CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75288

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-288

FIRM:

SCS Pharmaceuticals
Attn: Doranne Frano
4901 Searle Parkway
Skokie, Il 60077

DOSAGE FORM: Tablets

STRENGTH: 0.3 mg/0.03 mg

DRUG: Norgestrel & Ethinyl Estradiol Tablets USP, 0.3/0.03 mg
(Low-Ogestrel 0.3/30 21 and 28 Tablets)

CGMP STATEMENT/EIR UPDATED STATUS:
Last EER summary report for Overall Recommendation:
Acceptable (per 06/08/99, vol. 5.1).

BIO STUDY:
The *in vivo* bioequivalence study was reviewed and was accepted on 10/19/98. Bio review (final) can be found in vol. 3.1.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Methods Validation not required (USP has monographs for drug substances and drug product).

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
YES. Containers used in the stability studies are identical to those listed in container section (see CR#3).

LABELING:
Labeling is Satisfactory and was signed off by John Grace dated 06/14/99 (vol. 5.1).

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio/stability batch is the full scale as the production batch (for both active and placebo).

	Bio/stability	Production
Batch size (tablets)		
Batch size (Kg)		

Source of NDS: see table below--Referenced DMF are adequate. (see CR#3):

DS	Norgestrel, USP	Ethinyl Estradiol, USP
Supplier		
DMF#		
DMF Status	DMF last Updated(12/98) & Reviewed (01/13/99).	DMF last Updated(04/99) & Reviewed. (06/10/99).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Stability batch is the same as the bio batch (Lot# 002, tablets).

Bio/stability and stability batches are manufactured via same manufacturing process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Intended production batch size is tablets.

Manufacturing process for the intended production size is identical to that used for the bio/stability batch.

6/22/99

Bing Cai/06-15-99
Review Chemist
Division of Chemistry I
OGD/CDER

/S/ 6/22/99

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D1V

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO.: No. 1

2. ANDA #: 75-288

3. NAME AND ADDRESS OF APPLICANT:
SCS Pharmaceuticals
Attn: Doranne Frano
4901 Searle Parkway
Skokie, Il 60077

4. LEGAL BASIS FOR ANDA SUBMISSION:
505 j

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME:
Low-Ogestrel 0.3/30 21 and 28 tablets

7. NONPROPRIETARY NAME: Norgestrel and Ethinyl Estradiol Tablets

8. SUPPLEMENT(S) PROVIDE(S) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Searle:

12/24/97	Submission of ANDA (received on 12/29/97)
03/03/98	Methods verification sample Submission

FDA:

02/05/98	Accepted for filling.
02/06/98	EERs are issued.
03/27/98	Labeling review completed (Deficiencies).
04/29/98	Bio-review completed (Deficiencies).

10. PHARMACOLOGICAL CATEGORY:
Oral Contraceptive

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):
Innovator: Wyeth Ayerst Labs (Lo/Ovral, NDA 17802 & 17612)
DMF

DMF
DMF
DMF
DMF

13. DOSAGE FORM: Tablet

14. POTENCY: 0.3 mg/0.03 mg

15. CHEMICAL NAME AND STRUCTURE:
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(±)-.
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-.

16. RECORDS AND REPORTS: N/A

17. COMMENTS:
EER for has been issued with filing. EER for has to be issued.

Labeling review and bio review is completed, both of them have deficiencies.

CMC deficiencies could be found in item 38.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not approvable (Major Amendment).

19. REVIEWER: Bing Cai, Ph.D.
DATE COMPLETED: 06/12/98

cc: ANDA #75-288
DUP File
Division File
Field Copy

Endorsements:
HFD-625/CaiB/06/18/98
HFD-625/MSmela/06/22/98
HFD-625/DHuie/06/23/98

F/T: gp/06/29/98

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Chem Review #1

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-288
APPLICANT: SCS Pharmaceuticals
DRUG PRODUCT: Low-Ogestrel 0.3/30 21 and 28 Tablets

The deficiencies presented below represent Major deficiencies.

A. Deficiencies:

1. Please provide data to demonstrate that the [redacted]% overage for Ethinyl Estradiol is necessary for your production.

2. Please update your specification for Norgestrel as described in current USP/Supplement 8 (LOD test).

3. Please update your specifications for Lactose Monohydrate to current USP23, Supplement 8.

4. Please revise your COA for Microcrystalline Cellulose, to be consistent with your specifications.

5. Please update your specification for Lactose Anhydrous to current USP 23/Supplement 8. Since the vendor doesn't include the test for the content of [redacted] in their COA, you must run this test for every lot.

6. Please add spray rate limit range, as an in-process control, into your Master Batch Record

7. We believe that in order to ensure continued [redacted] for the lifetime of the drug product, you should provide for a [redacted] test and specification as a routine in-process control. An adequate testing schedule should be conducted to assure uniformity on a batch to batch basis. You may delete this testing with the approval of a supplemental application should adequate data become available to demonstrate it is unnecessary.

8. Please add individual tablet weight, as an in-process control, into your Master Batch Record.

9. Please provide test results for the container/closure system used in the biobatch (e.g., moisture permeation testing, IR, and pinhole test). Please also provide COAs for those packaging materials which were used in the biobatch.

10. Please provide a summary of your in-process controls and associated methods used in the production of the drug product.

11. Please add the disintegration test as it is required by USP to your product release specifications.

12. Please clarify the specification for "related substances." It is not clear what it means when you say NMT % (or %). Please explain if these numbers are calculated on content of Norgestrel or Ethinyl Estradiol? In addition, the specification for individual impurity should be less (e.g. %), unless the impurity is identified and justified with data.

13. Please explain your specification of the finished product for the Melting Point. It is recommended that the specification in the drug substance monograph be used.

14. Please improve your system suitability for your method for Related Substances. An RSD of % is excessive. Please also improve sensitivity for the Limit of Quantitation (LOQ) for Ethinyl Estradiol related substances. Please demonstrate that your method will allow one to detect the impurities at level of % or less.

15. Please provide a full degradation validation for your stability assay at stressed conditions such as acid, base, heat, oxidation, and light.

16. Please provide a <u>final</u> protocol/specification for your stability testing.

17. Please provide stability data, (at least Appearance), for your placebo tablets. The placebo tablets should be included in your post approval program.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data available.

2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.

3. Your response must also address the labeling deficiencies.

4. The USP analytical methods, as written, are considered regulatory for this product. Results from them shall prevail in an event of a dispute. You may not change your stability methods without approval of a supplemental application.

5. Bioequivalence of your product has not been demonstrated. Please refer to the deficiencies dated May 1, 1998. The acceptance of your dissolution test is dependent on the bioequivalence review. Please clarify the reference to lot #RCT 10242 for the bioequivalence study. CMC information (batch record, in-process and release data) are needed for the biobatch.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. CHEMIST'S REVIEW NO.: No. 2

2. ANDA #: 75-288

3. NAME AND ADDRESS OF APPLICANT:
SCS Pharmaceuticals
Attn: Doranne Frano
4901 Searle Parkway
Skokie, Il 60077

4. LEGAL BASIS FOR ANDA SUBMISSION: 505 j

5. SUPPLEMENT(S) N/A

6. PROPRIETARY NAME:
Low-Ogestrel 0.3/30 21 and 28 Tablets

7. NONPROPRIETARY NAME:
Norgestrel and Ethinyl Estradiol Tablets

8. SUPPLEMENT(S) PROVIDE(S) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Searle:

12/24/97	Submission of ANDA (received on 12/29/97)
03/03/98	Methods verification sample Submission
05/18/98	Bioequivalency Amendment
09/03/98	Bioequivalency Amendment (additional info)
10/16/98	Major CMC/Labeling Amendment

FDA:

02/05/98	Accepted for filling.
02/06/98	EERs are issued.
03/27/98	Labeling review/Deficiencies
04/29/98	Bio-review/Deficiencies letter.
07/14/98	CMC deficiency Letter.
10/19/98	Bio-review completed-Acceptable
01/11/99	Labeling review/Deficiencies.

10. PHARMACOLOGICAL CATEGORY:
Oral Contraceptive

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):
Innovator: Wyeth Ayerst Labs (Lo/Ovral, NDA 17802 & 17612)
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM: Tablet

14. POTENCY: 0.3 mg/0.03 mg

15. CHEMICAL NAME AND STRUCTURE:
18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(±)-, and
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-.

16. RECORDS AND REPORTS: N/A

17. COMMENTS:
EER are all acceptable (Per 06/26/98).

Labeling review (2nd round) is completed. It has deficiencies.

Bio-Review (2nd round) is completed. It is acceptable.

CMC deficiencies (FAX) are found in item 38.

18. CONCLUSIONS AND RECOMMENDATIONS:
Not approvable (FAX Amendment).

19. REVIEWER:	DATE COMPLETED:	DATE REVISED:
Bing Cai, Ph.D.	03/19/99	04/14/99

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Chem-Review #2

Chemistry Review

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #:** 75-288

3. **NAME AND ADDRESS OF APPLICANT:**
SCS Pharmaceuticals
Attn: Doranne Frano
4901 Searle Parkway
Skokie, Il 60077

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **SUPPLEMENT(S)** N/A

6. **PROPRIETARY NAME:**
Low-Ogestrel 0.3/30 21 and 28 Tablets

7. **NONPROPRIETARY NAME:**
Norgestrel and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Searle:

12/24/97	Submission of ANDA (received on 12/29/97)
03/03/98	Methods verification sample Submission
05/18/98	Bioequivalency Amendment
09/03/98	Bioequivalency Amendment (additional Info)
10/16/98	Major CMC/Labeling Amendment
05/27/99	FAX CMC/Labeling Amendment
06/10/99	Telephone Amendment

FDA:

02/05/98	Accepted for filling
02/06/98	EERs are issued
03/27/98	Labeling review/Deficiencies
04/29/98	Bio-review/Deficiencies letter
07/14/98	CMC deficiency Letter (1^{st}-Major)
10/19/98	Bio-review completed-Acceptable
01/11/99	Labeling review/Deficiencies
05/13/99	CMC deficiency Letter (2^{nd}-Minor)
06/10/99	Telecon

10. PHARMACOLOGICAL CATEGORY:
Oral Contraceptive

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):
Innovator: Wyeth Ayerst Labs (Lo/Ovral, NDA 17802 & 17612)
DMF
DMF
DMF
DMF

13. DOSAGE FORM: Tablet

14. POTENCY: 0.3 mg/0.03 mg

15. CHEMICAL NAME AND STRUCTURE:
18,19-Dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-,(17α)-(±)-

19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-.

16. RECORDS AND REPORTS: N/A

17. COMMENTS:
EER are all acceptable (Per 06/26/98).

Labeling review (3rd round) is not found in the jacket.

Bio-Review is acceptable (10/98).

CMC closed (06/10/99).

18. CONCLUSIONS AND RECOMMENDATIONS:
CMC closed, pending for labeling review.

19. REVIEWER:	DATE COMPLETED:	DATE REVISED:
Bing Cai, Ph.D.	06/10/99	

Labeling acceptable per DLPS/LRB review dated 6/14/99.
M Smela

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Chem. Review #3

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-288
APPLICANT: SCS Pharmaceuticals
DRUG PRODUCT: Norgestrel and Ethinyl Estradiol Tablets USP

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. Regarding use of % overage for Ethinyl Estradiol, please demonstrate that it is necessary or remove it prior to approval of this ANDA.

2. Please include the USP test for "Completeness of Solution" into your specification for Ethinyl Estradiol, USP.

3. Please revise your Master Batch Record to include following requirements.

   •Limit (range) for individual tablet weight.

   •Specification for Test:

   Sample Size: 1-3 dosage units equivalent;
   Acceptance Criteria: Mean of 90.0-110.0% with RSD no more than 5.0% for both active ingredients.

4. Please include a limit for the maximum drying time for the granulation into your Master Batch Record

5. Please clarify following issues:

   •Please indicate which supplier you will use for the aluminum foil for your container/closure system for the market place.

   •If you choose to use the C/C system using the aluminum from please provide 3-month accelerated stability on this system. Alternatively, you may withdraw as a vendor for aluminum foil.

- If you choose to use the C/C system using the aluminum form then please provide moisture permeation test result for the C/C system using the subject aluminum. You need to provide this information prior to approval of this **ANDA.**

6. Please revise your dissolution testing as following for your finished product specification and stability study based on OGD Division of Bioequivalence's Recommendation.

   The dissolution testing should be conducted in 500 mL of water with 5 ppm of Tween 80, at 37°C using USP apparatus 2 at 75 rpm. The test product should meet the following specifications:

   "Not less than % (Q) of the labeled amount of both ethinyl estradiol and norgestrel in the dosage form are dissolved in 60 minutes"

7. Please include a limit for "any unidentified individual impurity" of NMT % of the label claim (Quantitated Against an Ethinyl Estradiol Standard) into your finished product/stability specifications.

8. Please revise your room temperature storage conditions for both active and placebo tablets for your stability testing as follows:

   "25°C±2°C with 60%±5% relative humidity"

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data if available.

2. Your response must also address the labeling deficiencies.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

38. **Chemistry Comments to be Provided to the Applicant:**

ANDA: 75-288
APPLICANT: SCS Pharmaceuticals
DRUG PRODUCT: Low-Ogestrel 0.3/30 21 and 28 Tablets

The deficiencies presented below represent Major deficiencies.

A. Deficiencies:

1. Please provide data to demonstrate that the % overage for Ethinyl Estradiol is necessary for your production.

2. Please update your specification for Norgestrel as described in current USP/Supplement 8 (LOD test).

3. Please update your specifications for Lactose Monohydrate and Purified Water to current USP23, Supplement 8.

4. Please revise your COA for Microcrystalline Cellulose, to be consistent with your specifications.

5. Please update your specification for Lactose Anhydrous to current USP 23/Supplement 8. Since the vendor doesn't include the test for the content of in their COA, you must run this test for every lot.

6. Please add as an in-process control, into your Master Batch Record

7. We believe that in order to ensure continued for the lifetime of the drug product, you should provide for a test and specification as a routine in-process control. An adequate testing schedule should be conducted to assure uniformity on a batch to batch basis. You may delete this testing with the approval of a supplemental application should adequate data become available to demonstrate it is unnecessary.

8. Please add as an in-process control, into your Master Batch Record.

9. Please provide test results for the container/closure system used in the biobatch (e.g., moisture permeation testing, IR, and pinhole test). Please also provide COAs for those packaging materials which were used in the biobatch.

10. Please provide a summary of your in-process controls and associated methods used in the production of the drug product.

11. Please add the disintegration test as it is required by USP to your product release specifications.

12. Please clarify the specification for "related substances." It is not clear what it means when you say NMT % (or %). Please explain if these numbers are calculated on content of Norgestrel or Ethinyl Estradiol? In addition, the specification for individual impurity should be less (e.g. %), unless the impurity is identified and justified with data.

13. Please explain your specification of the finished product for the Melting Point. It is recommended that the specification in the drug substance monograph be used.

14. Please improve your system suitability for your method for Related Substances. An RSD of % is excessive. Please also improve sensitivity for the Limit of Quantitation (LOQ) for Ethinyl Estradiol related substances. Please demonstrate that your method will allow one to detect the impurities at level of % or less.

15. Please provide a full degradation validation for your stability assay at stressed conditions such as acid, base, heat, oxidation, and light.

16. Please provide a final protocol/specification for your stability testing.

17. Please provide stability data, (at least Appearance), for your placebo tablets. The placebo tablets should be included in your post approval program.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data available.

2. The CGMP status of the firms referenced in the ANDA will be evaluated by our Office of Compliance and an adequate evaluation is required prior to approval.

3. Your response must also address the labeling deficiencies.

4. The USP analytical methods, as written, are considered regulatory for this product. Results from them shall prevail in an event of a dispute. You may not change your stability methods without approval of a supplemental application.

5. Bioequivalence of your product has not been demonstrated. Please refer to the deficiencies dated May 1, 1998. The acceptance of your dissolution test is dependent on the bioequivalence review. Please clarify the reference to lot #RCT 10242 for the bioequivalence study. CMC information (batch record, in-process and release data) are needed for the biobatch.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center of Drug Evaluation and Research

for February 06, 1998

Application: **ANDA 75288/000**
Stamp: **29-DEC-1997** Regulatory Due:
Applicant: **SCS PHARMS**
4901 SEARLE PKY
SKOKIE, IL 60077

Priority:
Org Code: **600**
Action Goal:
District Goal: **28-FEB-1999**
Brand Name:
Established Name: **NORGESTREL; ETHINYL ESTRADIOL**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **0.3 MG 0.03MG-21&28 DAY**

FDA Contacts: **S. OKEEFE** **(HFD-617)** **301-827-5848 , Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848 , Team Leader**

Overall Recommendation:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **06-FEB-1998**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date **06-FEB-1998**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**