

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-166

CHEMISTRY REVIEW(S)

Addendum to CMC review # 2 of NDA 21-166

From: Rajiv Agarwal, Ph.D, Chemist
To: NDA # 21-166
Date: 09-FEB-2004
Subject: Phase 4 commitment to provide an in-vitro release specification

Comment: Applicant provided the following Phase 4 commitment via an amendment dated 09-FEB-2004.

As discussed, we agree to design and conduct a phase 4 study to establish an in-vitro release rate specification. We also agree to adhere to the following schedule:

1. Protocol submission: Within 2 months of this action letter, we will submit a detailed protocol for the study.
2. Study start: Within 2 months of reaching protocol agreement with DRUDP.
3. Final study submission: Within 1 year from the approval of the NDA, we will provide the final report via CBE-30 supplement.

APPENDIX
0100

NDA 21-166

**EstroGel 0.06%
(estradiol gel)**

Unimed Pharmaceuticals, Inc.

Rajiv Agarwal, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Chemistry Review Data Sheet

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APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

Chemistry Review Data Sheet

- 1. NDA # 21-166
- 2. REVIEW #: 2
- 3. REVIEW DATE: 09-FEB-2004
- 4. REVIEWER: Rajiv Agarwal
- 5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	13-AUG-1999
Amendment	20-SEP-1999
Amendment	11-SEP-1999
Amendment	21-JAN-2000

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	16-JUN-2003
Amendment	19-JUN-2003
Amendment	01-AUG-2003
Amendment	22-OCT-2003
Amendment	23-OCT-2003
Amendment	23-OCT-2003
Amendment	07-DEC-2003
Amendment	10-DEC-2003
Amendment	09-JAN-2004
Amendment	27-JAN-2004
Amendment	02-FEB-2004
Amendment	06-FEB-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Unimed Pharmaceuticals, Inc.
(A Solvay Pharmaceuticals Inc. Company)

Address: 901 Sawyer Rd., Marietta, GA 30062

Representative: Ms. Cicely N. Vaughn, MPH

Telephone: 770-578-5684

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: EstroGel
- b) Non-Proprietary Name (USAN): estradiol gel
- c) Code Name/# (ONDC only):

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Estrogen, Treatment of moderate to severe vasomotor symptoms in menopausal women.

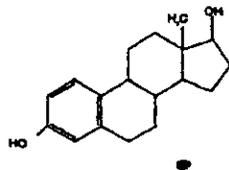
11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Estrodiol (0.06%).
(An EstroGel unit dose of 1.25 g contains 0.75 mg)

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Estradiol (estra-1, 3, 5 (10)-triene-3, 17 β -diol)**Molecular Formula:** C₁₈H₂₄O₂**Molecular weight:** 272.39

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II	/	Estradiol	3	Adequate	16-DEC-2002	Reviewed by Dr. Bing Cai, HFD-620, Chem. Review # 8. : C j
/	II	/	/	1	Adequate	28-JAN-2004	Reviewed by Dr. Rajiv Agarwal Chem. Review # 2
	III		/	1	Adequate	31-OCT-2003	Reviewed by Dr. Rajiv Agarwal Chem Review # 2

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

- Chemistry Review # 1 dated 09-MAY-2000
- IR letter dated 01-MAY-2000

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-FEB-2004	Office of Compliance
DMETS	Acceptable	21-OCT-2003	Ms. Alina R. Mahmud
Methods Validation	The method validation package will be sent to and validated by FDA laboratories.		

The Chemistry Review for NDA 21-368

The Executive Summary

*I. Recommendations**A. Recommendation and Conclusion on Approvability*

This NDA may be approved from the Chemistry, Manufacturing and Control point of view.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has made a commitment in the amendment dated 09-JAN-2004 to carry out studies to develop and validate a suitable dissolution method for the drug product. It would take approximately [] and [] production batches for establishing the in-vitro release rate specification.

*II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)***Drug product:**

The drug product, EstroGel, is a hydro-alcoholic gel for topical application and contains 0.06% of estradiol (17 β -estradiol), a drug substance. The Chemistry, Manufacturing and Control information of the "EstroGel" is located in the DMF [] for the Laboratories Besins International (formerly Laboratories Besins-Iscovesco) and it is adequate to support the NDA.

The two EstroGel formulations are made at two different sites. The formulation made by Bristol Myers Squibb (Buffalo, NY) contained [] alcohol and the formulation manufactured by Besins of France contained [] w/w of alcohol. The Bristol Myers Squibb formulation is used in clinical trials, whereas, Besins formulation is the proposed market formulation. In order to establish the pharmaceutical equivalency, a comparative in vitro release rate for estradiol from two EstroGel formulations is conducted. The formulations were evaluated at [] Two formulations showed similar estradiol release profiles. The confidence interval obtained from the slopes of the individual cells from the in vitro study was within the limits (75 to 133.33%) set by SUPAC-SS Guidance.

Pivotal clinical trials were conducted with EstroGel packaged in glamate tube and squeezed onto a measuring applicator to measure the dose. Multiple dose airless-metered dose pump dispenser is also a proposed container closure for the to-be-marketed drug product. Applicant is seeking approval for both the tube/applicator and pump dispenser. In order to establish that the mean doses of EstroGel delivered from the pump are comparable to doses delivered using the glamate tube/applicator, a comparative and consistency evaluation between the two is conducted. The mean dose delivered (comparative study) from pump dispenser is within [] of the mean dose delivered from the glamate tubes using applicator, while, the relative standard deviation of dose delivered (consistency study) from the pump dispenser is equal to or less than that delivered from the glamate tube/applicator.

The drug product is available in two different packaging configurations. Both glaninate tube and multiple dose airless metered-pump dispenser are used to package and deliver the gel. Each individually packaged tube and pump dispenser container contains 80 g and 93 g of gel, respectively and is capable of delivering sixty-four 1.25 g (0.75 mg estradiol) doses.

The quality of the gel is controlled by tests: appearance, identification, assay (estradiol and alcohol), pH, viscosity, microscopic examination, mean weight of content and bacteriological purity. Tests specific to the metered dose dispenser are also conducted to ensure in the consistency in the usable doses delivered by dispenser and they are uniformity of weight of doses, mean weight of dose and total number of doses. The test methods and respective acceptance criteria are deemed satisfactory.

Applicant commits to provide in-vitro release specification, once the method is developed and validated.

The trade name "EstroGel" has been accepted by DMETS (dated 21-OCT-2003). After revision, primary container/closure labels for tube and metered dose pump dispenser deemed adequate from the CMC and DMETS (dated 2-FEB-2004) standpoint.

The primary stability batches of the EstroGel are manufactured, packaged, and tested by Besins International (formerly Laboratoires Besins-Iscovesco) of France. The final recommendation from the Office of Compliance is **acceptable**.

Based on the updated stability data on primary stability batches, 36-months of expiration date is granted for the gel packaged in tube and metered dose pump dispenser.

Drug Substance:

The drug substance is estradiol, USP. The Chemistry, Manufacturing and Controls information of the drug substance is located in the _____'s DMF _____ and it is deemed adequate. The drug substance is accepted by the Laboratoires Besins-Iscovesco (France), drug product manufacturer, on the basis of Certificate of Analysis but is also tested by the drug product manufacturer for the physical and chemical attributes specified by the USP.

_____ manufacturing site in _____ is in compliance with cGMP.

B. Description of How the Drug Product is Intended to be Used

This product is indicated for treatment of moderate to severe vasomotor symptoms in menopausal women.

The recommended area of application is the arm, from wrist to shoulder. The EstroGel is available in the following two packaging configurations and should be used as described below:

Tube: Gently squeeze EstroGel from the tube on the provided applicator to fill the applicator to the halfway mark (1.25 mark) for 1.25 g dose and use you hand to spread the gel on the arm.

Airless Metered-dose pump container/dispenser: Prime the pump by depressing the pump twice. Discard the unused gel. After priming, pump is ready to use and one complete pump depression will dispense 1.25 g of EstroGel each time.

Chemistry Review Data Sheet

C. Basis for Approvability or Not-Approval Recommendation

- Outstanding issues from Chemistry Review # 1 (IR letter dated 01-MAY-2000) of NDA 21-166 have been satisfactorily resolved.
- The final recommendation from the Office of Compliance for the Manufacturing, Testing and Control sites is **Acceptable** (see Appendix-1).

III. Administrative

A. Reviewer's Signature Electronically captured in DFS

B. Endorsement Block

HFD-580/RAgarwal/ MRhee/ GLyght/ Date: 09-FEB-2004

C. CC Block None

APPEARS THIS WAY
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18 page(s) have been
removed because it
contains
trade secret
and/or
confidential information
that is not disclosable

D/E

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-166

DATE REVIEWED: 5/9/00

MAY 15 2000

REVIEW #: 1

REVIEWER: Rajiv Agarwal

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	13-8-99	17-8-99	28-10-99
Amendment-2	20-9-99	21-9-99	28-11-99
Amendment	11-9-99	11-10-99	11-12-99
Amendment	1-21-00	1-24-00	1-24-00
FAX	4-20-00		

NAME & ADDRESS OF APPLICANT:

UNIMED PHARMACEUTICALS, INC.
2150 E. Lake Cook Road
Suite 210
Buffalo Grove, IL 60089

DRUG PRODUCT NAME

Proprietary:
Established:
Code Name/#:
Chem. Type/Ther. Class:

ESTROGEL®
Estradiol, USP
None
3 S

PHARMACOL. CATEGORY/INDICATION:

Estrogen, Treatment of moderate to severe vasomotor symptoms in menopausal women

DOSAGE FORM:

Percutaneous Gel

STRENGTHS:

0.06% estradiol

ROUTE OF ADMINISTRATION:

Topical gel (to the arms)

Rx/OTC:

Rx OTC

SPECIAL PRODUCTS:

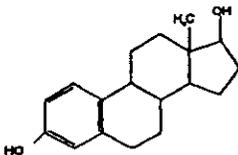
Yes No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Estradiol (estra-1, 3, 5 (10)-triene-3,17β-diol)
Molecular Formula: C₁₈H₂₄O₂
Molecular weight: 271.39

Structural Formula:



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
II/DMF []	Estradiol	[]	Adequate	5-9-00	N/A
II/DMF []	Estrogel 0.06%	Laboratories Besins-Iscovesco S.A. France	Inadequate	5-9-00	5-15-00
III/DMF []	[]	[]	Inadequate	5-10-00	5-15-00

RELATED DOCUMENTS (if applicable): None

CONSULTS:

- The EER inspection results are satisfactory (acceptable). See attached EER summary report.
- The OPDRA response is satisfactory for the use of the proprietary name, ESTROGEL (see attached review).
- The consult for Pump Dispenser was sent to Devices on 11/1/1999, review pending.
- The consult for Microbiological testing was sent to Microbiologist on: 11/10/1999. A satisfactory response is received (see attached review).

COMMENTS/REMARKS:

The Estrogel gel is composed of one active (Estradiol, USP) and four inactive (Carbomer 934P, Triethanolamine, ethyl alcohol and purified water) ingredients.

The drug substance, Estradiol (micro-) crystalline powder, is manufactured and supplied by _____, _____ as Type II DMF _____ for the drug substance, Estradiol. Dr. Amit Mitra reviewed this DMF on dated 7-13-99 and 9-10-99 in conjunction with the NDA 21-048 (see reviews in DMF _____) and the information in DMF _____ was found to be satisfactory. A supplement and an annual report was submitted to the DMF _____ on 11-4-1999 and 12-28-1999, respectively and reviewed in conjunction with the NDA 21-166. The DMF _____ was found to be adequate to support the NDA (see DMF _____ review dated 5-9-00 by Rajiv Agarwal).

The drug product is provided as a transdermal gel containing 0.6 mg of estradiol per gram of gel. The drug product will be packaged in two container/closure systems. The primary container/closure system is a pump dispenser manufactured by the _____ company. _____ This pump dispenser delivers a metered dose of ESTROGEL® (1.25 g/stroke). The other container/closure system consists of a glamate tube with a screw cap manufactured by _____ in _____ The tube will be utilized in conjunction with a metered spatula to deliver the required dose (spatula has markings for 1.25 and 2.5 g doses).

- The DMF _____ for the drug substance (Estradiol) has been found to be adequate to support the NDA 21-166.
- Majority of the CMC information is provided in the DMF _____ and it was reviewed separately. The DMF is inadequate to support the NDA 21-166.
- The DMF _____ for Glamate tube _____, has been found to be inadequate to support the NDA 21-166.
- The Amendment-2, dated 20-9-99 is for labels for all containers and packaging, inserts (physician and patient) for product packaged in tubes, complete street addresses and testing facilities.
- The Amendment dated 11-9-99 is provided for the clarification for the lots used in the clinical trials (information was requested by Dr. Rajiv Agarwal).

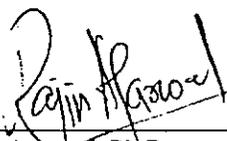
- The Amendment dated 1-21-00 is for the "response to agency request for additional information" (some information was requested by Dr. Rajiv Agarwal). It also contains the validation of the HPLC assay method for the determination of estradiol in in vitro release samples.
- A FAX was received on 4-20-00 including the following new informations:

- Change in the _____ utilized in the internal pouch from _____ to _____
- Change in the material utilized to manufacture upper and lower clack of the pump from _____ supplied by _____ to _____ (by _____)

A teleconference was setup on 4-24-00 with the sponsor in the presence of Ms. Spell-Lesane (Project Manager) and the comments were forwarded to the sponsor. An IR letter including the comments and questions related to the FAX and the deficiencies related to this NDA was also forwarded to the sponsor on 5-1-00.

CONCLUSIONS & RECOMMENDATIONS:

This application can be approved, when the sponsor of the NDA and holders of the DMFs have responded to the questions in the Draft Deficiency Letter of the NDA and DMF reviews and all responses should be reviewed and found satisfactory.



 Rajiv Agarwal, Ph.D
 Review Chemist

cc:
 Org. NDA 21-166
 HFD-580/Division File
 HFD-580/RAgarwal
 HFD-580/DSpellLesane
 HFD-580/MRhee
 R/D Init by:
 filename: NDA 21-166

MSpellLesane 5/15/00

**APPEARS THIS WAY
 ON ORIGINAL**

38 page(s) have been
removed because it
contains
trade secret
and/or
confidential information
that is not disclosable