend only to include in the NDA new, updated or revised information since our last ANDA correspondence.

2. We will request a waiver of the PDUFA fee based on the size of our company being less than 500 employees.

3. We plan to request a three (3) year marketing exclusivity based on our clinical study being required for NDA approval.

4. The labeling will include for the treatment of vasomotor symptoms, a recommended starting dose of 0.625 mg rather than the 1.25 mg indicated in the estrogen class labeling.

5. For the clinical study report:
   a) we do not plan to analyze or report the data by study center
   b) we do not plan to classify concomitant medications
   c) we do not plan to stratify or analyze any data by dosage strength

6. For the Human Pharmacokinetics and Bioavailability section we did not plan to report the pilot bioequivalence study performed prior to the 4 definitive studies. We plan to summarize the four definitive studies and reference the ANDA for complete results.

7. We have no plans for the submission of data or information in electronic format.

8. With regard to an environmental assessment, we intend to reference the [redacted]. For the drug product, we intend to prepare an abbreviated assessment in accordance with 21 CFR 25.31a (b)(5).

Attachment 2

Chemistry, Manufacturing, & Controls Discussion Points for Synthetic Conjugated Estrogens

This page presents information in response to issues raised in Duramed's meeting package. Other questions will likely arise during the review process and will be dealt with at that time.

ANDA Reference

It will be acceptable to refer to Duramed's ANDA submission, 40-115, for the CMC sections of the NDA that are unchanged from the ANDA. It is important that these references include the volume and page number of the ANDA to speed the review process.

Stability Data

To support the proposed 48 month expiration dating period, at least 24 months of room temperature and 12 months of accelerated stability data on 3 batches of the drug product would be generally be needed with appropriate data analysis.

The post-approval stability commitment should use ICH conditions, i.e. 25°C/65 RH.

Environmental Assessment

The NDA application should qualify for a categorical exemption to filing an EA per 21 CFR § 25.31 (a) and (b). This categorical exemption must be requested in the NDA application and can be granted if:

1. The expected introduction concentration of the drug substance is less than 1 ppb, and
2. There are no extraordinary circumstances

Impurities

Any unidentified impurity greater than 0.1% should be identified and qualified. The ICH Draft Guidance recommends limits of 2 ppm for benzene and 80 ppm for trichloroethylene.

Agenda

1.	Introduction	Mr. Rapoza
2.	Review of Chemistry, manufacturing and Controls Section	Mr. Rapoza
3.	Review of Clinical Study	Mr. Phelps
4.	Review of Labeling	Mr. Stoltman
5.	Discussion of pre-NDA Document	All

Attendees:

Ms. Kathryn Hanford, Sr. Biostatistician, MDS Harris
Mr. Ken Phelps, V.P. Corporate Projects, Duramed
Mr. John Rapoza, V.P. Regulatory Affairs, Duramed
Dr. Ruth Stevens, Director of Pharmacokinetics, Phoenix International
Mr. William Stoltman, Director Regulatory Compliance, Duramed
Dr. Suman Wason, Medical Director, Phoenix International
Dr. George Wright, Consultant

Synthetic Conjugated Estrogens
Vasomotor Study

Timeline

IND filed	July 18, 1997
First Dose	September 3, 1997
Last Dose	January 21, 1998
Database Lock	February 10, 1998
NDA Filing	March 1998

MINUTES of TELECON

Date: February 9, 1998 **Time:** 11:30 AM- 11:40 PM **Location:** Parklawn; Rm 17B-43

IND: **Drug Name:** Cenestin (synthetic conjugated estrogens) Tablets

External Participant: Duramed Pharmaceuticals, Inc

Type of Meeting: Statistics Guidance

Meeting Chair: Dr. Lisa Kammerman **External Participant Lead:** Mr. Ken Phelps

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

Diane Moore - Project Manager, DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Constituents:

Ms. Kathryn Hanford, Sr. Biostatistician, MDS Harris
Mr. Ken Phelps, V.P. Corporate Projects, Duramed

Meeting Objectives:

To clarify the previous discussion regarding the observations carried-forward in intent-to-treat patients who drop out of Duramed's vasomotor study prior to 4 weeks (see attached telefacimile dated February 4, 1998).

Background:

The intent-to-treat population was previously discussed in a Pre-NDA meeting with Duramed held on January 27, 1998.

Discussion Points: (See attached)

- the number of hot flushes from one patient was substantially higher than the rest of the study; this is most likely an outlier and could cause the data to be skewed if included in the analysis
- the sponsor plans to calculate the absolute change from baseline for their primary efficacy variable; they plan to perform non-parametric analyses if the normal distribution does not hold

Decisions reached:

- the most recent full week of data should be used for any patient who withdraws from the vasomotor study after 4 weeks regardless of when they withdraw
- the three patients who withdrew from the study prior to 4 weeks
  - the last observation should be carried forward for 4, 8 and 12 week analyses
  - data from those patients who did not receive the study drug could be left out of the analysis
- Outlier results
  - the outlier results for the one patient could be excluded from the statistical analysis; the sponsor will perform the primary calculations without that data and perform secondary calculations including the data for comparison
  - the sponsor can argue why it would not impact on the analyses and submit their justification to the NDA

Action Items: none

2/18/98

Signature, minutes preparer

Concurrence, Chair 2/18/98

drafted: dm/February 12, 1998/i53731tc.209

cc:
NDA Arch:
HFD-580
HFD-580/LRarick/LKammerman
HFD-580/JMercier

Concurrence:
LPauls 01.13.98/LKammerman 02.17.98

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MEMORANDUM OF TELECON

Date: March 25, 2998

APPLICATION NUMBER: IND , Cenestin (Synthetic Conjugated Estrogens)

BETWEEN:

Name: Kathy Hanford, Ph.D. - Sr. Biostatistician
Phone: (941) 434-6731
Representing: Duramed Pharmaceuticals, Inc.

AND

Name: Lisa Kammerman, Ph.D.
Division of Biometrics II, HFD-715

SUBJECT: Electronic SAS Data Files and Specific Software Programs requested by the Biometrics Discipline for NDA submission.

The following will be submitted to the NDA:

1. Two PC SAS datasets
   a. Demographic
   b. Weekly MSVS data and ITT dataset to include baseline value, weekly values, absolute change from baseline and percent change from baseline.

2. Programs used to generate the analyses.

Only the PC SAS datasets will be given to the sponsor; the programs are proprietary and will not be given to the sponsor.

The PC SAS datasets will be sent next week. The programs will follow within the next 2-3 weeks.

As the data is reviewed, the Agency may have additional requests for further information.

/s/ 4/14/98

Lisa Kammerman, Ph.D.
Biometrics Team Leader

cc: Original IND
HFD-580/Div. File
HFD-580/Lisa Kammerman, Ph.D.
HFD-580/Dmoore

TELECON

MINUTES of TELECON

Date: May 6, 1998 **Time:** 3:30 - 3:50 PM **Location:** Parklawn; Rm. 17B-43

NDA: 20-992 **Drug Name:** Cenestin (synthetic conjugated estrogens) Tablets

External Participant: Duramed Pharmaceuticals, Inc.

Type of Meeting: Chemistry Guidance

Meeting Chair: Dr. Moo-Jhong Rhee **External Participant Lead:** Mr. John Rapoza

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)

External Constituents:

Mr. John Rapoza, V. P. Regulatory Affairs, Duramed
Mr. Ken Phelps, V. P. Corporate Projects, Duramed
Ms. Annette Arlinghaus, Regulatory Affairs
Jim Banchback, Quality Control

Meeting Objectives:

To clarify the designation of the components of the drug substance presented in the NDA.

Background:

The drug substance in the NDA is designated as a hydroalcoholic solution of nine different estrogens. Within this solution there are three active estrogens and six other estrogen components. Active ingredients need to be defined.

Discussion Points:

- although three of the nine components delineated in the NDA are classified as active, the other six components are not well defined
- the sponsor does not seek to change the formulation; some of the components were added to mimic the composition of conjugated estrogens derived from pregnant mare's urine
- the term, concomitant components, is not appropriate because one of the concomitant components as defined in the USP is now one of the active ingredients

Decisions reached:

- an amendment should be submitted to the NDA to clearly indicate the distinction between active ingredients and non-active ingredients as follows: Sodium estrone sulfate, Sodium equilin sulfate, and Sodium 17α-dihydroequilin sulfate will be listed as active ingredients
- 17α-estradiol sulfate, 17 β-estradiol sulfate and 17 β-dihydroequilin sulfate will be listed as excipients
- Sodium equilenin sulfate, sodium 17α-dihydroequilenin sulfate and Sodium 17 β- dihydroequilenin sulfate will be listed as degradation products

Action Items:

• **Item**	**Responsible Person:**	**Due:**
• submit chemistry and labeling amendments	Duramed	two weeks

5/15/98
Signature, minutes preparer

5/15/98
Concurrence, Chair

drafted: dm/May 7, 1998/N20992tc.506

cc:
NDA Arch:
HFD-580
HFD-580/LRarick/MMann/MRhee/DLin
HFD-580/JMercier

Concurrence:
LPauls, DLin 05.11.98/MRhee 05.14.98

MINUTES of TELECON

Date: June 16, 1998 **Time:** 3:00 - 3:06 PM **Location:** Parklawn; Rm 17B-43

NDA: 20-992 **Drug Name:** Cenestin (synthetic conjugated estrogens) Tablets

External Participant: Duramed Pharmaceuticals, Inc

Type of Meeting: Advice

Meeting Chair: Dr. Moo-Jhong Rhee **External Participant Lead:** Mr. John Rapoza

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)

External Constituents:

Mr. John Rapoza, V. P. Regulatory Affairs, Duramed
Mr. Ken Phelps, V. P. Corporate Projects, Duramed
Ms. Annette Arlinghaus, Regulatory Affairs

Meeting Objectives:

To discuss the calculations for the sum total of the product components and the issue of the nomenclature for the established name for synthetic conjugated estrogens.

Discussion Points:

- proposals to designate the active ingredients in the Duramed synthetic conjugated estrogens product were discussed in an internal FDA meeting; the sponsor's proposal to designate the nine components of Cenestin was as follows:
    - estrone sulfate, equilin sulfate, and 17 α-dihydroequilin sulfate were designated as active ingredients
    - 17 β-dihydroequilin sulfate, 17 α-estradiol sulfate, and 17 β-estradiol sulfate were designated as excipients, and
    - equilenin sulfate, 17 α-dihydroequilenin sulfate and 17 β-dihydroequilenin sulfate were designated as degradation products
- it was determined that it would be inappropriate to designate only three of the components as active ingredients because the designation would be misleading; if the product is approved with three active

ingredients, future generic applications would base their drug products on only three of the nine components listed for this product

- it was determined that the whole mixture should be treated as active ingredients so that future generic drug products must contain all nine components
- upper limits for the 17 β-dihydroequilin sulfate, 17 β-estradiol sulfate, equilenin sulfate, 17 α-dihydroequilenin sulfate and 17 β-dihydroequilenin sulfate components were designated as "no more than"; zero is not acceptable as a lower range limit

Decisions reached:

- the sponsor agreed that all components should be designated as active because it is a synthetic product; therefore, specifications should be established for each component
- the specifications for the ranges of each component should be recalculated so that they all add up to 100% using actual data ranges; the raw data from the 103 batches already studied can be used for the calculations
- the calculations for the percentage range should be made from the total nine ingredients instead of the previous calculations using only estrone and equilin
- a lower range percentage must be designated for each degradation product; a 0.1% range is acceptable as a lower limit; however, the upper limit should be based on the actual batch records
- because the 17 β-estradiol sulfate component is a potent estrogen, and not a degradation product, the specification range should be tighter than the other component specificities;
  - the specifications now read "no more than 2.5%"
  - the actual ranges should be selected from the data base
- the most viable established name is "synthetic conjugated estrogen" with a Greek alphabet letter depending on the composition of the proposed product; the Greek letter as a suffix would distinguish synthetic conjugated estrogens products with differing estrogenic components
- the Agency will discuss with USAN regarding the acceptability of the established name

Action Items:

• **Item**	**Responsible Person:**	**Due:**
• submit revised calculations for the nine synthetic estrogen components	Duramed	one week

7/15/98

Signature, minutes preparer

7/15/98

Concurrence, Chair

drafted: dm/June 22, 1998/N20992TC61698.doc

cc:
NDA Arch:
HFD-580
HFD-580/LRarick/MRhee/DLin
HFD-580/DMoore/JMercier

Concurrence:
LPauls 06.25.98/DLin 06.27.98/MRhee 07.14.98

MEETING MINUTES

Date: July 22, 1998 **Time:** 2:10 - 2:30 PM **Location:** Parklawn; Conference Room "B"

NDA: 20-992 **Drug Name:** Cenestin (synthetic conjugated estrogens) Tablets

External Participant: Duramed Pharmaceuticals, Inc.

Type of Meeting: Pre-IND Chemistry advice

Meeting Chair: Dr. Moo-Jhong Rhee **External Participant Lead:** Mr. Ken Phelps

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Mei-Ling Chen, Ph.D. - Director, Division of Pharmaceutical Evaluation II (DPE II; HFD-870), Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

External Constituents:

Mr. John Rapoza, V. P. Regulatory Affairs, Duramed
Mr. Ken Phelps, V. P. Corporate Projects, Duramed

Meeting Objectives:

To discuss the consideration of equilinens as degradants with upper limits.

Discussion Points:

- equilinens are not added to the drug substance; they are degradants of the manufacturing process
- equilinens are not considered active by the sponsor
- the amount of 17 β dihydroequililen is below
- the constituent component issue has been discussed at the Center level
- components are considered part of an "active whole"
- all clinical trials were performed with the nine component product
- all current batches of Cenestin™ tablets contain the nine components

Decisions reached:

- any change in the component profile causes the drug product to be considered as a "new" product
- future tablet production batches must contain all nine components
- after NDA approval, the sponsor should submit a chemistry supplement to acknowledge acceptance of the six-component drug substance, but validate that the tablets will still contain the 9 components

Signature, minutes preparer 8/21/98

Concurrence, Chair 8/21/98

drafted: dm/June 22, 1998/N20992MM72298.doc

cc:
NDA Arch:
HFD-580
HFD-580/LRarick/MRhee/DLin
HFD-580/DMoore/JMercier
HFD-870/MChen

Concurrence:
LPauls 07.28.98/DLin 07.29.98/LRarick 08.06.98/MChen 08.07.98